Minimal/Measurable Residual Disease Testing for Hematologic Cancers

Date of Origin: 09/2022 **Last Review Date: 02/28/2024** **Effective Date: 03/01/2024**

Dates Reviewed: 2/2023, 2/2024

Developed By: Medical Necessity Criteria Committee

I. Description

Hematological (blood) cancers begin in the cells of the immune system or in blood-forming tissue, such as bone marrow. They impact the normal production and function of blood cells and often begin where stem cells develop into white blood cells, red blood cells, or platelets. These types of cancers occur when an uncontrolled growth of abnormal cells overtakes the development of normal blood cells, interfering with the regular functions of those cells. There are three main types of hematologic malignancies: lymphomas, leukemias, and myelomas. Lymphomas start in the lymph system, the part of the immune system that fights infection. Since the lymph system is found throughout the body, lymphoma can begin almost anywhere. Myeloma is a cancer of the plasma cells, the white blood cells that make antibodies that protect against infection. Leukemia is a cancer of the blood cells and bone marrow (the soft, sponge-like tissue in the center of most bones) that makes blood cells. Several types of leukemia are grouped by whether it grows faster (acute) or slower (chronic) and starts in lymphocytic cells or myelogenous cells.

Minimal Residue Disease (MRD) is defined by the persistence of very low levels of residual malignant cells in posttreatment cancer patients. It refers to the small number of cancer cells that remain in the body after treatment. An MRD-positive test means that the residual disease is detected.
MRD testing for cancer is a rapidly sensitive and specific method for monitoring the relative amounts of tumor-derived genetic material circulating in the blood of cancer patients. Some MRDs include Acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma.

The role of Minimal Residue Disease (MRD) assessment in patient care is significant. After treating cancer, any remaining cancer cells in the body can become active and start to multiply, causing a relapse of the disease. MRD testing can be used to diagnose cancer progression, recurrence, or relapse before there is clinical, biological, or radiographical evidence of progression, recurrence, or relapse. It can also be used to detect response to therapy by measuring the proportional changes in the amount of available tumor DNA. Detecting MRD may indicate that the treatment was not completely effective or that the treatment was incomplete. Tests for MRD may occur after the final cycle of combined therapy, after bone marrow transplantation, during treatment to confirm the depth of remission, after one year of maintenance therapy, and at regular intervals after treatment is completed. These decisions are based on the patient's disease and needs.

Techniques to detect MRD include highly sensitive methods such as polymerase chain reaction (PCR), flow cytometry, and Next Generation Sequencing (NGS). The tests use samples of bone marrow cells (taken by aspiration) and/or peripheral blood cells (taken through a vein).

Next-generation sequencing can rapidly examine stretches of DNA or RNA to accurately detect very small amounts of malignant cells and other genetic abnormalities in DNA extracted from a bone marrow aspirate sample. The FDA has approved 'ClonoSEQ' (Adaptive Biotechnologies), an NGS test to detect B- cell Acute Lymphoblastic Leukemia (ALL) and Myeloma. The test is utilized for monitoring residual disease, disease recurrence, and treatment response for solid tumors. MyMRD, an NGS gene panel, identifies pathogenic variants in AML. The test targets single nucleotide variants (SNVs), insertions, and deletions (indels) in coding exons of hotspots of 21 genes, and structural variants of potential genomic breakpoint hotspots within 3 somatic gene fusion partners.

Flow cytometry is a technique that evaluates individual cells, checking for the presence or absence of certain protein markers on the cell surface. A fresh bone marrow sample is required for reliable results.

Polymerase Chain Reaction (PCR) is a technique that expands trace amounts of DNA so that a specific segment of DNA can be studied. PCR can identify malignant cells based on their characteristic genetic abnormalities, such as mutations or chromosomal changes. Polymerase chain reaction essentially increases or "amplifies" small amounts of specific pieces of either DNA or RNA to make them easier to detect and count. As a result, genetic abnormalities can be detected by PCR even when a very small number of cancer cells remain.

II. Criteria: CWQI HCS 0311

A. Minimal residual disease testing (MRD) with FDA-approved tests for hematologic cancers is considered medically necessary when one or more of the following requirements are met;
   a. MRD testing by multi-parameter flow cytometry and/or NGS for **multiple myeloma** when ALL the following are met;
      i. During follow-up or surveillance after response to primary therapy
      ii. After each treatment state (i. e. after induction, high-dose therapy/autologous stem cell transplantation, consolidation, and maintenance)

   b. MRD testing by multiparameter flow cytometry (standardized ERIC method to at least a sensitivity of 10^{-4}) and **NGS** for individuals with **chronic lymphocytic leukemia** or **small lymphocytic lymphoma** and one of the following;
      i. During treatment
      ii. After the end of treatment
      iii. For consideration of therapy with lenalidomide for high-risk patients after first-line therapy

   c. MRD testing of bone marrow aspirate samples by multiparameter flow cytometry and NGS for individuals with **acute myeloid leukemia**, including;

i. On completion of first round of induction
ii. Before allogeneic transplantation
iii. Additional time points as guided by the regimen used

d. MRD testing of peripheral blood samples by **PCR-based techniques** for individuals with **acute myeloid leukemia**, including
   i. On completion of initial induction
   ii. Before allogeneic transplantation
   iii. Additional time points as guided by the regimen used
   iv. Serial monitoring in patients with molecular relapse or persistent low-level disease burden

e. MRD testing by flow cytometry, PCR-based techniques, and NGS for individuals with **acute lymphoblastic leukemia,** including;
   i. Baseline Cytometric and/or molecular characterization of leukemic clone to facilitate subsequent MRD analysis
   ii. On completion of initial induction
   iii. Additional time points as guided by the regimen used
   iv. Serial monitoring in patients with molecular relapse or persistent low-level disease burden

