MolDX: Molecular Diagnostic Tests (MDT)

Medicare Advantage Medical Policy No.: MNG-023

The Health Plan reserves the right to amend this policy and procedure at any time. Exceptions to this policy and procedure will be made on a case-by-case basis at the total discretion of the Health Plan.

Effective Date: June 18, 2024

Instructions for use

This policy serves to provide guidance in determining coverage based on medical necessity. It also gives a list of resources used to create these guidelines. Medical necessity determinations will be made in accordance with generally accepted standards of medical practice, taking into account credible scientific evidence published in peer reviewed medical literature generally recognized by the relevant medical community, physician specialty society recommendations, and the views of the physicians practicing in relevant clinical areas, and other relevant factors, as they relate to the member's clinical circumstances.

Medicare Advantage Members

Coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria will be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of the coverage criteria and is to be used by all plans and lines of business unless Federal or State law, contract language, including member or provider contracts, take precedence over the policy.

Basic Requirements for Clinical Appropriateness:

1. Before diagnostic or therapeutic intervention, a clinician must confirm the diagnosis or establish the likelihood based on a history and physical exam and, when appropriate, a review of laboratory studies, previous diagnostic testing and response to any prior interventions, specifically relevant to the clinical situation.
2. An alternative treatment or other appropriate intervention should not offer any greater benefit based on standards of medical practice and/or current literature.
3. The potential benefit to the patient should outweigh the risk of the diagnostic or therapeutic intervention.
4. A reasonable likelihood of the intervention changing management and/or leading to an improved outcome for the patient must exist, based on the clinical evaluation, current literature and standards of medical practice.

If these requirements are not apparent in the request for authorization, including the clinical documentation provided, the determination of appropriateness will most likely require a peer-to-peer

conversation to understand the individual and unique facts that would supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

Simultaneous ordering of multiple diagnostic or therapeutic interventions and/or repeated diagnostic or therapeutic interventions in the same anatomic area may be denied, unless individual circumstances support the medical necessity of performing interventions simultaneously or repeatedly. This should be apparent in the clinical documentation or in peer-to-peer conversations.

MolDX: Molecular Diagnostic Tests (MDT)

CMS National Coverage Policy

Title XVIII of the Social Security Act, §1862(a)(1)(A), states that no Medicare payment shall be made for items or services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of malformed body member."

Title XVIII of the Social Security Act, §(a)(1)(D), Investigational or Experimental.

45 CFR §162.1002 (a)(5), Medical data code sets

CMS Internet-Only Manual, Pub. 100-08, Medicare Program Integrity Manual, Chapter 13, §13.5.4 Reasonable and Necessary Provisions in LCDs

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This coverage policy provides the following information:

- Defines tests required to register for a unique identifier
- Defines tests required to submit a complete technical assessment (TA) for coverage determination
- Defines the payment rules applied to covered tests that are not reported with specific codes from a code set recognized in 45 CFR §162.1002 (a)(5), and termed “HIPAA compliant code sets” throughout the remainder of this coverage policy
- Lists specific covered tests that have completed the registration and TA process and meets Medicare’s reasonable and necessary criteria for coverage.

Tests evaluated through the application process and/or technical assessment will be reviewed to answer the following questions:

- Is the test performed in the absence of clinical signs and symptoms of disease?
- Will the test results provide the clinician with information that will improve patient outcomes and/or change physician care and treatment of the patient?
- Will the test results confirm a diagnosis or known information?
- Is the test performed to determine risk for developing a disease or condition?
- Will risk assessment change management of the patient?
- Is there a diagnosis specific indication to perform the test?

- Is the test performed to measure the quality of a process or for Quality Control/Quality Assurance (QC/QA), i.e., a test to ensure a tissue specimen matches the patient?

