MEDICAL POLICY

Medical Policy Title	**Measurable Residual Disease (MRD) Assessment Testing**
Policy Number	**2.02.54**
Current Effective Date	December 15, 2025
Next Review Date	August 2026

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

I. ClonoSEQ Assay test is considered **medically appropriate** for measurable residual disease (MRD) assessment for **ANY** of the following U.S. Food and Drug Administration (FDA) approved indications:

   A. Acute Lymphoblastic leukemia (ALL);

   B. Chronic Lymphocytic Leukemia (CLL);

   C. Multiple Myeloma (MM).

II. Flow cytometry is considered **medically necessary** to detect measurable residual disease (MRD) in patients with **ANY** of the following indications:

   A. Leukemia;

   B. Lymphoma;

   C. Multiple myeloma (MM).

III. MRD assessment is considered **investigational** for all other indications when using **ANY** of the following tests, including but not limited to:

   A. Signatera Test;

   B. MyMRD;

   C. Guardant Reveal;

   D. Northstar Response;

   E. Invitae PCM MRD Monitoring;

   F. PCM Tissue Profiling and MRD Monitoring;

   G. HPV-SEQ;

   H. M-insight Patient Definition Assay;

   I. M-insight Patient Follow-Up Assessment;

   J. UroAmp MRD.

RELATED POLICIES

Corporate Medical Policy

2.02.51 Molecular Testing of Tumor Tissue to Identify Targeted Therapies for Cancers

2.02.56 Circulating Tumor DNA for Management of Cancer (Liquid Biopsy)

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. Testing for MRD may be performed by either flow cytometry, next-generation sequencing (NGS) or PCR.

V. Testing for MRD by more than one (1) laboratory methods concurrently is not medically appropriate as it is duplicative testing.

DESCRIPTION

Measurable Residual Disease (MRD)

MRD, previously referred to as minimal residual disease, occurs after cancer treatment and remission when clonal cells, which are derived from a common “ancestor” cell, are present in concentrations below the threshold of detection by standard testing. However, after cancer treatment these residual tumor cells exist in quantities that are detectable using higher sensitivity testing methods. NGS can detect clonal cells with greater sensitivity than either flow cytometry or PCR, although next-generation flow techniques have reached a detection limit of 1 in 10^5 cells, which is equal to PCR and approaches the limit of detection of NGS.

There are three (3) main categories of hematologic malignancies, lymphomas, leukemias, and myelomas. Treatment of acute leukemias can lead to complete remission. Multiple myeloma and the chronic leukemias are treatable but generally incurable. Follow-up or surveillance after treatment may be accomplished with MRD analysis. MRD is used to assess subclinical residual disease. Patients with detectable MRD have an increased risk of relapse, but the absolute risk varies depending on the timing of MRD evaluation, the sensitivity of the method used and baseline characteristics of the patient and tumor. Not all patients who test MRD-positive will relapse clinically because some cells

with abnormal markers may lack the ability to create disease. Other patients will relapse despite MRD-negative detectable disease as a result of malignant progenitor cells that lack the initially identified markers. MRD is most commonly measured with polymerase chain reaction (PCR) and flow cytometry (FC).

MRD status (MRD-positive or MRD-negative) is a strong predictor of disease-free and overall survival after remission of certain hematologic malignancies. However, not all patients who test MRD-positive will relapse and some patients who test MRD-negative will experience disease recurrence. Nonetheless, MRD testing can help clinicians: make earlier assessments of how well malignancy responds to a completed course of treatment; yield prognostic data to identify patients who may be at higher risk of relapse; and detect cancer recurrence sooner than traditional testing. Therefore, assessing MRD-status can help identify patients who may benefit from additional treatment.

NGS can detect clonal cells with greater sensitivity than either flow cytometry or PCR, although next-generation flow techniques have reached a detection limit of 1 in 10^5 cells, which is equal to PCR and approaches the limit of detection of NGS.

