Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
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Plan: AmeriHealth Caritas Pennsylvania	**Submission Date**: February 28, 2020
Policy Number: CCP.1002	**Effective Date:** 9/2013 **Revision Date:** February 4, 2020
Policy Name: Maternal genetic testing	

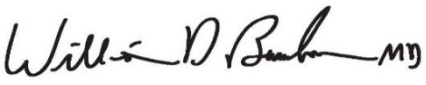
Type of Submission – Check all that apply:

- ☐ **New Policy**
- ☑ **Revised Policy***
- ☐ **Annual Review – No Revisions**
- ☐ **Statewide PDL**

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

Please see revisions below using tracked changes.

Name of Authorized Individual (Please type or print): William D. Burnham, MD	**Signature of Authorized Individual:** 

AmeriHealth Caritas Pennsylvania

Maternal genetic testing

Clinical Policy ID: CCP.1002

Recent review date: 2/2020

Next review date: 6/2021

Policy contains: DNA sequencing of maternal plasma; Harmony™ test (Ariosa Diagnostics, San Jose, Ca) for trisomy 21 and 18; MaterniT21® Plus (Sequenom Lab; San Diego, Ca) for trisomy 21, 18, and 13; QNatal® Advanced test (Quest Diagnostics) for trisomy 21, 18, and 13; verifi® prenatal test (Illumina, Inc.; San Diego, Ca) for trisomy 21, 18, and 13; Panorama™ test for aneuploidy at 13, 18, 21, X, Y, and triploidy

AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania's clinical policies are not guarantees of payment.

Coverage policy

Screening for aneuploidy for trisomies 21, 18, and 13 (first trimester screening, maternal analyte screening, or fetal cell free DNA sequencing of gestational maternal plasma) is clinically proven and, therefore, medically necessary when the following criteria are met (American College of Obstetricians and Gynecologists, 2016a; 2016b):

1. Testing should be discussed and offered to all women early in pregnancy (between 10 and 13 weeks of gestational age) or at the first prenatal visit if after 13 weeks).

2. The test is an analytically and clinically valid test (i.e., supported by peer-reviewed published research).

    a. The test is ordered by a trained professional. It should be accompanied by pre-test and post-test counseling by a trained professional (e.g., obstetrician/gynecologist, specialist in medical genetics, developmental-behavioral pediatrician, condition-specific subspecialist, maternal-fetal specialist, or perinatologist or neonatologist for neonates in the neonatal intensive care unit).

b. For women who consent to test, the test results will be discussed with the patient or guardian, including the limitations of the testing method, the risks and benefits of either continuing or stopping therapy based on the test, and current disease management guidelines.

c. There is a care-coordinating, multidisciplinary team available for genetic and behavioral counseling for a tiered evaluation, which includes the obstetric provider and a geneticist (who is a physician or a licensed genetic counselor).

d. The patient or guardian has a desire for engagement with the integrated multidisciplinary team that is documented in the clinical record.

3. Women with positive screening test results are offered further counseling and testing, including invasive prenatal diagnostic tests with amniocentesis or chorionic villus sampling.

Limitations

All other uses of DNA sequencing for maternal genetic testing are considered investigational and are therefore not medically necessary.

Alternative covered services

Alternatives include measurement of maternal serum markers such as alpha fetoprotein, unconjugated estriol, and inhibin A.

Other covered tests include ultrasound determination of nuchal translucency and crown-rump length, chorionic villous sampling, or amniocentesis.

Background

Genetic predisposition is reported to represent 30% of premature deaths (Schroeder, 2007). The number of diseases with a genetic basis expand the impact of genetic testing. Such laboratory analyses cover a wide range of molecular, chromosomal, cytogenetic, and biochemical methods. These tests have the promise of improving health if, as a result of such testing, therapeutic steps may be taken by the patient and treating physicians. However, testing that does not result in informing clinical decision-making is wasteful. Further, every test has potential false positive and false negative results, which may cause emotional or physical harm to tested patients.

Because of these hopes and concerns, the federal government in 2002 established The Secretary's Advisory Committee on Genetics, Health, and Society (Department of Health and Human Services, 2008). This body has worked to develop a framework for genetic and molecular testing to reduce confusion and improve the specificity of testing for individuals at risk for genetically-based clinical disorders. The Committee undertook the evaluation of genetic and molecular testing with consideration of the following attributes:

- Analytical and clinical validity.
- Proficiency testing and quality assurance essential for continuous quality management.
- Demonstration of clinical utility.
- Education and guidance for clinicians, laboratory personnel, and other health care professionals.
- Ongoing public health.

- Coordination of public- and private-sector activities.