Molecular Diagnostic Test (MDT) Policy Specific Definitions

MDT: Any test that involves the detection or identification of nucleic acid(s) deoxyribonucleic acid/ribonucleic acid (DNA/RNA), proteins, chromosomes, enzymes, cancer chemotherapy sensitivity and/or other metabolite(s). The test may or may not include multiple components. An MDT may consist of a single mutation analysis/identification, and/or may or may not rely upon an algorithm or other form of data evaluation/derivation.

Laboratory developed test (LDT): Any test developed by a laboratory developed without Food and Drug Administration (FDA) approval or clearance.

Applicable Tests/Assays

In addition to the MDT definition, this coverage policy applies to all tests that meet at least one of the following descriptions:

- All non-FDA approved/cleared laboratory developed tests (LDT)
- All modified FDA-approved/cleared kits/tests/assays
- All tests/assays billed with more than one code from a HIPAA compliant code set to identify the service, including combinations of method-based, serology-based, and anatomic pathology codes
- All tests that meet the first three bullets and are billed with a Not Otherwise Classified (NOC) code

CPT Codes:

81105, 81106, 81107, 81108, 81109, 81110, 81111, 81112, 81120, 81121, 81161, 81162, 81163, 81164, 81165, 81166, 81167, 81168, 81170, 81171, 81172, 81173, 81174, 81175, 81176, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81191, 81192, 81193, 81194, 81200, 81201, 81202, 81203, 81204, 81205, 81206, 81207, 81208, 81209, 81210, 81212, 81215, 81216, 81217, 81218, 81219, 81220, 81221, 81222, 81223, 81224, 81225, 81226, 81227, 81228, 81229, 81230, 81231, 81232, 81233, 81234, 81235, 81236, 81237, 81238, 81239, 81240, 81241, 81242, 81243, 81244, 81245, 81246, 81247, 81248, 81249, 81250, 81251, 81252, 81253, 81254, 81255, 81256, 81257, 81258, 81259, 81260, 81261, 81262, 81263, 81264, 81265, 81266, 81267, 81268, 81269, 81270, 81271, 81272, 81273, 81274, 81275, 81276, 81277, 81278, 81279, 81283, 81284, 81285, 81286, 81287, 81288, 81289, 81290, 81291, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81301, 81302, 81303, 81304, 81305, 81306, 81307, 81308, 81309, 81310, 81311, 81312, 81313, 81314, 81315, 81316, 81317, 81318, 81319, 81320, 81321, 81322, 81323, 81324, 81325, 81326, 81327, 81328, 81329, 81330, 81331, 81332, 81333, 81334, 81335, 81336, 81337, 81338, 81339, 81340, 81341, 81342, 81343, 81344, 81345, 81346, 81347, 81348, 81349, 81350, 81351, 81352, 81353, 81355, 81357, 81360, 81361, 81362, 81363, 81364, 81374, 81377, 81381, 81383, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81410, 81411, 81412, 81413, 81414, 81415, 81416, 81417, 81419, 81420, 81422, 81425, 81426, 81427, 81430, 81431, 81432, 81433, 81434, 81435, 81436, 81437, 81438, 81439, 81440, 81441, 81442, 81443, 81445, 81448, 81449, 81450, 81451, 81455, 81456, 81460, 81465, 81470, 81471, 81479, 81493, 81504, 81507, 81518, 81519, 81520, 81521, 81522, 81523, 81525, 81528, 81529, 81540, 81541, 81542, 81546, 81551, 81552, 81554, 81595, 0004M, 0006M, 0007M, 0011M, 0012M, 0013M, 0016M, 0017M,

