

Medicare Medical Policy

Next Generation Sequencing for Minimal Residual Disease Detection

MEDICARE MEDICAL POLICY NUMBER: 111

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INSTRUCTIONS FOR USE: Company Medicare Medical Policies serve as guidance for the administration of plan benefits and do not constitute medical advice nor a guarantee of coverage. Company Medicare Medical Policies are reviewed annually to guide the coverage or non-coverage decision-making process for services or procedures in accordance with member benefit contracts (otherwise known as Evidence of Coverage or EOCs) and Centers of Medicare and Medicaid Services (CMS) policies, manuals, and other CMS rules and regulations. In the absence of a CMS coverage determination or specific regulation for a requested service, item or procedure, Company policy criteria or applicable utilization management vendor criteria may be applied. These are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. 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.

The Company reserves the right to determine the application of Medicare Medical Policies and make revisions to these policies at any time. Any conflict or variance between the EOC and Company Medical Policy will be resolved in favor of the EOC.

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

PRODUCT AND BENEFIT APPLICATION

Medicare Only

MEDICARE COVERAGE CRITERIA

IMPORTANT NOTE: More than one Centers for Medicare and Medicaid Services (CMS) reference may apply to the same health care service, such as when more than one coverage policy is available (e.g., both an NCD and LCD exist). All references listed should be considered for coverage decision-making. The Company uses the most current version of a Medicare reference available at the time of publication; however, these websites are not maintained by the Company, so Medicare references and their corresponding hyperlinks may change at any time. If there is a conflict between the Company Medicare Medical Policy and CMS guidance, the CMS guidance will govern.

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 [PCR]) are not addressed in this Company medical policy, but may be included within the Medicare citations below.

Service	Medicare Guidelines
<p><i>Next Generation Sequencing (NGS) Minimal Residual Disease (MRD) Testing - General Criteria</i></p> <p><i>(e.g., ClonoSeq Assay B-Cell Reagent Set [81479], Signatera [0340U], Guardant Reveal)</i></p>	<p>General coverage criteria (for all indications):</p> <ul style="list-style-type: none"> • Local Coverage Determination (LCD) for MoIDX: Minimal Residual Disease Testing for Cancer <ul style="list-style-type: none"> ○ Testing performed in OR, WA, AK, ID, UT, AZ, MT, ND, SD, WY: L38816 ○ Testing performed in CA or NV: L38814 <p>Specific test coverage: LCDs L38816/L38814 require successful completion of a technical assessment (TA) by the Medicare Molecular Diagnostics (MoIDX) contractor. Not all commercially available tests may be medically necessary.</p>
<p>Important Note for All of the Following LCAs:</p> <ul style="list-style-type: none"> • <u>Clinical criteria:</u> The member must meet the <i>clinical</i> criteria from LCD L38816/ L38814 above (e.g., personal history of cancer, etc.). • <u>Test criteria:</u> The following LCAs list covered tests which have met the LCD <i>test</i> requirements. See “Policy Guidelines” for additional coverage information for select tests. If a test is not listed as “covered” for MRD testing within an LCA or within Table 1 in the “Policy Guidelines” of this medical policy, then the above LCD <i>test</i> requirement criteria are <u>not</u> met. 	
<p><i>NGS MRD Tests for Leukemias or Lymphoid Malignancies</i></p>	<ul style="list-style-type: none"> • LCA for Billing and Coding: MoIDX: Minimal Residual Disease Testing for Hematologic Cancers: <ul style="list-style-type: none"> ○ Testing performed in OR, WA, AK, ID, UT, AZ, MT, ND, SD, WY: A58997 ○ Testing performed in CA or NV: A58996

NGS MRD Tests for Solid Tumor Cancers

- LCAs for Billing and Coding: MoIDX: Minimal Residual Disease Testing for **Solid Tumor Cancers**:
 - Testing performed in OR, WA, AK, ID, UT, AZ, MT, ND, SD, WY: [A58456](#)
 - Testing performed in CA or NV: [A58454](#)

