BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.147 Next-Generation Sequencing for the Assessment of Measurable Residual Disease

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Related Policies:

None

Next-Generation Sequencing for the Assessment of Measurable Residual Disease

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 patients 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).

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

It is proposed that by using a highly sensitive and sequential MRD surveillance strategy, one could expect better outcomes when therapy is guided by molecular markers rather than hematologic relapse. 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 (eg, 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 Table 1, 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

OBJECTIVE

The objective of this evidence review is to determine whether next-generation sequencing for measurable residual disease improves the net health outcome in individuals with B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, multiple myeloma, diffuse large B-cell lymphoma, or mantle cell lymphoma tested for measurable residual disease.

POLICY STATEMENT

Next-generation sequencing (eg clonoSEQ) to detect measurable residual disease (MRD) at a threshold of 10^{-4} as an alternative test in individuals with acute lymphoblastic leukemia may be considered **medically necessary**.

Next-generation sequencing (eg clonoSEQ) to detect MRD at a threshold of less than 10^{-4} in individuals with acute lymphoblastic leukemia is considered **investigational**.

Next-generation sequencing (eg clonoSEQ) to detect MRD at a threshold of 10^{-4} as an alternative test in individuals with chronic lymphocytic leukemia may be considered **medically necessary**.

Next-generation sequencing (eg clonoSEQ) to detect MRD at a threshold of less than 10^{-4} in individuals with chronic lymphocytic leukemia is considered **investigational.**

Next-generation sequencing (eg clonoSEQ) to detect MRD at a threshold of 10^{-5} as an alternative test in individuals with multiple myeloma may be considered **medically necessary**.

Next-generation sequencing (eg clonoSEQ) to detect MRD at a threshold of less than 10^{-5} in individuals with multiple myeloma is considered **investigational**.

Next-generation sequencing (eg clonoSEQ) to detect MRD in individuals with diffuse large B-cell lymphoma is considered **investigational**.

Next-generation sequencing (eg clonoSEQ) to detect MRD in individuals with mantle cell lymphoma is considered **investigational**.

Next-generation sequencing to detect MRD is considered **investigational** in all other situations.

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

The clonoSEQ Minimal Residual Disease Test is offered by Adaptive Biotechnologies. clonoSEQ was previously marketed as clonoSIGHT™ (Sequenta), which was acquired by Adaptive Biotechnologies in 2015. clonoSIGHT™ was a commercialized version of the LymphoSIGHT platform by Sequenta 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).

RATIONALE

Summary of Evidence

For individuals with B-Cell (B-ALL) who are being monitored for residual disease following treatment who receive next-generation sequencing (NGS) for measurable residual disease (MRD) at a threshold of 10^{-4}, the evidence includes 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 flow cytometry (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 10000 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 chronic lymphocytic leukemia (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 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 in completed phase 2 and 3 trials. Two studies demonstrated an association between the level of MRD and progression-free survival (PFS) with lower risk of progression in patients who exhibit MRD negativity below 10^{-4} compared to patients who have detectable residual disease. In one study of participants treated with ibrutinib+venetoclax, PFS at one 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 10000 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 multiple myeloma (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 complete response 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 (eg, 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 multiple myeloma (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 hematopoietic stem cell transplant (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 multiple myeloma (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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

International Myeloma Working Group

The International Myeloma Working Group published consensus criteria in 2016 for response and minimal residual disease (MRD) assessment in multiple myeloma (Table 2).[12,]

Table 2. 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 (ie, 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 NetworkThe National Comprehensive Cancer Network has published guidelines of relevance to this review (see Table 3).

Table 3. Recommendations on Assessing Measurable Residual Disease

Guideline	Version	Recommendation
Acute lymphoblastic leukemia [1,]	3.2023	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 (eg, clonally rearranged Ig, TCR genes), and reverse transcriptase quantitative PCR (RT-qPCR) assays (eg, BCR/ABL1).High sensitivity flow cytometry with validated analysis algorithms or PCR methods can quantify leukemic cells at a sensitivity threshold of $1x10^{-4}$ (0.01%) bone marrow mononuclear cells (MNCs). NGS and some PCR methods can detect leukemic cells at a sensitivity threshold of $1x10^{-6}$ (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 [8,]	3.2023	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 [28,]	1.2024	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 10^5 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 10^5 nucleated cells or higher.

B-cell lymphomas [29,]	6.2023	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.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

Molecular Diagnostic Services Program has determined that clonoSEQ Assay testing is reasonable and necessary when performed on bone marrow specimens in patients with B-Cell acute lymphoblastic leukemia (ALL), CLL, multiple myeloma, or diffuse large B-cell lymphoma. Medicare will pay for a single episode of testing using clonoSEQ for a patient with ALL, CLL or multiple myeloma when clonoSEQ is being used according to its U.S. Food and Drug Administration cleared indications and clinical guidelines. An episode of testing will typically require a baseline assay and 3 follow-up assays.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2018	New Policy	Policy created with literature review through 6, 2018. Considered investigational.
March 2020	Replace policy	Policy updated with literature review through October 16, 2019; references added. The revised policy is focused on the two indications (acute lymphocytic leukemia and multiple myeloma) that have received de novo marketing clearance for ClonoSEQ. Next-generation sequencing for measurable residual disease may be considered medically necessary when reported at the same threshold as multiparameter flow cytometry and is investigational at more sensitive thresholds. Benefit Application section was added to this policy.
March 2021	Replace policy	Policy updated with literature review through October 12, 2020; references added. The indication of chronic lymphocytic leukemia was added to the policy at a threshold of 10-4. The threshold for measurable residual disease detection in patients with multiple myeloma was changed to 10-5.
March 2022	Replace policy	Policy updated with literature review through October 20, 2021; NCCN references updated. Minor editorial changes to policy statements, intent unchanged.
March 2023	Replace policy	Policy updated with literature through November 2, 2022; references added. The indications of diffuse large B-cell lymphoma and mantle cell lymphoma were added, and investigational policy statements added for these indications.
March 2024	Replace policy	Policy updated with literature through October 18, 2023; references added. Policy statements edited to clarify that MRD testing with NGS for individuals with diffuse large B-cell lymphoma and mantle cell lymphoma is INV at any sensitivity threshold.