Guidelines for Medical Necessity Determination for Maternal Cell-Free Fetal DNA Testing for Aneuploidy

These Guidelines for Medical Necessity Determination (Guidelines) identify the clinical information that MassHealth needs to determine medical necessity for noninvasive prenatal testing (NIPT) through analysis of cell-free DNA (cfDNA) in maternal blood. The majority of cfDNA in maternal blood originates from the mother herself, however about 10-20 percent is composed of fetal DNA originating from the placenta and freely circulating in maternal plasma, also known as cell-free fetal DNA (cffDNA) and can be indicative of aneuploidy risk. These Guidelines are based on generally accepted standards of practice, review of the medical literature, and federal and state policies and laws applicable to Medicaid programs.

Providers should consult MassHealth regulations at 130 CMR 401.000, 433.000, and 450.000; Subchapter 6 of the *Independent Clinical Laboratory Manual*; and Subchapter 6 of the *Physician Manual* for information about coverage, limitations, service conditions, and prior authorization (PA) requirements.

Providers serving members enrolled in a MassHealth-contracted accountable care partnership plan (ACPP), managed care organization (MCO), integrated care organization (ICO), senior care organization (SCO), or program of all-inclusive care for the elderly (PACE) should refer to the ACPP's, ICO's, MCO's, SCO's, or PACE's medical policies for covered services.

MassHealth requires PA for maternal cfDNA testing. MassHealth reviews requests for prior authorization on the basis of medical necessity. If MassHealth approves the request, payment is still subject to all general conditions of MassHealth, including member eligibility, other insurance, and program restrictions.

1 SECTION I. GENERAL INFORMATION

The American College of Obstetricians and Gynecologists (ACOG) recommends that all women, regardless of age, be offered prenatal assessment for fetal aneuploidy before 20 weeks of gestation. Screening for fetal aneuploidy can identify fetuses at increased risk for trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and trisomy 13 (patau syndrome), the three most common live-birth autosomal aneuploidies.

Prenatal screening for fetal aneuploidy traditionally uses a combination of serum analytes such as alpha-fetoprotein, human chorionic gonadotropin, unconjugated estriol, inhibin A, and pregnancy-associated plasma protein A (PAPP-A) commonly known as the quadruple screen or quad test. The quad test, combined with ultrasound markers (such as first trimester nuchal translucency and second trimester increased nuchal fold) can be used to detect risk for aneuploidy and neural tube defects. Cell-free DNA testing measures fetal DNA rather than proteins found in maternal plasma using multiple methods including determining the proportion of fetal DNA present for each chromosome. This testing methodology first became commercially available for prenatal aneuploidy screening in 2011.

Both cell-free DNA testing and the quad screen ultrasound combination are screens, not diagnostic tests, and assess the fetus's risk for prenatal aneuploidy. Thus, for both modalities of screening, if the screening indicates that the fetus is at high risk for prenatal aneuploidy, invasive procedures such as chorionic villus sampling (CVS) or amniocentesis, with their risks (including fetal loss), are required for diagnosis. In addition, the cell-free DNA test does not screen for risk of fetal anomalies such as neural tube defects or ventral wall defects.

The data regarding the performance of cfDNA screening in multiple gestations are limited, as the fraction of fetal DNA is a composite of all of the fetuses and cannot be individualized. Hence neither ACOG nor the Society for Maternal-Fetal Medicine (SMFM) recommends the use of cfDNA screening in multiple gestations.

While the sensitivity and specificity of cfDNA testing is reported as high, it is not 100 percent and false positive and false negative cfDNA screening results have been reported. The actual frequency of discordant results is unknown and there is no central registry for reports of false negatives and false positives. As well, in practice the rates of false positives and false negatives may be higher than the original studies showed. CfDNA testing does not replace the universal 11-13 week ultrasound scan and serum protein measures which detect fetal neural tube or ventral wall defects. It also does not replace the need for invasive diagnostic testing (e.g., CVS or amniocentesis) in high-risk pregnancies with abnormal screening results.

Both false negatives and false positives occur with cfDNA testing. False negatives can occur because of low levels of fetal DNA in the maternal serum related to early fetal age, maternal obesity, or sampling errors as a result of a failure to collect a sufficient volume of cfDNA. These situations cause falsely low proportions of fetal material resulting in a potential false negative screen. Some reasons for false positive results include maternal malignancies, maternal mosaicism for aneuploidy, or placental mosaicism. Maternal mosaicisms and malignancies can be associated with chromosomal anomalies. Both maternal and fetal DNA are sequenced in cfDNA testing making it possible that a maternal anomaly would interfere with the fetal risk assessment and create a false positive. With placental mosaicism, the placental cells which are measured in cfDNA testing may have an aneuploidic chromosome complement without the fetus having an aneuploidy, thus creating a false positive result. In this case the test would detect that aneuploidy even though the fetus may be normal because the primary source of cfDNA is the trophoblastic tissue which develops into the placenta. Another possible cause of a false positive is the demise of a co-twin which could result in higher than typical proportions for a singleton pregnancy. There are no formal guidelines to indicate how long after the demise of a co-twin the cffDNA from the demised fetus persists. As well, the loss of a twin is not always apparent either to the mother or to the physician. In addition unknown maternal karyotype abnormalities, such as low level maternal Turner syndrome and copy number variants, can affect interpretation of the results.

