HEALTH PLANS
UNIVERSITY OF UTAH

Medical Policy

Cell-free DNA (cfDNA) Testing for Fetal Aneuploidy

Policy MP-018

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Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.
3. Services requiring prior-authorization may not be covered, if prior-authorization is not obtained.
4. This Medical Policy does not guarantee coverage or payment of the service. The service must be a benefit in the member's plan and the member must be eligible for coverage at the time of service. Additional payment guidelines may be applied that are not included in this policy.

Description:

Chromosomal abnormalities can complicate pregnancy. Some chromosomal abnormalities such as trisomy (having three copies of a given chromosome or chromosome segment in each somatic cell rather than the normal number of 2) occur more commonly in children of women older than age 35 when they become pregnant and if certain other high risk indicators exist. The most common trisomy conditions to occur include Trisomy 21 (Downs syndrome), Trisomy 18 (Edwards syndrome), and Trisomy 13 (Patau syndrome).

To help families and pregnant women determine if these conditions may exist various prenatal testing is undertaken particularly in high risk individuals. Currently, several different blood tests in combination with nuchal translucency assessment by ultrasound are the standard of care for screening for presence of trisomy. Either amniocentesis or chorio-villous sampling are then performed as definitive test to determine if a trisomy condition is truly present.

With the discovery of cell free fetal DNA circulating in maternal blood new methods to test for trisomy have been developed. There are a number of companies currently providing this testing including Sequenom [Materniti21], Natera [Panorama], Roche/Ariosa [Harmony] and others. These tests or assays are based on the purification of cell-free DNA from maternal plasma applying recent high-tech developments in sequence (and bioinformatics) analysis of DNA fragments. It is not known whether or to what extent the results of these and other testing technologies would be in agreement.

It is hoped that the use of these more definitive tests to detect fetal trisomy will result in the need for fewer invasive procedures such as amniocentesis or chorio-villous sampling with an associated reduction in procedure complications resulting in miscarriages and loss of the pregnancy.

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans covers testing for fetal aneuploidy when the following criteria are met:

A. Pregnancy is a singleton pregnancy (with only one fetus) at greater than 10 weeks of gestation; **and**

B. **ONE** of the following are present:

i. Women with a first or second trimester positive screen; or

ii. Pregnant women 35 years of age or older at delivery*; or

iii. Previously affected pregnancy with a trisomy; or

iv. Documented first degree relative with a translocation specific for a common trisomy; or

v. Abnormal sonographic findings.

**In cases where the pregnant woman has received a 'donor' egg and is acting as a surrogate, it is the age of the donor that is relevant to the decision process not the age of the surrogate.*

U of U Health Plans does NOT cover testing for fetal aneuploidy in multiple gestation pregnancies or any other indications.

U of U Health Plans does NOT cover fetal chromosomal microdeletions syndromes and other chromosomal disorders using circulating cell-free fetal DNA testing.

2. Medicaid Plans

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at: https://medicaid.utah.gov/utah-medicaid-official-publications/ or the Utah Medicaid code Look-Up tool

CPT/HCPCS codes covered by Utah State Medicaid may still require further evaluation to determine medical necessity for coverage.

Clinical Rationale

A review of the literature performed in August 2012 identified 3 systematic reviews and 23 primary studies. A systematic review from the California Technology Assessment Forum (CTAF) summarized well the current testing methods and sensitivity and specificity rates of seven studies conducted to evaluate the use of cfDNA for screening for fetal aneuploidy. The analysis affirmed the accuracy of cfDNA for detecting Trisomy 21. Limitations cited of the studies were the low number of patients of normal patients enrolled in the studies which may influence the specificity, the studies only included high risk women, a lack of direct comparison to current screening methods for aneuploidy and lack of data outside of an investigational study.

Most published evidence on cfDNA is based on studies conducted on high-risk populations. There is now data on the performance of cfDNA in the general obstetric population. One study conducted in 2013 compared the clinical performance of cfDNA in detecting trisomies 21, 18 and 13 in 146,958 pregnancies in low-risk versus high-risk pregnancies. There was no significant difference in test performance between the 72 382 high-risk and 40 287 low-risk subjects (sensitivity, 99.21% *vs* 98.97% (*P* = 0.82); specificity, 99.95% *vs* 99.95% [*P* = 0.98]). However, due to the lower prevalence of aneuploidy in low-risk pregnancies (e.g., in women under the age of 35), the positive predictive value of this test is lower in the general obstetric population.

Two articles seminal to the determination of clinical validity are the studies of Palomaki et al. and Bianchi et al. Each evaluated 1 of the commercially available tests, Palomaki assessing the MaterniT21™ test and Bianchi assessing the Verify™ prenatal test. Each study demonstrated the detection for aneuploidies has high sensitivity and specificity for Trisomy 21 approaching 100% under the study conditions. Additionally, sensitivity and specificity for trisomies 13 and 18 are about 78% and 97% respectively, depending on the test method/vendor. Below are the abstracts of 2 major prospective studies.

Another study by Palomaki et al, in 2017, assessed the clinical utility of cfDNA-based screening for aneuploidies offered through primary obstetrical care providers to a general pregnancy population. Among 2,681 tests reported, 16 women (0.6%) were screen-positive for trisomy 21, 18 or 13. Twelve were confirmed (PPV, 75%) and four were false-positives (0.15%). Of 150 test failures (5.6%), 79% had a negative serum or subsequent cfDNA test. There were no reported cases of aneuploidy among cfDNA test failures. This first clinical utility study of cfDNA screening found higher uptake rates, patient understanding of basic concepts, and easy incorporation into routine obstetrical practices.

