MEDICAL POLICY	Next Generation Sequencing for Minimal Residual Disease Detection (All Lines of Business Except Medicare)
Effective Date: 4/1/2022  4/1/2022 Medical Officer Date	Medical Policy Number: 110 Medical Policy Committee Approved Date: 3/2020; 5/2021; 3/2022

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. Other MRD techniques (e.g., flow cytometry, polymerase chain reaction) are not addressed in this policy and may be considered medically necessary.

Lymphoid Malignancies

I. Minimal residual disease detection in lymphoid malignancies using next-generation sequencing (i.e. ClonoSeq) may be considered **medically necessary and covered** for the treatment of acute lymphocytic leukemia or multiple myeloma.

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

Solid Tumors

III. Minimal residual disease detection in solid tumors using next-generation sequencing (e.g. Signatera, Guardant Reveal) is considered **investigational and not covered.**

Link to Policy Summary

BILLING GUIDELINES

Clonoseq Assay (Adaptive Biotechnologies) will only pay when 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

CPT/HCPCS CODES

All Lines of Business Except Medicare	
Not Covered	
0306U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient 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
Unlisted Codes 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 **prior-authorization is required.**	
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).[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.

Lymphoid Malignancies

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

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding minimal residual disease detection using next-generation sequencing. Below is a summary of the available evidence identified through March 2021.

Lymphoid Malignancies

Systematic Reviews

In 2018 (updated 2020), 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 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.[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 2020, ECRI published a genetic test assessment evaluating the clinical validity and utility of the Signatera ctDNA test for molecular residual disease assessment and recurrence monitoring of solid tumor cancers.[3] In total, 4 relevant clinical validity studies were identified evaluating patients (n=4-130) with breast, colorectal and non-small cell lung cancers. Study results were limited by small sample sizes and the analysis of multiple indications. Each study acknowledged the need for additional studies to determine clinical validity and utility.[6-9]

- 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 2020, the NCCN published guidelines (version 2.2020) addressing the diagnosis and management of acute lymphoblastic leukemia.[14] Authors stated that NGS-based MRD tests based on quantification of immunoreceptor genes in patients with ALL is a "suitable" method for MRD quantification.[14] The guideline also noted that NGS-based assays are frequently used to detect clonal rearrangements in immunoglobulin and/or T-cell receptor genes.

- In 2021, the NCCN published guidelines (version 5.2021) addressing the diagnosis and management of multiple myeloma.[15] 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 2021, the NCCN published guidelines (version 2.2021) addressing the diagnosis and management of colon cancer.[16] 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." [16]

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.[17] 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."[17] Authors argued that "until prospective trials have validated its use, this technology should not be used to guide treatment decisions."[17]

POLICY 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 lymphoid malignancies as medically necessary. NCCN guidelines support the use of MRD testing as an essential component of management for patients with acute lymphoblastic leukemia (ALL) 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. NCCN guidelines do not endorse these assays for cancers other than ALL and MM. For this reason, minimal

residual disease detection using next-generation sequencing may be considered medically necessary for patients with lymphoid malignancies but investigational for patients with solid tumors.

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.

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 2021, neither has been approved by the FDA as companion diagnostics for cancer therapies.

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. 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.

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