



Louisiana

Next-Generation Sequencing for the Assessment of Measurable Residual Disease

Policy # 00656

Original Effective Date: 12/19/2018

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers next-generation sequencing for measurable residual disease to be **investigational**.*

Background/Overview DISEASE

There are 3 main types of hematologic malignancies: lymphomas, leukemias, and myelomas. Lymphoma is the most common type of hematologic malignancy and is typically divided into 2 categories, Hodgkin lymphoma (also known as Hodgkin disease) and non-Hodgkin lymphoma (NHL). Lymphoma begins in lymph cells of the immune system, which originate in bone marrow and collect in lymph nodes and other tissues. The 2 types of lymph cells that develop into NHL are B lymphocytes (B cells), which mature in the bone marrow, and T lymphocytes (T cells), which mature in the thymus.

Leukemia is caused by the overproduction of abnormal white blood cells in the bone marrow, which leads to a decrease in production of red blood cells and plasma cells. Leukemia may be acute or chronic, and affect either lymph or myeloid cells. The most common forms of leukemia are acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia. There are a number of less common forms of leukemia. Multiple myeloma (MM), also called plasma myeloma, is a malignancy of plasma cells in the bone marrow.

Hodgkin Lymphoma

Hodgkin lymphoma is a relatively uncommon B-cell lymphoma. In 2017, the estimated number of new cases in the United States was approximately 8260 with 1070 estimated deaths. The disease has a bimodal distribution, with most patients diagnosed between the ages of 15 and 30 years, with a second peak in adults aged 55 years and older.

Non-Hodgkin Lymphoma

NHL includes a heterogeneous group of lymphoproliferative malignancies. In general, NHL can be divided into 2 prognostic groups: indolent and aggressive. Follicular lymphoma is the most common indolent NHL (70%-80% of cases), and often the terms indolent lymphoma and follicular lymphoma are used synonymously. Indolent NHL has a relatively good prognosis, with a median survival of 10 years; however, it is not curable in advanced clinical stages. Histologic transformation to higher grade lymphoma occurs in up to 70% of patients with low-grade lymphoma, and median survival with conventional chemotherapy is 1

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year or less. Aggressive NHL has a shorter natural history; however, 30% to 60% of these patients can be cured with intensive combination chemotherapy regimens.

Acute Lymphoblastic Leukemia

Childhood ALL

ALL is the most common cancer diagnosed in children; it represents nearly 25% of cancers in children younger than 15 years. 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.

Adult ALL

ALL accounts for 20% of acute leukemias in adults. Between 60% and 80% of adults with ALL can be expected to achieve a complete response 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.

Chronic Lymphocytic Leukemia

CLL tends to present as asymptomatic enlargement of the lymph nodes and tends to be indolent, but can undergo transformation to a more aggressive form of the disease. The median age at diagnosis of CLL is approximately 72 years. Both low- and intermediate-risk CLL demonstrate relatively good prognoses, with a median survival of 6 to 10 years; however, the median survival of high-risk CLL may only be 2 years. Although typically responsive to initial therapy, CLL is rarely cured by conventional therapy, and nearly all patients die of their disease.

Acute Myeloid Leukemia

AML, also called acute nonlymphocytic leukemia, refers to a set of leukemias that arise from a myeloid precursor in the bone marrow. Clinical signs and symptoms are associated with neutropenia, thrombocytopenia, and anemia. The incidence of AML increases with age, with a median of 67 years. Molecular studies have identified a number of genetic abnormalities that can be used to guide prognosis and management of AML. Cytogenetically normal AML is the largest defined subgroup of AML, comprising approximately 45% of all AML cases. Despite the absence of cytogenetic abnormalities, these cases often have genetic variants that affect outcomes.

Chronic Myeloid Leukemia

Chronic myeloid leukemia accounts for about 15% of newly diagnosed cases of leukemia in adults and occurs in 1 to 2 cases per 100,000 adults. The natural history of the disease consists of an initial (indolent) chronic phase, lasting a median of 3 years, which typically transforms into an accelerated phase, followed

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by a “blast crisis,” which is usually the terminal event. Most patients present in chronic phase, often with nonspecific symptoms secondary to anemia and splenomegaly. Conventional-dose chemotherapy regimens used for chronic phase disease can induce multiple remissions and delay the onset of blast crisis to a median of 4 to 6 years. However, successive remissions are invariably shorter and more difficult to achieve than their predecessors.

