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

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 100000 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), and multiple myeloma (MM).

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 (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 Minimal 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 B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, and multiple myeloma 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 patients with acute lymphoblastic leukemia may be considered **medically necessary**.

Next-generation sequencing (eg clonoSEQ) to detect measurable residual disease (MRD) at a threshold of less than 10^{-4} in patients 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 patients with chronic lymphocytic leukemia may be considered **medically necessary**.

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

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

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

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

POLICY GUIDELINES

None

BENEFIT APPLICATION

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 MM. In 2020, clonoSEQ received marketing clearance from the FDA to detect MRD in patients with chronic lymphocytic leukemia.

RATIONALE

Summary of Evidence

For individuals with B-cell acute lymphoblastic leukemia (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 a retrospective comparison of data from 2 earlier trials by the Children's Oncology Group. 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 outcomes.

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 the earlier Children's Oncology Group 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 outcomes.

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 2 clinical trials. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, quality of life (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. Both 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. The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

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 2 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 outcomes.

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 a retrospective comparison 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}. Progression free survival (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}. Several 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 outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

International Myeloma Working Group

The International Myeloma Working Group developed consensus criteria for response and minimal residual disease (MRD) assessment in multiple myeloma (Table 2).[14,]

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 have the following recommendations regarding the assessment of MRD:[9,]

"The complete eradication of the leukemia is a desired end point. Use of sensitive multicolor flow cytometry, PCR, or next generation sequencing can detect MRD in many patients who
achieved a complete clinical response. Prospective clinical trials have provided substantial evidence that therapies that are able to eradicate MRD usually result in an improved clinical outcome. The techniques for assessing MRD have undergone a critical evaluation and have become well standardized. Six-color flow cytometry (MRD flow), allele-specific oligonucleotide PCR, or high-throughput sequencing using the ClonoSEQ assay are reliably sensitive down to a level of 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 Network

The 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[5.]	2.2020	Risk stratification after treatment induction by MRD positivity. MRD in ALL refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. The most frequently employed methods for MRD assessment are FC, RQ-PCR, and NGS. The concordance rate between these methods is generally high.
Chronic lymphocytic leukemia/small lymphocytic lymphoma https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf[10.]	1.2021	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[15.]	3.2021	Bone marrow aspirate with multiparameter flow cytometry is to be used as clinically indicated following treatment. MRD tests should be initiated only at the time of suspected CR. and can be assessed for prognostication after a shared decision with the patient. MRD criteria include NGF with the EuroFlow procedure or NGS with a sensitivity of 10^{-5}.

ALL: acute lymphoblastic leukemia, CR: complete response; ERIC: European Research Initiative on CLL; FC: flow cytometry; MRD: measurable residual disease; NGF: next generation flow; NGS: next-generation sequencing; RQ-PCR: real-time quantitative polymerase chain reaction.

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 ALL, CLL or multiple myeloma. Medicare will pay for a single episode of testing using ClonoSEQ for a patient with ALL 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.