MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Measurable Residual Disease Assessment Testing**
Policy Number	**2.02.54**
Category	**Technology Assessment**
Original Effective Date	**08/19/21**
Committee Approval Date	**08/19/21, 06/16/22, 06/22/23**
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Archived Date	**NA**
Archive Review Date	**NA**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), 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 STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, next-generation sequencing (NGS) for the assessment of measurable residual disease (MRD) is considered **medically appropriate** to detect measurable residual disease (MRD) at a threshold of 10^{-4} as an alternative test in patients with Leukemia, Lymphoma, and Multiple Myeloma.

II. Based upon our criteria and assessment of the peer-reviewed literature, NGS for the assessment of MRD is considered **investigational** for all other indications, including but not limited to Guardant Reveal and Signatera.

Refer to Corporate Medical Policy #2.02.51 Molecular Panel Testing of Tumor Tissue to Identify Targeted Therapies for Cancers.

Refer to Corporate Medical Policy #2.02.56 Circulating Tumor DNA for Management of Cancer (Liquid Biopsy).

Refer to Corporate Medical Policy #2.02.57 Flow Cytometry

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services.

POLICY GUIDELINES

I. The **ClonoSEQ** Assay is a United States Food and Drug Administration (FDA) cleared test produced by Adaptive Biotechnologies and uses multiplex polymerase chain reaction (PCR) and next generation sequencing (NGS) for in vitro diagnostic testing to evaluate MRD. In September 2018, it initially received de novo class II designation by the United States Food and Drug Administration (FDA) for using bone marrow aspirate to detect and monitor B-cell acute lymphoblastic leukemia (ALL) and multiple myeloma (MM). In August 2020, 510(k) clearance decision of substantially equivalent was granted to use peripheral blood and bone marrow for detection and monitoring of chronic lymphocytic leukemia (CLL).

II. The **Guardant Reveal** test produced by Guardant Health; Inc. uses NGS for in vitro MRD diagnostic testing of blood by detecting the presence of small fragments of circulating tumor DNA (ctDNA). The test has not received FDA approval.

III. The **Signatera** test produced by Natera uses multiplex PCR and NGS to detect ctDNA in plasma to monitor MRD in patients previously diagnosed with colorectal cancer. Signatera has received FDA Breakthrough Device Designations but has not been FDA-cleared or FDA-approved.

IV. Testing for MRD may be performed by either flow cytometry or next-generation sequencing (NGS). Testing for MRD by both laboratory methods concurrently is not medically appropriate as it is duplicative testing.

V. For criteria to detect MRD using Flow cytometry refer to policy #2.02.57 Flow Cytometry.

VI. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

DESCRIPTION

Measurable residual disease (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.

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. MRD testing performed by NGS proposes to detect one residual clonal sequence out of 10^6 cells and can be performed from a simple blood draw and without direct tumor tissue testing. In essence, MRD status allows for risk stratification that can be used as a guide for treatment decisions.

ClonoSEQ is a DNA-based test that identifies and quantifies specific nucleic acid sequences isolated from bone marrow aspirate and/or peripheral blood to estimate the percentage of cells that contain those specific sequences. This excludes circulating DNA in plasma. The test is intended for use as an aid to measure MRD to monitor the change in burden of disease for patients with hematological malignancy during and after treatment. The manufacturer states that results can be expected in approximately seven (7) days for fresh specimens and 14 days for stored specimens. The manufacturer also notes on their website that clonoSEQ is also available for use in other lymphoid cancers and specimen types as a CLIA-validated laboratory developed test.

The Guardant Reveal test is used in the assessment of MRD in early-stage colorectal cancer at least four (4) weeks after surgical treatment. *Guardant Reveal* does not require direct tumor tissue testing, so can be used for regular MRD surveillance or to identify patients with colorectal cancer who are at high-risk of recurrence and may benefit from adjuvant chemotherapy and active surveillance. The manufacturer states that results can be expected seven (7) days after a routine blood draw.

