Medicare Medical Policy

Next Generation Sequencing for Minimal Residual Disease Detection

MEDICARE MEDICAL POLICY NUMBER: 111

Effective Date: 7/1/2024

Last Review Date: 6/2024

Next Annual Review: 6/2025

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
Next Generation Sequencing (NGS) Minimal Residual Disease (MRD) Testing - General Criteria *(e.g., ClonoSeq Assay B-Cell Reagent Set [81479], Signatera [0340U], Guardant Reveal)*	**General coverage criteria (for all indications):** • Local Coverage Determination (LCD) for MolDX: Minimal Residual Disease Testing for Cancer ○ Testing performed in OR, WA, AK, ID, UT, AZ, MT, ND, SD, WY: L38816 ○ Testing performed in CA or NV: L38814 **Specific test coverage:** LCDs L38816/L38814 require successful completion of a technical assessment (TA) by the Medicare Molecular Diagnostics (MolDX) contractor. **Not all commercially available tests may be medically necessary**. Table 2 provides coverage information for tests performed in MolDX service areas, indicating whether they are listed as "covered" or "not covered."
Important Notes for the above LCDs and ALL of the Following LCAs: • **TESTING FREQUENCY**: MRD testing can be used to: ○ diagnose cancer progression, recurrence, or relapse before there is clinical, biological, or radiographical evidence of any of these; **or** ○ detect tumor response to therapy by measuring the proportional changes in the amount of available tumor DNA. • ***The intended purpose of the test for a given individual AND patient's personal history together determine the appropriateness of testing frequency. This means:*** ○ For patients with cancer: This means patients are actively undergoing therapeutic interventions for the cancer in question. Billing occurs at the start of the episode of	

testing. The unit of services is 1. The service may be performed once per patient per cancer diagnosis, ***unless*** there is clinical evidence of *a priori* change in genetic content.
    - For patients without cancer: This means there is no clinical, radiographical, or other biological evidence that tumor cells remain post treatment and subsequently the patient is no longer being subjected to therapeutic interventions for cancer. For these individuals, a series of tests may be appropriate. Billing occurs at each timepoint, and the unit of service is 1 for each date of testing. The frequency of MRD testing for each unique individual must be set in accordance with national or society guidelines or recommendations, but testing **cannot exceed** more than once in a month.
- **CLINICAL CRITERIA**: The member must meet the *clinical* criteria from LCD L38816/ L38814 above. This means one of the following apply:
    - The member meets NCD 90.2 clinical criteria (has advanced cancer, plans on being treated for said cancer, **and** has not been previously treated with the same test before, etc.), or
    - NCD 90.2 doesn't apply to the member, meaning the member has a personal *history* of cancer, but no evidence of tumor cells currently remain post-treatment, and the member is not currently undergoing therapeutic interventions for cancer.
- **TEST CRITERIA**: Not all commercially-available tests will meet LCD/LCA coverage requirements. The following LCAs list covered tests which **have** met the LCD *test* 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 2 in the "Policy Guidelines" of this medical policy, then additional research will be required.**

NGS MRD Tests for Leukemias or Lymphoid Malignancies	• LCA for Billing and Coding: MolDX: Minimal Residual Disease Testing for **Hematologic Cancers**: ○ 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: MolDX: 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

Medicare Coverage Criteria: "MA organizations may create publicly accessible internal coverage criteria… when coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs." *(§ 422.101(b)(6) – see Policy Guidelines below*)

- **Medicare Coverage Manuals:** Medicare does not have criteria for the MRD test listed below in a coverage manual.
- **National Coverage Determination (NCD):** Medicare does not have an NCD for the MRD test listed below.
- **NON-Noridian J-F Local Coverage Determination (LCD)/Local Coverage Article (LCA):** Novitas Solutions is the Medicare Administrative Contractor (MAC) for the service area where the MRD test below will be performed. While Novitas considers some MRD tests to be non-covered (see LCA A58917), they do **not** have an LCD with coverage criteria for MRD testing in general.

