


<b>MEDICAL POLICY</b>	<b>Minimal Residual Disease Detection in Lymphoid Malignancies (All Lines of Business Except Medicare)</b>	
<b>Effective Date: 6/1/2020</b>   <div style="text-align: right;">6/1/2020</div>	Section: LAB	Policy No: 425
	Medical Policy Committee Approved Date: 3/2020	
Medical Officer	Date	

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

**SCOPE:**

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

**APPLIES TO:**

All lines of business except Medicare

**BENEFIT APPLICATION**

Medicaid Members

*Oregon:* Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**POLICY CRITERIA**

**Note:** This policy only addresses the use of next generation sequencing (NGS) for minimal residual disease (MRD) detection in lymphoid malignancies (i.e., ClonoSeq). Other MRD techniques (e.g., flow cytometry, polymerase chain reaction) are not addressed in this policy and may be considered medically necessary.

- I. Minimal residual disease detection in lymphoid malignancies using next-generation sequencing (i.e. ClonoSeq) is considered **investigational and not covered**.

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Link to [Policy Summary](#)

### CPT/HCPCS CODES

All Lines of Business Except Medicare	
<p><b>Unlisted Codes</b></p> <p>All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then it will be <b>denied as not covered</b>.</p>	
81479	Unlisted molecular pathology procedure

### DESCRIPTION

Minimal Residual Disease

Minimal residual disease (MRD) refers to the small number of cancer cells that remain in the body following treatment. To test for MRD, samples are drawn from either the patient’s blood or bone marrow aspiration. MRD testing is used to determine cancer treatment’s efficacy, predict risk of relapse and guide subsequent treatment. The most common tests used to measure MRD are flow cytometry, polymerase chain reaction (PCR) and next-generation sequencing (NGS).<sup>1</sup>

Next Generation Sequencing

Next generation sequencing (NGS) is a form of MRD that rapidly examines stretches of DNA or RNA that purports to accurately detect very small amounts of malignant cells and other genetic abnormalities. The U.S. Food and Drug Administration approved ClonoSeq to detect MRD in B-cell acute lymphoblastic leukemia (ALL) and myeloma.<sup>1</sup>

ClonoSeq

The ClonoSeq assay is an *in vitro* diagnostic assay that uses multiplex polymerase chain reaction (PCR) and next-generation sequencing (NGS) to identify the frequency and distribution of clonal sequences consistent with a malignant lymphocyte in bone marrow samples. The Assay measures minimal residual disease (MRD) to monitor changes in burden of disease during and after treatment. An initial assay determines the presence of 1 or more dominant sequences and subsequent sample assays allow tracking of the dominant sequence(s).<sup>2</sup>

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Multiple Myeloma

Multiple myeloma is a cancer that in which cancerous plasma cells proliferate in the bone marrow and produce a monoclonal immunoglobulin, resulting in extensive skeletal destruction.

Leukemia

Leukemia refers to a group of blood cancers that occur in the body’s blood-forming tissues, including the bone marrow and lymphatic system.

**REVIEW OF EVIDENCE**

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding minimal residual disease detection in lymphoid malignancies using next-generation sequencing (i.e. ClonoSeq). Below is a summary of the available evidence identified through January 2020.

*Systematic Reviews*

In 2018, Hayes conducted a systematic review evaluating the analytical validity, clinical validity and clinical utility of ClonoSeq in the assessment of minimal residual disease (MRD) in lymphoid malignancies.<sup>2</sup> As of October 2018, 3 retrospective cohort studies were identified evaluating ClonoSeq’s clinical validity by comparing the assay to MRD detection by multiparametric flow cytometry (MPFC), and immunoglobulin heavy chain locus (IgH) ClonoSeq. Sample sizes ranged from 32 to 108 patients. No peer-reviewed studies were identified that assessed the assay’s analytical validity. While clinical validity studies reported a high to moderately high level of concordance between ClonoSeq and MPFC, Hayes concluded that the lack of clinical utility studies rendered evidence insufficient to support claims that ClonoSeq accurately measures MRD and improves patient outcomes. Moreover, studies only examined the ClonoSeq assay, and not the sequence generation and downstream data analyses that collectively constitute the ClonoSeq process. Citing “very low” quality evidence, authors ultimately assigned a “D2” rating (insufficient evidence) for the use of ClonoSeq in detecting and measuring MRD in bone marrow samples.

*Additional Studies*

Since the Hayes review discussed above, one additional peer-reviewed study was identified.