Multiple Myeloma

MM represents approximately 10% of all hematologic cancers. It is treatable but rarely curable. Treatment is usually reserved for patients with symptomatic disease (usually progressive myeloma), whereas 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 intermediate asymptomatic but the more advanced premalignant stage is recognized and referred to as smoldering MM. The overall risk of disease progression from smoldering to symptomatic MM is 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and 1% for the next 10 years.

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 the acute leukemias can lead to complete remission. MM and the chronic leukemias are treatable but generally incurable. Patients are typically followed by complete blood count and morphologic assessment of bone marrow. Complete hematologic response is defined as a bone marrow blast (immature cells) composition of less than 5% and hematologic recovery (normal neutrophil and platelet count) without the need for red blood cell transfusions.

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 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,

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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).

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

Centers for Medicare and Medicaid Services (CMS)

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

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Rationale/Source

NEXT-GENERATION SEQUENCING TO DETECT MEASURABLE RESIDUAL DISEASE

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Clinical Context and Test Purpose

The purpose of next-generation sequencing (NGS) to detect measurable residual disease (MRD) in patients who have been treated for hematologic cancers and achieved a complete response after induction therapy is to inform a decision regarding subsequent treatment.

The question addressed in this evidence review is: Does the use of NGS testing for MRD improve the net health outcome in patients with hematologic cancers?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients who have been treated for hematologic cancers and exhibit complete morphologic remission.

Interventions

The test being considered is NGS (eg, clonoSEQ). This test is proposed as an adjunct to existing methods of assessing MRD with complete blood count and cell morphology, and as an alternative to flow cytometry or polymerase chain reaction (PCR).

Comparators

The following tests are currently being used to detect MRD: flow cytometry and PCR. The reference standard is clinical (hematologic) relapse.

Outcomes

The general outcomes of interest are remission and relapse in the short term and survival at longer follow-up.

Beneficial outcomes of a true-positive test result would be intensification or continuation of an effective treatment leading to a reduction in relapse and improvement in overall survival (OS). The beneficial outcome of a true-negative test is the avoidance of unnecessary treatment and reduction of adverse events.

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Harmful outcomes of a false-positive test include an increase or continuation of unnecessary treatment resulting in treatment-related harms. Harmful outcomes of a false-negative test include a reduction in necessary treatment that would delay treatment, with a potential impact in progression-free survival (PFS) and OS.

Direct harms of the test are repeated bone marrow biopsy, although this test can also be performed in blood and would, therefore, reduce direct harms of the invasive test.

Timing

Relapse of acute hematologic malignancies may be measured in months and chronic hematologic malignancies measured in years. Changes in survival from acute hematologic malignancies would be observable at 2 years, while chronic hematologic malignancies would typically be observable by 10 years.

Setting

Evaluation of MRD would be in an outpatient care setting by a hematologic oncologist.

Study Selection Criteria

For the evaluation of clinical validity of the clonoSEQ test, studies that met the following eligibility criteria were considered:

- Included a suitable reference standard (relapse or OS or PFS)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Studies were excluded from the evaluation of the clinical validity of the test because they did not use the marketed or earlier version of the test, did not include information needed to calculate performance characteristics, did not use an appropriate reference standard or reference standard was unclear, did not adequately describe the patient characteristics, or did not adequately describe patient selection criteria.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Diagnostic Accuracy for Hematologic or Clinical Relapse

Characteristics and results of the diagnostic accuracy studies evaluating NGS for MRD are summarized in Tables 2 and 3. Kurtz et al (2015) reported a sensitivity of 31% and specificity of 100% to predict clinical relapse, with an MRD threshold of 10^{-6} . A malignant clonal sequence was identified in 83% of patients.