• Therefore, in the absence of established Medicare coverage criteria in a manual, NCD, LCD, or other regulatory guidance for the health plan's service area, Company criteria below are applied for medical necessity decision-making.	
For MRD Tests Performed in Non-MolDX Services Areas *Examples Include:* *HPV-SEQ Test (CPT 0470U) (Sysmex Inostics, Inc., Maryland)*	Company medical policy for Next Generation Sequencing for Minimal Residual Disease Detection I. These services may be considered **medically necessary** for Medicare when the Company medical policy criteria are met. II. These services are considered **not medically necessary** for Medicare when the Company medical policy criteria are not met. *See Policy Guidelines below.*

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 (MolDX) Program Contractor

While many Medicare contractors (MACs) have adopted guidelines developed and published by the Molecular Diagnostic Services (MolDX) Program for their service areas, the program is **not** national in scope. MolDX-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 MolDX Program was developed by Palmetto GBA in 2011. The MolDX 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 MolDX service area are required to undergo a technical assessment (TA) review by the MolDX Medicare Contractor, Palmetto. The LCDs in Table 1 detail this requirement:

Table 1: General MolDX 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 MolDX 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 MolDX 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 MolDX Program contractor.

Table 2: Related tests

Proprietary Test Name	Laboratory	MolDX 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 cancer or demonstrating no evidence of disease.)	Guardant Health (California)	Covered
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
UroAmp MRD (0467U)	Convergent Genomics, Inc. (California)	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.

Non-MolDX Service Area Testing

Services areas which have not adopted MolDX guidelines include testing performed in the following states: FL, CO, NM, OK, TX, AR, LA, MS, DE, MD, NJ, PA, IL, MN, WI, CT, NY, ME, MA, NH, RI, and VT.

Medicare and Medical Necessity

Only medically reasonable and necessary services or items which treat illness or injury are eligible for Medicare coverage, as outlined in *Title XVIII of the Social Security Act, §1862(a)(1)(A)*. MA organizations (MAOs) make medical necessity determinations based on coverage and benefit criteria, current standards of care, the member's unique personal medical history (e.g., diagnoses, conditions, functional status, co-morbidities, etc.), physician recommendations, and clinical notes, as well as involvement of a plan medical director, where appropriate. *(§ 422.101(c)(1))*

In addition:

> "MA organizations may create publicly accessible internal coverage criteria that are based on current evidence in widely used treatment guidelines or clinical literature when coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs. Current, widely-used treatment guidelines are those developed by organizations representing clinical medical specialties, and refers to guidelines for the treatment of specific diseases or conditions. Acceptable clinical literature includes large, randomized controlled trials or prospective cohort studies with clear results, published in a peer-reviewed journal, and specifically designed to answer the relevant clinical question, or large systematic reviews or meta-analyses summarizing the literature of the specific clinical question." *(§ 422.101(b)(6) and Medicare Managed Care Manual, Ch. 4, §90.5)*

The Plan's Medicare policy for *PHA Medicare Medical Policy Development and Application* (MP50) provides details regarding Medicare's definition of medical necessity and the hierarchy of Medicare references and resources during the development of medical policies, as well as the Plan's use of evidence-based processes for policy development.

For service areas which have not adopted MolDX guidelines, their applicable LCDs (L35000, L35062 / L35396, L34519) also require that each test have established clinical utility and analytical validity (CU/AV) in order to be eligible for Medicare coverage. Due to the large number of proprietary tests marketed and available, most genetic tests are not specifically called out within an LCD or LCA, nor do LCDs or LCAs provide the outcome for the peer-reviewed CU/AV for most tests. For these service areas, the Plan uses an objective, evidenced-based process to make coverage determinations and the Company medical policy criteria is applied to tests not called out within an LCD directly. See the "Evidence Summary" from the Company Medical Policy for *Next Generation Sequencing for Minimal Residual Disease Detection* (MP110) for additional information about these tests.

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

GENERAL

PLA code 0356U represents the NavDx® test by Naveris, Inc. (Massachusetts or North Carolina). While this test does evaluate for minimal (molecular) residual disease, it does **not** use next-generation sequencing methodology, and thus, is not addressed by the scope of this policy. In addition, PLA code 0422U represents the the Guardant360 Response™ test by Guardant Health Inc., which may also be used to evaluate for MRD, but since it is a cell-free circulating DNA test, it is not addressed by the scope of this policy. Both of these tests are addressed in the Medicare medical policy for *Circulating Tumor Cell and DNA Assays for Cancer Management*.

CODES*		
CPT	0049U	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative *(NPM1 MRD by NGS, by LabPMM LLC; California)*
	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 *(Invitae PCM Tissue Profiling and MRD Baseline Assay, by Invitae Corp.; California)*
	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, by Invitae Corp.; California)*
	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 *(Signatera™, by Natera Inc.; California)*
	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, by Adaptive Biotechnologies; Washington)*
	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, by Convergent Genomics, Inc.; California)*
	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, by Sysmex Inostics, Inc.; Maryland)*
	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 MolDX/Medicare
7/2024	Annual review and Q3 2024 code updates; no changes to criteria