In 2018, Perrot and colleagues conducted a post-hoc analysis of data from a recent clinical trial to assess the prognostic value of next-generation sequencing to obtain MRD measurements.<sup>3</sup> It is unclear if ClonoSeq was the next generation sequencing process utilized. In total, data from 127 patients at 50-month follow-up were reported. Authors reported that MRD was a strong prognostic factor for both progression-free survival (HR, 0.22; 95% CI 0.15-0.34; P < .001) and overall survival (HR, 0.24; 95%

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confidence interval, 0.11-0.54; P = .001). Patients who were MRD negative had a higher probability of prolonged progression-free survival than patients with detectable residual disease, regardless of subsequent treatments and other baseline characteristics. However, patients with undetectable MRD also continued to show a linear risk of relapse after stopping treatment. Authors concluded that NGS-determined MRD status may be used as a prognostic biomarker in patients with multiple myeloma. The study is limited however by its retrospective design, as post-hoc correlations may be vulnerable to confounding by multiple variables. Additional studies comparing next-generation sequencing to PCR and flow cytometry are necessary to establish superiority.

**CLINICAL PRACTICE GUIDELINES**

National Comprehensive Cancer Network (NCCN)

- In 2020, the NCCN published guidelines addressing the diagnosis and management of acute lymphoblastic leukemia.<sup>4</sup> ClonoSeq was not mentioned by name. Authors argued that MRD assessment is “an essential component of patient evaluation over the course of sequential therapy” but also stated that next-generation sequencing assays “are not recommended for minimal residual disease quantification outside the context of a clinical trials.”<sup>4</sup> The guidance’s “discussion section” is currently being updated and clarifications/further recommendations may be forthcoming.
- In 2020, the NCCN published guidelines addressing the diagnosis and management of multiple myeloma.<sup>5</sup> The guideline utilizes employed the International Myeloma Working Group criteria, which considers NGS a technique for MRD detection. Nonetheless, no clear recommendation is regarding the use of NGS in MRD detection.

American Society of Clinical Oncology/Cancer Care Ontario (ASCO/CCO)

In 2019, ASCO/CCO published a clinical practice guideline evaluating the treatment of multiple myeloma.<sup>6</sup> Recommendations were made on the basis of expert opinion and a non-systematic literature review. Investigators stated that while multiple studies have reported improved outcomes among patients with MRD negative status, “there is no universal agreement as to which method is preferred, when the testing should be performed, and at what interval.”<sup>6</sup> Authors argued that “until prospective trials have validated its use, this technology should not be used to guide treatment decisions.”<sup>6</sup>

**POLICY SUMMARY**

Evidence is currently insufficient to support the use of minimal residual disease detection in lymphoid malignancies using next-generation sequencing (i.e. ClonoSeq). Longitudinal RCTs that concurrently compare clinical outcomes in patients managed with ClonoSeq, alternative tests and/or no tests are

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needed to support conclusions of clinical utility. To date, no such studies have been conducted and patient selection criteria have yet to be validated. NCCN guidelines support the use of MRD testing as an essential component of acute lymphoblastic leukemia (ALL) and multiple myeloma (MM). Nonetheless, authors recommended against NGS assays for the treatment of ALL and issued no clear recommendation regarding the role of NGS in MRD detection. A joint guideline from the ASCO/CCO called for prospective trials validating the efficacy and treatment parameters of NGS assays prior to its utilization in guiding treatment.

**INSTRUCTIONS FOR USE**

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

**REGULATORY STATUS**

U.S. Food and Drug Administration (FDA)

In September 2018, the FDA granted De Novo designation for the ClonoSeq® Minimal Residual Disease assay (Adaptive Biotechnologies®, Seattle, WA) in patients with multiple myeloma or acute lymphoblastic leukemia.

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

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## MEDICAL POLICY CROSS REFERENCES

### REFERENCES

1. Leukemia and Lymphoma Society. Minimal Residual Disease (MRD) - Fact Sheet. [https://www.lls.org/sites/default/files/National/USA/Pdf/Publications/FS35\\_MRD\\_Final\\_2019.pdf](https://www.lls.org/sites/default/files/National/USA/Pdf/Publications/FS35_MRD_Final_2019.pdf). Published 2019. Accessed 2/12/2020.
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3. 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;132(23):2456-2464. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6284215/>.
4. National Comprehensive Cancer Network (NCCN). Acute Lymphoblastic Leukemia - Version 1.2020. [https://www.nccn.org/professionals/physician\\_gls/pdf/all.pdf](https://www.nccn.org/professionals/physician_gls/pdf/all.pdf). Published 2020. Updated 1/15/2020. Accessed 1/16/2020.
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6. Mikhael J, Ismaila N, Cheung MC, et al. Treatment of multiple myeloma: ASCO and CCO joint clinical practice guideline. *Journal of Clinical Oncology*. 2019;37(14):1228-1263. <https://ascopubs.org/doi/pdfdirect/10.1200/JCO.18.02096>.