Hematopoietic Neoplasm Evaluation and Monitoring

Hematopoietic neoplasm evaluation and monitoring is the most common use of flow cytometry. Immunophenotyping for assignment of lineage, identification of prognostic subgroups, and post-therapeutic monitoring for diagnosing and monitoring hematopoietic neoplasms is obtained via flow cytometry.

MRD Tests Available

Name of Test	Company	Type of Test	Sample	Description
ClonoSeq Assay Test	Adaptive Biotechnologies	Multiplex PCR and (Next Generation Sequencing (NGS)	Bone marrow aspirate Peripheral blood and bone marrow	Detects and monitors B-cell acute lymphoblastic leukemia (ALL) and multiple myeloma (MM). Detects and monitors chronic lymphocytic leukemia (CLL).
Guardant Reveal	Guardant Health inc.	NGS	Blood	Detects the presence of small fragments of circulating tumor DNA (ctDNA).
Signatera MRD	Natera	Multiplex PCR and NGS	Primary tissue sample	Detects ctDNA to monitor MRD in a variety of cancer types (breast, colorectal,

				lung, bladder and ovarian) and for monitoring response to immune-checkpoint inhibitor therapy for patients with any solid tumors.
Northstar Response	BillionToOne, Inc.	NGS	Blood	This pan-cancer test (12 cancer types, including lung, colorectal, and pancreatic) measures the number of methylated, ctDNA molecules in each sample, reflecting the patient's tumor burden. The test uses an algorithm to report quantitative measurement of methylation as a correlate of tumor fraction.
HPV-SEQ	Sysmex Inostics, Inc.	NGS	Plasma	The test detects ctDNA for treatment monitoring of disease burden in HPV-related cancers. The test uses next-generation sequencing (NGS) based quantification of 8 DNA targets, cell free HPV 16 and 18 DNA from plasma, to detect minimal residual disease (MRD).
UroAmp MRD	Convergent Genomics	NGS	Urine	The test is purported to help monitor disease progression, recurrence, and response to therapeutic interventions. The test interrogates 60 urothelial cancer genes and broadly measures changes across the whole genome. It also uses an algorithm reported as minimal residual disease (MRD) status positive or negative and quantitative disease burden; a measure of

				a patient's disease burden compared to bladder cancer patients previously tested with UroAmp.
Invitae PCM MRD monitoring	Invitae Corporation	NGS	Blood	Detects ctDNA related to the patient's tumor profile identified in the Invitae PCM Tissue Profiling and MRD baseline assay. Used to monitor for recurrence and identify the presence of cancer cells following treatment.
Invitae PCM Tissue Profiling and MRD monitoring	Invitae Corporation	NGS	Blood	Detects ctDNA to identify patient-specific somatic mutations for subsequent minimal residual disease (MRD) evaluation. Indicated for baseline testing.
MyMRD	Invivoscribe	NGS	Blood or Bone Marrow	Detects all classes of variants identified in a defined set of targets that commonly drive myeloid malignancies including AML, MPN and MDS. It can detect detection of low-level mutations in patients. Testing with MyMRD allows for studying important mutations in known genes implicated in the causation, prognosis, and reoccurrence of myeloid disorders.
M-insight Patient Definition Assay	Corgenix Clinical Laboratory	Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS)	Blood serum	Identifies specific protein pieces, known as clonotypic peptides, that come from cells in a patient with multiple myeloma (MM). The results are reported as baseline presence or absence of

				detectable clonotypic peptides.
M-insight Patient Follow-Up Assessment	Corgenix Clinical Laboratory	LC-MS/MS	Blood serum	Quantifies specific clonotypic peptides from cells in a patient with multiple myeloma. The test includes comparison with the separately reported baseline test, M–inSight Patient Definition Assay, and determines the abundance of monoclonal protein (M–protein).

SUPPORTIVE LITERATURE

Measurable Residual Disease

A meta-analysis by Short et al (2020) included four studies that used NGS to evaluate MRD-status to predict outcome survival (OS) and disease-free survival (DFS). This NGS sub-group analysis showed a hazard ratio (HR) 0.43 (0.24-0.75) at 95 percent CI for OS and HR 0.45 (0.25-0.80) 95 percent CI DFS. This indicates that patients who tested MRD-negative were predicted to have better OS and DFS compared to patients who tested MRD-positive. A limitation of this meta-analysis is that the four NGS studies examined comprised only 6% of the overall studies while the remainder of the studies had been conducted by MFC, PCR or other methods.

