Medicare Medical Policy

Minimal Residual Disease Testing

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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.

Service	Medicare Guidelines

Minimal Residual Disease (MRD) Testing - General Criteria	**IMPORTANT NOTE: General MRD testing coverage criteria (for all indications) are based on the following LCDs and LCAs. Criteria for individual tests are provided in separate rows below:**
	
	• 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, as well as CA or NV: L38814
	  ○ Testing performed in AL, GA, TN, SC, VA, WV, NC: L38779
	• 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, as well as CA or NV: A58454
	  ○ Testing performed in AL, GA, TN, SC, VA, WV, NC: A58376
	• 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, as well as CA or NV: A58996
	  ○ Testing performed in AL, GA, TN, SC, VA, WV, NC: A58988

	Specific test coverage: LCDs L38814/L38779 require successful completion of a technical assessment (TA) by the Medicare Molecular Diagnostics (MolDX) contractor. **Not all commercially available tests may be considered medically necessary**. **Fully Established CMS criteria:** While the CMS guidance is fully established with regard to medical necessity criteria, it does **not** provide specific guidance regarding frequency or the use of same or similar tests that are duplicative of MRD services requested. Thus, these CMS criteria are considered "not fully established" under CFR § 422.101(6)(i)(A) as additional criteria are needed to interpret or supplement these general coverage provisions in order to determine medically appropriate testing frequencies consistently for all Plan Medicare Advantage members. The use of these additional criteria provides clinical benefits highly likely to outweigh any clinical harms, including from delayed or decreased access to items or services, because these additional criteria, based clinical practice guidelines (e.g., National Comprehensive Cancer Network [NCCN]), evaluate how test results are expected to improve diagnosis, improve patient management, change treatment decisions and improve health outcomes. Under Medicare rules, tests must meet analytical and clinical validity standards and demonstrate clinical utility to fulfill the CMS "reasonable and necessary" requirement. Tests without proven clinical utility and/or analytical validity pose risk to patients in a number of ways, which include, but may not be limited to, avoiding high false positive or false negative test results. False positives can lead to an individual undergoing additional unnecessary testing and/or an unnecessary invasive procedure, and false negatives may result in the selection of ineffective treatments, or treatment not being initiated in a timely manner. Additional negative impacts of improper or unnecessary testing may also include privacy and discrimination issues, emotional distress, and/or financial consequences.[1,2]
MRD TESTING FOR SOLID TUMOR CANCERS	
*Signatera (0340U) (Natera) – **Initial** Testing (**WITH** Active Cancer*)* ***Active cancer** is defined by L38814 as clinical, radiographical, or other biological evidence that tumor cells remain post	I. **Initial** Signatera testing for individuals **WITH** active cancer* may be considered **medically necessary** when **both** of the following (A and B) are met (based on LCD L38814 and LCA A58454): A. Testing is for the type and staging within the intended use of Signatera **and** those intended uses have met Medicare's clinical validity (CV) criteria, which are any **one** of following:

treatment and the patient is subjected to therapeutic interventions for cancer.		1. Testing for the diagnosis of disease progression, recurrence or relapse for the following **advanced cancers**: a) **Colorectal cancer** (stages II, III or IV) in the adjuvant setting[3,4]; **or** b) **Muscle-invasive bladder cancer** (MIBC) (stages II or III)[3,5]; or c) **Ovarian cancer** (stages II, III or IV) in the adjuvant setting[3,6]; **or** d) **Breast cancer** (stages IIb, III or IV) in the neoadjuvant or adjuvant setting[3,7]; **or** 2. Testing to monitor response to immune checkpoint inhibitor (ICI) therapy[3,8] for any solid tumor (may also be referred to immunotherapy or IO Monitoring) (the plan will consider testing for monitoring response to ICI therapy when **either** the member is actively receiving ICI treatment **OR** the member has received an ICI within the last 90 days[9]); **and** B. Member intends on pursuing treatment for the cancer undergoing MRD testing.
*Signatera – **Repeat** testing (**WITH** Active Cancer*)*	II.	**Repeat** Signatera testing for individuals **WITH active** cancer (as defined by L38814) may be considered **medically necessary** when the member meets **both** of the following (A and B) (based on LCD L38814 and LCA A58454):