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Table 2. Characteristics of Diagnostic Accuracy Studies Assessing NGS for MRD

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Median Follow-Up, mo	Test Version
Kurtz et al (2015)	Adult B-cell lymphoma	Prospective	Clinical relapse	MRD at 10 ⁻⁶	34	LymphoSIGHT

MRD: measurable residual disease; NGS: next-generation sequencing

Table 3. Results of Diagnostic Accuracy Studies Assessing NGS for MRD

Study	N	% With an Identified Clonal Sequence	Clinical Validity (95% Confidence Interval), %			
			Sens	Spec	PPV	NPV
Kurtz et al (2015)	75	83	31	100		

MRD: measurable residual disease; NGS: next-generation sequencing; NPV: negative predictive value; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

The purpose of the gaps tables (see Tables 4 and 5) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 4. Relevance Gaps

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Kurtz et al (2015)				2. A chain of evidence of decisions that would be affected by the test have not been explicated	

The evidence gaps 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 5. Study Design and Conduct Gaps

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Kurtz et al (2015)	2. Study inclusion based in part on availability of sufficient blood samples with only 8 of 140 patients from 1 of the sites included					1. Confidence intervals and/or p values not reported

The evidence gaps 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 (ie, 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.

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^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 to other tests not reported.

Prognosis

Tables 6 and 7 describe studies that have evaluated prognosis based on MRD detected by either flow cytometry or NGS, or for studies that have evaluated prognosis based on the level of MRD from 10^{-3} to 10^{-6} . Outcome measures of these studies varied, which complicates analysis, but overall, higher levels of MRD are associated with worse prognosis. In the study by Wood et al (2018), higher levels of sensitivity were associated with a decrease in specificity, and the maximal hazard ratio was obtained at 10^{-4} .

Table 6. Characteristics of Prognostic Studies Assessing NGS for MRD

Study	Study Population	Design ^a	Source	Reference Standard	Threshold for PIT	FU, y	Test Version
Wood et al (2018)	Pediatric B-ALL	Nonconcurrent from banked samples	Bone marrow	Event-free survival	MRD at 10^{-4} and 10^{-5}	5	ImmunoSEQ
Pulsipher et al (2015)	Pediatric ALL	Nonconcurrent from banked samples	Pre- and post-HCT bone marrow	Time to relapse following HCT	FC at 10^{-3} NGS at 10^{-5}		ImmunoSEQ
Martinez-Lopez et al (2014)	Multiple myeloma	Retrospective	Bone marrow	Time to progression	MRD at 10^{-3} and 10^{-5}		LymphoSIGHT

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

Table 7. Results of Prognostic Studies Assessing NGS for MRD

Study	N	% With a Trackable Sequence	MRD Threshold	Results				
				TTP, mo	5-Year EFS, %	Relapse Rate at 2 Years, %	Hazard Ratio	p
Wood et al (2018)	607	95.4	$<10^{-4}$		98.1		Maximal at 10^{-4}	
Pulsipher et al (2015)	40		Pre-HCT FC negative			16		
			Pre-HCT NGS negative			0		
Martinez-Lopez et al (2014)	133	91	$>10^{-3}$	27				
			10^{-3} to 10^{-5}	48				
			$<10^{-5}$	80			TTP=3.97	<0.001

EFS: event-free survival; FC: flow cytometry; HCT: hematopoietic cell transplantation; MRD: measurable residual disease; NGS: next-generation sequencing; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; TTP: time to progression.

Gaps in relevance and design and conduct are shown in Tables 8 and 9.

Table 8. Relevance Gaps

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of FU ^e
Wood et al (2018)		3. Used		1, 2. Study does not	1. Duration of FU

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	ImmunoSEQ rather than OncoSEQ	elucidate how health outcomes would be improved by the prognostic information	insufficient to evaluate overall survival
Pulsipher et al (2015)	3. Used ImmunoSEQ rather than OncoSEQ	1, 2. Study does not elucidate how health outcomes would be improved by the prognostic information	
Martinez-Lopez et al (2014)		1, 2. Study does not elucidate how health outcomes would be improved by the prognostic information	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. FU: follow-up.

^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.

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^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 9. Study Design and Conduct Gaps

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Wood et al (2018)		1. Blinding not described				
Pulsipher et al (2015)						
Martinez-Lopez et al (2014)		1. Blinding not described				

The evidence gaps 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 (ie, convenience).

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^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 to other tests not reported.