B. When MRD is not covered
   a. Minimal residue disease detection in solid tumors using next-generation sequencing is considered **Investigational and not covered**
   b. All other MRD testing by multiparameter flow cytometry, PCR, or next-generation sequencing is considered investigational

C. Minimal Residue Disease tests approved by FDA
   a. ClonoSEQ® Assay
   b. MyMRD NGS panel

D. Tests NOT FDA approved and considered experimental & investigational
   a. Guardant Reveal
   b. Natera Signatera Molecular Monitoring (MRD) for breast cancer

III. Information Submitted with the Prior Authorization Request:

1. Clinical chart/notes

IV. CPT or HCPC codes covered:

Codes	Description
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 or 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
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
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
81479	Unlisted molecular procedure
81599	Unlisted multianalyte assay with algorithmic analysis
88184	Flow cytometry, cell surface, cytoplasmic, or nuclear marker, technical component only; first marker
88185	Flow cytometry, cell surface, cytoplasmic, or nuclear marker, technical component only; each additional marker (List separately in addition to code for first marker)
88187	Flow Cytometry, interpretation; 2 to 8 markers
88188	9 to 15 markers
88189	16 or more markers

V. CPT or HCPC codes NOT covered:

Codes	Description

VI. Annual Review History

Review Date	Revisions	Effective Date
02/2023	New policy	03/01/2023
05/2023	CPT code updates	
02/2024	Annual Review: added code for clonoSEQ adaptive technologies, Grammar updates	03/01/2024

VII. References

1. Sanchez, Ayala, Martin Lopez-Minimal residual disease monitoring with next-generation sequencing methodologies in hematological malignancies. International journal of molecular science. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6600313/
2. MolDX: Minimal Residual Disease Testing for Cancer. L38779. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38779&ver=4
3. Leukemia & Lymphoma Society: Minimal Residual Disease (MRD). Retrieved from https://www.lls.org/sites/default/files/National/USA/Pdf/Publications/FS35_MRD_Final_2019.pdf
4. Tierens et al (2021); Consensus Recommendations for MRD Testing in Adult B-Cell Acute Lymphoblastic Leukemia in Ontario
5. Schuurhuis et al 2018. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5865231/
6. Colmenares et al. (2022). The Minimal Residual Disease Using Liquid Biopsies in Hematological Malignancies. Cancers journal. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8909350/
7. Xie et al 2018. Monitoring Minimal Residual Disease in Acute Myeloid Leukemia Using Genomic or cfDNA with MyMRD®, a Targeted NGS Panel. Retrieved from https://www.sciencedirect.com/science/article/pii/S0006497119413682
8. National Comprehensive Cancer Network NCCN https://www.nccn.org/professionals/physician_gls/pdf/all.pdf
9. Kostopolous et al 2020: Minimal Residual Disease in Multiple Myeloma: Current Landscape and Future Applications With Immunotherapeutic Approaches. Retrieved from https://www.frontiersin.org/articles/10.3389/fonc.2020.00860/full
10. Xie et al (2018). Monitoring Minimal Residual Disease in Acute Myeloid Leukemia Using Genomic or cfDNA with MyMRD®, a Targeted NGS Panel. https://www.sciencedirect.com/science/article/pii/S0006497119413682
11. Kuiper et al (2021). Minimal residual disease (MRD) detection in acute lymphoblastic leukemia based on fusion genes and genomic deletions: towards MRD for all. https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.17744
12. Hematologic Cancer Incidence, Survival, and Prevalence. U.S. Cancer Statistics Data Briefs, No. 30 September 2022 Retrieved from https://www.cdc.gov
13. Hematologic Malignancies. Retrieved from https://www.accc-cancer.org/home/learn/cancer-types/hematologic-malignancies
14. MRD (Minimal Residual Disease) Testing Market Size 2023 Industry Analysis, Key Players, Regional Demand, Opportunity and Forecast 2028

Appendix 1 – Applicable Diagnosis Codes:

Codes	Description
C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in remission
C90.02	Multiple myeloma in relapse
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse
Z85.6	Personal history of leukemia [when specified as ALL]
Z85.79	Personal history of other malignant neoplasms of lymphoid, hematopoietic and related tissues [when specified as multiple myeloma]

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD) and Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD):

Jurisdiction(s): 5, 8	NCD/LCD Document (s): L38779
Noridian Local Coverage Determination L38779 Minimal Residual Disease Testing for Cancer	

NCD/LCD Document (s):

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	Applicable State/US Territory	Contractor
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC