CLINICAL MEDICAL POLICY	
Policy Name:	Fetal Aneuploidy Testing Using Noninvasive Cell-Free Fetal DNA
Policy Number:	MP-020-MC-ALL
Responsible Departments:	Medical Management; Medical Policy
Provider Notice Date:	07/01/2017
Original Effective Date:	08/01/2017
Annual Approval Date:	06/01/2018
Revision Date:	N/A
Products:	Ohio Medicare Assured
Application:	All participating and nonparticipating hospitals and providers
Page Number(s):	1 of 9

DISCLAIMER

Gateway Health℠ (Gateway) clinical 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

Gateway Health℠ provides coverage for laboratory benefit under the medical benefits of the Company's Medicare 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).

Gateway Health℠ 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.

DEFINITIONS

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 following tests are commercially available:
   a) Harmony™ Prenatal Test
   b) MaterniT21™ Plus
   c) verifi® Prenatal Test
   d) Panorama
   e) informaSeq℠

2) These tests are considered eligible as advanced screening technology for pregnant women at high risk, as determined by the following medical necessity:
   a) Advanced maternal age (pregnant women aged 35 years and older at expected time of delivery); AND
   b) Testing is offered between 9 and 13 weeks gestational age in women with singleton gestation;-AND
   c) Fetal ultrasonography findings predictive of increased risk of fetal aneuploidy (i.e., 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
   d) Positive screening test for an aneuploidy, including first trimester, sequential, or integrated screen, or a positive quadruple screen; OR
   e) History of a prior maternal pregnancy with an aneuploidy; OR
   f) Parental balanced Robertsonian translocation with increased risk for fetal trisomy 13 or trisomy 21.
   g) 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.
   h) Use of noninvasive prenatal testing using the cell-free DNA test for the determination of fetal sex or fetal RHD genotyping is typically not medically necessary and will require case-by-case review.
   i) Women with positive cfDNA tests should be offered invasive prenatal diagnostic tests with amniocentesis or chorionic villus sampling.

j) Genetic counseling is strongly recommended prior to testing in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person.

3) When Noninvasive Cell-Free Fetal DNA is not covered
   - 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 will require case-by-case review.
   - Services for DNA-based prenatal microdeletion and microduplication syndromes are unproven and not medically necessary.

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

5) 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 counseling for mutations. This service is necessary in order to inform persons being tested about the benefits and limitations of a specific genetic test for the specific patient. Genetic testing for mutation requires documentation of medical necessity from one of the following providers who has evaluated the patient and intends to see the person after testing has been performed for counseling:
   a) Board Eligible or Board Certified Genetic Counselor
   b) Advanced Genetics Nurse
   c) Genetic Clinical Nurse
   d) Advanced Practice Nurse in Genetics
   e) Board Eligible or Board Certified Clinical Geneticist
   f) A physician with experience in cancer genetics
   g) A physician specializing in the care for the indication(s) for genetic testing

6) Place of Service
   The place of service for testing to be administered 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.

Additional information is available online at:
http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm.

Coverage Determination
Gateway Health℠ follows the coverage determinations made by CMS as outlined in either the national coverage determinations (NCD) or the state-specific local carrier determination (LCD).

For Ohio, please use the following for CGS Administrators, LLC list of LCDs:
https://www.cms.gov/medicare-coverage-database/indexes/lcd-list.aspx?Cntrctr=228&name=CGS%20Administrators,%20LLC%20(15102,%20MAC%20-%20Part%20B)&DocType=All&DocStatus=Active&ContrVer=2&CntrctrSelected=228*2&s=22&bc=AggAAAQAAAAAAA%3d%3d&#ResultsAnchor

CODING REQUIREMENTS

Procedure Codes

CPT Codes	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
0009M	Fetal aneuploidy (trisomy 21, and 18) DNA sequencing of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy

Noncovered Experimental Procedure Code
All requests for this service must be reviewed by a Medical Director

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

Diagnosis Codes

ICD-10 Codes	Description
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
O09.299	Supervision of pregnancy with other poor reproductive or obstetric history, unspecified 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
O09.519	Supervision of elderly primigravida, unspecified 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
O09.529	Supervision of elderly multigravida, unspecified trimester

O28.1	Abnormal hematological finding on antenatal screening of mother
O28.2	Abnormal cytological 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
O28.9	Unspecified abnormal finding on antenatal screening of mother
O35.0XX9	Maternal care for (suspected) chromosomal nervous system malformation in fetus, other fetus
O35.1XX0	Maternal care for (suspected) chromosomal abnormality in fetus, not applicable or unspecified
O35.1XX1	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 1
O35.1XX9	Maternal care for (suspected) chromosomal abnormality 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
Q92.6	Marker chromosomes
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 screening for other specified diseases and disorders
Z31.438	Encounter for other genetic testing of female for procreative management

REIMBURSEMENT

Participating facilities will be reimbursed per their Gateway Health℠ contract.

