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***Current Policy Effective Date: 11/1/25**
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Title: Genetic Testing – Next Generation Sequencing for Assessment of Measurable Residual Disease (e.g., ClonoSEQ) in Hematological Malignancies

Description

Measurable residual disease (MRD), also known as minimal residual disease, refers to residual clonal cells in blood or bone marrow following treatment for hematologic malignancies. MRD is typically assessed by flow cytometry (FC) or polymerase chain reaction, which can detect 1 clonal cell in 100,000 cells. It is proposed that next-generation sequencing (NGS), which can detect 1 residual clonal sequence out of 1,000,000 cells, will improve health outcomes in individuals who have been treated for hematologic malignancies such as acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), diffuse large B-cell lymphoma (DLBCL), and mantle cell lymphoma (MCL).

Medical Policy Statement

The efficacy of next generation sequencing (e.g. clonoSEQ) to detect measurable residual disease has been established. It may be considered a useful option when specific criteria are met.

Inclusionary and Exclusionary Guidelines

Inclusions:

Next generation sequencing (e.g., clonoSEQ) to detect measurable residual disease (MRD) in any **one** of the following hematologic malignancies:

- B-Cell acute lymphoblastic leukemia
- Chronic lymphocytic leukemia
- Multiple myeloma

Exclusions:

- Next-generation sequencing (e.g. clonoSEQ) to detect MRD in all other situations.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81479 0364U

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Background

Disease

There are 3 main types of hematologic malignancies: lymphomas, leukemias, and myelomas. Lymphoma begins in lymph cells of the immune system, which originate in the bone marrow and collect in lymph nodes and other tissues. Leukemia is caused by the overproduction of abnormal white blood cells in the bone marrow, which leads to a decrease in the production of red blood cells and plasma cells. The most common forms of leukemia are acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, and chronic myeloid leukemia. Multiple myeloma (MM), also called plasma myeloma, is a malignancy of plasma cells in the bone marrow. The present evidence review will address B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, multiple myeloma, diffuse large B-cell lymphoma, and mantle cell lymphoma. As B-Cell acute lymphoblastic leukemia and B-Cell lymphoblastic lymphoma are generally considered clinically indistinct, reference to B-Cell acute lymphoblastic leukemia is intended to encompass both entities.

Treatment

Treatment depends on the type of malignancy and may include surgery, radiotherapy, chemotherapy, targeted therapy, plasmapheresis, biologic therapy, or hematopoietic cell transplant. Treatment of acute leukemias can lead to complete remission. Multiple myeloma and the chronic leukemias are treatable but generally incurable. Outcomes of lymphoma vary by subtype, and some forms are curable.

Measurable Residual Disease

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, 1 could expect better outcomes when therapy is guided by molecular markers rather than hematologic relapse. 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. One available test (clonoSEQ) uses both PCR and NGS to detect clonal DNA in blood and bone marrow. ClonoSEQ Clonality (ID) PCR assessment is performed when there is a high disease load (e.g., initial diagnosis or relapse) to identify dominant or “trackable” sequences associated with the malignant clone. NGS is then used to monitor the presence and level of the associated sequences in follow-up samples. As shown in Table1, 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 (see Table 1).

Table 1. Sensitivity of Methods for Detecting Measurable Residual Disease

Technique	Sensitivity	Detection limit of blasts per 100,000 Nucleated Cells
Microscopy (complete response)		50,000
Multiparameter flow cytometry	10^{-4}	10
Next-generation flow cytometry	10^{-5}	1.0
Polymerase chain reaction	10^{-5}	1.0
Quantitative next-generation sequencing	10^{-5}	1.0
Next-generation sequencing	10^{-6}	0.1

Summary of Evidence

For individuals with B-cell ALL who are being monitored for residual disease following treatment who receive NGS for MRD at a threshold of 10^{-4} , the evidence includes a retrospective comparisons of data from trials. Relevant outcomes are overall survival (OS), disease-specific survival, test validity, change in disease status, quality of life (QOL), and treatment-related morbidity. Comparison of NGS and the established standard of FC showed good concordance when the same threshold (10^{-4}) was used for both NGS and FC. OS in pediatric patients with MRD positivity was significantly lower than in pediatric patients who were MRD negative at this threshold. The relatively small subset of patients who were

discordant for FC and NGS results had outcomes that were midway between patients who were concordant as MRD positive or MRD negative for both tests. As the vast majority of patients had concordant results for NGS and FC at a threshold of 10^{-4} , NGS can be considered an alternative to FC for monitoring MRD in patients with B-ALL.

The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with B-ALL who are being monitored for residual disease following treatment who receive NGS for MRD at a threshold of less than 10^{-4} , the evidence includes retrospective analysis of prognosis from trials. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. NGS can be more sensitive than FC to detect the presence of residual leukemic cells, but specificity may be decreased at the more sensitive thresholds resulting in potential harm from overtreatment. Further study is needed to clarify whether MRD at levels lower than 1 in 10,000 cells represents clinically significant disease and if the more sensitive test can be used to risk-stratify patients with B-ALL. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with CLL who are being monitored for residual disease following treatment who receive NGS for MRD at a threshold of 10^{-4} , the evidence includes analysis of samples from 2 clinical trials. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. These studies evaluated the association between the level of MRD detected by NGS in bone marrow or blood and progression-free survival (PFS) in completed phase 2 and 3 trials. Two studies demonstrated an association between the level of MRD and PFS with lower risk of progression in patients who exhibit MRD negativity below 10^{-4} compared to patients who have detectable residual disease. In 1 study of participants treated with ibrutinib + venetoclax, PFS at 1 year was high regardless of MRD status using threshold of 10^{-4} at the end of treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with CLL who are being monitored for residual disease following treatment who receive NGS for MRD at a threshold of less than 10^{-4} , the evidence includes analysis of samples from clinical trials. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. NGS can be more sensitive than FC to detect the presence of residual leukemic cells, but it is not clear if prognosis is improved at the lower thresholds. Currently, no additional treatment is offered to eradicate low-level MRD ($<10^{-4}$) after first-line treatment of CLL. Further study is needed to clarify whether MRD at levels lower than 1 in 10,000 cells represents clinically significant disease and if the more sensitive test can be used for prognosis in patients with CLL. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with MM who have achieved a complete response (CR) following treatment who receive NGS for MRD at a threshold of 10^{-5} , the evidence includes retrospective comparisons of NGS and FC data from MM treatment trials and from a clinical series. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. Concordance has been demonstrated between NGS and the established standard of FC at 10^{-4} as well as with next generation flow cytometry (NGF) at a threshold of 10^{-5} . PFS in patients with MRD positivity is significantly shorter than in patients who are MRD negative at these thresholds. The relatively small subset of patients who were

discordant for FC and NGS results had outcomes that were, on average, midway between patients who were concordant as MRD positive or MRD negative for both tests. Retrospective studies also indicate improved PFS when MRD is less than 10^{-5} compared to patients who have MRD greater than 10^{-5} . This threshold is consistent with current guideline-based care for prognostication using either NGF or NGS. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with MM who have achieved a CR following treatment who receive NGS for MRD at a threshold of less than 10^{-5} , the evidence includes retrospective studies on prognosis. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. There is some evidence that MRD may be a prognostic marker, but there is insufficient evidence on the number of false positives in patients with CR at the more sensitive threshold provided by NGS for prognostication or to guide therapy. A chain of evidence regarding management changes based on the assessment of MRD with NGS to detect 1 malignant clonal sequence out of 1,000,000 cells cannot be completed. Direct evidence from randomized controlled trials is needed to evaluate whether patient outcomes are improved by changes in postinduction care (e.g., continuing or discontinuing therapy, avoiding unnecessary adverse events) following NGS assessment of residual disease at a threshold lower than 10^{-5} . Trials that will test the effectiveness of NGS to guide therapy in MM are ongoing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with DLBCL who are being monitored for residual disease following treatment who receive NGS for MRD, the evidence includes an analysis from a single-center, prospective trial. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. Although both PFS and OS are correlated with MRD positivity, the trial is limited by its small sample-size and inclusion of only patients eligible for HSCT from a single center. Guideline support for using MRD with any method or threshold to make management decisions is lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with MCL who are being monitored for residual disease the evidence includes retrospective analyses of NGS testing during therapeutic clinical trials. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. A retrospective analysis of a "research version" of an NGS test has demonstrated concordance between NGS and FC at 10^{-4} during induction therapy. MRD positivity as determined by either the "research version" of NGS or FC was associated with worse PFS. An exploratory analysis found improved survival in patients who were MRD negative after 2 cycles of induction; however, this is based on a small number of samples with an undefined threshold for NGS testing. Overall, the literature is limited, and guidelines for NGS testing to detect MRD in patients with MCL are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific

outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms. The following is a summary of the key literature to date.

Next-Generation Sequencing to Detect Measurable Residual Disease in B-Cell Acute Lymphoblastic Leukemia

Clinical Context and Test Purpose

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed in children; it represents nearly 25% of cancers in children younger than 15 years and 20% of acute leukemias in adults. Remission of disease is now typically achieved with pediatric chemotherapy regimens in 98% of children with ALL, with up to 85% long-term survival rates. The prognosis after the first relapse is related to the length of the original remission. For example, the leukemia-free survival rate is 40% to 50% for children whose first remission was longer than 3 years compared with 10% to 15% for those who relapse less than 3 years after treatment. Between 60% and 80% of adults with ALL can be expected to achieve a complete response (CR) after induction chemotherapy; however, only 35% to 40% can be expected to survive 2 years. “Poor prognosis” genetic abnormalities such as the Philadelphia chromosome (translocation of chromosomes 9 and 22) are seen in 25% to 30% of adult ALL but infrequently in childhood ALL. Other adverse prognostic factors in adult ALL include age greater than 35 years, poor performance status, male sex, and leukocytosis count of greater than 30,000/ μ L (B-cell lineage) or greater than 100,000/ μ L (T-cell lineage) at presentation.