The MaterniT21® Plus test is based upon circulating cell-free DNA purified from the plasma component of anti-coagulated maternal whole blood. The DNA is analyzed and converted into a genomic library for the determination of chromosome 21, 18, 13, fetal sex, and sex chromosome aneuploidies, based on massively parallel DNA sequencing (Sequenom, 2015). Studies to date have suggested that the MaterniT21® Plus has had an acceptable specificity and sensitivity for the more common aneuploidies but, due to low frequency in the overall population, it remains challenging to validate findings for screening for the more rare forms of aneuploidies. Therefore, MaterniT21® Plus is not recommended as a screening test.

Findings

There are several FDA-approved tests for fetal aneuploidy. These cell-free tests rely on measurement of fractured fetal DNA found circulating in the maternal bloodstream. The American College of Obstetricians and Gynecologists reviewed these tests in May of 2016 (American College of Obstetricians and Gynecologists, 2016a). The Committee Opinion recommends that all women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age:

> "The choice of screening test is affected by many factors, including a desire for information before delivery, prior obstetric history, family history, and the number of fetuses. Other factors to be considered include gestational age at presentation, the availability of a reliable nuchal translucency measurement, screening test sensitivity and limitations, the cost of screening, the constraints of long-term care of an affected child, and options for pregnancy care or termination for an abnormal diagnostic test result. No one test is superior for all test characteristics and not every test is available at all centers. Each test has advantages and disadvantages that should be discussed with each patient, with the appropriate test offered based on her concerns, needs, and values. Obstetrician–gynecologists and other obstetric care providers should become familiar with the available screening and diagnostic testing options for their patients within their practice and adopt a standard approach for counseling. Regardless of which screening tests are offered, information about the detection (sensitivity) and positive screening and false-positive rates, advantages, disadvantages, and limitations should be communicated to the patient. At the time of counseling regarding aneuploidy screening, the benefits and risks of diagnostic testing (amniocentesis and CVS) also should be discussed. After counseling, patients may decline screening or diagnostic testing for any reason."

References

On November 5, 2019, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "genetic testing" (MeSH), "maternal testing" (MeSH), and "laboratory test." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

American College of Obstetricians and Gynecologists. Prenatal Diagnostic Testing for Genetic Disorders. American College of Obstetricians and Gynecologists Committee Practice Bulletin No. 162. *Obstet Gynecol* 2016a;127(5):e108-122. Doi: 10.1097/AOG.0000000000001405

American College of Obstetricians and Gynecologists, Committee on Practice Bulletins—Obstetrics, Committe on Genetics, and Society for Maternal–Fetal Medicine. Practice Bulletin No. 163: Screening for Fetal Aneuploidy. *Obstet Gynecol.* 2016b;127(5):e123-e137. Doi: 10.1097/AOG.0000000000001406

Badeau M, Lindsay C, Blais J, et al. Genomics-based non-invasive prenatal testing for detection of fetal chromosomal aneuploidy in pregnant women. *Cochrane Database Syst Rev.* 2017;11:Cd011767. Doi: 10.1002/14651858.CD011767.pub2

Canick JA, Kloza, Lambert-Messerlain GM, et al. DNA sequencing of maternal plasma to identify Down syndrome and other trisomies in multiple gestations. *Prenat Diagn*. 2012 Aug;32(8):730-734. Doi: 10.1002/pd.3892

Carlson LM, Vora NL. Prenatal diagnosis: Screening and diagnostic tools. *Obstet Gynecol Clin North Am*. 2017;44(2):245-256. Doi: 10.1016/j.ogc.2017.02.004

Chiu RW, Akolekar R, Zheng YW, et al. Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. *BMJ*. 2011 Jan 11;342:c7401. Doi: 10.1136/bmj.c7401.2

Chiu RW, Lo YM. Noninvasive prenatal diagnosis empowered by hih-throughput sequencing. *Prenat Diagn.* 2012; 32(4):401-406. Doi: 10.1002/pd.3822

Hardisty EE, Vora NL. Advances in genetic prenatal diagnosis and screening. *Curr Opin Pediatr*. 2014; 26(6):634-638. Doi: 10.1097/MOP.0000000000000145

Iwarsson E, Jacobsson B, Dagerhamn J, Davidson T, Bernabe E, Heibert Arnlind M. Analysis of cell-free fetal DNA in maternal blood for detection of trisomy 21, 18 and 13 in a general pregnant population and in a high risk population - a systematic review and meta-analysis. *Acta Obstet Gynecol Scand.* 2017;96(1):7-18. Doi: 10.1111/aogs.13047

Natoli JL, Ackerman DL, McDermott S, Edwards JG. Prenatal diagnosis of Down syndrome: a systematic review of termination rates (1995-2011). *Prenat Diagn.* 2012; 32:142-153. Doi: 10.1002/pd.2910

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; 207:374.e1-6. Doi: 10.1016/j.ajog.2012.08.033

Norton, M., Brar, H., Weiss, J., Karimi, A., 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; 207(2):137.e1-8. Doi: 10.1016/j.ajog.2012.05.021

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. Doi: 10.1038/gim.2011.73

Pan M, Huang LY, Zhen L, Li DZ. A cost-effectiveness analysis comparing two different strategies in advanced maternal age: Combined first-trimester screening and maternal blood cell-free DNA testing. *Taiwan J Obstet Gynecol.* 2018;57(4):536-540. Doi: 10.1016/j.tjog.2018.06.011

Quest Diagnostics. About QNatal® Advanced. 2018a. https://www.questdiagnostics.com/home/physicians/testing-services/by-test-name/noninvasive/about.html Accessed November 6, 2019.

Quest Diagnostics. About QNatal® Advanced. 2018b. https://www.questdiagnostics.com/home/physicians/testing-services/by-test-name/noninvasive/faq.html Accessed November 6, 2019.

Schroeder SA, We can do better — improving the health of the American people. *N Engl J Med.* 2007; 357:1221-8. Doi: 10.1056/NEJMsa073350

Strom CM, Anderson B, Tsao D, et al. Improving the positive predictive value of non-invasive prenatal screening (NIPS). *PloS one.* 2017;12(3):e0167130. Doi: 10.1371/journal.pone.0167130

Sequenom Laboratories. MaterniT 21PLUS® provider information. https://laboratories.sequenom.com/tests/reproductive-health/maternit21-plus#provider-overview/. Accessed November 6, 2019.

U.S. system of oversight of genetic testing: a response to the charge of the Secretary of Health and Human Services (HHS) Report of the Secretary's Advisory Committee on Genetics, Health, and Society. *Per Med*. 2008;5(5): 521–528. doi: 10.2217/17410541.5.5.521

Verweij EJ, van den Oever JM, et al. Diagnostic accuracy of noninvasive detection of fetal trisomy 21 in maternal blood: a systematic review. *Fetal Diagn Ther.* 2012; 31(2):81-6. Doi: 10.1159/000333060

Walsh JME, Goldberg JD. Fetal aneuploidy detection by maternal plasma DNA sequencing: a technology assessment. *Prenat Diagn.* 2013 Jun;33(6):514-20. doi: 10.1002/pd.4109

Zhao Y, Abuhamad A, Fleenor J, et al. Prenatal and postnatal survival of fetal tetralogy of fallot: a meta-analysis of perinatal outcomes and associated genetic disorders. *J Ultrasound Med*. 2016;35(5):905-15. Doi: 10.7863/ultra.15.04055

Policy updates

12/2012: initial review date and clinical policy effective date: 9/2013

11/2016: Publications updated:

- A narrative review (Hardisty, 2014) identified prenatal tests routinely offered to pregnant women and identified the use of chromosomal microarray analysis as a first-tier test in place of standard karyotype in selected cases. The authors also reiterated the place of prominence cell-free DNA prenatal testing for the detection of aneuploidy has assumed in the high-risk population and noted a variety of new applications (e.g., microdeletion syndromes) that were not previously evaluated.

- A systematic review (Zhao, 2016) compared the genetic testing results in three subtypes of tetralogy of Fallot (tetralogy of Fallot with pulmonary stenosis, tetralogy of Fallot with pulmonary atresia, and tetralogy of Fallot with an absent pulmonary valve). The survival rates (termination of pregnancy was considered fetal death) for prenatally diagnosed tetralogy of Fallot with pulmonary atresia and tetralogy

of Fallot with an absent pulmonary valve at the end of the neonatal period were significantly lower than the survival rate for tetralogy of Fallot with pulmonary stenosis. The authors concluded that prenatal differentiation by providers among the subtypes of tetralogy of Fallot can help specialists better counsel their patients.

1/2018: References updated:

- In Practice Bulletin 163, the American College of Obstetricians and Gynecologists described and reviewed the available testing options for fetal aneuploidy, noting that combined first- and second-trimester screening with either integrated, sequential, or contingent screening protocol provides a higher detection rate than one-step screening (2016b). The American College of Obstetricians and Gynecologists recommends that all pregnant women, regardless of age, be offered aneuploidy screening or prenatal diagnostic testing for genetic disorders, and makes several recommendations and conclusions which are included in Appendix A.

