

Next Generation Sequencing for Minimal Residual Disease Detection

MEDICAL POLICY NUMBER: 110

Effective Date: 7/1/2025	COVERAGE CRITERIA	2
Last Review Date: 6/2024	POLICY CROSS REFERENCES.....	2
Next Annual Review: 6/2026	POLICY GUIDELINES.....	3
	REGULATORY STATUS.....	4
	CLINICAL EVIDENCE AND LITERATURE REVIEW	4
	HEALTH EQUITY CONSIDERATIONS.....	7
	BILLING GUIDELINES AND CODING	8
	REFERENCES.....	10
	POLICY REVISION HISTORY.....	11

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 Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. 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. 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. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

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

PLAN PRODUCT AND BENEFIT APPLICATION

☒ Commercial

☒ Medicaid/OHP*

☐ Medicare**

*Medicaid/OHP 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.

**Medicare Members

This Company policy may be applied to Medicare Plan members only when directed by a separate Medicare policy. Note that investigational services are considered “**not medically necessary**” for Medicare members.

COVERAGE CRITERIA

Note: This policy only addresses the use of next generation sequencing (NGS) for minimal residual disease (MRD) detection. 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 (MRD) detection using next-generation sequencing (e.g., ClonoSeq, MyMRD NGS Panel) may be considered **medically necessary** for the treatment of any of the following indications (A.-D.):
 - A. Acute lymphocytic leukemia
 - B. Acute myeloid leukemia
 - C. Chronic lymphocytic leukemia/small lymphocytic lymphoma
 - D. Multiple myeloma.
- II. Minimal residual disease detection using next-generation sequencing is considered **not medically necessary** when criterion I. above is not met, including but not limited to use in solid tumors (e.g., Signatera, Guardant Reveal).

Link to [Evidence Summary](#)

POLICY CROSS REFERENCES

- [Circulating Tumor Cell and DNA Assays for Cancer Management](#), MP122

The full Company portfolio of current Medical Policies is available online and can be [accessed here](#).

POLICY GUIDELINES

BACKGROUND

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).¹

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.¹

ClonoSeq (Adaptive Biotechnologies)

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).²

Signatera (Natera, Inc.)

Signatera is a blood-based liquid biopsy test that analyzes cell-free, circulating tumor DNA (ctDNA) using next-generation sequencing to detect 16 cancer-associated single-nucleotide variants (SNVs). The test is intended to monitor for residual disease, disease recurrence, and treatment response in patients with solid tumors.³

Guardant Reveal (Guardant Health Inc.)

Guardant Reveal is a blood-only liquid biopsy test for residual disease and recurrence monitoring for early-stage colorectal cancer.⁴ The assay purports to identify high-risk patients who are most likely to recur and may benefit most from adjuvant chemotherapy and active surveillance by detecting minimal residual disease.

MyMRD NGS Panel, (Invivoscribe)

MyMRD® is a panel that detects minimal residual disease in patients with acute myeloid leukemia, myelodysplastic syndrome, or myeloproliferative neoplasms to monitor and evaluate for refractory and relapsed disease.

Lymphoid Malignancies

Lymphoid malignancies are cancers that originate from lymphocytes. Examples include multiple myeloma, non-Hodgkin lymphoma, Hodgkin lymphoma and lymphocytic leukemias.

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

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.

A search of the FDA device database on of “minimal residual disease” and “MRD” resulted in no additional pertinent results. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high- complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use (e.g., MyMRD NGS Panel (Invivoscribe)).

Other next generation assays that purport to detect minimal residual disease include Signatera (Natera, Inc.) and Guardant Reveal (Guardant Health Inc.) assays. As of April 2023, neither has been approved by the FDA as companion diagnostics for non-solid tumor cancer therapies.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

Lymphoid Malignancies

Systematic Reviews

In 2024, 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.² As of 2022, 2 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. Was study was 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 noted that the lack of clinical utility studies rendered evidence insufficient to support claims that ClonoSeq accurately measures MRD and improves patient outcomes. Hayes concluded, "The overall body of evidence is rated as low in quality. The Rating is based solely on the published evidence, suggesting that the clonoSEQ test results are comparable with those of other MRD tests. However, substantial uncertainty remains regarding the impact of test results on health outcomes."

ClonoSEQ was given a C rating to measure minimal residual disease (MRD) to monitor changes in the burden of disease during and after treatment for clinical decision making in conjunction with other clinicopathological factors.

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.⁵ 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% 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.