Induction therapy aims to reduce the leukemic cell population below the cytological detection limit (about 10^{10} cells or 1 malignant cell for every 20 to 100 normal cells), but it is believed that remaining leukemic cells that are below the level of clinical and conventional morphologic detection lead to relapse if no further treatment were given. Consolidation and intensification therapy is intended to eradicate this residual disease. The type of post-remission therapy (chemotherapy or autologous or allogeneic hematopoietic cell transplantation [HCT]) depends on the expected rate of relapse and patient characteristics such as age and comorbidities. Bone marrow is examined every 3 to 6 months for a minimum of 2 years to determine clinical relapse. If a patient is in CR for 7 to 8 years they are considered cured. Most children and up to one-half of adults will have prolonged disease-free survival, but up to 20 percent of adults will have a resistant disease, and a majority of adults and some children will eventually relapse and die of leukemia.

Measurable, or minimal, residual disease (MRD) is used to assess the 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. In addition, not all patients with MRD positivity will relapse clinically because some cells with abnormal markers may lack the ability to create disease. Other patients will relapse despite no 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 assays are routinely used in the clinical care of children and increasingly in adults with ALL and guidelines state that MRD quantification is an essential component of patient

evaluation.(1) The choice of tests may depend on how the results will impact patient care. FC may be preferred if there are plans to escalate care because results are rapidly available and the likelihood of relapse with this less sensitive test is high. PCR may be preferred to identify patients with a low risk of relapse when a reduction in treatment intensity is being considered. Some clinicians use more than 1 technique to minimize false-negative results, or at multiple time points to assess disease trajectory, and ongoing trials are evaluating whether children who demonstrate a rapid clearance of tumor cells during induction therapy may be candidates for less intensive therapy. In adults who have a high rate of relapse, MRD is being studied to identify patients who require intensified treatment.

Next-generation sequencing (NGS) is a newer technique that is commercially available (e.g., clonoSEQ). NGS is more sensitive than other methods and can detect up to 1 leukemic cell in 1,000,000 cells if there is sufficient DNA in the sample (see Table 1), but other performance characteristics are not well established.

The main use of measurement of MRD with NGS is to risk-stratify and inform treatment management.(1)

Tables 2, 3, and 4 describe studies that have evaluated prognosis based on MRD levels detected by FC and NGS. Overall, higher levels of MRD are associated with a worse prognosis. In a study by Wood et al (2018), there was high concordance between FC and NGS at a threshold of 10^{-4} in pediatric B-ALL (data are shown graphically in the publication).(3) A subset of these results was submitted to the U.S. Food and Drug Administration in support of the de novo clearance. OS in pediatric patients with MRD positivity was significantly lower than in pediatric patients who were MRD negative at this threshold. At an MRD threshold of 10^{-4} , NGS identified 55 patients as MRD-positive who were MRD-negative by FC, while 17 patients were MRD-positive by FC but MRD-negative by NGS (see Table 3). Patients who were FC negative/NGS positive had outcomes that were midway between patients who were concordant as MRD positive or MRD negative for both tests.

Notably, higher levels of sensitivity were associated with a decrease in clinical specificity, with a larger fraction of MRD-positive patients with relatively good outcome (data not shown in the publication). With MRD negativity set at a threshold of 10^{-6} , OS was 100% in the standard-risk group and 95.1% in the high-risk group (see Table 4), but at this threshold, there was not a statistically significant difference in OS between the MRD positive and MRD negative patients for either group. The maximal HR for NGS was obtained at 10^{-4} , which is the sensitivity of FC. A smaller study by Pulsipher et al (2015) compared NGS at 10^{-6} with FC assessed before and after HCT in pediatric patients with ALL.(4) NGS was more successful at predicting the relapse probability and OS compared to FC. The major limitations of these studies are shown in Tables 5 and 6. A limitation in Wood et al (2018) is that samples were only available at the end of induction, so the results only apply to the end of induction. In addition, the data on sensitivity and specificity at other thresholds were not reported, although the study did assess the threshold with the greatest HR, which was calculated to be 10^{-4} (the same as FC). Both studies were conducted in pediatric ALL patients, and results may not apply fully to adults or be applicable to other periods in the treatment course.

In an analysis of samples from 2 multicenter studies, Pulsipher et al (2022) compared FC at a threshold of 10^{-4} with NGS at thresholds of 10^{-4} , 10^{-5} , 10^{-6} , and any detectable level (approximately 10^{-7}) in pediatric and young adult patients with B-ALL who received

tisagenlecleucel.(5) In 95 patients with both NGS and FC results, 18% of samples were MRD-positive with FC compared with 22%, 29%, 33%, and 41% with NGS at cutoff values of 10^{-4} , 10^{-5} , 10^{-6} , and any detectable level, respectively. No samples were positive by FC and negative by NGS.

Liang et al (2023) reported results of a study of the prognostic performance of the clonoSEQ assay in 111 adult participants with B-cell or T-cell ALL who underwent allogeneic HCT at Stanford University or Oregon Health & Science University between 2014 and 2021.(6) Participants were followed for leukemia relapse and/or death for up to 2 years after HCT. Relapse was defined as morphologic or clinical. The MRD samples came from either peripheral blood or bone marrow. The median age of the patients was 44 years (range, 19 to 70 years), 62 (56%) were male, and 95 (86%) had B-cell ALL.

Table 2. Characteristics of Prognostic Studies Assessing NGS for MRD in B-cell ALL

Study	Study Population	Design ^a	Reference Standard	Threshold for PIT	FU	Test Version
Liang et al (2023)	Blood and bone marrow samples from adults with B-cell (86%) or T-cell ALL undergoing HCT	Retrospective from banked samples; assessed by NGS	Relapse	Presence of a detectable IgH clonotype in B-cell ALL or the presence of a detectable TCR β or TCR γ clonotype in T-cell ALL. Stratified as undetectable (0), low ($<10^{-4}$), high ($\geq 10^{-4}$ to $\leq 10^{-3}$), or very high ($>10^{-3}$)	Up to 2 years	clonoSEQ
Pulsipher et al (2022)	Blood and bone marrow samples from 143 patients in tisagenlecleucel trials	Retrospective from banked samples with comparison of FC and NGS	Relapse	FC at 10^{-4} ; NGS at 10^{-4} or less	38.4 mo	clonoSEQ
Wood et al (2018)	619 paired bone marrow samples from pediatric B-ALL patients before and after induction chemotherapy in COG trials	Retrospective from banked samples with comparison of FC and NGS	Event-free survival and overall survival	FC at 10^{-4} ; NGS at 10^{-4} and 10^{-5}	5 y	ImmunoSEQ
Pulsipher et al (2015)	Before (n=41) and after HCT (n=57) marrow samples from pediatric ALL patients in COG trials	Retrospective from banked samples with comparison of FC and NGS	Time to relapse following HCT	FC at 10^{-4} ; NGS at 10^{-6}		ImmunoSEQ

ALL: acute lymphoblastic leukemia; COG: Children's Oncology Group; FC: flow cytometry; FU: follow-up; HCT: hematopoietic cell transplantation; MRD: measurable residual disease; NGS: next-generation sequencing; PIT: positive index test.

Table 3. Concordance Between FC and NGS at a Threshold of 10^{-4} from Wood et al (2018)(3)

		Flow Cytometry		
		+	-	Total
NGS	+	87	55	142
	-	17	409	426

Total	104	464	568
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FC: flow cytometry; NGS: next-generation sequencing.

Table 4. Results of Prognostic Studies Assessing NGS for MRD in B-cell ALL

Study	N	MRD Threshold	Results	5-Year EFS, % (SD)	OS, % (SD)	Hazard Ratio
			Relapse, %			
Liang et al (2023)	111 (95 B-cell ALL)	MRD before HCT: Undetectable (n=82) Low (<10 ⁻⁴ ; n=24), High (>10 ⁻⁴ to ≤10 ⁻³ ; n=11) Very high (>10 ⁻³ ; n=5)	Undetectable, <10% Low, ~35% High, ~30% Very high, ~55%			Undetectable, Reference Low, HR=3.6 (1.4 to 9.2) High, HR=2.9 (0.8 to 11.2) Very high, HR=7.0 (2.1 to 22.9)
Pulsipher et al (2022)	143	As low as "any detectable level" (roughly corresponding to 10 ⁻⁷)	Relapse before 12 months occurred without MRD detection in 50% of patients by FC, 31% by NGS at 10 ⁻⁶ , and 0% of those with NGS below the 10 ⁻⁶ level			
Wood et al (2018)	282 Standard Risk	EOI NGS negative <10 ⁻⁶ (n=56)		98.1 (2)	100 (0)	Maximal at 10 ⁻⁴
	297 High Risk	EOI NGS negative <10 ⁻⁶ (n=89)		92.7 (4)	95.1 (3)	
Relapse Probability at 2 Years, %						
Pulsipher et al (2015)	41	Pre-HCT FC negative	16			
		Pre-HCT NGS negative	0			
		Pre-HCT FC positive	46			
		Pre-HCT NGS positive	53			

EFS: event-free survival; EOI: end of induction; FC: flow cytometry; HCT: hematopoietic cell transplantation; MRD: measurable residual disease; NGS: next-generation sequencing; OS: overall survival; PPV: positive predictive value; SD: standard deviation; TTP: time to progression.

Limitations in study relevance, and study design and conduct are shown in Tables 5 and 6.