Additionally, there are concerns about how the testing will fit into existing clinical care pathways. A recently published economic study, funded by the manufacturer of the Verify prenatal test suggested the greatest benefit of the testing may come from a reduction in miscarriages due to invasive testing. In the modeled population, invasive diagnostic-induced miscarriages are reduced by 66%. When an invasive procedure is not used following a positive test result, miscarriages are further reduced to about 81%. The study also suggests annual savings related to prenatal screening and diagnosis of fetal aneuploidy to be about 1%. These measures are most impacted by the cost of the cfDNA test; secondarily by the cost of amniocentesis, the rate of second trimester ultrasound and the specificity of prenatal screening.

Some evidence supports the statistical and clinical validity of fetal cell-free DNA as a means of identifying aneuploidy issues in high risk populations. Many unanswered questions remain regarding its exact clinical role, but evidence exists which supports use of the test in the appropriate setting has potential cost effectiveness and improves quality of life.

A study by Grace et al, in 2016, found that since 2011 the American College of Obstetrics and Gynecology (ACOG) and the Society for Maternal Fetal Medicine (SMFM), the International Society for Prenatal Diagnosis (ISPD), the National Society for Genetic Counselors, and the American College of Medical Genetics and Genomics only recommended cfDNA screening in singleton pregnancies, of women who are considered "high risk" defined by: 1. Their maternal age is 35 or older at time of birth; 2. Having a previous effected pregnancy with a trisomy; 3. Having a positive first or second trimester screening; 4. Having an abnormal ultrasonic finding; and 5. Parental balanced Robertsonian translocation that increases the risk of Trisomy 21 or 13. As more research became available validating the performance of cfDNA screening in general obstetric populations, some societies softened previous recommendations to limit cfDNA screening to high-risk patient populations (i.e., ISPD and The American College of Medical Genetics and Genomics).

In 2015 ACOG and SMFM published a joint committee opinion on the use of cfDNA testing concluded that "given the performance of traditional screening methods and the limitations of cfDNA, conventional screening methods remain the most appropriate choice for first-line screening for most women in the general obstetric population." However, if low risk women choose to have the screening they should have pre and post-test counseling of the limitations and benefits and should not make any pregnancy management decisions, including termination based on this test alone.

A 2015 statement from the Society for Maternal-Fetal Medicine (SMFM), indicates their recommendation for cell-free DNA aneuploidy testing should not be offered to all pregnant women, only "high risk" pregnancies described above. When it comes to patient autonomy, SMFM believes any woman who requests additional testing should be given the option of this test, even though professional societies do not recommend testing in "low risk" pregnancies. Furthermore, SMFM suggests that insurance coverage should not be required for any "low risk" pregnancies.

ACOG recently modified its guidance regarding cfDNA testing for fetal aneuploidy. It now states "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." These recommendations are based on limited evidence and Hayes in their 2022 update noted the benefits of this testing in a low risk population remains uncertain.

The 2022 Hayes clinical utility report, goes on to note, over the past few decades, the incidence of multifetal gestations has increased remarkably in the United States. Nonetheless, maternal serum screening has several limitations. In twin gestations, conventional maternal serum screening can be complicated by the presence of analytes from the normal and affected fetuses. Analyte levels are effectively averaged together, masking the abnormal levels from the affected fetus. Several aneuploidy screening methods are available for twin gestations, summarized, along with clinical performance for trisomy 21. However, there is only limited information available in screening for trisomy 18 and 13.

CfDNA provides information on the three most common aneuploidies but has not been validated for screening of microdeletions, thus cannot be recommended for clinical use. Given the low prevalence of microdeletion disorders, the significance of the results from cfDNA screening is unknown. Detection of a microdeletion would require diagnostic testing using microarray of fetal cells obtained from chorionic villus sampling or amniocentesis.

Several systemic reviews and meta-analyses of studies on the diagnostic accuracy of sequencing based tests for the detection of fetal aneuploidies have been published. For instance, a study by Iwarsson et al in 2017, reviewed the performance of noninvasive prenatal testing (NIPT) for detection of trisomy 21, 18 and 13 (T21, T18, and T13) in a general pregnant population as well as on high risk pregnancies. In the

general pregnant population, there is moderate evidence that the pooled sensitivity is 0.993 (95% CI, 0.955-0.999) and specificity was 0.999 (95% CI, 0.998-0.999) for the analysis of T21. Pooled sensitivity and specificity for T13 and T18 was not calculated in this population due to the low number of studies. In the high risk pregnant population, there is moderate evidence that the pooled sensitivities for T21 and T18 are 0.998 (95% CI, 0.981-0.999) and 0.977 (95% CI, 0.958-0.987) respectively, and low evidence that the pooled sensitivity for T13 is 0.975 (95% CI, 0.819-0.997). The pooled sensitivity for all three trisomies is 0.999 (95% CI, 0.998-0.999). The authors concluded, this is the first meta-analysis using GRADE that shows that NIPT performs well as a screen for trisomy 21 in general pregnant population. Although the false positive rate is low compared with first trimester combined screening, women should still be advised to confirm a positive result by invasive testing if termination of pregnancy is under consideration.

In conclusion, current published evidence demonstrates strong clinical validity for cfDNA testing for aneuploidy; the clinical utility is also well-established for "high risk" patients and less so for "low" or "average" risk patients given the infrequency of these genetic changes in these populations. Further study is necessary to determine if clinical utility and economic utility exist for "low" and "average risk" patients. In addition the evidence does not support use in multiple gestation pregnancies and the testing has not been validated in this setting. Lastly, the use of this testing for microdeletions is not supported due to the lack of clinical utility studies demonstrating meaningful action based on the findings from this testing.

Applicable Coding

CPT Codes

Covered codes if criteria are met:

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

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 codes:

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

HCPCS Codes

No specific codes found

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