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

Effective Date: January 15, 2019

Related Policies: None

Genetic

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 or polymerase chain reaction, which can detect one clonal cell in 100,000 cells. It is proposed that next-generation sequencing (NGS), which can detect one residual clonal sequence out of 1,000,000 cells, will improve health outcomes in patients who have been treated for hematologic malignancies.

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 blood or bone marrow 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 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 (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 and is transitioning from “bench-to-bedside” for clinical use.

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 relapse 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. There is currently no consensus on which method provides clinically meaningful assessment of MRD. A 2018 international consensus paper recommended that flow cytometry presents a high enough sensitivity to be used in routine clinical practice, but for a more sensitive result and if MRD eradication is the goal for the selected patient, then allele-specific PCR should be used.1 It is notable that next-generation flow techniques have reached a detection limit of one in 10^{-5} cells, which is equal to PCR and approaches the limit of detection of NGS (see Table 1).

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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" B- or T-cell 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. It is not known whether the increase in sensitivity from 10^{-5} to 10^{-6} represents a clinically meaningful difference in MRD.

Table 1. Sensitivity of Methods for Detecting Minimal Residual Disease

Technique	Sensitivity	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 improves the net health outcome in individuals tested for measurable residual disease.

POLICY STATEMENT

Next-generation sequencing for measurable residual disease is **investigational**.

POLICY GUIDELINES

There is no specific code for next generation sequencing for measurable residual disease monitoring.

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.

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

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 Food and Drug Administration through the de novo classification process to detect MRD in patients with ALL or MM.

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RATIONALE

Summary of Evidence

For individuals who have achieved a complete response and are being evaluated for MRD who receive NGS for MRD, the evidence includes studies on diagnostic accuracy and prognosis. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, quality of life, and treatment-related morbidity. The evidence is insufficient to determine the clinical validity of NGS for assessing MRD, and no chain of evidence can be constructed to establish clinical utility in hematologic malignancies. NGS can identify more blast cells with an identified clonal sequence by a factor of 10. However, the clinical utility of this increase in the detection of clonal sequences is uncertain. Direct evidence from randomized controlled trials is needed to evaluate whether patient outcomes are improved by changes in postinduction care (eg, continuing therapy, escalating to hematopoietic cell transplant, avoiding unnecessary therapy) following NGS detection of MRD at 10^{-6} compared with the established methods of flow cytometry or polymerase chain reaction (at 10^{-5}). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with B-ALL who are in remission who are being considered for treatment with blinatumomab who receive NGS for MRD, the evidence is lacking. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, quality of life, and treatment-related morbidity. Direct evidence from RCTs is needed to evaluate whether patient outcomes are improved by directing treatment with blinatumomab based on NGS assessment of MRD at 10^{-6} compared with the threshold of 10^{-3} approved by the Food and Drug Administration. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Practice Guidelines and Position Statements

The National Comprehensive Cancer Network has published guidelines of relevance to this review (see Table 2).

Table 2. Recommendations on Assessing Measurable Residual Disease

Guideline	Version	Recommendation
Acute lymphoblastic leukemia[7]	1.2018	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.
Chronic lymphocytic leukemia[8]	1.2019	Response assessment involves both physical examination and evaluation of blood parameters. MRD-negative status in peripheral blood correlates with better PFS. Therapy is not guided by MRD status.
Hairy cell leukemia[9]	2.2019	An immunohistochemical assessment of the percentage of MRD will enable patients to be separated into those with CR with or without evidence of MRD.
Multiple myeloma[10]	1.2019	Treatment for progressive disease based on MRD with NGF or NGS on bone marrow at a minimum sensitivity of 10^{-5}

ALL: acute lymphoblastic leukemia, CR: complete response; FC: flow cytometry; MRD: measurable residual disease; NGF: next-generation flow cytometry; NGS: next-generation sequencing; PFS: progression-free survival; RQ-PCR: real-time quantitative polymerase chain reaction.

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U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Tomuleasa C, Selicean C, Cismas S, et al. Minimal residual disease in chronic lymphocytic leukemia: A consensus paper that presents the clinical impact of the presently available laboratory approaches. Crit Rev Clin Lab Sci. Aug 2018;55(5):329-345. PMID 29801428
2. Kurtz DM, Green MR, Bratman SV, et al. Noninvasive monitoring of diffuse large B-cell lymphoma by immunoglobulin high-throughput sequencing. Blood. Jun 11 2015;125(24):3679-3687. PMID 25887775
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):3501-3508. PMID 25862561
5. 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):3073-3079. PMID 24646471
6. U.S. Food and Drug Administration. Prescribing information for BLINCYTO. 2018; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125557s013lbl.pdf. Accessed October 5, 2018.
7. National Comprehensive Care Network. NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia. Version 1.2018. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed September 27, 2018.
8. National Comprehensive Care Network. NCCN Clinical Practice Guidelines in Oncology: Chronic lymphocytic leukemia. Version 1.2019. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed September 27, 2018.
9. National Comprehensive Care Network. NCCN Clinical Practice Guidelines in Oncology: Hairy Cell Leukemia. Version 2.2019. https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf. Accessed September 27, 2018.
10. National Comprehensive Care Network. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 1.2019. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed September 27, 2018.
11. 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* 2018, Sep 24. pii: blood 2018-06-858613

POLICY HISTORY

Date	Action	Description
December 2018	New Policy	Policy created with literature review through 6, 2018. Considered investigational.