Table 5. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Liang et al (2023)	4. Included participants with B-cell or T-cell ALL		2. No comparator		1. Limited follow-up duration
Pulsipher et al (2022) ⁵	4. Results specific to patients treated with tisagenlecleucel				1. Limited follow-up duration
Wood et al (2018) ³	4. Results are specific to pediatric B-ALL. Stored samples were available only at the end of induction.	3. Used ImmunoSEQ rather than clonoSEQ			

Pulsipher et al (2015) ⁴ .	4. Results are specific to pediatric ALL.	3. Used ImmunoSEQ rather than clonoSEQ
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The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. ALL: acute lymphoblastic leukemia.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 6. Study Design and Conduct Limitations

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Liang et al (2023)	2. Selection based on availability of samples from prior studies	1. Blinding was not described				
Pulsipher et al (2022) ⁵ .	2. Selection based on availability of samples from prior studies	1. Blinding was not described	2. FC analysis was part of the original trials; NGS was performed on frozen samples post hoc			
Wood et al (2018) ³ .	2. Selection based on availability of tissue samples from prior studies			2. NGS at 10 ⁻⁴ was not prespecified. The lack of specificity with other thresholds was mentioned.		
Pulsipher et al (2015) ⁴ .	2. Selection based on availability of tissue samples from prior studies	1. Blinding was not described				

NGS: next-generation sequencing.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

There is sufficient evidence on test performance when NGS results are reported at 10⁻⁴, which is comparable to other established methods of measuring MRD such as FC. However, performance characteristics at lower thresholds are uncertain, and there is some evidence that

false-positives may be increased with a more sensitive test. Therefore, a chain of evidence cannot be constructed regarding the clinical utility of measurement of MRD at less than 10^{-4} in patients with ALL.

Section Summary: Next Generation Sequencing to Detect Measurable Residual Disease in B-cell Acute Lymphoblastic Leukemia

Evidence on the clinical validity of NGS to risk-stratify patients includes 2 retrospective studies in pediatric patients with ALL who had participated in earlier trials by the Children's Oncology Group and 2 retrospective studies in adults. The largest study was conducted in stored samples from before and after induction therapy, and MRD negativity was 1 of several factors that were used to risk-stratify patients. Comparison with FC showed comparable results when the same threshold (10^{-4}) was used for both NGS and FC, and OS in pediatric patients with MRD positivity was significantly lower than in pediatric patients who were MRD negative. However, NGS at the limit of detection (10^{-6} or 1 leukemic cell in 1,000,000 normal cells) was found to have lower specificity. Thus, in 1 study of over 600 pediatric patients with B-ALL undergoing induction, risk stratification based on NGS and FC were comparable at a threshold of 10^{-4} , but NGS had more false-positives with lower thresholds. In another retrospective study in pediatric and young adult patients who were enrolled in tisagenlecleucel clinical trials, NGS was only of prognostic importance at levels below the threshold of 10^{-6} .

Guidelines state that MRD quantification is an essential component of patient evaluation. Evidence is sufficient to support the clinical utility of using NGS to measure MRD when patient management is based on test results at a sensitivity of 10^{-4} . Evidence is insufficient to evaluate benefits and harms when treatment decisions are made based on NGS results at thresholds lower than 10^{-4} . Few studies have been performed to assess whether the identification of 1 in 1,000,000 cells identifies clinically significant residual disease, and false-positives may be increased resulting in harm from overtreatment. Further study is needed to clarify which threshold of NGS should be considered when risk stratifying patients and whether treatment decisions based on the more sensitive assay improves the net health outcome.

Next-Generation Sequencing to Detect Measurable Residual Disease in Chronic Lymphocytic Leukemia

Clinical Context and Test Purpose

Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries, representing approximately 25% to 30% of all leukemias. CLL is characterized by progressive accumulation of functionally incompetent monoclonal B lymphocytes. It occurs primarily in older adults, but occurrence in younger adults is not unusual. The incidence of CLL increases with age with a median age at diagnosis of 70 years. Malignant cells in CLL and the non-Hodgkin lymphoma small lymphocytic lymphoma have identical pathologic and immunophenotypic features. The term CLL is used when the disease manifests primarily in the blood, whereas the term small lymphocytic lymphoma is used for primarily nodal manifestation.

Not all patients with CLL will require treatment at the time of diagnosis. Median survival for patients with asymptomatic CLL is 10 years, and some patients with early stage CLL may be asymptomatic without treatment for decades. Importantly, randomized trials evaluating immediate versus delayed treatment strategies have found no improvement in long-term survival with early treatment, survival in some patients will not be different from the normal population, and with the exception of HCT, there is currently no cure for CLL. Therefore, the

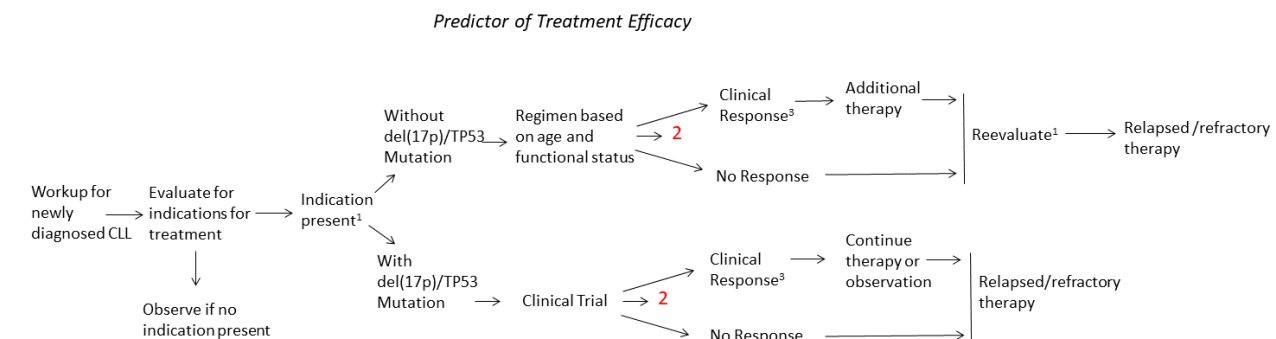
standard of care for patients with early stage asymptomatic CLL is observation rather than immediate treatment.

Treatment is indicated for patients with disease-related complications, termed "active disease" by the International Workshop on Chronic Lymphocytic Leukemia.(6) Criteria for active disease include 1 or more of the following: progressive marrow failure, splenomegaly, lymphadenopathy, progressive lymphocytosis, autoimmune anemia and/or thrombocytopenia, extranodal involvement (e.g., skin, kidney, lung, spine), and constitutional symptoms such as weight loss, fatigue, fever, and night sweats. The goal of therapy is to ameliorate symptoms and improve PFS and OS. The choice of therapy is based on patient and tumor characteristics and goals of therapy. Most patients will have an initial complete or partial response to treatment but will eventually relapse. Relapse may be asymptomatic but is monitored closely for progression to active disease.

The main use of MRD with NGS in patients with CLL is to predict treatment efficacy.

The analytic framework for the use of MRD for CLL, based on guidelines from the National Comprehensive Cancer Network,(7) is shown in Figure 1.

Figure 1. Analytic Framework for the use of MRD to Inform Treatment Management in CLL.



CLL: chronic lymphocytic leukemia; HCT: hematopoietic cell transplant; MRD: measurable residual disease; Ph: Philadelphia chromosome; TKI: tyrosine kinase inhibitor

¹ Evaluate for del (17p), TP53 mutation status, CpG-stimulated karyotype, IGHV mutation status (if not previously done), imaging as appropriate

² Measurable residual disease (MRD) assessment:

"Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end of treatment is an important predictor of treatment efficacy"

"MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized ERIC method or standardized NGS method"

³ Response is determined by lymph nodes, liver and/or spleen size, constitutional symptoms, circulating lymphocyte count, platelet count, hemoglobin, marrow, and neutrophils without growth factor.

Study characteristics and results are described in Tables 7 and 8. Study limitations are described in Tables 9 and 10.

Material submitted for U.S. Food and Drug Administration (FDA) approval included data analyzed from 2 studies that assessed MRD with clonoSeq using available blood samples from 2 clinical trials (NCT02242942 and NCT00759798).(9) The primary endpoint of the first study was to evaluate whether MRD at a threshold of 10^{-5} at 3 months after treatment could predict PFS. Secondary objectives were to assess different cutoff values and repeated measurements. Patients with MRD greater than 10^{-5} had a 6.64-fold higher event risk compared to MRD negative patients (95% CI, 3.65-12.1). The primary distinction was at a cutoff of 10^{-4} , where only 16.5% of patients with MRD in blood greater than 10^{-4} were

progression free at 4 yr follow-up, compared to 44%, 49%, and 47% with MRD less than 10^{-6} , 10^{-5} , and 10^{-4} , respectively.

The second study was published by 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 FC (N=63) in a phase 2 clinical trial.(10) 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 months, range 28 to 112 months) compared with PFS of 67 months (bone marrow) or 74 months (blood). The percent of patients who were progression free with MRD less than 10^{-6} , 10^{-5} , and 10^{-4} was 85%, 75%, and 67.5%, respectively. The authors note that "At this time, no additional treatment is offered to eradicate low-level MRD ($<10^{-4}$) after first-line treatment of CLL, given the generally favorable prognosis for such patients."

Munir et al (2023) reported results of the prognostic performance of clonoSEQ in participants from the GLOW study.(11) GLOW (NCT03462719; n=211) was a phase III trial comparing fixed-duration ibrutinib + venetoclax to chlorambucil + obinutuzumab in participants with previously untreated CLL who were older and/or had comorbidities. MRD was assessed by clonoSEQ from samples collected every 3-4 months from peripheral blood and at 9 and 18 months from bone marrow. Detectable MRD defined as having ≥ 1 CLL cell per 10,000 leukocytes. Median follow-up was 34 months. PFS at 12 months after the end of treatment with ibrutinib + venetoclax was high regardless of MRD status at the end of treatment: 96% versus 93% in patients with undetectable MRD versus detectable MRD.