Thompson et al (2019), analyzed MRD with NGS in stored samples of bone marrow (n=57), blood (n=29) and plasma (n=32) from 62 patients who had previously tested negative for MRD by flow cytometry (FC) (n=63) in a phase 2 clinical trial. MRD rates by NGS varied according to sample type with fewer patients with undetectable MRD in bone marrow (25%) than blood (55%) or plasma (75%). MRD at the end of treatment was predictive of PFS. Patients with undetectable MRD did not progress by the end of the study (mean 82 mo., range 28 to 112) compared with PFS of 67 months (bone marrow) or 74 months (blood). The percent of patients who were progression free with MRD < 10^{-6}, 10^{-5}, and 10^{-4} was 85%, 75%, and 67.5%, respectively. MRD is a critical prognostic feature, however whether a patient will relapse or when, is more complex and other factors must be considered. Patients with M-IGHV compared with UM-IGHV and trisomy 12 were more likely to achieve MRD at 10^{-6} and longer PFS. Optimal sample types are yet to be determined, however NGS using blood to determine MRD is reasonable.

ClonoSeq

Costa et al (2023) reported results from the single-arm, open-label, multicenter, phase 2 trial,

Minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma (MASTER). Eligible participants were 18 years old or older with newly diagnosed multiple myeloma, a life expectancy of at least 12 months, and an Eastern Cooperative Oncology Group performance status of 0–2 and had received no previous treatment for multiple myeloma except up to one cycle of therapy containing bortezomib, cyclophosphamide, and dexamethasone. The primary endpoint was reaching MRD negativity ($<10^{-5}$). Participants who reached MRD negativity after or during two consecutive phases stopped treatment and began observation with MRD surveillance (MRD-SURE); participants who did not reach two consecutive MRD-negative results received maintenance lenalidomide. Secondary endpoints included progression-free survival and cumulative incidence of progression. For 118 (96%) participants, MRD was evaluable by clonoSEQ, (having a detection threshold of MRD is less than 10^{-6}), the remaining five had an absence of sufficiently unique clonogenic sequences to enable tracking by the assay. Of the 118 participants for whom MRD was evaluable, 84 (71%, 62–79) reached MRD of less than 10^{-6}, comprising 34 (68%, 53–80) of 50 participants with no high-risk chromosome abnormalities (HRCAs), 35 (80%, 65–90) of 44 participants with one HRCA, and 15 (63%, 41–81) of 24 participants with two or more HRCAs.

Martinez-Lopez et al (2020) reported a retrospective analysis of patients (N=234) treated at their center for newly diagnosed or relapsed MM who had been evaluated for MRD by NGS. MRD assessment by clonoSEQ was performed after a CR, but there was no consistent time after treatment; most were performed within 1 year. Successful identification of at least1 trackable sequence in the pretreatment sample was obtained in 234 out of 251 (93%) patients. Sensitivity was assessed at 10^{-4}, 10^{-5}, and 10^{-6}. Out of all patients, 91 (39%) had MRD less than 10^{-6} and 129 (55%) had MRD less than 10^{-5}. For both newly diagnosed MM and relapsed MM patients, MRD less than 10^{-5} or less than 10^{-6} was associated with prolonged survival. In patients who had repeat testing, rising MRD levels preceded clinical relapse by a median of 13 months (range 1 to 28 months). Patients who reached a molecular response at 10^{-5} had similar outcomes to those who achieved MRD negativity at 10^{-6}.

