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Medicare Advantage Policy Manual **Policy ID:** M-GT88

Minimal Residual Disease (MRD) Testing for Cancer

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IMPORTANT REMINDER

The Medicare Advantage Medical Policy manual is not intended to override the member Evidence of Coverage (EOC), which defines the insured's benefits, nor is it intended to dictate how providers are to practice medicine. Physicians and other health care providers are expected to exercise their medical judgment in providing the most appropriate care for the individual member, including care that may be both medically reasonable and necessary.

The Medicare Advantage medical policies are designed to provide guidance regarding the decision-making process for the coverage or non-coverage of services or procedures in accordance with the member EOC and Centers of Medicare and Medicaid Services (CMS) policies and manuals, along with general CMS rules and regulations. In the event of a conflict, applicable CMS policy or EOC language will take precedence over the Medicare Advantage Medical Policy. In the absence of a specific CMS coverage determination for a requested service, item or procedure, the health plan may apply CMS regulations, as well as their Medical Policy Manual or other applicable utilization management vendor criteria developed with an objective, evidence-based process using scientific evidence, current generally accepted standards of medical practice, and authoritative clinical practice guidelines.

Some services or items may appear to be medically indicated for an individual but they may also be a direct exclusion of Medicare or the member's benefit plan. Medicare and member EOCs exclude from coverage, among other things, services or procedures considered to be investigational (experimental) or cosmetic, as well as services or items considered not medically reasonable and necessary under Title XVIII of the Social Security Act, §1862(a)(1)(A). In some cases, providers may bill members for these non-covered services or procedures. Providers are encouraged to inform members in advance when they may be financially responsible for the cost of non-covered or excluded services. Members, their appointed representative, or a treating provider can request coverage of a service or item by submitting a pre-service organization determination prior to services being rendered.

DESCRIPTION

Minimal residual disease (MRD), also known as measurable residual disease, refers to residual cells in blood or bone marrow following treatment for solid tumor cancers or hematologic malignancies. MRD testing can be performed with various technologies, including flow cytometry, polymerase chain reaction (PCR) and next-generation sequencing (NGS). Often, MRD testing requires baseline testing on tumor tissue or blood, followed by later testing to detect the presence or recurrence of the cancer after treatment.

MEDICARE ADVANTAGE POLICY CRITERIA

Notes: The Medicare references in this policy represent the guidance available at publication; please see the Medicare Coverage Database for the latest guidance. This policy includes links to external webpages that are not maintained by the health plan.

National Coverage Determinations (NCDs)

For Medicare Coverage Determinations and Articles, see the Medicare Coverage Database

- Next Generation Sequencing (NGS) (NCD 90.2)

This NCD applies only to only NGS testing and only for individuals that currently have cancer. NCD 90.2 provides coverage for somatic cancer tests (including MRD tests) that are FDA approved or cleared for their intended use, when additional patient-specific criteria are met, including either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer.

MRD tests with FDA approval or clearance for specific indications include (may not be all inclusive, see FDA website for most current information):

- clonoSEQ®
  - B-cell acute lymphoblastic leukemia (B-ALL)
  - chronic lymphocytic leukemia (CLL)
  - multiple myeloma
- Signatera™:
  - muscle-invasive bladder cancer (MIBC)

See local guidance below for tests and indications that are not FDA approved or cleared, and for individuals without active cancer, which is defined as "no clinical, radiographical, or other biological evidence that tumor cells remain post treatment and subsequently the patient is no longer being subjected to therapeutic interventions for cancer."[1]

Noridian Healthcare Solutions (Noridian) Local Coverage Determinations (LCDs) and Articles

For Medicare Coverage Determinations and Articles, see the Medicare Coverage Database

Laboratories in AK, ID, OR, WA, UT, AZ, MT, ND, SD, WY, CA, NV:

- MolDX: Minimal Residual Disease Testing for Cancer (L38814)

For solid tumor cancers:

- Billing and Coding: MolDX: Minimal Residual Disease Testing for Solid Tumor Cancers (A58454)

For hematologic malignancies:

- Billing and Coding: MolDX: Minimal Residual Disease Testing for Hematologic Cancers (A58996)

The LCD includes several requirements related to the intended use of the tests and states that the technical assessment (TA) will "confirm that the analytical validity, clinical validity, and clinical utility criteria set in this policy. The DEX® Diagnostics Exchange Registry includes information regarding the TA status and intended use of the test**.**

Tests that have completed a TA and are covered for specific indications are listed in the

"Billing and Coding" articles. Coverage is limited only to the indications listed as covered in the applicable Billing and Coding article above, and use of the tests for other indications is considered **not medically necessary**. See "Additional Information" below for information about specific tests.