0001U, 0005U, 0016U, 0017U, 0018U, 0019U, 0022U, 0023U, 0026U, 0027U, 0029U, 0030U, 0031U, 0032U, 0033U, 0034U, 0036U, 0037U, 0040U, 0045U, 0046U, 0047U, 0048U, 0049U, 0050U, 0055U, 0060U, 0069U, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U, 0078U, 0079U, 0084U, 0087U, 0088U, 0089U, 0090U, 0091U, 0094U, 0101U, 0102U, 0103U, 0111U, 0112U, 0113U, 0114U, 0118U, 0120U, 0129U, 0130U, 0131U, 0132U, 0133U, 0134U, 0135U, 0136U, 0137U, 0138U, 0153U, 0154U, 0155U, 0156U, 0157U, 0158U, 0159U, 0160U, 0161U, 0162U, 0169U, 0170U, 0171U, 0172U, 0173U, 0175U, 0177U, 0179U, 0180U, 0181U, 0182U, 0183U, 0184U, 0185U, 0186U, 0187U, 0188U, 0189U, 0190U, 0191U, 0192U, 0193U, 0194U, 0195U, 0196U, 0197U, 0198U, 0199U, 0200U, 0201U, 0203U, 0204U, 0205U, 0209U, 0211U, 0212U, 0213U, 0214U, 0215U, 0216U, 0217U, 0218U, 0221U, 0222U, 0229U, 0230U, 0231U, 0232U, 0233U, 0234U, 0235U, 0236U, 0237U, 0238U, 0239U, 0242U, 0244U, 0245U, 0246U, 0250U, 0258U, 0260U, 0262U, 0264U, 0265U, 0266U, 0267U, 0268U, 0269U, 0270U, 0271U, 0272U, 0273U, 0274U, 0276U, 0277U, 0278U, 0282U, 0285U, 0286U, 0287U, 0288U, 0289U, 0290U, 0291U, 0292U, 0293U, 0294U, 0296U, 0297U, 0298U, 0299U, 0300U, 0306U, 0307U, 0313U, 0314U, 0315U, 0318U, 0319U, 0320U, 0323U, 0326U, 0327U, 0329U, 0330U, 0331U, 0332U, 0333U, 0335U, 0336U, 0339U, 0340U, 0341U, 0347U, 0348U, 0349U, 0350U, 0355U, 0356U, 0362U, 0363U, 0439U, 0440U, 0444U, 0448U, 0449U

Unique Test Identifier Requirement

Because the available language in the current HIPAA compliant code sets used to describe the pathology and laboratory categories and the tests included in those categories are not specific to the actual test results provided, all MDT services must include an identifier as additional claim documentation. Test providers must receive an identifier specific to the applicable test and submit the test assigned identifier with the claim for reimbursement. The assigned identifier will provide a crosswalk between the test's associated detail information on file and the submitted claim detail line(s) required to adjudicate each test's claim. The unique identifier limits the need to submit the required additional information about the test on each claim.

Technology Assessments (TA)

Molecular Diagnostic Services Program (MolDX®) will review all new test/assay clinical information to determine if a test meets Medicare's reasonable and necessary requirement. Labs must submit a comprehensive dossier on each new test/assay prior to claim submission. MolDX® will only cover and reimburse tests that demonstrate analytical and clinical validity, and clinical utility at a level that meets the Medicare reasonable and necessary requirement.

Sources of Information

Current Procedural Terminology® (CPT) American Medical Association. American Medical Association Press, ISBN9781603592178, 2011, UpToDate.

References

1. Adams DR, Eng CM. Next-Generation Sequencing to Diagnose Suspected Genetic Disorders. N Engl J Med 2018;379:1353.
2. Amendola LM, Jarvik GP, Leo MC, et al. Performance of ACMG-AMP Variant-Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium. Am J Hum Genet 2016;98:1067.
3. Armstrong GL, MacCannell DR, Taylor J, et al. Pathogen Genomics in Public Health. N Engl J Med 2019;381:2569.