MyMRD

Balagopal et al (2019) conducted a retrospective case-control study to assess the performance and utility of NGS-based MRD detection in patients with AML following hematopoietic cell transplantation (HCT). The researchers developed a hybrid-capture NGS panel utilizing unique molecular identifiers (UMIs) to detect at 0.1% Variant allele frequency (VAF) or below across 22 genes frequently mutated in myeloid disorders an applied it to a set of blood and bone marrow DNA samples that were negative for disease. The 30 patients that had trackable mutations in the 22 genes at eventual relapse via standard NGS analysis, they were able to definitively detect relapse-associated mutations in 18/30 (60%) at previously disease -negative timepoints collected 20-100 days prior to relapse date. MRD was detected in bone marrow (15/28. 53.6%) and peripheral blood samples (9/18, 50%), while demonstrating technical specificity in the sample set. Specificity was confirmed by the disappearance of all MRD signals with increasing time prior to relapse (>100 days), even using genes commonly associated with clonal hematopoiesis of intermediate potential (CHIP). The researchers did note that in one patient, VAF's were found in bone marrow even when the peripheral blood was negative and stated that bone marrow is preferred specimen type for MRD analysis.

HPV-SEQ

Sanz-Garcia et al (2024) conducted a prospective study to evaluate the methods and optimal timepoint for detecting MRD in patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC). A total of 32 patients, three did not have a baseline plasma collection, both follow-up plasma samples were collected in in 25 patients; the rest of the patients only had one. There was an even number of HPV positive and negative disease patients. The methods used to detect MRD were circulating tumor DNA (ctDNA) using tumor-informed (RaDaR), and tumor-naïve (CAPP-seq). HPV DNA was measured using HPV-sequencing (HPV-seq) and digital PCR (HPV dPCR). Sensitivity and specificity for MRD at FU2 using RaDaR was 40% and 100% versus 20 and 90.5% using CAPP-seq. Sensitivity and specificity for MRD during follow-up using HPV-seq was 100% and 91.7%. versus 50% and 100% using dPCR. The RaDaR assay but not CAPP-seq may detect MRD in patients who relapse within 1 year. HPV-seq may be more sensitive than dPCR for MRD detection.

Invitae

Zhao et al (2023) conducted a study to assess the Invitae Personalized Cancer Monitoring assay and its use for monitoring MRD and recurrent disease to assist with prognostic information, and monitoring therapy responses in patients with solid tumors. The authors validated the assay's tumor WES and ctDNA detection components using 250 unique human specimens and nine commercial reference samples that generated 1349 WES and cell-free DNA (cfDNA)-derived libraries. A comparison of tumor and germline specimen via WES was used to identify patient-specific tumor variant signatures and generate patient-specific panels, followed by targeted NGS of plasma-derived cfDNA using the patient-specific panels with anchored multiplex polymerase chain reaction (PCR) chemistry leveraging unique molecular identifiers. The authors found that WES resulted in a sensitivity of 99.8% and specificity of greater than 99.9%. The ctDNA portion of the study resulted in greater than 99.9% specificity and a sensitivity of 96.3%. A limitation of the study is that ctDNA methods are prone to biological limitation including false positives. Releasing of cell-free DNA (cfDNA) and ctDNA and the rates that they are shed and cleared can vary based on factors such as vascularization, temporal variability and field effects. In conclusion the Invitae Personalized Cancer Monitoring assay, that has flexible patient-specific panel design with 18–50 variants, demonstrated high sensitivity and specificity for detecting ctDNA at variant allele frequencies as low as 0.008%

M-insight

Langerhorst et al (2021) conducted a study to assess blood-based targeted mass spectrometry (MS-MRD) as a sensitive, minimally invasive alternative to measure multiple myeloma (MM) disease activity. The study included 41 individuals with MM that were enlisted in the IFM-2009 clinical trial was assessed with MS-MRD on frozen sera and compared to routine monoclonal protein (M-protein) diagnostics and next-generation sequencing (NGS-MRD). Clonotypic M-protein specific peptides were identified, and they were able to perform sera-based MS-MRD measurements in all 41 individuals. The consistency between NGS-MRD and MS-MRD status in 81 paired bone marrow/serum samples was 79%. Individuals with either NGS-positive or MS-positive directly after maintenance treatment had a 50% progression free survival (PFS) was identical at 49 months. Individuals that were NGS-negative and MS-negative had a 50% PFS at 69 and 89 months, respectively. Individuals that were MRD-negative for both methods had the longest 50% PFS (96 months). MS-MRD relapse during

maintenance treatment was significantly correlated to poor PFS. The data indicates that MS-MRD evaluation in blood is feasible and an alternative to NGS-MRD that is tested on bone marrow. Clinical validation in a larger and independent cohort is being recommended to assess the prognostic value of MS-MRD and its complementary value in MRD evaluation of patients with MM.