SUMMARY OF LITERATURE

In 2015, the American College of Obstetricians and Gynecologists (ACOG) reported that noninvasive prenatal testing using cell-free fetal DNA from the plasma of pregnant women is an important screening tool for fetal aneuploidy. In addition, the ACOG society identified the following indications as appropriate for cell-free DNA:

- Maternal age 35 years or older at time of delivery
- Fetal ultra-sonographic findings predicting increased risk of fetal aneuploidy
- History of prior pregnancy with aneuploidy; positive screening test for aneuploidy, including first trimester, sequential, or integrated screen, or a positive quadruple screen
- Parental balanced Robertsonian translocation with increased risk for fetal trisomy 13 or trisomy 21

ACOG commented that cell-free DNA testing should not be offered to low-risk women or women with multiple gestations, or be part of routine prenatal laboratory testing because the test has not been evaluated in these groups.

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.

The Society for Maternal Fetal Medicine (2015) stated cell-free DNA screening is largely recommended in patients at higher risk for aneuploidy and not the lower risk populations since there is limited studies on this population. The Society for Maternal Fetal Medicine (SMFM) does not consider cell-free DNA screening as first-line screening and that conventional screening methods should be utilized in this group.

In the analysis performed by Norton and colleagues (2013), it was stated that the use of the cell-free DNA in maternal plasma represents a tremendous advance in prenatal diagnosis. In this analysis, it was noted that true cost-utility analysis is necessary to determine the actual clinical effectiveness of this screening in the general prenatal population.
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. (2015) 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.

Fetal chromosomal microdeletions in genomic sequence analysis are chromosomal deletions that are too small to be detected by microscopy or conventional cytogenetic methods. Microdeletions and microduplications are known as copy number variations (CNVs). There are several genomic disorders associated with microdeletions such as DiGeorge syndrome and Cri-du-chat syndrome. These disorders may have distinctive and serious clinical features such as cardiac anomalies, immune deficiency, palatal defects, and developmental delay.

The clinical utility of microdeletion testing is unknown. At this time, there is no data on whether testing for microdeletions improves outcomes in comparison to the current standards of care. Additional clinical studies are needed to gain experience with routine genetic screening for microdeletions as well as clarity on clinical follow-up for detected microdeletions. The American College of Medical Genetics and Genomics (2016) does not recommend microdeletion screening. If this level of information is desired, then appropriate diagnostic testing (e.g., amniocentesis) is recommended.

POLICY SOURCE(S)

Ashoor G, Syngelaki A, Wagner M, et al. Chromosome-selective sequencing of maternal plasma cell-free DNA for first-trimester detection of trisomy 21 and trisomy 18. Am J Obstet Gynecol. 2012; 206(4):322.e1-5. Accessed on January 21, 2016 and available at: http://www.ajog.org/article/S0002-9378(12)00060-9/pdf.

Palomaki GE, Deciu C, Kloza EM, et al. DNA sequencing of maternal plasma reliably identifies trisomy 18 and trisomy 13 as well as Down syndrome: an international collaborative study.

Genet Med. 2012; 14(3):296-305. Accessed on January 21, 2106 and abstract available at: http://www.nature.com/gim/journal/v14/n3/full/gim201173a.html.

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; 206(4):319.e1-9. Accessed on January 16, 2016 and abstract available at: http://www.ajog.org/article/S0002-9378(12)00061-0/abstract.

Garfield SS, Armstrong SO. Clinical and cost consequences of incorporating a novel non-invasive prenatal test into the diagnostic pathway for fetal trisomies. Journal of Managed Care Medicine. 2012; 15(2):34-41. Accessed on January 17, 2016 and available at: http://www.namcp.org/journals/jmcm/articles/15-2/Non%20Invasive%20Penatal.pdf.

Norton M.E., Brar H., Weiss J., et al. Non-Invasive Chromosomal Evaluation (NICE) study: results of a multicenter, prospective, cohort study for detection of fetal trisomy 21 and trisomy 18. Am J Obstet Gynecol. 2012 Aug; 207(2):137.e1-8. Accessed on January 20 2016 and available at: http://www.ajog.org/article/S0002-9378%2812%2900584-4/pdf.