LCDs and Articles for Other Jurisdictions

Note: The health plan is required to use LCDs and articles published by the contractor with jurisdiction over the service area in which the tests are performed.[2,3] See below for contractor guidance in other jurisdictions:

Laboratories in AL, GA, TN, SC, NC, VA, WV:

- MolDX: Minimal Residual Disease Testing for Cancer (L38779) and articles (A58376, A58988)

Laboratories in IA, KS, MO, NE, IN, MI:

- MolDX: Minimal Residual Disease Testing for Cancer (L38835) and articles (A58468, A59004)

Laboratories in KY, OH:

- MolDX: Minimal Residual Disease Testing for Cancer (L38822) and articles (A58434, A58998)

Additional research may be needed to determine coverage for tests or indications not addressed in the LCD and article.

Additional Information

See below for tests that may be considered medically necessary for the indications listed, when testing is performed in a MolDX jurisdiction (may not be all inclusive, see the *Medicare Coverage Database* for most recent guidance).

FOR SOLID TUMOR CANCERS:

- Guardant Reveal™:
  - colorectal cancer
- Guardant360 Response™:
  - monitoring response to immune checkpoint inhibitors* for inoperable/metastatic cancers
- NavDx®:
  - HPV-driven oropharyngeal and anal squamous cell cancers
- NeXT Personal®:
  - non-small cell lung cancer
  - breast cancer
  - monitoring response to immune checkpoint inhibitors* for stage IV (metastatic) solid tumors

- Oncodetect™:
    - colorectal cancer
- Pathlight™:
    - advanced breast cancer
- RaDaR®:
    - HPV-negative head and neck squamous cell carcinoma
    - advanced breast cancer
- Signatera™:
    - colorectal cancer
    - muscle-invasive bladder cancer
    - breast cancer
    - ovarian cancer
    - non-small cell lung cancer
    - monitoring response to immune checkpoint inhibitors* for advanced cancers
- TrueMRD™:
    - muscle-invasive bladder cancer

*Immune checkpoint inhibitors include but are not limited to: ipilimumab (Yervoy), tremelimumab (Imjudo), cemiplimab (Libtayo), dostarlimab (Jemperli), nivolumab (Opdivo), pembrolizumab (Keytruda), penpulimab-kcqx (Anikora, Anniko), retifanlimab-dlwr (Zynyz), tislelizumab (Tevimbra), atezolizumab (Tecentriq), avelumab (Bavencio), and durvalumab (Imfinzi).

FOR HEMATOLOGIC MALIGNANCIES:

- clonoSEQ®:
    - acute lymphoblastic leukemia (ALL)
    - multiple myeloma
    - chronic lymphocytic leukemia (CLL)
    - diffuse large B-cell lymphoma (DLBCL)
    - mantle cell lymphoma
- Single gene tests:
    - *BCR-ABL1*: chronic myeloid/myelogenous leukemia (CML), ALL
    - *NPM1* or *PML-RARA*: acute promyelocytic leukemia (APL).
    - *RUNX1-RUNX1T1*, *CBFB-MYH11*, or *NPM1*: acute myeloid leukemia, when that gene variant is present.
    - Ig and T-cell receptor genes (*IGH*, *IGK*, *TRB*, *TRG*): lymphoma or leukemia

The following tests have completed a TA and are listed as “not covered”, and are therefore considered **not medically necessary**:

- Haystack MRD®
- Heme-STAMP MRD
- Labcorp® Plasma Detect™
- Precise MRD

- Tempus xM

POLICY GUIDELINES

REQUIRED DOCUMENTATION

The following information is required in order to determine medical necessity and potential Medicare coverage for a genetic or molecular diagnostic test. *[See Title XVIII of the Social Security Act, §1833(e), which states no payment may be made unless information necessary to determine payment has been submitted].*

1. The specific name of the test (or gene, for single-gene testing);
2. Name and location of the performing laboratory;
3. Applicable CPT and/or HCPCS code(s);
4. Brief explanation of how the results of the testing are necessary to guide treatment decisions relevant to the member's medical condition.
5. Medical records relevant to the testing being performed. This includes:
   - History and physical examinations by the referring physician;
   - Conventional testing and outcomes; and
   - Conservative treatment provided, if applicable.