UroAmp

Rac et al (2023) conducted a prospective, cohort study to assess the utility of urinary comprehensive genomic profiling (uCGP) for predicting recurrence risk following a transurethral resection of bladder tumor (TURBT) and evaluating longitudinal intravesical therapy (IVT) response. Urine was collected before and after IVT instillation and uCGP testing via UroAmp. Following TURBT baseline uCGP identified patients with high (61%) and low (39%) recurrence risk. At 24 months, recurrence-free survival (RFS) was 100% for low-risk and 45% for high-risk patients with a hazard ratio (HR) of 9.3. Longitudinal uCGP classified patients as MRD Negative, IVT Responder, or IVT Refractory with 24-month RFS of 100%, 50%, and 32%, respectively. Compared with MRD Negative patients, IVT Refractory patients had a HR of 10.5. The limitations of the study included, small cohort size, and only consisted of Caucasian males, and urine samples were not taken during post induction maintenance cycles, and induction treatments were not consistent. The study suggests that uCGP could inform surveillance cystoscopy schedules and identify high-risk patients in need of additional therapy.

Hematopoietic Neoplasm Evaluation and Monitoring

Immunophenotyping by flow cytometry has become standard practice in the evaluation and monitoring of patients with hematopoietic neoplasia. The 2006 Bethesda International Consensus Recommendations on the Flow Cytometric Immunophenotypic Analysis of Hematolymphoid Neoplasia (Davis et al., 2007) indicated that flow cytometry is useful for the evaluation of cytopenia, elevated leukocyte count, observation of atypical cells or blasts and evaluation of body fluids, plasmacytosis or monoclonal gammopathy, organomegaly and tissue masses, and certain patient monitoring indications such as staging disease to document the extent of involvement, detecting potential therapeutic targets, assessment of response to therapy, documentation of progression or relapse, diagnosis of addition intercurrent treatment-related or coincidental hematolymphoid neoplasm, evaluate of disease acceleration or transformation, and prognostication. Flow cytometry is general not indicated for mature neutrophilia, polyclonal hypergammaglobulinemia, polycythemia, thrombocytosis, or basophilia because they are not usually associated with hematolymphoid malignancy or associated with hematolymphoid neoplasms that are not detectable by flow cytometry. The flow cytometric testing performed should be comprehensive enough to identify all major categories of hematopoietic neoplasia relevant to the clinical circumstances, including, but not limited to, the submitted medical indication(s) and account for all major cell populations present in the specimen, but does not need to identify all hematopoietic cell types.

PROFESSIONAL GUIDELINE(S)

The National Comprehensive Cancer Network (NCCN) Guidelines Relevant to This Policy