Table 7. Characteristics of Prognostic Studies Assessing NGS for MRD in CLL

Study	Study Population	Design ^a	Reference Standard	Threshold for PIT	FU (range)	Test Version
clonoSEQ Technical Summary	Patients treated for CLL with blood samples at 3 mo after treatment (n=337)	Analysis of prospectively collected blood samples from a phase 3 trial (NCT02242942)	PFS	NGS at 10^{-6} , 10^{-5} , 10^{-4} in blood	4 yr	clonoSEQ
Thompson et al (2019)	Patients with CLL treated with up to 6 courses of FCR and MRD negative by FC (n=62)	Analysis of prospectively collected samples from a phase 2 trial (NCT00759798)	PFS	NGS at 10^{-6} , 10^{-5} , 10^{-4} in blood, plasma, or bone marrow	82 mo (28-112)	clonoSEQ
Munir et al (2023)	Patients with CLL treated with ibrutinib + venetoclax	Analysis of prospectively collected samples from the phase 3 GLOW trial (NCT03462719)	PFS	NGS at 10^{-4}	1 yr	clonoSEQ

CLL: chronic lymphocytic leukemia; FC: flow cytometry; FCR: fludarabine, cyclophosphamide, and rituximab; FU: follow-up; MRD: measurable residual disease; NGS: next-generation sequencing; PIT: positive index test; PFS: progression-free survival.

Table 8. Results of Prognostic Studies Assessing NGS for MRD in CLL

Study	N	Tissue Source	Progression Free at End of Study n/N (%)				
			EOT MRD $<10^{-6}$	EOT MRD $>10^{-6}$	EOT MRD $<10^{-5}$	EOT MRD $>10^{-5}$	EOT MRD $<10^{-4}$ EOT MRD $>10^{-4}$

clonoSEQ Technical Summary			33/75 (44.0%)	50/106 (47.2%)			24/49 (49.0%)	17/103 (16.5%)
Thompson et al (2019)	53	Bone Marrow	11/13 (84.6%)	21/40 (52.5%)	18/24 (75.0%)	14/29 (48.3%)	27/40 (67.5%)	5/13 (38.4%)
	29	Blood	7/8 (87.5%)	8/13 (61.5%)				
Munir et al (2023)	211 (106 ibrutinib + venetoclax)	Bone marrow					Ibrutinib + venetoclax, 96%	Ibrutinib + venetoclax,, 93%
							Chlorambucil + obinutuzumab, 83%	Chlorambucil + obinutuzumab, 59%

EOT: end of treatment; MRD: measurable residual disease; NGS: next-generation sequencing; PFS: progression free survival
Limitations in study relevance, and study design and conduct are shown in Tables 9 and 10.

Table 9. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
clonoSEQ Technical Summary			3. Did not compare results to FC		
Thompson et al (2019)					1. Mean FU was 82 months (range of 28 to 118 mo) which is insufficient to determine PFS in CLL
Munir et al (2023)			3. Did not compare results to FC		1. Follow-up of 1 year

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CLL: chronic lymphocytic leukemia; FC: flow cytometry; FU: follow-up; PFS: progression-free survival.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 10. Study Design and Conduct Limitations

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
clonoSEQ Technical Summary		1. Blinding was not described		2. Details from the technical summary are limited and did not discuss the minimal difference of the different thresholds.		
Thompson et al (2019)	2. Selection based on availability of tissue samples from prior studies	1. Blinding was not described				

Munir et al (2023)	1. Blinding was not described
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The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

No RCTs assessing the clinical utility of MRD by NGS to guide therapy were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. MRD levels that are less than 10^{-4} are associated with improved PFS compared to patients who have MRD levels greater than 10^{-4} . The studies are insufficient to demonstrate improved prognostic performance at thresholds lower than 10^{-4} .

Section Summary: Next Generation Sequencing to Detect Measurable Residual Disease in Chronic Lymphocytic Leukemia

The evidence on NGS for detection of MRD includes 2 studies that were submitted to the FDA and an exploratory analysis of samples from the GLOW clinical trial. These studies evaluated the association between the level of MRD detected by NGS in the bone marrow or blood and PFS in samples of blood or bone marrow from completed phase 2 and 3 trials. Both studies submitted to FDA demonstrated an association between the level of MRD and PFS with lower risk of progression in patients who exhibit MRD negativity below 10^{-4} compared to patients who have detectable residual disease. Analysis of samples from the GLOW study suggests that for participants treated with ibrutinib + venetoclax, PFS was high regardless of MRD status using threshold of 10^{-4} at the end of treatment.

Evidence is sufficient to support the clinical utility of using NGS to measure MRD for prognosis based on test results at a sensitivity of 10^{-4} . Currently, no additional treatment is offered to eradicate low-level MRD ($<10^{-4}$) after first-line treatment of CLL. Further study is needed to clarify which threshold of NGS should be considered when risk stratifying patients and whether prognosis based on the more sensitive thresholds improves the net health outcome.

Next-Generation Sequencing to Detect Measurable Residual Disease in Multiple Myeloma

Clinical Context and Test Purpose

Multiple myeloma (MM) represents approximately 17% of all hematologic cancers, largely occurring in patients over 60 years of age. It is characterized by the proliferation of plasma cells in the bone marrow producing a monoclonal immunoglobulin. The clonal plasma cells frequently result in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures; additional complications can include hypercalcemia, renal insufficiency, anemia, and infections.

MM is treatable but is typically incurable, with treatment reserved for patients with symptomatic disease (usually progressive). Without effective therapy, symptomatic patients die within a median of 6 months. Asymptomatic patients are observed because there is little evidence that early treatment of asymptomatic MM prolongs survival compared with therapy delivered at the time of symptoms or end-organ damage. In some patients, an asymptomatic but more advanced premalignant stage is referred to as smoldering MM. Patients with smoldering MM may remain stable for prolonged periods, with an overall risk of disease progression from smoldering to symptomatic MM of 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and 1% for the next 10 years.

Prognosis and treatment for MM depend on risk stratification based on underlying genetic variants, age, performance status, comorbidities, stage, and response to therapy. Patients are assessed to determine eligibility for HCT because HCT has been shown to prolong both event-free and OS compared with chemotherapy alone. The response to treatment is usually determined by a morphologic evaluation and visual quantitation of the percentage of plasma cells in the bone marrow. Most patients with MM will have an initial response to treatment, but will ultimately progress with serial relapse, and will be treated with most available agents at some point during their disease course. Other patients will not respond to initial treatment (refractory disease).

Response to treatment is categorized into clinical response, MRD response, and imaging response. A complete (clinical) response is defined by the International Myeloma Working Group and the National Comprehensive Cancer Network as shown in Table 11.(12) MRD response is defined as a CR plus the absence of clonal plasma cells by NGF or NGS at a minimum sensitivity of 1 in 10⁻⁵ nucleated cells in bone marrow, and there is a category of “imaging plus MRD-negative” in which patients are determined to have a CR, be MRD negative in the bone marrow, and have also achieved positron emission tomography (PET)/computed tomography (CT)-negativity. “Sustained MRD negativity” is achieved when both imaging plus MRD are negative in assessments that are a minimum of 1 year apart. It is not known whether patients with sustained MRD negative status can be considered cured. MRD measured by NGS is currently used as a surrogate outcome measure in clinical trials, and there are ongoing trials to test the effectiveness of using NGS-MRD to guide therapy.(13)

Table 11. Definitions of Complete Response and Measurable Residual Disease Criteria from the International Myeloma Working Group

Standard Response Criteria	
Complete response	"Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates"
MRD Response Criteria (requires a complete response)	
Sequencing MRD-negative	Absence of clonal plasma cells with a minimum sensitivity of 1 in 10 ⁻⁵ nucleated cells
Imaging plus MRD-negative	MRD negativity by NGF or NGS plus imaging criteria

MRD: minimal residual disease; NGF: next-generation flow; NGS: next-generation sequencing

The main use of measurement of MRD is to inform treatment management.

Measures of MRD can be used to assess whether a patient has responded to treatment, has not fully responded to treatment, or has progressed. The National Comprehensive Cancer Network guidelines provide an analytic framework for the use of MRD in MM.(11) If a patient

meets the criteria for CR and MRD, the patient could proceed with maintenance therapy or observation. If, however, a patient meets the criteria for nonresponse or for progression, the clinical decision would be to proceed to the next line of therapy for the previously treated disease. The National Comprehensive Cancer Network guidelines recommend follow-up/surveillance after treatment with multiparameter FC (threshold of 10^{-4}), with NGF or NGS used for prognostication (threshold of 10^{-5}) after shared decision with the patient.

Martinez-Lopez et al (2014) assessed the time to progression (TTP) stratified by MRD at levels from 10^{-3} to less than 10^{-5} and found that the TTP was associated with the level of MRD.(14) Specifically, median progression was 27 months for patients with MRD greater than 10^{-3} , 48 months for individuals with MRD between 10^{-3} and 10^{-5} , and 80 months for patients with MRD less than 10^{-5} , giving a HR of 3.97 for higher levels of MRD ($p < .001$, see Table 9). In the subgroup of patients with CR, TTP was 131 months in MRD negative patients and 35 months in MRD positive patients (HR of 2.87, $p < .001$). When compared to multiparameter FC, 82 of 99 results (83%) were concordant. NGS identified an additional 12 patients with MRD that were MRD-negative by FC, while 5 patients were found to be flow MRD+/NGS MRD-. One of 5 flow+/NGS- patients progressed. Patients who were NGS+/flow- had an intermediate TTP (50 months) compared to NGS-negative patients (TTP not reached; $p < .0001$).

In Perrot et al (2018), a threshold of 10^{-6} was used to evaluate the association between MRD and PFS, finding that the dichotomous division into MRD positive and MRD negative (no detectable MRD at the limit of detection) was highly predictive of PFS with an HR for MRD negative/MRD positive of 0.19 ($p < .001$). (15) The median PFS was 29 months in patients who were positive for MRD and was not reached among patients with no detectable MRD.

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.(16) 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 least 1 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} .