	A. Member meets **one** of the following (1 or 2): 1. Testing for monitoring response to ICI therapy for any solid tumor type (actively receiving treatment or have received an ICI within the prior 90 days[9])[3,8]; **or** 2. The member meets both of the following (a and b) a) Testing is for the diagnosis of disease progression, recurrence or relapse for **one** of the following advanced cancers: (1) **Advanced colorectal cancer** (stages II, III or IV); **or** (2) **Muscle-invasive bladder cancer** (stages II or III)[3,5]; **or** (3) **Ovarian cancer** (stages II, III or IV) in the adjuvant setting[3,6]; **or** (4) **Breast cancer** (stages IIb, III or IV) in the neoadjuvant or adjuvant setting[3,7]; **and** b) There is clinical evidence of *a priori* change in genetic content (LCD L38814 and NCD 90.2 both allow for repeat NGS testing when clinical evidence of *a priori* change in genetic content is present, such as development of resistance to a targeted therapy); **and** B. Testing is performed within the appropriate timeframes for the applicable cancer type (See Table 2 for MRD testing schedules). **NOTE:** These criteria for repeat Signatera testing (timepoints) are based on LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (L38814) and the companion billing and coding article (A58454). These Medicare coverage policies are not considered "fully established." See "Summary and Sources of Evidence" below for a summary of clinical practice guidelines and other references used in supplemental criteria.
*Signatera – **Initial** testing (**WITHOUT** Active Cancer*)*	III. **Initial** Signatera testing for individuals **WITHOUT** active cancer* may be considered **medically necessary** when **both** of the following (A and B) are met (based on LCD L38814 and LCA A58454): A. Member meets **one** of the following (1 or 2):

*According to LCD L38814, an individual is considered "without active cancer" when "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."	1. Any solid tumor when testing is for monitoring response to ICI therapy (actively receiving treatment or have received an ICI within the prior 90 days[9])[3,8]; **or** 2. For other surveillance testing (diagnosis of disease progression, recurrence, or relapse), the member has **one** of the following: a) **Advanced colorectal cancer** (stages II, III or IV)[3,4,10]; or b) **Muscle-invasive bladder cancer** (stages II or III)[3,4]; or c) **Non-small cell lung cancer (NSCLC)** (any stage)[3,11]; or d) **Ovarian, fallopian tube or primary peritoneal cancer** (stages II, III or IV); **or** e) **Breast cancer** (stages IIb, III or IV) (includes those with a personal history of advanced breast cancer and/or those on long-term endocrine prophylaxis)[3,7]; f) personal history of **non-small cell lung cancer** (NSCLC); **and** B. Testing is performed within the appropriate timeframes for the applicable cancer type (See Table 2 for MRD testing schedules). **NOTE:** These criteria for repeat Signatera testing (timepoints) are based on LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (L38814) and the companion billing and coding article (A58454). These Medicare coverage policies are not considered "fully established." See "Summary and Sources of Evidence" below for a summary of clinical practice guidelines and other references used in supplemental criteria.
*Signatera – **Repeat** testing (**WITHOUT** Active Cancer*)*	IV. **Repeat** Signatera testing for individuals **WITHOUT** active cancer (i.e., there is no clinical, radiographical, or other biological evidence that tumor cells remain post treatment and the patient is no longer being subjected to therapeutic interventions for cancer") may be considered **medically necessary** when the member meets **all** of the following (based on LCD L38814 and LCA A58454):

	A. Member meets **one** of the following (1 or 2): 1. Any solid tumor when testing is for monitoring response to ICI therapy (actively receiving treatment or have received an ICI within the prior 90 days[9])[3,8]; **or** 2. For other surveillance testing (diagnosis of disease progression, recurrence, or relapse), the member has **one** of the following: a) **Colorectal cancer** (stages II, III or IV)[3,4,10]; **or** b) **Muscle-invasive bladder cancer** (stages II or III)[3,5]; or c) **NSCLC** (any stage)[3,11]; or d) **Ovarian, fallopian tube or primary peritoneal cancer** (stages II, III or IV); **or** e) **Breast cancer** (stages IIb, III or IV) (includes those with a personal history of advanced breast cancer and/or those on long-term endocrine prophylaxis)[3,7]; **and** B. Testing is performed within the appropriate timeframes for the applicable cancer type (See Table 2 for MRD testing schedules). **NOTE:** These criteria for repeat Signatera testing (timepoints) are based on LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (L38814) and the companion billing and coding article (A58454). These Medicare coverage policies are not considered "fully established." See "Summary and Sources of Evidence" below for a summary of clinical practice guidelines and other references used in supplemental criteria.
NavDx (0356U) (Naveris Inc.)	V. **NavDx** may be considered **medically necessary** when monitoring for recurrence of *HPV-driven* (aka HPV-positive or HPV-associated) *oropharyngeal cancers* **and** *anal squamous cell cancers* when testing is performed within appropriate timeframes for the applicable cancer type (See Table 2 for MRD testing schedules)[12,13]: VI. **NavDx** for *HPV-driven oropharyngeal or anal squamous cell cancers* is considered **not medically necessary** when testing frequencies are exceeded. According to LCD L38779 and LCA A58376,