IMPORTANT NOTICE: While some services or items may appear medically indicated for an individual, they may also be a direct exclusion of Medicare or the member's benefit plan. Such excluded services or items by Medicare and member EOCs include, but are not limited to, services or procedures considered to be cosmetic, not medical in nature, or those considered not medically reasonable or necessary under *Title XVIII of the Social Security Act, §1862(a)(1)(A)*. If there is uncertainty regarding coverage of a service or item, please review the member EOC or submit a pre-service organization determination request. Note that the Medicare Advance Beneficiary Notice of Noncoverage (ABN) form **cannot** be used for Medicare Advantage members. (*Medicare Advance Written Notices of Non-coverage. MLN006266 May 2021*)

POLICY CROSS REFERENCES

None

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

POLICY GUIDELINES

BACKGROUND

Medicare's Molecular Diagnostic (MoIDX) Program Contractor

While many Medicare contractors (MACs) have adopted guidelines developed and published by the Molecular Diagnostic Services (MoIDX) Program for their service areas, the program is **not** national in scope. MoIDX-related reference materials only apply to genetic and molecular tests performed in the following states: OR, WA, AK, ID, UT, AZ, MT, ND, SD, WY, CA, NV, HI, NC, SC, AL, GA, TN, VA, WV, KY, OH, IA, KS, MO, NE, IN, and MI.³

The MoIDX Program was developed by Palmetto GBA in 2011. The MoIDX Contractor performs the following functions^{3,4}:

- Establish clinical utility expectations.
- Complete technical assessments of published test data to determine clinical utility and coverage of individual tests.
- Develop unique test identifiers (Z-codes), adding to the DEX™ register of molecular diagnostic tests to allow for automated claims processing and to track utilization.
- Establish reimbursement.

Genetic tests performed within a MoIDX service area are required to undergo a technical assessment (TA) review by the MoIDX Medicare Contractor, Palmetto. The LCDs in Table 1 detail this requirement:

Table 1: General MoIDX Requirements by LCD

Note: This list was accurate at the time of publication, but it is subject to change at any time by the Medicare MoIDX Program contractor.

	LOCATION/MEDICARE CONTRACTOR				
	NORIDIAN J-F OR, WA, AK, ID, UT, AZ, MT, ND, SD, and WY	NORIDIAN J-E CA and NV	PALMETTO GBA J-J AND J-M NC, SC, AL, GA, TN, VA, and WV	WPS J-5 AND J- 8 IA, KS, MO, NE, IN, and MI	CGS J-15 KY and OH
General MoIDX Requirements	L36256	L35160	L35025	L36807	L36021

The outcome of these TA reviews is maintained in the DEX™ Diagnostics Exchange registry catalog and when possible, the coverage outcome is included within this medical policy to assist with coverage decision-making.

- Tests listed as “covered” in this catalog have completed the required TA review and have been determined to be **medically reasonable or necessary** for Medicare under §1862(a)(1)(A); however, this coverage is not automatic, as both of the following must be met:
 - Applicable NCD, LCD, and LCA criteria are met; and,
 - The member has signs/symptoms of a relevant disease or condition.
- Tests listed as “not covered” in this catalog have had clinical utility and analytical validity (CU/AV) reviewed and were determined to be **not medically reasonable or necessary** for Medicare under *Social Security Act, §1862(a)(1)(A)*.
- Tests which have **not yet** completed the required TA review are by default also considered to be **not medically reasonable or necessary** for Medicare under §1862(a)(1)(A).

If a test is not specifically called out in this medical policy, additional research is required to determine coverage.

Related panel tests include those found in Table 1 below.

Note: This list was accurate at the time of publication, but it is subject to change at any time by the Medicare MoIDX Program contractor.