4. Ashley EA, Butte AJ, Wheeler MT, et al. Clinical assessment incorporating a personal genome. Lancet 2010;375:1525.
5. Association for Molecular Pathology v. Myriad Genetics, Inc. No. 12-398. 569 U.S ___ (2013). Text available at: www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf.
6. Bamshad MJ, Ng SB, Bigham AW, et al. Exome sequencing as a tool for Mendelian disease gene discovery. Nat Rev Genet 2011;12:745.
7. Beck TF, Mullikin JC, NISC Comparative Sequencing Program, Biesecker LG. Systematic Evaluation of Sanger Validation of Next-Generation Sequencing Variants. Clin Chem 2016;62:647.
8. Beitsch PD, Whitworth PW, Hughes K, et al. Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle? J Clin Oncol 2019;37:453.
9. Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. N Engl J Med 2014;370:2418.
10. Bennett ST, Barnes C, Cox A, et al. Toward the 1,000 dollars human genome. Pharmacogenomics 2005;6:373.
11. Burki T. UK explores whole-genome sequencing for newborn babies. Lancet 2022;400:260.
12. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill 2020;25.
13. Dai W, Zhang B, Jiang XM, et al. Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. Science 2020; 368:1331.
14. Dimmock D, Caylor S, Waldman B, et al. Project Baby Bear: Rapid precision care incorporating rWGS in 5 California children's hospitals demonstrates improved clinical outcomes and reduced costs of care. Am J Hum Genet 2021;108:1231.
15. Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med 2015;372:2243.
16. Evaluation of automatic class III designation for MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets). Available at: www.accessdata.fda.gov/cdrh_docs/reviews/DEN170058.pdf (Accessed on November 16, 2017).
17. FDA announces approval, CMS proposes coverage of first breakthrough-designated test to detect extensive number of cancer biomarkers. Available at: www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2017-Press-releases-items/2017-11-30-2.html (Accessed on December 04, 2017). www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id290.pdf (Accessed on December 04, 2017).
18. FDA unveils a streamlined path for the authorization of tumor profiling tests alongside its latest product action. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585347.htm (Accessed on November 16, 2017).

19. Gilissen C, Hehir-Kwa JY, Thung DT, et al. Genome sequencing identifies major causes of severe intellectual disability. Nature 2014;511:344.
20. Goldfaden RL, Wall DP, Khoury MJ, et al. Human Genome Sequencing at the Population Scale: A Primer on High-Throughput DNA Sequencing and Analysis. Am J Epidemiol 2017;186:1000.
21. Hong YC, Liu HM, Chen PS, et al. Hair follicle: a reliable source of recipient origin after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2007;40:871.
22. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med 2017;19:249.
23. King MC, Levy-Lahad E, Lahad A. Population-based screening for BRCA1 and BRCA2: 2014 Lasker Award. JAMA 2014;312:1091. https://clinicalgenome.org/ (Accessed on August 20, 2019).
24. Kames J, Holcomb DD, Kimchi O, et al. Sequence analysis of SARS-CoV-2 genome reveals features important for vaccine design. Sci Rep 2020;10:15643. www.cdc.gov/genomics/implementation/toolkit/tier1.htm (Accessed on June 14, 2019).
25. Kuehn BM. NIH's Undiagnosed Diseases Program expands: 6 new sites offer potential answers to more patients. JAMA 2014;312:587.
26. Lazaridis KN, Schahl KA, Cousin MA, et al. Outcome of Whole Exome Sequencing for Diagnostic Odyssey Cases of an Individualized Medicine Clinic: The Mayo Clinic Experience. Mayo Clin Proc 2016;91:297. www.nccn.org/professionals/physician_gls/default.aspx (Accessed on May 10, 2019).
27. Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. JAMA 2014;312:1880.
28. Logsdon GA, Vollger MR, Eichler EE. Long-read human genome sequencing and its applications. Nat Rev Genet 2020;21:597.
29. Long EF, Ganz PA. Cost-effectiveness of Universal BRCA1/2 Screening: Evidence-Based Decision Making. JAMA Oncol 2015;1:1217.
30. Lupski JR, Reid JG, Gonzaga-Jauregui C, et al. Whole-genome sequencing in a patient with Charcot-Marie-Tooth neuropathy. N Engl J Med 2010;362:1181.
31. Manchanda R, Patel S, Gordeev VS, et al. Cost-effectiveness of Population-Based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 Mutation Testing in Unselected General Population Women. J Natl Cancer Inst 2018;110:714.
32. Miller DT, Lee K, Chung WK, et al. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2021;23:1381.
33. Rehm HL, Bale SJ, Bayrak-Toydemir P, et al. ACMG clinical laboratory standards for next-generation sequencing. Genet Med 2013;15:733.
34. Rehm HL, Berg JS, Brooks LD, et al. ClinGen--the Clinical Genome Resource. N Engl J Med 2015;372:2235.

