MOLINA HEALTHCARE

Molina Healthcare of South Carolina

South Carolina Molina Clinical Policy Aneuploidy

State(s):	South Carolina	Policy #:	SC_MCP_603 Aneuploidy
Lines of Business:	Medicaid	Original Effective Date:	7/10/2018
		MCPC Approved:	9/19/2022
Next Review Date:	September 2024	Review Date:	9/11/2023
	*Full version control see approval history below	Revision Date(s):	9/19/2022

DISCLAIMER

This South Carolina Molina Clinical Policy (SC-MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this SC_MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Noninvasive cell-free DNA (cfDNA) testing is a prenatal screening test used to detect common chromosome aneuploidies that result in various congenital conditions. The most common of these conditions is trisomy 21 (T21, or Down syndrome), which results from the presence of an extra copy of chromosome 21. Other common conditions include trisomy 18 (T18, or Edwards syndrome), trisomy 13 (T13, or Patau syndrome), Klinefelter syndrome (47,XXY), triple X syndrome (47,XXX), and 47,XYY syndrome.

Currently, there are a number of cfDNA tests available in the United States including the MaterniT21 PLUS, the Verifi Prenatal Test, the Harmony Prenatal Test, the InformaSeq, Invitae NIPS, Prequel prenatal screen, QNatal Advanced Screen, and the Panorama Prenatal Test. The tests work by sequencing cell-free fetal DNA (cffDNA) fragments present in the maternal blood stream. Each assay is different with respect to its exact methodology and algorithms for data analysis and each commercial laboratory has its own proprietary platform and bioinformatics pipeline. Techniques used to study cffDNA include quantitative polymerase chain reaction (PCR), mass spectrometry, digital PCR, and massively parallel DNA sequencing (DynaMed, 2018).

Cell-free DNA testing is the most sensitive screening option for aneuploidies involving chromosomes 21, 18, and 13. The proposed advantages of cfDNA tests are that the detection rate is much higher (approximately MHSC MEDICAL COVERAGE POLICY Original Effective Date: 6/1/2022 Subject: CELL FREE DNA TESTING FOR CHROMOSOMAL ANEUPLOIDY Policy Number: SC-MCP-680 Revision Date(s): 7/1/2022 Approval Date: 8/1/2022 Richard Shrouds, Chief Medical Officer Review Date: 8/10/2022 SC Healthcare Services Committee Approval Date: 8/18/2022 Page 2 of 7 © Copyrighted and proprietary to Molina Healthcare South Carolina, Inc. 2022 99.5% for T21, 97.7% for T18, and 96.1% for T13) and the false-positive rate is much lower (< 0.1%), when compared with other screening options (Palomaki, et. al., 2021). Therefore, it is expected that using this test prior to chorionic villus sampling (CVS) or amniocentesis will increase the overall detection of fetal aneuploidies, decrease the number of unnecessary invasive testing procedures performed, and decrease the number of procedure-related pregnancy losses.

Alternatives include traditional prenatal screening tests, such as first-trimester screening, second-trimester maternal serum screening, a combination of first- and second-trimester screens (i.e., integrated or sequential screening), and a detailed ultrasound evaluation in the second trimester. It is important to note that cfDNA screening does not assess risk for other fetal anomalies such as neural tube defects or ventral wall defects. Also, cfDNA screening for aneuploidy is not diagnostic, so patients with positive results should be referred for genetic counseling and potentially for diagnostic tests such as CVS or amniocentesis (i.e., invasive prenatal diagnosis).

Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. However, CLIA regulations are restricted to certifying internal procedures and qualifications of laboratories rather than the safety and efficacy of specific

tests. Clinical laboratories may develop and validate tests inhouse and market them as a laboratory service. Laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories offering LDTs must be licensed by CLIA for high-complexity testing.

SOUTH CAROLINA COVERAGE POLICY

Please check individual state health plan regulations and benefit contracts before applying this MCP. Coverage of female sterilization is applicable to individual State and Federal Health Plan Medicaid regulations and benefit contracts that supersede this policy. All State and Federal Health Plan eligibility requirements including any applicable consent forms must be met and completed.