Cavo et al (2022) analyzed pooled data from 4 phase 3 studies in patients with relapsed or refractory MM who were ineligible for transplant.(17) MRD was assessed at a sensitivity of 10^{-5} . Patients who achieved a complete response or better and were MRD negative had improved PFS and an 80% reduction in the risk of disease progression or death compared with those who failed to reach CR or were MRD positive (HR, 0.20; $p < .0001$).

Oliva et al (2023) reported results of analyses of MRD status from samples available from the FORTE trial.(18) The FORTE trial was a phase 2, multicenter RCT including participants with newly diagnosed, transplant-eligible multiple myeloma randomized between 2015 and 2021 to 1 of 3 induction-intensification-consolidation strategies. Multiparameter flow cytometry (MFC) status was assessed in patients with at least a very good partial response first at premaintenance and then every 6 months during maintenance treatment until progressive

disease. The cut-off for MFC MRD positivity was set at ≥ 20 clonal plasma cells out of the total of nucleated cells, with a sensitivity of $\geq 10^{-5}$. NGS was performed in a subset of participants with at least a suspected complete response at pre-maintenance and monitored every 6 months during maintenance treatment until progressive disease using the clonoSEQ® assay with sensitivities at 10^{-5} and 10^{-6} . 2020 samples were available for analysis of MFC MRD status and 728 samples were available for the analysis of the correlation between MFC and NGS in the “suspected complete response population”. Median follow-up was 62 months. The hazard ratios for PFS in MFC-MRD and NGS-MRD-negative vs -positive patients were 0.29 (95% CI, 0.20 to 0.40) and 0.27 (95% CI, 0.18 to 0.39), respectively; see Table 13. Concordance between MFC and NGS is shown in Table 14 and concordance between NGS and NGF is shown in Table 15.

The major limitations of these studies are described in Tables 16 and 17.

Table 12. Characteristics of Studies Assessing NGS for MRD in MM

Study	Study Population	Design	Reference Standard	Threshold	Test Version
Martinez-Lopez et al (2014)	Patients with available bone marrow samples from GEM myeloma trials ^a	Retrospective	TTP	MRD at 10^{-3} and 10^{-5}	LymphoSIGHT
Perrot et al (2018)	Patients with myeloma enrolled in the IFM 2009 clinical trial ^b	Retrospective	PFS and OS	MRD at 10^{-6}	clonoSEQ
Martinez-Lopez et al (2020)	Patients with MM who had been treated at their clinic between 2005 and 2018 (N=234)	Retrospective	PFS	MRD at 10^{-5}	clonoSEQ
Cavo et al (2022)	Patients with bone marrow samples from POLLUX, CASTOR, ALCYONE, and MAIA trials ^c	Retrospective	PFS	MRD at 10^{-5}	clonoSEQ
Oliva et al (2023)	Patients with bone marrow samples from FORTE trial	Retrospective	PFS	MRD at 10^{-5} and 10^{-6}	clonoSEQ

MRD: measurable residual disease; NGS: next-generation sequencing; OS: overall survival; PFS: progression-free survival; TTP: time to progression.

^a GEM (Grupo Español de Mieloma) myeloma treatment trials

^b IFM 2009 was phase 3 trial from the Intergroupe Francophone du Myelome, conducted between 2010 and 2012, which evaluated the role of autologous cell transplantation in patients with newly diagnosed myeloma.

^c POLLUX, CASTOR, ALCYONE, and MAIA were daratumumab-based studies in patients with newly diagnosed MM.

Table 13. Results of Prognostic Studies Assessing NGS for MRD in MM

Study	N	MRD Threshold	TTP, mo (95% CI)
Martinez-Lopez et al (2014)	133	$>10^{-3}$	27
		10^{-3} to 10^{-5}	48
		$<10^{-5}$	80
Hazard Ratio for Time to Progression			3.97
p-Value			<.001
Subset of patients with CR	26	$<10^{-5}$	131 (51-154)
Subset of patients with CR	36	$>10^{-5}$	35 (30-41)
Hazard Ratio for Time to Progression			2.87
p-Value			<.001

Perrot et al (2018)	509	10 ⁻⁶	MRD negative/MRD positive	
Hazard Ratio for Progression Free Survival (95% CI)			0.19 (0.13 to 0.26)	
p-Value			<0.001	
Martinez-Lopez et al (2020)			PFS, mo	3-year survival
Newly Diagnosed		<10 ⁻⁶		90% (81% to 98.78%)
		<10 ⁻⁵	87	85.9% (78.2% to 94.5%)
		>10 ⁻⁵	32	46.8% (33.9% to 64.7%)
HR (95% CI)			3.54 (1.94 to 6.45)	
p-Value			<.001	
Relapsed	27/75 (36%)	<10 ⁻⁶	not reached	
	35/75 (47%)	<10 ⁻⁵	42	
		>10 ⁻⁵	17	
HR (95% CI)			2.45 (1.25 to 4.82)	
p-Value			.01	
Cavo et al (2022)			48-month PFS, %	
	2510	10 ⁻⁵	70.4	
Complete response or better and MRD negative			23.9	
Less than very good partial response or MRD positive				
Oliva et al (2023)			48-month PFS, %	48-month OS, %
MRD positive			46%	78%
MRD negative			83%	94%
HR (95% CI)			0.27 (0.18 to 0.39)	0.31 (0.17 to 0.54)
p-Value			<.01	<.01

CI: confidence interval; CR: complete response; HR: hazard ratio; MRD: measurable residual disease; NGS: next-generation sequencing; PFS: progression free survival; TTP: time to progression.

Table 14. Concordance Between NGS and FC

		Flow Cytometry		
		+	-	Total
Martinez-Lopez (2014)				
NGS	+	60	12	72
	-	5	22	27
	Total	65	34	99
Oliva (2023)				
NGS	+	85	59	144
	-	17	428	445
	Total	102	487	589

FC: flow cytometry; NGS: next-generation sequencing.

Kriegsmann et al (2020) found moderate concordance between NGS and NGF in a study of 113 patients with MM (Table 17). (19) Concordance between methods was obtained in 68% of patients while discordant results were found in 28 patients (11.2% in each direction). Cohen's kappa coefficient for interrater agreement between the MRD status of the 2 methods was 0.536 (n = 113, p <.001). A threshold of 10⁻⁵ was chosen as the best-fit MRD cut-off for

evaluation as it met the international guidelines and resulted in a tolerable proportion of nonassessable cases in both methods (1.6%, n=2 in NGS and 8.0%, n=10 in NGF).

Table 15. Concordance Between NGS and NGF

		NGF		
		+	-	Total
Kriegsmann (2020)				
NGS	+	42	14	56
	-	14	43	57
	Total	56	57	
Oliva (2023)¹⁸				
NGS	+	32	22	54
	-	2	83	85
	Total	34	105	139

NGF: next generation flow cytometry; NGS: next-generation sequencing.

Table 16. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Martinez-Lopez et al (2014)				3. No data were reported using a threshold of 10 ⁻⁶ since most of the samples had less input cells than is needed for this level of sensitivity	
Perrot et al (2018)	4. The study included patients from the IFM 2009 trial who had at least a very good partial response but did not report separately on patients with a complete response				
Martinez-Lopez et al (2020)			3. No comparison to other tests for MRD		
Cavo et al (2022)			3. No comparison to other tests for MRD		
Oliva et al (2023)	4. MFC status was assessed in patients with at least a very good partial response and NGS was assessed in patients with at least a suspected complete response				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or

risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 17. Study Design and Conduct Limitations

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Martinez-Lopez et al (2014)	2. Selection based on availability of tissue samples from prior studies	1. Blinding not described				1. The analysis by level of MRD does not appear to be prespecified.
Perrot et al (2018)	2. Selection based on availability of tissue samples in the original study	1. Blinding not described				1. Post-hoc exploratory analysis, not adjusted for multiple comparisons
Martinez-Lopez et al (2020)	2. Retrospective assessment of clinical data	1. Blinding not described	2. There was no uniform timing of the test.			
Cavo et al (2022)			2. MRD assessed at different time points in individual studies.			
Oliva et al (2023)	2. Retrospective assessment of clinical data	1. Blinding not described				

MRD: measurable residual disease

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

No RCTs assessing the clinical utility of MRD by NGS to guide therapy were identified.

Costa et al (2023) reported results of the MASTER multicenter (5 centers), single-arm, phase 2 study conducted in the US between 2018 and 2020. (20) MASTER was the first study to use prospective adaptation of treatment duration based on MRD status but MRD status was used to guide therapy in all participants with sufficient unique clonogenic sequences. There is no comparison to management without MRD status. Instead MASTER demonstrates the feasibility of using MRD to guide therapy. MASTER included 123 adults with newly diagnosed multiple myeloma, life expectancy >12 months, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and no previous treatment except up to 1 cycle of therapy containing bortezomib, cyclophosphamide, and dexamethasone. 70 (57%) of the participants were men; 94 (76%) of participants were non-Hispanic White, 25 (20%) were non-Hispanic

Black. The median age was 61 years (IQR, 55 to 68). 53 (43%) had no high-risk chromosome abnormalities (HRCA), 46 (37%) had 1 HRCA, and 24 (20%) had 2 or more HRCAs. The median follow-up duration was 42 months (IQR, 35 to 46). MRD status was assessed by clonoSEQ using a detection threshold of 10^{-5} to adjudicate response-adapted therapy. Five participants had an absence of sufficiently unique clonogenic sequences to enable tracking by the clonoSEQ assay. Eighty-four participants who reached MRD negativity after or during 2 consecutive treatment phases stopped treatment and began observation with MRD surveillance. 20 participants who did not reach 2 consecutive MRD-negative results received maintenance lenalidomide. Ten participants discontinued treatment early: 3 died, 5 had disease progression, and 2 chose to discontinue. Of the 84 participants who transitioned to MRD surveillance, 36-month progression-free survival (PFS) was 88% (95% CI, 77 to 96) for those with no HRCAs, 85% (95% CI, 73 to 96) for those with 1 HRCA, and 60% (95% CI, 35 to 82) for those with 2 or more HRCAs. Twenty-three of the 84 participants (27%) resumed therapy due to MRD resurgence or disease progression not preceded by MRD resurgence.(20)

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. High concordance has been shown between NGS and FC at a threshold of 10^{-4} , indicating that NGS may be considered an alternative to NGF at this threshold. Retrospective studies also indicate improved PFS when MRD is less than 10^{-5} compared to individuals who have MRD greater than 10^{-5} . This threshold is consistent with current guideline-based care for prognostication. Prospective studies will be needed to determine whether treatment can be guided by this test.