Guideline	Version	Recommendations

Acute Lymphoblastic Leukemia	1.2025	The NCCN Panel acknowledges FDA approval of an NGS-based MRD test based on quantification of immunoreceptor genes in patients with ALL, but panel members agreed that both multiparameter flow cytometry or FDA-approved NGS approach are suitable methods for MRD quantification. Six-color flow cytometry can detect leukemic cells at a sensitivity threshold of fewer than 1×10^{-4} (<0.01%) bone marrow mononuclear cells (MNCs), and PCR or NGS methods can detect leukemic cells at a sensitivity threshold of fewer than 1×10^{-6} (<0.0001%) bone marrow MNCs.
Acute Myeloid Leukemia	2.2025	• There are commercially available tests that can be used for MRD assessments, as well as further testing methods at certain academic centers. • The most frequently employed methods for MRD assessment include quantitative molecular assays such as real-time quantitative PCR (RQ-PCR) and multicolor flow cytometry (MFC) assays specifically designed to detect abnormal MRD immunophenotypes. • The Panel recommends RQ-PCR for detection of NPM1, CBFB::MYH11, and RUNX1::RUNX1T1. Utilization of an assay with minimum limit of detection of $\leq 10^{-4}$ is recommended. • For detection of FLT3-ITD, the Panel recommends a highly sensitive, NGS-based, targeted, deep-sequencing assay with a sensitivity level of $\leq 10^{-5}$. The Panel does not routinely recommend other NGS–based assays to detect mutated genes (targeted sequencing, 20–50 genes per panel) for MRD assessment due to inferior sensitivity.
B-Cell Lymphomas	2.2025	If end-of treatment PET is positive, consider repeat biopsy or if biopsy not feasible, consider circulating tumor DNA (ctDNA) for minimal residual disease (MRD) (ctDNA-MRD) assessment (category 2B), using a test with a detection limit of <1 part/million, prior to therapy.

Bladder Cancer	1.2025	• Muscle-Invasive Blader Cancer (MIBC)/Resectable: There is insufficient data for ctDNA results to determine the course of surveillance or therapy after complete surgical resection. Advanced Disease: Studies have demonstrated that ultrasensitive ctDNA assays may track the response to therapy and progression. However, there are insufficient data that changes in therapy based on ctDNA significantly improve outcomes. Additionally, there are no data to date that ctDNA clearance should be used to make decisions to alter or discontinue therapy.
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	3.2025	MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized European Research Initiative on CLL (ERIC) method or standardized NGS method.
Colon Cancer	3.2025	The Panel believes that there are insufficient data to recommend the use of multigene assays, Immunoscore, or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy.
Multiple Myeloma	2.2025	• Panel suggests that in certain circumstances to consider baseline clone identification and storage of aspirate sample for future MRD testing by NGS. • Panel recommends assessing for MRD during follow-up as indicated prognostication after shared decision-making with patient.
Myeloproliferative Neoplasms (MPN)	1.2025	• There are no recommendations for MRD assessment for MPNs.
Myelodysplastic Syndromes (MDS)	2.2025	• There are no recommendations for MRD assessment for MDS.
Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions	2.2025	• NGS to detect gene fusions is now being increasingly adopted by clinical diagnostic laboratories and may be used for both diagnosis of and monitoring for MRD. • Monitoring hematologic response, cytogenetic response (FISH), and molecular response (if RT-

		qPCR is available) every 3 and 6 months is recommended for patients achieving a durable complete response to initial treatment.
Non-Small Cell Lung Cancer (NSCLC)	3.2025	• There is no recommendation to use MRD testing for NSCLC.
Pancreatic Adenocarcinoma	2.2025	• There is no recommendation to use MRD testing for pancreatic adenocarcinoma.

The National Comprehensive Cancer Network (NCCN) guidelines note that flow cytometry may be used to assess the following hematologic lymphoid cancers: acute lymphoblastic leukemia, chronic myeloid leukemia, lymphomas, hairy cell leukemia, myeloproliferative neoplasms, myelodysplastic disorders, multiple myeloma, systemic mastocytosis, and Waldenstrom's macroglobinemia. Flow cytometry is not mentioned as a laboratory method used for the diagnosis or management of solid tumors, including any of the following: bladder, brain, breast, colon, endometrium, gastric, kidney, lung, neuroblastoma, ovary, prostate, or rectum.

A November 2019 consensus statement from an Ontario expert multidisciplinary working group recommended that: "All adult patients with B-ALL should receive MRD testing after induction chemotherapy. Philadelphia chromosome (Ph)-positive patients should have ongoing monitoring of MRD during treatment and thereafter, while samples from Ph-negative B-ALL patients should be tested at least once later during treatment, ideally at 12 to 16 weeks after treatment initiation. In Ph-negative adult B-ALL patients, standardized, ideally centralized, protocols must be used for MRD testing, including both flow cytometry and immunoglobulin (Ig) heavy chain and T-cell receptor (TCR) gene rearrangement analysis. For Ph-positive B-ALL patients, MRD testing using a standardized protocol for reverse transcription real-time quantitative PCR (RT-qPCR) for the BCR-ABL1 gene fusion transcript is recommended, with Ig/TCR gene rearrangement analysis done in parallel likely providing additional clinical information."