South Carolina Department of Health and Human Services (SCDHHS) regulations are defined below for Aneuploidy:

Non-Invasive Prenatal Testing (NIPT) using maternal serum cell-free fetal DNA (cffDNA) to screen for fetal aneulploidy (trisomy 13, 18, and 21) **may be considered medically necessary** for members meeting **ALL** the following criteria which includes elements outlined in the SC-DHHS Physician Services Provider Manual, version January 2022.

- Laboratory is a qualified Molina par provider; and
- Underwent pretest counseling; and
- Current pregnancy greater than or equal to 10 weeks and less than 23 weeks at the time blood will be drawn; and
- High risk for fetal aneuploidy as evidenced by ANY of the following indications [ONE]:
    - o Maternal age greater than or equal to 35 years at delivery
    - o Maternal history of child affected with trisomy
    - o Abnormal fetal ultrasound findings indicating an increased risk of aneuploidy
    - o Positive test result for aneuploidy, including first trimester, sequential or integrated screen or quadruple screen.
    - o A parent carrying a balanced Robertsonian translocation with increased risk of trisomy 13 or trisomy 21.

SOUTH CAROLINA COVERAGE EXCLUSIONS AND LIMITATIONS

COVERAGE EXCLUSIONS AND LIMITATIONS

ALL of the following clinical and billing conditions are considered **NOT** medically necessary and are excluded from coverage:

- Screening of an average or low-risk pregnancy
- Multiple gestation pregnancy
- Parallel or simultaneous testing with multiple screening methodologies for fetal aneuploidy
- Screening for sex chromosome aneuploidies
- Screening in pregnancies with multifetal gestations if a fetal demise, vanishing twin, or anomaly is identified in one fetus
- Screening for nonmedical traits (e.g., screening for gender identification)
- Screening for microdeletions and single-gene mutations by cell-free DNA
- No more than one cell-free fetal DNA test performed per pregnancy
- When karyotyping, aneuploidy FISH, and/or array CGH have already been performed on the pregnancy within 10 weeks of the cell-free fetal DNA test
- Duplicative or repeat testing due to low fetal fraction or test failure
- Non-specific procedure codes (e.g., 81479, 81599, 84999) or any procedure codes that do not accurately describe the test methodology performed

END South Carolina Department of Health and Human Services (SCDHHS) regulations

DOCUMENTATION REQUIREMENTS. *Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.*

CODING & BILLING INFORMATION

CPT Codes

CPT	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, and 21
81422	Non-invasive prenatal screening for fetal chromosomal microdeletions
81105-81479	Non-invasive prenatal screening for single-gene mutations
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

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.*

REFERENCES

Government Agency

1. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database. National coverage determination forcytogenic studies (190.3). Available from CMS. Effective July 16, 1998. Accessed February 1, 2022.
2. South Carolina Medicaid Physician Services Provider Manual. Non-Invasive Prenatal Screening (NIPS). January 2022

Evidence Based Reviews and Publications

1. AMR Peer Review. Policy reviewed February 7, 2022 by a board-certified physician practicing in Clinical Molecular Genetics.
2. DynaMed. Screening for down syndrome. Ipswich (MA): EBSCO Information Services. Record No. T902971. Updated November 30, 2018. https://www.dynamed.com. Registration and login required. Accessed February 1, 2022.
3. eviCore National Lab Management Policy on Noninvasive Prenatal Testing (NIPT). 2020.
4. Hayes. Clinical utility evaluation: Cell-free DNA (cfDNA) screening for fetal chromosomal copy number variants. https://evidence.hayesinc.com/. Published November 9, 2017. Accessed December 15, 2021. Registration and login required.
5. Hayes. Clinical utility evaluation: Cell-free DNA (cfDNA) screening for fetal rare autosomal trisomies. https://evidence.hayesinc.com/. Published December 21, 2021. Accessed January 31, 2022. Registration and login required.
6. Hayes. Clinical utility evaluation: Cell-free DNA (cfDNA) screening for fetal sex chromosome aneuploidy. https://evidence.hayesinc.com/. Published October 26, 2017. Updated September 23, 2021. Accessed December 15, 2021. Registration and login required.
7. Hayes. Clinical utility evaluation: Cell-free DNA (cfDNA) screening for fetal trisomy 21, 18, and 13 in low-risk women with singleton pregnancy. https://evidence.hayesinc.com/. Published October 5, 2017. Updated April 19, 2021. Accessed December 15, 2021. Registration and login required.
8. Hayes. Clinical utility evaluation: Cell-free DNA (cfDNA) screening for fetal trisomy 21, 18, and 13 in women with twin pregnancies.https://evidence.hayesinc.com/. Published July 7, 2021. Accessed December 15, 2021. Registration and login required.
9. Palomaki G, Messerlian G, Halliday J. Prenatal screening for common aneuploidies using cell-free DNA. http://www.uptodate.com. Updated November 23, 2021. Accessed December 15, 2021. Registration and login required.

Peer Reviewed Publications

1. Ashoor G, Syngelaki A, Wagner M, Birdir C, Nicolaides KH. Chromosome-selective sequencing of maternal plasma cell-free DNA for first-trimester detection of trisomy 21 and trisomy 18. Am J Obstet Gynecol. 2012 Apr;206(4):322.e1-5. doi: 10.1016/j.ajog.2012.01.029.
2. Ashoor G, Syngelaki A, Wang E, et al. Trisomy 13 detection in the first trimester of pregnancy using a chromosome-selective cell-free DNA analysis method. Ultrasound Obstet Gynecol. 2013;41(1):21-25.
3. Bianchi DW, Platt LD, Goldberg JD, Abuhamad AZ, Sehnert AJ, Rava RP et al. Maternal blood is source to accurately diagnose fetal aneuploidy (MELISSA) study group. Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. Obstet Gynecol. 2012 May;119(5):890-901.
4. Bianchi DW, Parker RL, Wentworth J, et al.; CARE Study Group. DNA sequencing versus standard prenatal aneuploidy screening. N Engl J Med. 2014;370(9):799-808.
5. Brar H, Wang E et al. The fetal fraction of cell-free DNA in maternal plasma is not affected by a priori risk of fetal trisomy. The Journal of Maternal-Fetal and Neonatal Medicine, 2012; Early Online: 1–3. doi: 10.3109/14767058.2012.722731.

