Policy Statement

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

Policy Guidelines

There is no specific code for next generation sequencing for measurable residual disease monitoring. ClonoSEQ® Minimal Residual Disease Test may be billed with the following unlisted codes:

- **81599**: Unlisted multianalyte assay with algorithmic analysis
- **81479**: Unlisted molecular pathology procedure

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.

Related Policies

- Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- Hematopoietic Cell Transplantation for Acute Myeloid Leukemia
- Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia Small Lymphocytic Lymphoma
- Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia
- Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
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 Acute Lymphoblastic Leukemia (ALL) or Multiple myeloma (MM).

Rationale

Background 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 8,260 with 1,070 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 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 relapsed 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/μL (B-cell lineage) or greater than 100,000/μL (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 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 a symptomatic 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 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).

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” 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                            |

**Literature Review**

**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 (e.g., 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.

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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Design</th>
<th>Reference Standard</th>
<th>Threshold for Positive Index Test</th>
<th>Median Follow-Up, mo</th>
<th>Test Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurtz et al (2015)²</td>
<td>Adult B-cell lymphoma</td>
<td>Prospective</td>
<td>Clinical relapse</td>
<td>MRD at $10^{-6}$</td>
<td>34</td>
<td>LymphoSIGHT</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>% With an Identified Clonal Sequence</th>
<th>Clinical Validity (95% Confidence Interval), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurtz et al (2015)²</td>
<td>75</td>
<td>83</td>
<td>31 Sens, 100 Spec</td>
</tr>
</tbody>
</table>

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

The purpose of the gap 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Duration of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurtz et al (2015)²</td>
<td></td>
<td></td>
<td></td>
<td>2. A chain of evidence of decisions that would be affected by the test have not been explicated</td>
<td></td>
</tr>
</tbody>
</table>

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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>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Designa</th>
<th>Source</th>
<th>Reference Standard</th>
<th>Threshold for PIT</th>
<th>FU, y</th>
<th>Test Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurtz et al (2015)²</td>
<td>Pediatric B-ALL</td>
<td>Nonconcurrent from banked samples</td>
<td>Bone marrow</td>
<td>Event-free survival</td>
<td>MRD at 10⁻⁴ and 10⁻⁵</td>
<td>5</td>
<td>ImmunoSEQ</td>
</tr>
<tr>
<td>Pulsipher et al (2015)²</td>
<td>Pediatric ALL</td>
<td>Nonconcurrent from banked samples</td>
<td>Pre- and post- HCT bone marrow</td>
<td>Time to relapse following HCT</td>
<td>FC at 10⁻³ NGS at 10⁻⁵</td>
<td>ImmunoSEQ</td>
<td></td>
</tr>
</tbody>
</table>

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 10⁻⁴.³
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 GS for MRD

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>% With a Trackable Sequence</th>
<th>MRD Threshold</th>
<th>5-Year EFS, %</th>
<th>Relapse Rate at 2 Years, %</th>
<th>Hazard Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood et al (2018)³</td>
<td>607</td>
<td>95.4</td>
<td>&lt;10⁻⁴</td>
<td>98.1</td>
<td>Maximal at 10⁻⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulsipher et al (2015)⁴</td>
<td>40</td>
<td></td>
<td>Pre-HCTFC negative</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martinez-Lopez et al (2014)⁵</td>
<td>133</td>
<td>91</td>
<td>&gt;10⁻³</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10⁻³ to 10⁻⁵</td>
<td>48</td>
<td></td>
<td>TTP=3.97</td>
<td>&lt;0.00</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationᵃ</th>
<th>Interventionᵇ</th>
<th>Comparatorᶜ</th>
<th>Outcomesᵈ</th>
<th>Duration of FUᵉ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3. Used ImmunoSEQ rather than OncoSEQ</td>
<td></td>
<td>1. Study does not elucidate how health outcomes would be improved by the prognostic information</td>
<td>1. Duration of FU insufficient to evaluate overall survival</td>
<td></td>
</tr>
<tr>
<td>Pulsipher et al (2015)⁴</td>
<td>3. Used ImmunoSEQ rather than OncoSEQ</td>
<td></td>
<td>1. Study does not elucidate how health outcomes would be improved by the prognostic information</td>
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</tr>
<tr>
<td>Martinez-Lopez et al (2014)⁵</td>
<td></td>
<td></td>
<td>1. Study does not elucidate how health outcomes would be improved by the prognostic information</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
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 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 (e.g., 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 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).6

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 (e.g., 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.

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.
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 (e.g., 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 $10^{-3}$). 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
The National Comprehensive Cancer Network has published guidelines of relevance to this review (see Table 10).

Table 10. Recommendations on Assessing Measurable Residual Disease

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Version</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukemia7</td>
<td>1.2018</td>
<td>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.</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia8</td>
<td>1.2019</td>
<td>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.</td>
</tr>
<tr>
<td>Hairy cell leukemia9</td>
<td>2.2019</td>
<td>An immunohistochemical assessment of the percentage of MRD will enable patients to be separated into those with CR with or without evidence of MRD.</td>
</tr>
<tr>
<td>Multiple myeloma10</td>
<td>1.2019</td>
<td>Treatment for progressive disease based on MRD with NGF or NGS on bone marrow at a minimum sensitivity of $10^{-5}$.</td>
</tr>
</tbody>
</table>

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.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
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.
Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 11.

Table 11. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCTNo.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>DNA Sequencing-Based Monitoring of Minimal Residual Disease to Predict Clinical Relapse in Aggressive B-cell Non-Hodgkin Lymphomas</td>
<td>500</td>
<td>Oct 2019</td>
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<tr>
<td>NCT02633111</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>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 Hematopoietic Cell Transplantation (HCT) Next-generation-sequence (NGS) Minimal Residual Disease (MRD) Negative (ENRAD)</td>
<td>95</td>
<td>Apr 2022</td>
</tr>
<tr>
<td>NCT03509961</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td></td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>None</td>
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</tr>
</tbody>
</table>

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/01/2018</td>
<td>BCBSA Medical Policy Adoption</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an
authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.