CROSS REFERENCES

1. Genetic and Molecular Diagnostics – Testing for Cancer Diagnosis, Prognosis, and Treatment Selection, Genetic Testing, Policy No. 83

REFERENCES

1. Local Coverage Determination L38814. MolDX: Minimal Residual Disease Testing for Cancer
2. Medicare Claims Processing Manual, Chapter 1 - General Billing Requirements, §10.1.5.4 - Independent Laboratories
3. Medicare Managed Care Manual, Chapter 4 - Benefits and Beneficiary Protections, §90.4.1 - MAC with Exclusive Jurisdiction over a Medicare Item or Service

CODING

Codes	Number	Description
CPT	0040U	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
	0171U	Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence
	0306U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient specific panel for future comparisons to evaluate for MRD
	0307U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent

	assessment with comparison to previously analyzed patient specimens to evaluate for MRD
0340U	Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate
0356U	Oncology (oropharyngeal or anal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence
0364U	Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or absence of minimal residual disease (MRD) with quantitation of disease burden, when appropriate
0422U	Oncology (pan-solid tumor), analysis of DNA biomarker response to anti-cancer therapy using cell-free circulating DNA, biomarker comparison to a previous baseline pre-treatment cell-free circulating DNA analysis using next-generation sequencing, algorithm reported as a quantitative change from baseline, including specific alterations, if appropriate
0467U	Oncology (bladder), DNA, next generation sequencing (NGS) of 60 genes and whole genome aneuploidy, urine, algorithms reported as minimal residual disease (MRD) status positive or negative and quantitative disease burden
0470U	Oncology (oropharyngeal), detection of minimal residual disease by next-generation sequencing (NGS) based quantitative evaluation of 8 DNA targets, cell-free HPV 16 and 18 DNA from plasma
0560U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood and tumor tissue, baseline assessment for design and construction of a personalized variant panel to evaluate current MRD and for comparison to subsequent MRD assessments
0561U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood, subsequent assessment with comparison to initial assessment to evaluate for MRD
0569U	Oncology (solid tumor), next-generation sequencing analysis of tumor methylation markers (>20,000 differentially methylated regions) present in cell-free circulating tumor DNA (ctDNA), whole blood, algorithm reported as presence or absence of ctDNA with tumor fraction, if appropriate
0641U	Oncology (minimal residual disease [MRD]), tumor DNA, next-generation sequencing (NGS), using formalin-fixed paraffin-embedded (FFPE) tissue and blood samples, initial (baseline) assessment
0642U	Oncology (minimal residual disease [MRD]), tumor DNA, next-generation sequencing (NGS), whole blood, comparison to previously performed analyses, reported as trend in circulating tumor DNA (ctDNA) level
0644U	Oncology (leukemia), minimal residual disease (MRD) detection for rearrangements, blood or bone marrow, personalized assay design and baseline quantification
0645U	Oncology (leukemia), minimal residual disease (MRD) detection for rearrangements, based on digital PCR, blood or bone marrow, reported as not detected or detected with estimated abundance
0646U	Oncology (molecular residual disease), whole genome sequence analysis, cell-free DNA, whole blood, and formalin-fixed paraffin embedded (FFPE) tumor tissue DNA, baseline assessment
0647U	Oncology (molecular residual disease), whole genome sequence analysis, cell-free DNA (cfDNA), whole blood, assessment utilizing patient specific

	tumor information, reported as negative or percent circulating tumor DNA (ctDNA)
0688U	Oncology (colorectal cancer), analysis of minimal residual disease (MRD), next-generation sequencing (NGS), circulating tumor DNA (ctDNA) analysis in whole blood and tumor for baseline assessment to evaluate current MRD status and for comparisons to subsequent MRD assessments
0689U	Oncology (colorectal cancer), analysis of minimal residual disease (MRD) using patient-specific assays, reported as amount of circulating tumor DNA (ctDNA) detection and trend over time
0693U	Oncology (head and neck), circulating tumor DNA (ctDNA), tumor-informed next-generation sequencing (NGS) analysis for 699 genes of patient-specific somatic variants identified from primary tumor tissue, postoperative lymphatic exudate specimen, algorithm reported as presence or absence of ctDNA
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81261	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)
81263	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis
81264	IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81310	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
81334	RUNX1 (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (eg, exons 3-8)
81340	TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)
81342	TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81445	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
81450	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or

		rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
	81479	Unlisted molecular pathology procedure
HCPCS	None	