The retrospective studies are insufficient to demonstrate clinical validity at thresholds lower than 10^{-5} . Levels of MRD are associated with average prognosis, but improved performance characteristics have not been demonstrated at lower thresholds. A potential benefit of NGS assessment of MRD would be if individuals were able to forgo maintenance therapy if there was no detectable MRD. However, it is unknown whether therapy can be safely guided based on this test.

Section Summary: Next-generation Sequencing to Detect Measurable Residual Disease in Multiple Myeloma

The evidence on clinical validity of NGS for detection of MRD includes 6 published retrospective studies in individuals with MM. These studies evaluated the association between the level of MRD detected by NGS in the bone marrow and the TTP or PFS from the completed phase 3 trials or from a clinical population. All of the studies demonstrated an association between the level of MRD and PFS with longer TTP in individuals who exhibit MRD negativity below 10^{-5} or 10^{-6} compared to individuals who have detectable residual disease. There was also high concordance between NGS and FC. Participants who were discordant for the 2 tests had outcomes that were intermediate between individuals who were positive for both tests and those who were negative for both tests.

In exploratory analysis of the largest clinical validity study, the median PFS was 29 months in individuals who were positive for MRD and was not reached among patients with no detectable clones, suggesting that assessment of MRD might have utility in guiding therapy. About one-quarter of MRD negative individuals progressed within 36 months in these trials, raising questions about whether NGS could be used to guide therapy. It is unknown whether progression is due to very low levels of residual disease or to new clonal rearrangements in MM. Direct evidence from RCTs is needed to evaluate whether patient outcomes are improved

by changes in postinduction care (e.g., continuing or discontinuing therapy, avoiding unnecessary adverse events) following NGS assessment of residual disease. Trials that test the effectiveness of MRD to guide therapy in MM are ongoing.

Next-Generation Sequencing to Detect Measurable Residual Disease in Diffuse Large B-Cell Lymphoma

Clinical Context and Test Purpose

Lymphoma refers to any cancer that starts in the lymph system and includes 2 broad categories of disease, Hodgkin lymphoma and non-Hodgkin lymphoma.(21) There are multiple forms of non-Hodgkin lymphoma with B-cell malignancies comprising 85% of cases.(22) Of the B-cell lymphomas, diffuse large B-cell lymphoma (DLBCL) accounts for approximately one-third of cases. DLBCL occurs most commonly in older individuals with the mean age of diagnosis of approximately 60 years of age. Although aggressive, DLBCL generally responds well to treatment, and 75% of individuals have no signs of disease after initial treatment. Historically, PET and CT imaging have been used to assess lymphoma tumor burden and disease response; however, techniques such as flow cytometry, PCR-based methods, and NGS-based techniques are being increasingly used.(23)

The main use of MRD with NGS in individuals with DLBCL is to inform treatment management.

There are 2 studies assessing the prognostic value of NGS for MRD specifically in individuals with DLBCL. One prospective, single-center, observational study by Chase et al (2021) attempted to correlate MRD with prognosis in individuals with newly diagnosed DLBCL receiving conventional treatment; however, attrition limited outcome assessment.(21) Only 3 individuals had early clinical relapse, and no conclusions can be drawn. Tables 18 and 19 describe the characteristics and results of the other prognostic study in individuals with DLBCL, and Tables 20 and 21 describe limitations of this study.

In a phase 2, single-center, prospective trial in patients with DLBCL undergoing HSCT, Kambhampati et al (2021) assessed 15 individuals for MRD with NGS.(25) Of the 14 individuals with available MRD samples after salvage therapy, 11 were MRD negative and 3 were MRD positive. MRD tests were predictive of survival in these individuals.

Table 18. Characteristics of Studies Assessing NGS for MRD in DLBCL

Study	Study Population	Design	Reference Standard	Threshold	Test Version
Kambhampati et al (2021)	Patients with relapsed/refractory DLBCL undergoing HSCT enrolled in a phase 2 trial	Single-center, prospective	PFS/OS	NR	clonoSEQ

DLBCL: diffuse large B-cell lymphoma; HSCT: hematopoietic stem cell transplant; NR: not reported; OS: overall survival; PFS: progression-free survival.

Table 19. Results of Prognostic Studies Assessing NGS for MRD in DLBCL

Study	N	Median OS, mo	Median PFS, mo
Kambhampati et al (2021)	27 (14 with MRD samples after salvage therapy)		
MRD negative		Not reached	Not reached
MRD positive		3.5	1.3

MRD: measurable residual disease; OS: overall survival; PFS: progression-free survival.

Table 20. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Kambhampati et al (2021)		1. Threshold not reported	3. No comparator MRD measure		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 21. Study Design and Conduct Limitations

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Kambhampati et al (2021)		1. Blinding not described				2. No comparator MRD measure

MRD: measurable residual disease

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

No RCTs assessing the clinical utility of MRD by NGS to guide therapy were identified.

Section Summary: Next-Generation Sequencing to Detect Measurable Residual Disease in Diffuse Large B-Cell Lymphoma

The evidence on NGS for detection of MRD in DLBCL includes an analysis from a single-center, prospective trial that did not include comparison to another MRD measure. Although both PFS and OS correlated with MRD positivity, the trial included 27 participants eligible for HSCT from a single center and is not sufficient to establish clinical validity or clinical utility.

Next-Generation Sequencing to Detect Measurable Residual Disease in Mantle Cell Lymphoma

Clinical Context and Test Purpose

A small percentage of B-cell lymphomas (about 5%) are categorized as mantle cell lymphoma (MCL).(19) Similar to DLBCL, it occurs most commonly in patients over 60 years of age and tends to be an aggressive lymphoma; however, the response to treatment has traditionally been poor. Most patients present with advanced stage disease, and treatment is dependent on stage and eligibility for HSCT. Historically, PET and CT imaging have been used to assess lymphoma tumor burden and disease response; however, techniques such as flow cytometry, PCR-based methods, and NGS-based techniques are being increasingly used.(20)

The main use of measurement of MRD with NGS in patients with MCL is to inform treatment management.

Characteristics and results of studies evaluating NGS for MRD in MCL are summarized in Tables 22 and 23, and limitations of these trials are summarized in Tables 24 and 25. Smith et al. (2019) conducted a retrospective review of samples from individuals enrolled in the ECOG1411 trial which evaluated MCL patients treated with bendamustine-rituximab induction followed by rituximab (with or without lenalidomide) consolidation and evaluated MRD by both FC and NGS.(26) Concordance between tests was high both after cycle 3 and end of induction. MRD status correlated with PFS. For patients who were MRD negative after cycle 3 by either method, PFS was 58.9 months. For those who were MRD positive by NGS, PFS was 26.9 months and PFS was 29.9 months for those who were positive by FC. The authors concluded both NGS and FC were feasible to assess MRD.

Lakhotia et al (2022) conducted an exploratory review of circulating tumor DNA analyzed by NGS from a trial of bortezomib induction in 53 MCL patients found patients who had undetectable MRD after 2 induction cycles had longer PRS and OS than those with MRD.(24) As this was an exploratory analysis, key details are not included, and no firm conclusions can be drawn.

Table 22. Characteristics of Studies Assessing NGS for MRD in patients with MCL

Study	Study Population	Design	Reference Standard	Threshold	Test Version
Smith et al (2019)	Patients with MCL enrolled in ECOG1411	Retrospective	PFS	MRD at 10^{-4}	"Research version" of clonoSEQ
Lakhotia et al (2022)	Patients with MCL enrolled in a trial of bortezomib induction treatment	Retrospective	PFS	NR	Not specified; however, test supplied by Adaptive Biotechnologies

ECOG: Eastern Cooperative Oncology Group; MCL: mantle cell lymphoma; MRD: measurable residual disease; NR: not reported; PFS: progression free survival.

Table 23. Results of Prognostic Studies Assessing NGS for MRD in patients with MCL

Study	N	MRD Threshold	MRD Negative, (%) ^a	PFS	OS
Smith et al (2019)	214	MRD at 10^{-4}			
FC			95 (peripheral blood)		
NGS			91 (peripheral blood)/90 (bone marrow)		
MRD negative (by NGS)				58.9 mo	
MRD positive (by NGS)				26.9 mo	
Lakhotia et al (2022)	53				
MRD negative ^b				2.7 yr	13.8 yrs
MRD positive ^b				1.8 yr	7.4 yrs

FC: flow cytometry; MRD: measurable residual disease; NGS: next-generation sequencing; OS: overall survival; PFS: progression free survival.

^a Results reported at end of induction.

^b After 2 cycles of induction.

Table 24. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Smith et al (2019)		2. Unclear if "research version" of clonoSEQ® used in study is same as commercially available test.			1. Data reported from mid-induction or end of induction

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 25. Study Design and Conduct Limitations

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Smith et al (2019)		1. Blinding not described				
Lakhotia et al (2022)	2. Selection based on availability of tissue samples in the original study	1. Blinding not described				1. Post-hoc exploratory analysis

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

No RCTs assessing the clinical utility of MRD by NGS to guide therapy were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. High concordance has been shown between NGS and FC at a threshold of 10^{-4} , indicating that NGS may be considered an alternative to FC at this threshold. Further studies are needed to determine whether treatment can be guided by this test.