Table 2: Related tests

Proprietary Test Name	Laboratory	MoIDX TA Review Outcome (as found in the DEX™ Diagnostics Exchange registry)
Invitae PCM Tissue Profiling and MRD Baseline Assay (0306U)	Invitae Corporation (California)	Not Covered
Invitae PCM MRD Monitoring (0307U)	Invitae Corporation (California)	Not Covered
Signatera (0340U)	Natera Inc. (California)	Covered
Guardant Reveal	Guardant Health (California)	Not Covered
Guardant Reveal Post-Surgery Minimal Residual Disease Bundle (This bundle of tests is initiated within 3 months of curative intent treatment for patients with	Guardant Health (California)	Covered

cancer or demonstrating no evidence of disease.)		
NPM1 MRD by NGS (0049U)	LabPMM (California)	Not Covered
ClonoSeq (See notes below for more information regarding this portfolio of tests)	Adaptive Biotechnologies (Washington)	See below:
ClonoSEQ® B-Cell Set (81479)		Covered
ClonoSEQ® B-Cell Single (81479)		Not Covered
ClonoSEQ® (with no additional words in the title) (This is a T-Cell Test; 81479)		Not Covered
ClonoSEQ® when reported with 0364U		Not Covered

ClonoSEQ®

According to communication received from the MolDX Program contractor, the ClonoSEQ® test consists of two parts:

- Part 1 identifies DNA changes associated with a tumor. *This is the ClonoSEQ ID assessment.*
- Part 2 is a bundle of assays that track those changes in the tumor over time. *This is the ClonoSEQ MRD or Tracking assessment.*

There are three (3) entries related to ClonoSEQ® found in the DEX™ Exchange Registry, each with its own coverage/non-coverage determination by MolDX:

- **ClonoSEQ® B-Cell Set** is a combination of those two parts and is for patients who have cancer that are then followed throughout their treatment. *This is the FDA approved test, and thus is listed in the DEX™ Exchange Registry as **covered** (or medically necessary when criteria are met).*
- **ClonoSEQ® B-Cell Single** test is for patients who had cancer, but no longer do and are being monitored. *This is listed in the DEX™ Exchange Registry as **non-covered**.*
- **ClonoSEQ® (with no additional words in the title)** is for T-cells. *This is also listed in the DEX™ Exchange Registry as **non-covered**.*

PLA code 0364U represents both a single timepoint out of the set in a patient with cancer and a single time point in a patient without cancer. This code **does not have** a corresponding entry in the DEX™ Exchange Registry. Therefore, it is also considered to be **non-covered** because it has not completed the required technical assessment (TA) review by the MolDX Program.

REGULATORY STATUS

U.S. FOOD & DRUG ADMINISTRATION (FDA)

While clearance by the Food and Drug Administration (FDA) is a prerequisite for Medicare coverage, the 510(k) premarket clearance process does not in itself establish medical necessity. Medicare payment policy is determined by the interaction of numerous requirements, including but not limited to, the availability of a Medicare benefit category and other statutory requirements, coding and pricing guidelines, as well as national and local coverage determinations and clinical evidence.

BILLING GUIDELINES AND CODING

CODES*		
CPT	0049U	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative (<i>NPM1 MRD by NGS, by LabPMM LLC; California</i>)
	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 (<i>Invitae PCM Tissue Profiling and MRD Baseline Assay, by Invitae Corp.; California</i>)
	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 (<i>Invitae PCM MRD Monitoring, by Invitae Corp.; California</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 germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate (<i>Signatera™, by Natera Inc.; California</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 (<i>clonoSEQ® Assay, by Adaptive Biotechnologies; Washington</i>)
	81479	Unlisted molecular pathology procedure
HCPCS	None	

***Coding Notes:**

- The code list above 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. According to Medicare, "presence of a payment amount in the MPFS and the Medicare physician fee schedule database (MPFSDB) does not imply that CMS has determined that the service may be covered by Medicare." The issuance of a CPT or HCPCS code or the provision of a payment or fee amount by Medicare does **not** make a procedure medically reasonable or necessary or a covered benefit by Medicare. (*Medicare Claims Processing Manual, Chapter 23 - Fee Schedule Administration and Coding Requirements, §30 - Services Paid Under the Medicare Physician's Fee Schedule, A. Physician's Services*)
- 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.

REFERENCES

None

POLICY REVISION HISTORY

DATE	REVISION SUMMARY
10/2022	Q4 2022 code updates (converted to new format 2/2023)
4/2023	Q2 2023 code updates (added 0364U)
7/2023	Annual review; no changes to criteria, but added 0049U (NPM1 MRD by NGS, by LabPMM LLC) to the policy
12/2023	Interim update. Update coverage for ClonoSEQ tests as defined by MoIDX/Medicare