- A systematic review (Badeau, 2017) examined and compared the diagnostic accuracy of massively parallel shotgun sequencing and targeted massively parallel sequencing for genomics-based non-invasive prenatal testing in the following two populations: as a first-tier test in unselected pregnant women being screened for aneuploidies or as a second-tier test in pregnant women categorized as high risk subsequent to first-tier screening for common fetal aneuploidies. Both tests performed similarly for detecting fetal T31, T18, T13, and sex chromosome aneuploidy in terms of sensitivity and specificity, but the two tests were not compared in any of the included studies. The laboratory Quest Diagnostics developed the non-invasive prenatal test QNatal® Advanced, which is based on cell-free DNA technology and tests for trisomies 21, 18, and 13, fetal sex aneuploidies, and select copy number variants (Quest, 2018a; Strom, 2017). According to Quest, the test is intended for high-risk and multiple-gestation pregnancies as well as pregnancies from in vitro fertilization of donor eggs, and can be ordered at 10 weeks' gestation for high-risk patients who are 35 or older, have had an abnormal ultrasound, have had a previous pregnancy with one of the chromosomal anomalies that this test screens for, or have a positive maternal serum screening test (Quest, 2018b). The test should not be used for women who have had a bone marrow transplant.

11/2018: References updated. The policy ID changed from 02.01.01 to CCP.1002.

11/2019: References updated.

Appendix A

Excerpt from American College of Obstetricians and Gynecologists, Committee on Practice Bulletins — Obstetrics, Committee on Genetics, and Society for Maternal-Fetal Medicine. Practice Bulletin No. 163: Screening for Fetal Aneuploidy. *Obstet Gynecol.* 2016b;127(5):e123 – e137. This practice bulletin was reaffirmed in 2018.

Summary of Recommendations and Conclusions

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

- Women who have a negative screening test result should not be offered additional screening tests for aneuploidy because this will increase their potential for a false-positive test result.

- If an enlarged nuchal translucency, an obvious anomaly, or a cystic hygroma is identified on

ultrasonography, the patient should be offered genetic counseling and diagnostic testing for aneuploidy as well as follow-up ultrasonography for fetal structural abnormalities.

- Patients with an enlarged nuchal translucency or cystic hygroma and normal fetal karyotype should be offered an anatomic evaluation in the second trimester, fetal cardiac ultrasonography, and further counseling regarding the potential for genetic syndromes not detected by aneuploidy screening.

- Women who undergo first-trimester screening should be offered second-trimester assessment for open fetal defects (by ultrasonography, MSAFP screening, or both) and ultrasound screening for other fetal structural defects.

- Because cell-free DNA is a screening test, it has the potential for false-positive and false-negative test results and should not be used as a substitute for diagnostic testing.

- All women with a positive cell-free DNA test result should have a diagnostic procedure before any irreversible action, such as pregnancy termination, is taken.

- Women whose cell-free DNA screening test results are not reported, are indeterminate, or are uninterpretable (a no call test result) should receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy.

- Women with a positive screening test result for fetal aneuploidy should be offered further detailed counseling and testing.

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

- Cell-free DNA screening tests for microdeletions have not been validated clinically and are not recommended at this time.

- Patients who conceive after preimplantation genetic screening for aneuploidy should be offered aneuploidy screening and diagnosis during pregnancy.

- No method of aneuploidy screening is as accurate in twin gestations as it is in singleton pregnancies. Because data generally are unavailable for higher-order multifetal gestations, analyte screening for fetal aneuploidy should be limited to singleton and twin pregnancies.

The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):

- Screening for aneuploidy should be an informed patient choice, with an underlying foundation of shared decision making that fits the patient’s clinical circumstances, values, interests, and goals.

- Aneuploidy screening or diagnostic testing should be discussed and offered to all women early in pregnancy, ideally at the first prenatal visit.

- All women should be offered the option of an aneuploidy screening, or diagnostic testing for fetal genetic disorders, regardless of maternal age.

- If an isolated ultrasonographic marker for aneuploidy is detected, the patient should be offered aneuploidy screening if it was not offered previously.

- Some women who receive a positive test result from traditional screening may prefer to have cell-free DNA screening rather than undergo definititive testing. This approach may delay definitive diagnosis and management and may fail to identify some fetuses with aneuploidy.

- Parallel or simultaneous testing with multiple screening methodologies for aneuploidy is not cost-effective and should not be performed.

- In multifetal gestations, if fetal demise or an anomaly is identified in one fetus, serum-based aneuploidy screening should be discouraged. There is a significant risk of an inaccurate test result in these circumstances.

For more information:
The American College of Obstetricians and Gynecologists has identified additional resources on topics related to this document that may be helpful for obgyns, other health care providers, and patients. You may view these resources at www.acog.org/more-info/AneuploidyScreening.
These resources are for information only and are not meant to be comprehensive. Referral to these resources does not imply the American College of Obstetricians and Gynecologists' endorsement of the organization, the organization's web site, or the content of the resource. The resources may change without notice.