Solid Tumors

- In 2023, ECRI published a genetic test assessment evaluating the clinical validity and utility of the Signatera ctDNA test for Assessing Molecular Residual Disease and Monitoring Recurrence of Colorectal Cancer.³ In total, 5 relevant clinical validity studies were identified evaluating patients with various solid tumors. Study results were limited by small sample sizes and the analysis of multiple indications. No studies assessed clinical utility. Each study acknowledged the need for additional studies to determine clinical validity and utility.⁶⁻⁹ ECRI determined that Signatera has "potential benefits but no clinical data."
- In 2020, Cullinane and colleagues published a systematic review and meta-analysis assessing the association of circulating tumor DNA with disease-free survival (DFS) in breast cancer.¹⁰ Investigators systematically searched the literature through October 2019, identified eligible

studies, assessed study quality, extracted data and pooled results. In total, 8 studies (n = 739) were included for review. The primary outcome was the association of ctDNA with DFS or relapse-free survival in breast cancer. Secondary outcomes focused on subgroup analysis in the setting of early breast cancer and metastatic breast cancer. Results indicated that ctDNA gene variation detection (both before and after treatment) was statistically significantly associated with shorter DFS (HR, 4.44; 95% CI, 2.29-8.61; P < .001). Detection of ctDNA was statistically significantly associated with a reduction in DFS in both the early breast cancer subgroup (HR, 8.32; 95% CI, 3.01-22.99; P < .001) and the metastatic or locally advanced subgroup (HR, 1.91; 95% CI, 1.35-2.71; P < .001). Pretreatment plasma detection of ctDNA was statistically significantly associated with reduced DFS (HR, 3.30; 95% CI, 1.98-5.52; P < .001). Posttreatment sampling of ctDNA failed to achieve statistical significance (HR, 8.17; 95% CI, 1.01-65.89; P = .05). Investigators concluded that elevated plasma ctDNA was associated with a high risk of relapse. This finding suggests that plasma ctDNA may help stratify risk and personalize patient follow-up. Limitations included the heterogeneity of included studies and heterogeneous techniques employed to quantify ctDNA.

- Additional systematic reviews assessing the efficacy of clinical validity and utility of ctDNA analysis for colorectal cancer patients were identified.¹¹⁻¹³ Studies reported that KRAS mutations may be considered a prognostic biomarker for colorectal cancer. Investigators called for additional, well-designed prospective studies to verify results reported to date.

CLINICAL PRACTICE GUIDELINES

National Comprehensive Cancer Network (NCCN)

- In 2025, the NCCN published guidelines (Version 3.2025) addressing Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. The guidelines state, “evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end of treatment is an important predictor of treatment efficacy... MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized ERIC method or standardized NGS method.”¹⁴
- In 2025, the NCCN published guidelines (Version 2.2025) addressing the diagnosis and management of acute myeloid leukemia in adults.¹⁵ Authors stated that MRD is a component of disease evaluation over the course of sequential therapy, and recommended MRD assessment upon completion of initial induction, before allogeneic HCT and at additional time points guided by the regimen used.
- In 2025, the NCCN published guidelines (Version 1.2025) addressing the diagnosis and management of acute lymphoblastic leukemia.¹⁶ Authors stated that NGS-based MRD tests based on quantification of immunoreceptor genes in patients with ALL is a “suitable” method for MRD quantification.¹⁶ The guideline also noted that NGS-based assays are frequently used to detect clonal rearrangements in immunoglobulin and/or T-cell receptor genes.

- In 2025, the NCCN published guidelines (version 2.2025) addressing the diagnosis and management of multiple myeloma.¹⁷ The guideline utilizes employed the International Myeloma Working Group criteria, which considers NGS a technique for MRD detection. The guidelines also recommend NGS panels on bone marrow as useful adjunct in allowing further risk categorization through the identification of additional abnormalities that may be of prognostic/or therapeutic value.
- In 2025, the NCCN published guidelines (Version 3.2025) addressing the diagnosis and management of colon cancer.¹⁸ Investigators stated that “insufficient data to recommend the use of multigene assays, Immunoscore or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy.”¹⁸

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.¹⁹ 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.”¹⁹ Authors argued that “until prospective trials have validated its use, this technology should not be used to guide treatment decisions.”¹⁹

EVIDENCE SUMMARY

There is sufficient support from the evidence base and from clinical practice guideline organizations to consider the use of next-generation sequencing for minimal residual disease detection (MRD) in certain indications as medically necessary. NCCN guidelines support the use of MRD testing as an essential component of management for patients with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL) and multiple myeloma (MM). In contrast, there are not enough large, well-designed studies that assess these tests in patients with solid tumors. These studies will need to compare outcomes between patients managed with next generation assays versus patients managed with alternative tests and/or no tests. For this reason, minimal residual disease detection using next-generation sequencing may be considered medically necessary for patients with lymphoid malignancies but not medically necessary for patients with solid tumors.

HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) defines health equity as the state in which everyone has a fair and just opportunity to attain their highest level of health. Achieving health equity requires addressing health disparities and social determinants of health. A health disparity is the occurrence of diseases at greater levels among certain population groups more than among others. Health disparities are linked to social determinants of health which are non-medical factors that influence health outcomes such as the conditions in which people are born, grow, work, live, age, and

the wider set of forces and systems shaping the conditions of daily life. Social determinants of health include unequal access to health care, lack of education, poverty, stigma, and racism.

The U.S. Department of Health and Human Services Office of Minority Health calls out unique areas where health disparities are noted based on race and ethnicity. Providence Health Plan (PHP) regularly reviews these areas of opportunity to see if any changes can be made to our medical or pharmacy policies to support our members obtaining their highest level of health. Upon review, PHP creates a Coverage Recommendation (CORE) form detailing which groups are impacted by the disparity, the research surrounding the disparity, and recommendations from professional organizations. PHP Health Equity COREs are updated regularly and can be found online [here](#).

BILLING GUIDELINES AND CODING

Clonoseq Assay (Adaptive Biotechnologies) may be considered medically necessary if billed with any of the following ICD-10 codes:

Multiple Myeloma

- C90.00 Multiple myeloma not having achieved remission
- C90.01 Multiple myeloma in remission
- C90.02 Multiple myeloma in relapse

Acute Lymphoblastic Leukemia

- C91.00 Acute lymphoblastic leukemia not having achieved remission
- C91.01 Acute lymphoblastic leukemia, in remission
- C91.02 Acute lymphoblastic leukemia, in relapse

Chronic Lymphocytic Leukemia

- C91.1 Chronic lymphocytic leukemia of B-Cell type
- C91.10 Chronic lymphocytic leukemia of B-Cell type not having achieved remission
- C91.11 Chronic lymphocytic leukemia of B-Cell type in remission
- C91.12 Chronic lymphocytic leukemia of B-Cell type in relapse

CODES*			
CPT	0171U	Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence	MyMRD NGS Panel, <i>Invivoscribe</i>
	0306U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient-	Invitae PCM Tissue Profiling and MRD Baseline Assay, <i>Invitae Corporation</i>

		specific panel for future comparisons to evaluate for MRD	
	0307U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD	Invitae PCM MRD Monitoring, <i>Invitae Corporation</i>
	0340U	Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and	Signatera, TM <i>Natera, Inc.</i>
	0364U	Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or absence of minimal residual disease (MRD) with quantitation of disease burden, when appropriate	clonoSEQ [®] Assay, <i>Adaptive Biotechnologies</i>
	0467U	Oncology (bladder), DNA, next-generation sequencing (NGS) of 60 genes and whole genome aneuploidy, urine, algorithms reported as minimal residual disease (MRD) status positive or negative and quantitative disease burden	UroAmp MRD, <i>Convergent Genomics</i>
	0470U	Oncology (oropharyngeal), detection of minimal residual disease by next-generation sequencing (NGS) based quantitative evaluation of 8 DNA targets, cell-free HPV 16 and 18 DNA from plasma	HPV-SEQ Test, <i>Sysmex Inostics</i>
	0560U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood and tumor tissue, baseline assessment for design and construction of a personalized variant panel to evaluate current MRD and for comparison to subsequent MRD assessments	Haystack MRD Baseline, <i>Quest Diagnostics</i>
	0561U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood, subsequent assessment with comparison to initial assessment to evaluate for MRD	Haystack MRD Monitoring, <i>Quest Diagnostics</i>
	0569U	Oncology (solid tumor), next-generation sequencing analysis of tumor methylation markers (>20000 differentially methylated regions) present in cell-free circulating tumor DNA (ctDNA), whole blood, algorithm reported as presence or absence of ctDNA with tumor fraction, if appropriate	Guardant Reveal, <i>Guardant Health, Inc</i>
	81479	Unlisted molecular pathology procedure	
HCPCS	None		

*Coding Notes:

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company [Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website](#) for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as “medically unlikely edits” (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
4/2023	Q2 2023 code set update
9/2023	Annual review. Changed denial type from “investigational” to “not medically necessary.” Re-formatted criteria and coding table. Added acute myeloid leukemia to list of medically necessary indications. Added relevant CPT code to coding table.
7/2024	Annual review and Q3 2024 code set update. 2 codes added, no other changes.
7/2025	Annual review. No changes to criteria. Q3 code set update. 3 codes added.