Section Summary: Clinically Valid

The performance characteristics of NGS at 10⁻⁶ to detect relapse are not well defined. One prospective study was identified and it evaluated the diagnostic accuracy of NGS. In this study, a clonal sequence could be identified in only 83% of the samples, which can be compared with the 100% identification of clonal cells by flow cytometry. At a detection limit of 10⁻⁶, NGS had 31% sensitivity and 100% specificity to detect

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clinical relapse. Several prognostic studies have reported on the association between MRD at various sensitivities and relapse prediction. The percentage of cases in which a clonal sequence could be identified ranged from 91% to 95.4%. The timing of the test and the outcome measures of these studies were variable, which complicates analysis, but overall, higher levels of MRD were associated with worse prognosis. One study, however, found that the maximal hazard ratio was obtained at a sensitivity of 10^{-4} , the same as flow cytometry and that higher levels of sensitivity were associated with a decrease in specificity. Thus, the clinical validity of NGS to detect MRD is uncertain.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs assessing the clinical utility of NGS to detect malignant clonal sequences were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The evidence is insufficient to demonstrate clinical validity, and it is not known whether management changes based on the increase in sensitivity with NGS to detect malignant clonal sequences would improve health outcomes.

Section Summary: Clinically Useful

The evidence is insufficient to determine the test performance of NGS for detecting MRD, and no chain of evidence can be constructed to establish clinical utility in hematologic malignancies. Direct evidence from RCTs are needed to evaluate whether patient outcomes are improved by changes in postinduction care (eg, continuing therapy, escalating to hematopoietic cell transplantation, avoiding unnecessary adverse events) following NGS detection of MRD at 10^{-6} compared with the established methods of flow cytometry or PCR at 10^{-5} .

NGS TO INFORM TREATMENT OF B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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 patients and to managing the course of that condition. Validated outcome measures are necessary to

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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.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Clinical Context and Test Purpose

The purpose NGS to detect MRD in patients who are in remission for B-cell acute lymphoblastic leukemia (B-ALL) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

In 2018, blinatumomab received approval from the Food and Drug Administration for the treatment of MRD positive B-cell precursor ALL in first or second complete remission with MRD positivity of 0.1% or greater (10^{-3} or 1 in 1000 cells).

The question addressed in this evidence review is: Does the use of NGS testing for MRD improve the net health outcome in patients with B-ALL who are being considered for treatment with blinatumomab?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients who have been treated for B-ALL and exhibit complete morphologic remission.

Interventions

The test being considered is NGS (eg, liter). This test is proposed as an adjunct to existing methods of assessing MRD with complete blood count and cell morphology, and as an alternative to flow cytometry or PCR.

Comparators

The following tests are currently being used to inform treatment decisions for those with B-ALL in remission: flow cytometry and PCR. The reference standard is clinical (hematologic) relapse.

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Outcomes

The general outcomes of interest are remission and relapse in the short term and survival at longer follow-up.

Beneficial outcomes of a true-positive test result would be the administration of an effective treatment leading to a reduction in relapse and improvement in OS. The beneficial outcome of a true-negative test is the avoidance of unnecessary treatment and reduction of adverse events.

Harmful outcomes of a false-positive test are unnecessary treatment resulting in treatment-related harms. Harmful outcomes of a false-negative test are a reduction in necessary treatment that would delay treatment, with a potential impact in PFS and OS.

Direct harms of the test are repeated bone marrow biopsy, although this test can also be performed in blood and would, therefore, reduce direct harms of the invasive test.

Timing

Relapse of B-ALL may be measured in months. Changes in survival from B-ALL would be observable at 2 years.

Setting

Evaluation of MRD would be in an outpatient care setting by a hematologic oncologist.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Clinical Studies

No studies were identified that assessed the clinical validity or clinical utility of using NGS to inform a decision to treat B-ALL patients in remission with blinatumomab.

Section Summary: NGS to Inform Treatment of B-Cell Acute Lymphoblastic Leukemia

The evidence is insufficient to determine the utility of using NGS to inform a decision to treat B-ALL patients in remission with blinatumomab. Direct evidence from RCTs is needed to evaluate whether patient outcomes are improved by directing treatment with blinatumomab following NGS detection of MRD at 10^{-6} compared with the Food and Drug Administration–directed threshold of 10^{-3} or more.

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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.

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