2 SECTION II. CLINICAL GUIDELINES

A. CLINICAL COVERAGE

MassHealth bases its determination of medical necessity for maternal cfDNA testing for trisomies 21, 18, and 13 on clinical data including, but not limited to, indicators that would affect the relative risks and benefits of the test. These criteria, which are adapted from ACOG Practice Bulletin Number 163, May 2016 and ACOG Committee Opinion Number 640, September 2015 include, but are not limited to, the following.

1. The test is being used as a primary screening test in a pregnant woman with a singleton gestation who is at an increased risk of aneuploidy, as evidenced by meeting any of the following indications (a-d):
    a. Women aged 35 years and older, at expected time of delivery; or
    b. Fetal ultrasonographic findings predict an increased risk of fetal aneuploidy (absent or hypoplastic nasal bone, choroid plexus cyst, echogenic bowel, echogenic intracardiac focus, fetal pyelectasis, nuchal translucency, nuchal fold, ventriculomegaly, and shortened femur or humerus); or
    c. Women with a history of a prior pregnancy affected with a trisomy; or
    d. A parent carrying a balanced Robertsonian translocation with increased risk of trisomy 13 or trisomy 21; or
2. The test is being used as a secondary screening test in a member with a positive screening test for an aneuploidy, including first trimester, sequential, or integrated screen, or a positive quadruple screen.

B. NONCOVERAGE

MassHealth does not consider maternal cfDNA testing to be medically necessary under certain circumstances. Examples of such circumstances include, but are not limited to, the following.

1. Maternal cfDNA testing in women with multiple gestations.
2. Maternal cfDNA testing performed at laboratories that do not report results as a numerical risk score for each trisomy, as recommended by ACOG and American College of Medical Genetics (ACMG).
3. Applications of maternal cfDNA testing for reasons other than screening for fetal aneuploidy, such as other chromosomal disorders.
4. Maternal cfDNA testing in women who are not at increased risk of aneuploidy.
5. Maternal cfDNA testing for the purpose of determining the sex or gender of the fetus including for the diagnosis of sex-linked genetic disorders.
6. Maternal cfDNA testing in egg donor pregnancies.
7. Maternal cfDNA testing performed at laboratories that are not contracted with MassHealth.

3 SECTION III. SUBMITTING CLINICAL DOCUMENTATION

Requests for PA for maternal cfDNA testing must be accompanied by clinical documentation that supports the medical necessity for this procedure.

A. Documentation of medical necessity must include all of the following.

   1. A copy of the completed test requisition, which has been signed and dated by the ordering physician;

   2. Primary diagnosis name and ICD-10 code pertinent to clinical scenario; and

   3. Documentation of the clinical history and/or results of prior testing that meet clinical coverage criteria (see Section II.A "Clinical Coverage").

B. Clinical information must be submitted by the clinical laboratory performing the genetic testing. Providers are strongly encouraged to submit requests electronically. Providers must submit the request for PA and all supporting documentation using the Provider Online Service Center (POSC), or by completing a MassHealth *Prior Authorization Request (*PA-1 form) found at www.mass.gov/masshealth and attaching all supporting documentation. Questions about POSC access should be directed to the MassHealth Customer Service Center at (800) 841-2900.

Select References

1. ACOG Committee on Genetics Committee Opinion No. 640: Cell-free DNA screening for fetal aneuploidy. *Obstet Gynecol.* 2015 Sep;126(3):e31-7.

2. ACOG Committee on Practice Bulletins ACOG Practice Bulletin No. 163: screening for fetal aneuploidy. *Obstet Gynecol.* 2016 May;127(5):e123-37.

3. Grace MR, Hardisty E, Dotters-Katz SK, Vora NL, Kuller JA. Cell-Free DNA Screening: Complexities and Challenges of Clinical Implementation. *Obstet Gynecol Surv.* 2016 Aug;71(8):477-87.

4. Mennuti MT, Cherry AM, Morrissette JJ, *et al.* Is it time to sound an alarm about false-positive cell-free DNA testing for fetal aneuploidy? *Am J Obstet Gynecol.* 2013 Nov;209(5):415-9.

5. Nicolaides KH, Syngelaki A, Ashoor G, *et al.* Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. *Am J Obstet. Gynecol.* 2012 Nov;207(5):374 e1-6.

6. Norton ME, Jelliffe-Pawlowski LL, Currier RJ. Chromosome abnormalities detected by current prenatal screening and noninvasive prenatal testing. *Obstet Gynecol.* 2014 Nov; 124:979–986.

7. Sparks AB, Struble CA, Wang ET, *et al.* Noninvasive prenatal detection and selective analysis of cell-free DNA obtained from maternal blood: evaluation for trisomy 21 and trisomy 18. *Am J Obstet Gynecol.* 2012 Apr;206(4):319.el-9.

8. Verweij EJ, de Boer MA, Oepkes D. Non-invasive prenatal testing for trisomy 13: more harm than good? *Ultrasound Obstet Gynecol.* 2014 Jul;44 (1):112–14.

These Guidelines are based on review of the medical literature and current practice in maternal cell-free fetal DNA testing for aneuploidy. MassHealth reserves the right to review and update the contents of these Guidelines and cited references as new clinical evidence and medical technology emerge.

This document was prepared for medical professionals to assist them in submitting documentation supporting the medical necessity of the proposed treatment, products or services. Some language used in this communication may be unfamiliar to other readers; in this case, contact your healthcare provider for guidance or explanation.

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