Section Summary: Next-Generation Sequencing to Detect Measurable Residual Disease in Mantle Cell Lymphoma

The evidence on NGS for detection of MRD in patients with MCL includes a retrospective study and an exploratory analysis of patients enrolled in treatment clinical trials. When compared with FC, NGS had strong correlation, and MRD positivity with either method was associated with worse PFS. However, the relevance of these findings to the commercial version of clonoSEQ® is unclear as a "research version" was used in the study. An exploratory analysis in patients with MCL enrolled in a treatment trial found improved survival in patients who were MRD negative after 2 cycles of induction. However, interpretation was limited by imprecision and unspecified NGS testing level.

Supplemental Information:

International Myeloma Working Group

The International Myeloma Working Group published consensus criteria (2016) for response and minimal residual disease (MRD) assessment in multiple myeloma (Table 26).(12)

Table 26. IMWG Criteria

Standard Response Criteria	
Complete response	"Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates"
Stringent complete response	"Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)"
MRD Response Criteria (requires a complete response)	
Sequencing MRD-negative	Absence of clonal plasma cells by NGS using the LymphoSIGHT platform (or validated equivalent) with a minimum sensitivity of 1 in 10 ⁵ nucleated cells
Imaging plus MRD-negative	MRD negativity by NGF or NGS plus imaging criteria
Sustained MRD-negative	MRD negativity by NGF or NGS, and by imaging, at a minimum of 1 year apart.

FLC: free light chain; IMWG: International Myeloma Working Group; MRD: minimal residual disease; NGF: next-generation flow; NGS: next-generation sequencing.

International Workshop on Chronic Lymphocytic Leukemia

The 2018 guidelines from the International Workshop on Chronic Lymphocytic Leukemia (CLL) have the following recommendations regarding the assessment of MRD:(7)

"The complete eradication of the leukemia is a desired end point. Use of sensitive multicolor flow cytometry, PCR [polymerase chain reaction], 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 1 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 6 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,1 CLL cell per 10,000 leukocytes."

The National Comprehensive Cancer Network

The National Comprehensive Cancer Network has published guidelines of relevance to this review (see Table 27).

Table 27. Recommendations on Assessing Measurable Residual Disease

Guideline	Version	Recommendation
Acute lymphoblastic leukemia	3.2024	MRD refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods or standard immunophenotyping. The most frequently employed methods for MRD assessment include an FDA-approved NGS-based assay to detect fusion genes or clonal

		rearrangements in Ig and T-cell receptor (TCR) loci (does not require patient-specific primers) (preferred), flow cytometry assays specifically designed to detect MRD immunophenotypes at low frequency, real-time quantitative polymerase chain reaction (RQ-PCR) assays (e.g., clonally rearranged Ig, TCR genes), and reverse transcriptase quantitative PCR (RT-qPCR) assays (e.g., BCR/ABL1). High sensitivity flow cytometry with validated analysis algorithms or PCR methods can quantify leukemic cells at a sensitivity threshold of 1×10^{-4} (0.01%) bone marrow mononuclear cells (MNCs). NGS and some PCR methods can detect leukemic cells at a sensitivity threshold of 1×10^{-6} (0.0001%) MNCs. If MRD is negative by flow cytometry, an FDA-approved NGS assay should be considered to confirm negativity.
Chronic lymphocytic leukemia/small lymphocytic lymphoma	3.2025	Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end of treatment is an important predictor of treatment efficacy. MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized ERIC method or standardized NGS method.
Multiple myeloma	2.2025	Consider baseline clone identification and storage of aspirate sample for future minimal residual disease (MRD) testing by NGS. Surveillance for smoldering disease: Bone marrow aspirate and biopsy with FISH, SNP array, NGS, or multiparameter flow cytometry may be used as clinically indicated. Consider MRD testing as indicated for prognostication after shared decision with patient. International Myeloma Working Group (IMWG) response criteria: Flow MRD-negative: Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 105 nucleated cells or higher. Sequencing MRD-negative: Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated equivalent method with a minimum sensitivity of 1 in 105 nucleated cells or higher.
B-cell lymphomas	2.2025	MRD surveillance is not included in the current guidelines.

ALL: acute lymphoblastic leukemia, CR: complete response; ERIC: European Research Initiative on CLL; FC: flow cytometry; FISH: fluorescence in situ hybridization; MRD: measurable residual disease; NGF: next generation flow; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 20.

Table 28. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05625971	Non-Invasive Minimal Residual Disease (MRD) Assessment in Multiple Myeloma Via Functional Imaging and Liquid Biopsy	88	Sep 2024
NCT03509961	A Phase II Pilot Trial to Estimate Survival After a Non-total Body Irradiation (TBI) Based Conditioning Regimen in Patients Diagnosed With Acute Lymphoblastic Leukemia (ALL) Who Are Pre-allogeneic	95	Jul 2026

	Hematopoietic Cell Transplantation (HCT) Next-generation-sequence (NGS) Minimal Residual Disease (MRD) Negative (ENRAD)		
NCT05255354	Optimizing ctDNA-based MRD Assessment in DLBCL, MCL, and FL Patients Undergoing CAR Therapy	300	Mar 2027
Unpublished			
NCT04545333a	Real World Observational Study Using clonoSEQ® Next Generation Sequencing in Hematologic Malignancies: The 'Watch' Registry	465 (actual)	Oct 2023 (terminated, sufficient data collected)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Regulatory Status

The clonoSEQ® Minimal Residual Disease Test is offered by Adaptive Biotechnologies. clonoSEQ® was previously marketed as clonoSIGHT™ (Sequentia), which was acquired by Adaptive Biotechnologies in 2015. clonoSIGHT™ was a commercialized version of the LymphoSIGHT platform by Sequentia for clinical use in MRD detection in lymphoid cancers. In September 2018, clonoSEQ received marketing clearance from the U.S. Food and Drug Administration (FDA) through the de novo classification process to detect MRD in patients with acute lymphoblastic leukemia or multiple myeloma. In 2020, clonoSEQ received marketing clearance from the FDA to detect MRD in patients with chronic lymphocytic leukemia. clonoSEQ is available for use in other lymphoid cancers, such as diffuse large B-cell lymphoma (DLBCL), as a CLIA-validated laboratory developed test (LDT).

Government Regulations

National:

Next Generation Sequencing (NGS). 90.2 Effective date: 1/27/20; Revision Date: 11/13/20

A. General

Clinical laboratory diagnostic tests can include tests that, for example, predict the risk associated with one or more genetic variations. In addition, in vitro companion diagnostic laboratory tests provide a report of test results of genetic variations and are essential for the safe and effective use of a corresponding therapeutic product. Next Generation Sequencing (NGS) is one technique that can measure one or more genetic variations as a laboratory diagnostic test, such as when used as a companion in vitro diagnostic test.

This National Coverage Determination (NCD) is only applicable to diagnostic lab tests using NGS for somatic (acquired) and germline (inherited) cancer. Medicare Administrative Contractors (MACs) may determine coverage of diagnostic lab tests using NGS for RNA sequencing and protein analysis.

Indications and Limitations of Coverage

B. Nationally Covered Indications

1. Somatic (Acquired) Cancer

Effective for services performed on or after March 16, 2018, the Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

- a. Patient has:
 - i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
 - ii. not been previously tested with the same test using NGS for the same cancer genetic content, and
 - iii. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
- b. The diagnostic laboratory test using NGS must have:
 - i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
 - ii. an FDA-approved or -cleared indication for use in that patient's cancer; and,
 - iii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

2. Germline (Inherited) Cancer

Effective for services performed on or after January 27, 2020, CMS has determined that NGS as a diagnostic laboratory test is reasonable and necessary and covered nationally for patients with germline (inherited) cancer, when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

- a. Patient has:
 - i. ovarian or breast cancer; and,
 - ii. a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer; and,
 - iii. a risk factor for germline (inherited) breast or ovarian cancer; and
 - iv. not been previously tested with the same germline test using NGS for the same germline genetic content.
- b. The diagnostic laboratory test using NGS must have all of the following:
 - i. FDA-approval or clearance; and,
 - ii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

C. **Nationally Non-Covered Indications**

- iv. 1. Somatic (Acquired) Cancer
- v. Effective for services performed on or after March 16, 2018, NGS as a diagnostic laboratory test for patients with acquired (somatic) cancer are non-covered if the cancer patient does not meet the criteria noted in section B.1., above.

D. **Other**

1. Somatic (Acquired) Cancer

- vi. Effective for services performed on or after March 16, 2018, Medicare Administrative Contractors (MACs) may determine coverage of NGS as a diagnostic laboratory test for patients with advanced cancer only when the test is

performed in a CLIA-certified laboratory, when ordered by a treating physician, and when the patient has:

- a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and,
- b. not been previously tested with the same test using NGS for the same cancer genetic content, and
- c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

2. Germline (Inherited) Cancer

- vii. Effective for services performed on or after January 27, 2020, MACs may determine coverage of NGS as a diagnostic laboratory test for patients with germline (inherited) cancer only when the test is performed in a CLIA-certified laboratory, when ordered by a treating physician, when results are provided to the treating physician for management of the patient and when the patient has:
 - a. any cancer diagnosis; and,
 - b. a clinical indication for germline (inherited) testing of hereditary cancers; and,
 - c. a risk factor for germline (inherited) cancer; and,
 - d. not been previously tested with the same germline test using NGS for the same germline genetic content.

Local:

MolDX: **Minimal Residual Disease Testing for Cancer.** L38835. Effective date: 12/26/21.

Revision date: 10/26/23

This Contractor provides limited coverage for MRD testing in cancer when ALL of the following are true:

If Next-Generation Sequencing (NGS) methodology is used in testing, the conditions set by NCD 90.2 are fulfilled (summarized: the patient has advanced cancer; plans on being treated for said cancer, and has not been previously tested with the same test for the same genetic content) or are not applicable (the patient does not have cancer as defined below)

The patient has a personal history of cancer, the type and staging of which is within the intended use of the MRD test.