Cell-free DNA screening for fetal aneuploidy. Committee Opinion No. 640. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2015; 126:e31-7. Accessed on January 21, 2016 and available at: https://www.acog.org/-/media/Committee-Opinions/Committee-on-Genetics/co640.pdf?dmc=1&ts=20160121T1130445567.

Palomaki G.E., Kloza E.M., Lambert-Messerlian G.M., et al. DNA sequencing of maternal plasma to detect Down syndrome: An international clinical validation study. Genetics in Medicine. 2011 Nov; 13(11):913-920. Accessed on January 20, 2016 and available at: http://www.nature.com/gim/journal/v13/n11/full/gim2011155a.html.

Gil M.M., Quezada M.S., Bregant B., et al. Implementation of maternal blood cell-free DNA testing in early screening for aneuploidies. Ultrasound Obstet Gynecol. 2013; 42(1):34-40. Accessed on January 17, 2016 and abstract available at: http://onlinelibrary.wiley.com/doi/10.1002/uog.12504/abstract.

Nicolaides K.H., Syngelaki A., Gil M., et al. Validation of targeted sequencing of single-nucleotide polymorphisms for non-invasive prenatal detection of aneuploidy of chromosomes 13, 18, 21, X, and Y. Prenat Diagn. 2013; 33(6):575-9. Accessed on January 17, 2016 and available at: http://onlinelibrary.wiley.com/doi/10.1002/pd.4103/abstract.

Pergament E., Cuckle H., Zimmermann B., et al. Single-nucleotide polymorphism-based noninvasive prenatal screening in a high-risk and low-risk cohort. Obstet Gynecol. 2014; 124(2 Pt 1):210-8. Accessed on January 20, 2016 and available at: http://journals.lww.com/greenjournal/Fulltext/2014/08000/Single_Nucleotide_Polymorphism_Based_Noninvasive.3.aspx.

Dar P., Curnow K.J., Gross S.J., et al. Clinical experience and follow-up with large scale single- nucleotide polymorphism—based noninvasive prenatal aneuploidy testing. Am J Obstet Gynecol. 2014; 211: 527. Accessed on January 20, 2016 and abstract available at: http://www.ajog.org/article/S0002-9378%2814%2900818-7/abstract.

Bianchi D, Parker R, Wentworth J, et al. DNA sequencing versus standard prenatal aneuploidy screening. CARE Study Group. N Engl J Med. 2014; 370(9):799-808. Accessed on January 17, 2016 and available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1311037.

The American College of Medical Genetics and Genomics (ACMG). ACMG statement on noninvasive prenatal screening for fetal aneuploidy. Genet Med. 2013; 15(5):395-398. Accessed on January 20, 2016 and available at: https://www.acmg.net/docs/nips-GiM_galley_text_130301.pdf.

Society for Maternal Fetal Medicine (SMFM). SMFM Statement: Maternal serum cell-free DNA screening in low risk women. Accessed on January 21, 2016 and available at: https://www.smfm.org/publications/193-cell-free-dna-screening.

Curnow KJ, Wilkins-Haug L, Ryan A, Kirkizlar E, Stosic M, Hall MP, et al. Detection of triploid, molar, and vanishing twin pregnancies by a single-nucleotide polymorphism-based noninvasive prenatal test. Am J Obstet Gynecol. 2015; 212:79.e1–79.e9. Accessed on January 17, 2016 and abstract available at: http://www.ajog.org/article/S0002-9378(14)01054-0/abstract.

Langlois S, Brock JA, et al. Current status in non-invasive prenatal detection of Down syndrome, trisomy 18, trisomy 13 using cell free DNA in maternal plasma. J Obstet Gynaecol Can. 2013 Feb; 35(2):177-83. Accessed on January 22, 2016 and available at: http://www.ncbi.nlm.nih.gov/pubmed/23470070.

Gregg AR, Skotko BG, Benkendorf JL, Monaghan KG, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. 2016 Oct; 18(10); 1056-1065. Accessed on May 4, 2017 and available at: http://www.acmg.net/docs/ACMG_NIPS_FINAL_STATEMENT_GIM_Oct%202016.pdf.

Pennsylvania Department of Human Services. Technology Assessment Group (TAG) Coverage Decisions. TAG meeting on 5/3/2017 review of fetal chromosome analysis; procedure code 81422. Managed Care Operations Memorandum to be published.

Policy History

Date	Activity
06/02/2017	Initial policy developed
06/21/2017	QI/UM Committee approval
08/01/2017	Provider effective date