The consensus statement from the European Leukemia Net Working party on AML (2021) notes that since their 2018 statement they have replaced the term "minimal risk disease" with "measurable residual disease". A "positive" or "negative" MRD test result refers to the detection, or not, of measurable disease above specific thresholds that may vary by assay and by laboratory. It is recommended that clinicians are advised to clarify the interpretation of individual MRD results with MRD laboratory colleagues. It is important to recognize that a negative MRD result does not necessarily indicate disease eradication, but rather represents disease below the assay's threshold in the tested sample and patients may still experience a relapse. MRD assessment in AML can be used as (1) a prognostic/predictive biomarker to refine risk assessment and inform treatment decision-making, (2) a monitoring tool to identify impending relapse, and (3) a potential surrogate end point for overall survival in clinical trials to accelerate the development of novel treatment strategies.

The International Workshop on Chronic Lymphocytic Leukemia (2018) stated the following: "The complete eradication of the leukemia is a desired end point. Use of sensitive multicolor flow cytometry, PCR, or next generation sequencing can detect MRD in many patients who achieved a

complete clinical response. Prospective clinical trials have provided substantial evidence that therapies that are able to eradicate MRD usually result in an improved clinical outcome. The techniques for assessing MRD have undergone a critical evaluation and have become well standardized. Six-color flow cytometry (MRD flow), allele-specific oligonucleotide PCR, or high-throughput sequencing using the ClonoSEQ assay are reliably sensitive down to a level of one CLL cell in 10,000 leukocytes. Refinement and harmonization of these technologies has established that a typical flow cytometry–based assay comprises a core panel of six markers (i.e., CD19, CD20, CD5, CD43, CD79b, and CD81). As such, patients will be defined as having undetectable MRD (MRD-neg) remission if they have blood or marrow with less than one CLL cell per 10,000 leukocytes."

The American Society for Clinical Pathology (2018) Choosing Wisely statement, “Do not perform peripheral blood flow cytometry to screen for hematological malignancy in the settings of mature neutrophilia, basophilia, erythrocytosis, thrombocytosis, isolated anemia, or isolated thrombocytopenia.” The role of peripheral blood flow cytometry for hematologic neoplasia is limited to settings in which either there are morphologically abnormal cells identified on a peripheral blood smear review (blasts, lymphoma cells) or there are clinical and/or laboratory findings that suggest a high pre-test probability for the presence of a disorder amenable to the immunophenotypic detection of neoplastic cells in the blood. The latter includes patients with neutropenia, absolute lymphocytosis, lymphadenopathy, or splenomegaly. The likelihood of flow cytometry of blood producing diagnostic results in the settings enumerated in the recommendation above is extremely low; bone marrow sampling with morphologic analysis (and appropriate ancillary diagnostic testing) may be indicated in those scenarios.

REGULATORY STATUS

Refer to the FDA Medical Device website. Available from: https://www.fda.gov/medical-devices [accessed 2025 May 28]

FDA Approved Tests

- ClonoSEQ Assay, produced by Adaptive Biotechnologies- For only CLL, ALL and MM

Non-FDA Approved Tests

- Guardant Reveal test produced by Guardant Health; Inc
- Signatera test produced by Natera
- MyMRD by Laboratory for Personalized Molecular Medicine
- Invitae PCM MRD Monitoring by Invitae Corporation
- Invitae PCM Tissue Profiling and MRD Baseline Assay by Invitae Corporation
- M-inSight Patient Definition Assay by Corgenix Clinical Laboratory
- M-inSight Patient Follow-Up Assessment by Corgenix Clinical Laboratory
- HPV-SEQ Test by Sysmex Inostics, Inc
- Nothstar Response by BillionToOne Laboratory