35. Rennert H, Leonard DG, Cushing M, et al. Avoiding pitfalls in bone marrow engraftment analysis: a case study highlighting the weakness of using buccal cells for determining a patient's constitutional genotype after hematopoietic stem cell transplantation. Cytotherapy 2013;15:391.
36. Rizzo JM, Buck MJ. Key principles and clinical applications of "next-generation" DNA sequencing. Cancer Prev Res (Phila) 2012;5:887.
37. Selkirk CG, Vogel KJ, Newlin AC, et al. Cancer genetic testing panels for inherited cancer susceptibility: the clinical experience of a large adult genetics practice. Fam Cancer 2014;13:527.
38. Sintchenko V, Holmes EC. The role of pathogen genomics in assessing disease transmission. BMJ 2015;350:h1314.
39. Splinter K, Adams DR, Bacino CA, et al. Effect of Genetic Diagnosis on Patients with Previously Undiagnosed Disease. N Engl J Med 2018;379:2131.
40. Strom SP, Lee H, Das K, et al. Assessing the necessity of confirmatory testing for exome-sequencing results in a clinical molecular diagnostic laboratory. Genet Med 2014; 16:510.
41. Tarailo-Graovac M, Shyr C, Ross CJ, et al. Exome Sequencing and the Management of Neurometabolic Disorders. N Engl J Med 2016;374:2246.
42. Taylor JC, Martin HC, Lise S, et al. Factors influencing success of clinical genome sequencing across a broad spectrum of disorders. Nat Genet 2015;47:717.
43. Thiede C, Prange-Krex G, Freiberg-Richter J, et al. Buccal swabs but not mouthwash samples can be used to obtain pretransplant DNA fingerprints from recipients of allogeneic bone marrow transplants. Bone Marrow Transplant 2000;25:575.
44. Van Driest SL, Wells QS, Stallings S, et al. Association of Arrhythmia-Related Genetic Variants With Phenotypes Documented in Electronic Medical Records. JAMA 2016;315:47.
45. Vassy JL, Christensen KD, Schonman EF, et al. The Impact of Whole-Genome Sequencing on the Primary Care and Outcomes of Healthy Adult Patients: A Pilot Randomized Trial. Ann Intern Med 2017;167:159.
46. Waddell N, Pajic M, Patch AM, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature 2015;518:495.
47. Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A 2011;108:18032.
48. Wilson MR, Naccache SN, Samayoa E, et al. Actionable diagnosis of neuroleptospirosis by next-generation sequencing. N Engl J Med 2014;370:2408.
49. Wright CF, Fitzgerald TW, Jones WD, et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. Lancet 2015;385:1305.
50. Wright CF, McRae JF, Clayton S, et al. Making new genetic diagnoses with old data: iterative reanalysis and reporting from genome-wide data in 1,133 families with developmental disorders. Genet Med 2018;20:1216.

51. Yang Y, Muzny DM, Reid JG, et al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. N Engl J Med 2013;369:1502.
52. Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. JAMA 2014;312:1870.
53. Zehir A, Benayed R, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 2017;23:703. https://cancergenome.nih.gov/ (Accessed on February 20, 2018). www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s024lbl.pdf (Accessed on November 27, 2017).
54. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727.
55. 100,000 Genomes Project Pilot Investigators, Smedley D, Smith KR, et al. 100,000 Genomes Pilot on Rare-Disease Diagnosis in Health Care - Preliminary Report. N Engl J Med 2021;385:1868.

Policy History

Chief Medical Officer Review: 06/18/2024

Utilization Management Committee review and Approval: 06/18/2024