6. Canick JA, Kloza EM, Lambert-Messerlian GM, Haddow JE, Ehrich M, van den Boom D, et al. DNA sequencing of maternal plasma to identify Down syndrome and other trisomies in multiple gestations. Prenat Diagn. 2012 Aug;32(8):730-4. doi: 10.1002/pd.3892.
7. Chiu RW, Akolekar R, Zheng YW, Leung TY, Sun H, Chan KC, 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.
8. Dar P, Curnow KJ, Gross SJ, et al. Clinical experience and follow-up with large scale single-nucleotide polymorphism-based noninvasive prenatal aneuploidy testing. Am J Obstet Gynecol. 2014;211(5):527.e1-527.e17.
9. Ehrich M, Deciu C, Zwiefelhofer T, Tynan JA, Cagasan L, Tim R, et al. Noninvasive detection of fetal trisomy 21 by sequencing of DNA in maternal blood: a study in a clinical setting. Am J Obstet Gynecol. 2011 Mar;204(3):205.e1-11.
10. Futch T, Spinosa J, Bhatt S, de Feo E, Rava R, Sehnert A. Initial clinical laboratory experience in noninvasive prenatal testing for fetal aneuploidy from maternal plasma DNA samples. Prenat Diagn. 2013;33(6):569-74.
11. Gil MM, Galeva S, et al. Screening for trisomies by cfDNA testing of maternal blood in twin pregnancy: update of The Fetal Medicine Foundation results and meta-analysis. Ultrasound Obstet Gynecol. 2019 Jun;53(6):734-742. doi: 10.1002/uog.20284. Accessed January 31, 2022.
12. Gil MM, Quezada M, Bregnant B, Ferraro M, Nicolaides KH. Implementation of maternal blood cell-free DNA testing in early screening for aneuploidies, ULTRASOUND Obstet Gynecol. (2013). doi: 10.1002/uog.12504. Accessed here.
13. Guy C, Haji-Sheikhi F, Rowland CM, Anderson B, Owen R, Lacbawan FL, Alagia DP. Prenatal cell-free DNA screening for fetal aneuploidy in pregnant women at average or high risk: Results from a large US clinical laboratory. Mol Genet Genomic Med. 2019 Mar;7(3):e545. doi: 10.1002/mgg3.545. Accessed February 8, 2022.
14. Kagan KO, et al. False-Positive Rate in First-Trimester Screening Based on Ultrasound and Cell-Free DNA versus First-Trimester Combined Screening with Additional Ultrasound Markers. Fetal Diagn Ther. 2019;45(5):317-324. doi: 10.1159/000489121. Accessed January 31, 2022.
15. Kagan KO, et al. First-trimester risk assessment based on ultrasound and cell-free DNA vs combined screening: a randomized controlled trial. Ultrasound Obstet Gynecol. 2018 Apr;51(4):437-444. doi: 10.1002/uog.18905. Accessed January 31, 2022.
16. Khalil A, Archer R, et al. Noninvasive prenatal screening in twin pregnancies with cell-free DNA using the IONA test: a prospective multicenter study. Am J Obstet Gynecol. 2021 Jul;225(1):79.e1-79.e13. doi: 10.1016/j.ajog.2021.01.005. Accessed February 1, 2022.
17. Luo Y, Hu H, et al. A retrospective analysis the clinic data and follow-up of non-invasive prenatal test in detection of fetal chromosomal aneuploidy in more than 40,000 cases in a single prenatal diagnosis center. 2020 Sep;63(9):104001. doi: 10.1016/j.ejmg.2020.104001. Accessed February 2, 2022.
18. McCullough RM, Almasri EA, Guan X, et al. Non-invasive prenatal chromosomal aneuploidy testing--clinical experience: 100,000 clinical samples. PloS One. 2014;9(10):e109173.
19. Migliorini S et al., First-trimester screening based on cell-free DNA vs combined screening: A randomized clinical trial on women's experience. Prenat Diagn. 2020 Jul 19. doi: 10.1002/pd.5800. Accessed January 31, 2022.
20. Nicolaides KH, Syngelaki A, Ashoor G, Birdir C, Touzet G. Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. Am J Obstet Gynecol. 2012 Nov;207(5):374.e1-6. doi: 10.1016/j.ajog.2012.08.033.
21. Nicolaides KH, Syngelaki A, Gil M, Atanasova V, Markova D. 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):575-579.
22. Norton ME, Brar H, Weiss J, Karimi A, Laurent LC, Caughey AB, 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. doi: 10.1016/j.ajog.2012.05.021.
23. Norton ME, Jacobsson B, Swamy GK, et al. Cell-free DNA analysis for noninvasive examination of trisomy. N Engl J Med. 2015 Apr 23;372(17):1589-97.
24. Norton ME, Baer RJ, Wapner RJ, et al. Cell-free DNA vs sequential screening for the detection of fetal chromosomal abnormalities. Am J Obstet Gynecol. 2016 Jun;214(6):727.e1-6.
25. Palomaki GE, Deciu C, Kloza EM, Lambert-Messerlian GM, et al. (2012 Mar). DNA sequencing of maternal plasma reliably identifies trisomy 18 and trisomy 13 as well as Down syndrome: an international collaborative study. Genet Med, 14(3):296-305. doi: 10.1038/gim.2011.73.
26. Palomaki GE, Kloza EM, Lambert-Messerlian GM, Haddow JE, Neveux LM, Ehrich M, et al. DNA sequencing of maternal plasma to detect Down syndrome: an international clinical validation study. Genet Med. 2011 Nov;13(11):913-20.
27. Sparks AB, Struble CA, Wang ET, Song K, Oliphant A. 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. 2012b;206(4):319.e1-e9.
28. Sparks AB, Wang ET, Struble CA, et al. Selective analysis of cell-free DNA in maternal blood for evaluation of fetal trisomy. Prenat Diagn. 2012a;32(1):3-9.
29. Verweij EJ, van den Oever JM, de Boer MA, Boon EM, Oepkes D. Diagnostic accuracy of no

National and Specialty Organizations

1. American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin #226. Screening for Fetal Chromosomal Abnormalities. Obstet Gynecol. 2020 Oct;136(4):e48-e69. doi: 10.1097/AOG.0000000000004084. Accessed February 1, 2022.
2. American College of Obstetricians and Gynecologists (ACOG). Practice Advisory. Cell-free DNA to screen for single-gene disorders. 2019 Feb. Available at: https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Advisories/Cell-freeDNA-to-Screen-for-Single-Gene-Disorders
3. Benn P, Borell A, Chiu R, et al. Position statement from the Aneuploidy Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis. Prenat Diagn. 2013; 33(7):622-9.
4. Gregg AR, Skotko BG, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement
5. of the American College of Medical Genetics and Genomics. 2016 Oct;18(10):1056-65. doi: 10.1038/gim.2016.97. Accessed February 1, 2022.
6. National Society of Genetic Counselors Position Statements: Prenatal cell-free DNA screening. Released October 11, 2016. Updated April 23, 2021. Available from NSGC. Accessed February 1, 2022.
7. Prabhu M, Kuller JA, Biggio JR. Society for Maternal-Fetal Medicine Consult Series #57: Evaluation and management of isolated soft ultrasound markers for aneuploidy in the second trimester: (Replaces Consults #10, Single umbilical artery, October 2010; #16, Isolated echogenic bowel diagnosed on second-trimester ultrasound, August 2011; #17, Evaluation and management of isolated renal pelviectasis on second-trimester ultrasound, December 2011; #25, Isolated fetal choroid plexus cysts, April 2013; #27, Isolated echogenic intracardiac focus, August 2013). Society Am J Obstet Gynecol. 2021 Oct;225(4):B2-B15. doi: 10.1016/j.ajog.2021.06.079. Accessed February 8, 2022.
8. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. SMFM Consult Series #36 Prenatal aneuploidy screening using cell-free DNA. Am J Obstetr Gynecol. 2015 Jun;212(6):711-6. doi: 10.1016/j.ajog.2015.03.043. Accessed February 1, 2022.

Other Resources

1. Illumina. Verifi prenatal test services. Available from Illumina.
2. Sequenom®CMM® website. MateriT21™ PLUS. http://www.sequenomcmm.com
3. Ariosa™ Diagnostics website. Harmony™ Prenatal Test. http://www.ariosadx.com/
4. ParanormaTM website. Panorama Prenatal Test. http://www.panoramatest.com

APPROVAL HISTORY

Revision	Review	MCP-Committee Approval Date	Comments
	9/11/2023	9/11/2023	HCS Committee reviewed and approved
9/19/2022	9/19/2022	9/19/2022	SC MCP Updated formatting and disclaimers no change in content from 8/15/2022, Approved by D Enigl and Dr. Shrouds
7/1/2022	8/10/2022	8/15/2022	SC MCP Policy reviewed, updated for South Carolina Medicaid Coverage Policy based on the DHHS Physicians Services Provider Manual v.Jan 2022.
		6/1/2022	SC MCP created
		2/9/2022	MCP Policy reviewed; renamed from Noninvasive Prenatal Testing; updated Overview, Summary of Evidence and Reference sections
		6/8/2021	MCP Removed CPT code 0009M, deleted 1/1/2020 by AMA.
		12/9/2021	MCP Updated references and added summary for ACOG Practice Bulletin #226. This policy was re-reviewed internally, and no changes have been made to the criteria based on the new ACOG guidelines
		6/17/2020	MCP Policy reviewed, updated coding (added CPT codes 81422, 81105-81479), updated professional guideline
		6/19/2019	MCP Policy reviewed, no changes to criteria; updated references.
		7/10/2018	MCP Policy reviewed, no changes to criteria; updated references.
		6/22/2017	MCP Policy reviewed, revised, and reinstated. This MCP supersedes Evicore criteria; clinical criteria section did not change; updated Exclusions, Summary of Medical Evidence, Professional Guidelines, and Reference section
		6/22/2014	MCP Policy retired and replaced by Evicore DNADirect criteria.
		12/11/2013	MCP Policy created