The identification of recurrence or progression of disease within the intended use population of the test is identified in the National Comprehensive Cancer Network (NCCN) or other established guidelines as a condition that requires a definitive change in patient management.

The test is demonstrated to identify molecular recurrence or progression before there is clinical, biological, or radiographical evidence of recurrence or progression AND demonstrates sensitivity and specificity of subsequent recurrence or progression comparable with or superior to radiographical or other evidence (as per the standard of care for monitoring a given cancer type) of recurrence or progression.

To be reasonable and necessary, it must also be medically acceptable that the test being utilized precludes other surveillance or monitoring tests intended to provide the same or similar information unless they either (a) are required to follow-up or confirm the findings of this test or (b) are medically required for further assessment and management of the patient.

If the test is to be used for monitoring a specific therapeutic response, it must demonstrate the clinical validity of its results in published literature for the explicit management or therapy indication (allowing for the use of different drugs within the same therapeutic class, so long as they are considered 'equivalent and interchangeable' for the purpose of MRD testing, as determined by national or society guidelines).

Clinical validity (CV) of any analytes (or expression profiles) measured must be established through a study published in the peer-reviewed literature for the intended use of the test in the intended population.

The test is being used (a) in a patient who is part of the population in which the test was analytically validated and (b) according to the intended use of the test.

The MRD test [(unless it is a Food and Drug Administration (FDA)-approved and established standard-of-care single-gene polymerase chain reaction (PCR)] satisfactorily completes a technical assessment (TA) that will evaluate and confirm that the analytical validity, clinical validity, and clinical utility criteria set in this policy are met to establish the test as Reasonable and Necessary.

Tests utilizing a similar methodology or evaluating a similar molecular analyte to a test for which there is a generally accepted testing standard or for which existing coverage exists must demonstrate equivalent or superior test performance (i.e., sensitivity and/or specificity) when used for the same indication in the same intended-use population.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Bone Marrow Transplant - Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- Bone Marrow Transplant – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma – Autologous and Allogeneic
- Bone Marrow Transplant - Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS

References

1. National Comprehensive Care Network. NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia. Version 3.2024.
https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed: May 12, 2024.
2. Berry DA, Zhou S, Higley H, et al. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. JAMA Oncol. Jul 13 2017; 3(7): e170580. PMID 28494052

3. Wood B, Wu D, Crossley B, et al. Measurable residual disease detection by high-throughput sequencing improves risk stratification for pediatric B-ALL. *Blood*. Mar 22 2018; 131(12): 1350-1359. PMID 29284596
4. Pulsipher MA, Carlson C, Langholz B, et al. IgH-V(D)J NGS-MRD measurement pre- and early post-allotransplant defines very low- and very high-risk ALL patients. *Blood*. May 28 2015; 125(22): 3501-8. PMID 25862561
5. Pulsipher MA, Han X, Maude SL, et al. Next-Generation Sequencing of Minimal Residual Disease for Predicting Relapse after Tisagenlecleucel in Children and Young Adults with Acute Lymphoblastic Leukemia. *Blood Cancer Discov*. Jan 2022; 3(1): 66-81. PMID 35019853
6. Liang EC, Dekker SE, Sabile JMG, et al. Next-generation sequencing-based MRD in adults with ALL undergoing hematopoietic cell transplantation. *Blood Adv*. Jul 25 2023; 7(14): 3395-3402. PMID 37196642.
7. Hallek M, Cheson BD, Catovsky D, et al. "NCCN guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL." *Blood*. Jun 21 2018; 131(25): 2745-2760. PMID 29540348
8. National Comprehensive Care Network. NCCN clinical care practice guidelines in Oncology: Chronic lymphocytic leukemia/small lymphocytic lymphoma. Version 3.2025. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed: May 12, 2025.
9. clonoSEQ Assay: Technical Information. <https://www.clonoseq.com/technical-summary/>. Accessed: November 7, 2025.
10. Thompson PA, Srivastava J, Peterson C, et al. Minimal residual disease undetectable by next-generation sequencing predicts improved outcome in CLL after chemoimmunotherapy. *Blood*. Nov 28 2019; 134(22): 1951-1959. PMID 31537528
11. Munir T, Moreno C, Owen C, et al. Impact of Minimal Residual Disease on Progression-Free Survival Outcomes After Fixed-Duration Ibrutinib-Venetoclax Versus Chlorambucil-Obinutuzumab in the GLOW Study. *J Clin Oncol*. Jul 20 2023; 41(21): 3689-3699. PMID 37279408
12. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. Aug 2016; 17(8): e328-e346. PMID 27511158
13. Bal S, Weaver A, Cornell RF, et al. Challenges and opportunities in the assessment of measurable residual disease in multiple myeloma. *Br J Haematol*. Sep 2019; 186(6): 807-819. PMID 31364160
14. Martinez-Lopez J, Lahuerta JJ, Pepin F, et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. *Blood*. May 15 2014; 123(20): 3073-9. PMID 24646471
15. Perrot A, Lauwers-Cances V, Corre J, et al. Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. *Blood*. Dec 06 2018; 132(23): 2456-2464. PMID 30249784
16. Martinez-Lopez J, Wong SW, Shah N, et al. Clinical value of measurable residual disease testing for assessing depth, duration, and direction of response in multiple myeloma. *Blood Adv*. Jul 28 2020; 4(14): 3295-3301. PMID 32706892
17. Cavo M, San-Miguel J, Usmani SZ, et al. Prognostic value of minimal residual disease negativity in myeloma: combined analysis of POLLUX, CASTOR, ALCYONE, and MAIA. *Blood*. Feb 10 2022; 139(6): 835-844. PMID 34289038
18. Oliva S, Genuardi E, Paris L, et al. Prospective evaluation of minimal residual disease in the phase II FORTE trial: a head-to-head comparison between multiparameter flow

- cytometry and next-generation sequencing. *EClinicalMedicine*. Jun 2023; 60: 102016. PMID 37396800.
19. Kriegsmann K, Hundemer M, Hofmeister-Mielke N, et al. Comparison of NGS and MFC Methods: Key Metrics in Multiple Myeloma MRD Assessment. *Cancers (Basel)*. Aug 18 2020; 12(8). PMID 32824635
 20. Costa LJ, Chhabra S, Medvedova E, et al. Minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma (MASTER): final report of the multicentre, single-arm, phase 2 trial. *Lancet Haematol*. Sep 27 2023. PMID 37776872
 21. Hematologic Cancer Incidence, Survival, and Prevalence. Centers for Disease Control and Prevention. <https://www.cdc.gov/cancer/uscs/about/data-briefs/no30-hematologic-incidence-surv-prev.htm>. Accessed: November 7, 2024
 22. Types of B-cell lymphoma. American Cancer Society. Revised January 19, 2019. <https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/b-cell-lymphoma.html>. Accessed: November 7, 2024.
 23. Herrera AF, Armand P. Minimal Residual Disease Assessment in Lymphoma: Methods and Applications. *J Clin Oncol*. Dec 01 2017; 35(34): 3877-3887. PMID 28933999
 24. Chase ML, Merryman R, Fisher DC, et al. A prospective study of minimal residual disease in patients with diffuse large B-cell lymphoma using an Ig-NGS assay. *Leuk Lymphoma*. Feb 2021; 62(2): 478-481. PMID 33236969
 25. Kambhampati S, Hunter B, Varnavski A, et al. Ofatumumab, Etoposide, and Cytarabine Intensive Mobilization Regimen in Patients with High-risk Relapsed/Refractory Diffuse Large B-Cell Lymphoma Undergoing Autologous Stem Cell Transplantation. *Clin Lymphoma Myeloma Leuk*. Apr 2021; 21(4): 246-256.e2. PMID 33288485
 26. Smith M, Jegede O, Parekh, et al. Minimal Residual Disease (MRD) Assessment in the ECOG1411 Randomized Phase 2 Trial of Front-Line Bendamustine-Rituximab (BR)-Based Induction Followed By Rituximab (R) Lenalidomide (L) Consolidation for Mantle Cell Lymphoma (MCL). 2019;134(Suppl_1):751. https://ashpublications.org/blood/article/134/Supplement_1/751/427083/Minimal-Residual-Disease-MRD-Assessment-in-the. Accessed: November 7, 2024.
 27. Lakhotia R, Melani C, Dunleavy K, et al. Circulating tumor DNA predicts therapeutic outcome in mantle cell lymphoma. *Blood Adv*. Apr 26 2022; 6(8): 2667-2680. PMID 35143622
 28. National Comprehensive Care Network. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 2.2025. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed: May 12, 2025.
 29. National Comprehensive Care Network. NCCN clinical care practice guidelines in Oncology: B-cell lymphomas. Version 2.2025. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed: May 12, 2025.
 30. Centers for Medicare & Medicaid Services: National Coverage Determination. "Next Generation Sequencing (NGS)." 2020. 100-3; (90.2):2. <https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=372&ncdver=2&keyword=Next%20Generation%20Sequencing&keywordType=starts&areald=s27&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1>. Accessed: May 12, 2025.
 31. Centers for Medicare & Medicaid Services. Local Coverage Determination: MolDX: Minimal Residual Disease Testing for Cancer (L38835). 2021. <https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38835&ver=4&keyword=clonoSEQ&keywordType=all&area>

[Id=s27&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1](#). Accessed: May 12, 2025.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 12, 2025, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/23	8/21/23		Joint policy established (slp) Vendor managed: N/A
11/1/24	8/20/24		Routine maintenance (slp) Vendor managed: N/A
11/1/25	8/19/25		Routine maintenance (slp) Vendor managed: N/A Formatting updated

Next Review Date: 3rd Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING – NEXT GENERATION SEQUENCING FOR ASSESSMENT OF
MEASURABLE RESIDUAL DISEASE (E.G., CLONSEQ) IN HEMATOLOGICAL
MALIGNANCIES

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria applies
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.