- UroAmp MRD by Convergent Genomics, Inc

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis
86356	Mononuclear cell antigen, quantitative (e.g., flow cytometry), not otherwise specified, each antigen
88182	Flow cytometry, cell cycle or DNA 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	Flow cytometry, interpretation; 9 to 15 markers
88189	Flow cytometry, interpretation; 16 or more markers
0171U (E/I)	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 (MyMRD NGS Panel, Laboratory for Personalized Molecular Medicine)
0306U (E/I)	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 (Invitae PCM Tissue Profiling and MRD Baseline Assay; Invitae Corporation)
0307U (E/I)	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 (Invitae PCM MRD Monitoring; Invitae Corporation)

Code	Description
0340U (E/I)	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. (Signatera Natera, Inc, Natera, In)
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 (ClonoSEQ Assay, Adaptive Biotechnologies)
0450U (E/I)	Oncology (multiple myeloma), liquid chromatography with tandem mass spectrometry (LC-MS/MS), monoclonal paraprotein sequencing analysis, serum, results reported as baseline presence or absence of detectable clonotypic peptides (M-inSight Patient Definition Assay, Corgenix Clinical Laboratory)
0451U (E/I)	Oncology (multiple myeloma), LC-MS/MS, peptide ion quantification, serum, results compared with baseline to determine monoclonal paraprotein abundance (M-inSight Patient Follow-Up Assessment, Corgenix Clinical Laboratory)
0467U (E/I)	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 (UroAmp MRD, Convergent Genomics, Inc)
0470U (E/I)	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 (HPV-SEQ Test, Sysmex Inostics, Inc)
0486U (E/I)	Oncology (pansolid tumor), next generation sequencing analysis of tumor methylation markers present in cell free circulating tumor DNA, algorithm reported as quantitative measurement of methylation as a correlate of tumor fraction (Nothstar Response, BillionToOne Laboratory)
0569U (E/I)	Oncology (solid tumor), next-generation sequencing analysis of tumor methylation markers (>20000 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

HCPCS Codes

Code	Description
Not Applicable	

ICD10 Codes

Code	Description
C81.00 – C81.99	Hodgkin lymphoma (code range)
C82.0 - C82.99	Follicular lymphoma (code range)
C83.0-C83.99	Non-follicular lymphoma (code range)
C84.0-C84.99	Mature T/NK-cell lymphomas (code range)
C85.1-C85.99	Other specified and unspecified types of non-Hodgkin lymphoma (code range)
C86.0-C86.6	Other specified types of T/NK-cell lymphoma (code range)
C88.0-C88.9	Malignant immunoproliferative diseases and certain other B-cell lymphomas (code range)
C90.00-C90.32	Multiple myeloma and malignant plasma cell neoplasms (code range)
C91.0-C91.92	Lymphoid leukemia (code range)
C92.0-C92.92	Acute myeloblastic leukemia (code range)
C93.0-C93.92	Monocytic leukemia (code range)
C94.00-C94.82	Other leukemias of specified cell type (code range)
C95.0-C95.92	Leukemia of unspecified cell type (code range)
C96.0- C96.9	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue (code range)

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for gene expression analysis for Minimal Residual Disease Testing for Cancer.

Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (NCA CAG-00450R) - Decision Memo [accessed 2025 Apr 24]

Next Generation Sequencing (NGS) (NCD 90.2) [accessed 2025 Apr 24]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION

Committee Approval Dates

08/19/21, 06/16/22, 06/22/23, 06/20/24, 08/21/25

Date	Summary of Changes
04/14/26	• Code 0569U re-added to the policy as it was removed unintentionally.
08/21/25	• Annual review, policy statement was revised to delete lymphoma and specify ALL, CLL and MM as the only FDA approved indications for ClonoSeq. Flow cytometry content for MRD was merged from CMP Flow Cytometry 2.02.57. Code edits: added codes 017U, 0306U, 0307U and removed code 81450. Investigational statement was expanded to address more MRD tests.
01/01/25	• Summary of changes tracking implemented.
08/19/21	• Original effective date