The Signatera test uses tumor tissue and matched-normal whole exome sequencing to characterize the clonal mutations of a tumor, creating a unique signature integrated from genomic and epigenomic cancer signatures. Some studies have also been conducted for other cancers including breast, early-stage non-small cell lung and bladder cancers, but these are not definitive.

RATIONALE

Measurable Residual Disease

The three main categories of hematologic malignancies are 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).

Relapse is believed to be due to residual clonal cells that remain following "complete response" after induction therapy but are below the limits of detection using conventional morphologic assessment. Residual clonal cells that can be detected in the bone marrow or blood are referred to as measurable residual disease (MRD), also known as minimal residual disease. MRD assessment is typically performed by flow cytometry or polymerase chain reaction (PCR) with primers for common variants. Flow cytometry or next generation flow cytometry evaluates blasts based on the expression of characteristic antigens, while PCR assesses specific chimeric fusion gene transcripts, gene variants, and overexpressed genes. PCR is sensitive for specific targets, but clonal evolution may occur between diagnosis, treatment, remission, and relapse that can affect the detection of MRD. Next-generation sequencing (NGS) has 10- to 100-fold greater sensitivity for detecting clonal cells, depending on the amount of DNA in the sample (see Table 1) and does not require patient-specific primers. For both PCR and NGS a baseline sample at the time of high disease load is needed to identify tumor-specific sequences. MRD with NGS is frequently used as a surrogate measure of treatment efficacy in drug development.

It is proposed that by using a highly sensitive and sequential MRD surveillance strategy, one could expect better outcomes when therapy is guided by molecular markers rather than hematologic relapse based on morphologic assessment. However, some patients may have hematologic relapse despite no MRD, while others do not relapse despite residual mutation-bearing cells. Age-related clonal hematopoiesis, characterized by somatic variants in leukemia-associated genes with no associated hematologic disease, further complicates the assessment of MRD. 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.

The National Comprehensive Cancer Network (NCCN) Guidelines of relevance to this policy:

Guideline	**Version**	**Recommendations**
Acute Lymphoblastic Leukemia	1.2022	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 this 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.
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	2.2023	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.
Multiple Myeloma	3.2023	Next generation sequencing (NGS) panel on bone marrow help provide a more detailed evaluation of MM genetics allows for further risk categorization through the identification of additional abnormalities that may be of prognostic and/or therapeutic

		value.33 Therefore, the NCCN Multiple Myeloma Panel has included these tests as useful adjunct in certain circumstances.
B-Cell Lymphomas	4.2023	If a high suspicion of a clonal process remains and other techniques have not resulted in a clear identification of a clonal process, then next-generation sequencing (NGS) can be used

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."

Thompson et al (2019), who 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 taken into account. 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.

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."

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.

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.

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}.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), 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
81599	Unlisted multianalyte assay with algorithmic analysis
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 (MyMRD® NGS Panel, Laboratory for Personalized Molecular Medicine, Laboratory for Personalized Molecular Medicine)
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 (Invitae PCM Tissue Profiling and MRD Baseline Assay; Invitae Corporation)
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 (Invitae PCM Tissue Profiling and MRD Baseline Assay; 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) *(effective 04/1/2023)*

HCPCS Codes

Code	Description
No codes	

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)
C88.0-C88.9	Malignant immunoproliferative diseases and certain other B-cell lymphomas (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)
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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*Key Article

KEY WORDS

Measurable residual disease, MRD, Minimal residual disease, Molecular residual disease, Liquid biopsy

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a National Coverage Analysis (NCA) for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=290&keyword=ClonoSEQ&keywordType=starts&areaId=s41&docType=NCA%2cCAL%2cNCD%2cMEDCAC%2cTA%2cMCD%2c6%2c3%2c5%2c1%2cF%2cP&contractOption=all&sortBy=relevance&bc=1

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