	testing schedules are set based on the validity established of the individual test for the given indication/cancer type. VII. According to LCA A58454, **NavDx** does **not** have established clinical utility for other intended uses. Therefore, NavDx is considered **not medically necessary** for *other cancer types*. **NOTE:** Naveris has two primary laboratory locations – Massachusetts and North Carolina. To ensure consistent coverage determinations, these criteria for NavDx testing are based on the Palmetto GBA LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (L38779) and the companion billing and coding article (A58376). These Medicare coverage policies are not considered "fully established." See "Summary and Sources of Evidence" below for a summary of clinical practice guidelines and other references used in supplemental criteria.
*Guardant360 Response (0422U) (Guardant Health) (**WITH** Active Cancer)* ***Active cancer** is defined by L38814 as clinical, radiographical, or other biological evidence that tumor cells remain post treatment and the patient is subjected to therapeutic interventions for cancer. *According to the DEX Registry, this test is intended to be used to assess patient response to therapy by measuring the change in ctDNA levels between a pre-treatment Guardant360 or Guardant360 CDx and a single*	VIII. **Guardant360 Response** may be considered **medically necessary** when both of the following are met (based on LCD L38814 and LCA A58454): A. CRC for monitoring of response to ICI therapy (received an ICI within the prior 90 days[9])[3,8]; **and** B. Testing initiated between 4 – 10 weeks after treatment initiation with immunotherapy[14]. **NOTE:** These criteria for Guardant Response testing are based on LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (~~L38816~~ L38814) and the companion billing and coding article (~~A58456~~ A58454).

post-therapy Guardant360 Response time point.	
*Guardant Reveal (0569U) CRC Post-Surgery MRD Bundle** (Guardant Health) (**WITH** Active Cancer)* ***According to the DEX REgistry, the Guardant Reveal CRC Post-Surgery MRD Bundle is a set of 3 Guardant Reveal single plasma tests which must be initiated within 3 months of surgical curative intent. This is a different test from the Guardant Reveal Advanced Cancer Therapy Monitoring Bundle, which is listed as "Not covered" in the DEX Registry.*	IX. The **Guardant Reveal** CRC Post-Surgery MRD bundle assay may be considered **medically necessary** when both of the following are met (based on LCD L38814 and LCA A58454): A. Patient has active cancer; **and** B. **One** of the following (1 or 2): 1. CRC for monitoring of response to ICI therapy (received an ICI within the prior 90 days[9])[3,8]; **or** 2. CRC (stages II, III or IV) in the adjuvant setting; **and** C. Testing is performed once per individual per cancer diagnosis. **NOTE:** These criteria for Guardant Reveal testing are based on LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (L38814) and the companion billing and coding article (A58454).
*Guardant Reveal (0569U) single timepoint plasma test (**WITHOUT** Active Cancer)* *According to LCD L38814, an individual is considered "without active cancer" when "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	X. The **Guardant Reveal** single plasma test for individuals **WITHOUT** active cancer (i.e., there is no clinical, radiographical, or other biological evidence that tumor cells remain post treatment and the patient is no longer being subjected to therapeutic interventions for cancer") may be considered **medically necessary** when **both** of the following (A **and** B) are met (based on LCD L38814 and LCA A58454): A. **One** of the following (1 or 2): 1. Personal history of CRC for monitoring of response to ICI therapy (received an ICI within the prior 90 days[9])[3,8]; **or** 2. Personal history of CRC (stages II, III or IV) with no evidence of active cancer; **and** B. Testing is performed within the appropriate timeframes (See Table 2).

therapeutic interventions for cancer."	**NOTE:** These criteria for Guardant Reveal testing are based on LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (L38814) and the companion billing and coding article (A58454).
*RaDaR (NeoGenomics Laboratories, Inc) (**WITH** Active Cancer*)* ***Active cancer** is defined by L38814 as clinical, radiographical, or other biological evidence that tumor cells remain post treatment and the patient is subjected to therapeutic interventions for cancer.	XI. **RaDaR** may be considered **medically necessary** for individuals for **either** of the following conditions: A. Active *HPV-negative head and neck squamous cell carcinoma* (HNSCC) (based on LCD L38814 and LCA A58454)[15;] **or** B. Advanced breast cancer (stages II, III or IV). XII. According to LCA A58454, **RaDaR** does **not** have established clinical utility for other intended uses for individuals with active cancer. Therefore, RaDaR is considered **not medically necessary** for *other cancer types*. **NOTE:** These criteria for RaDaR testing are based on LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (L38814) and the companion billing and coding article (A58454).
*RaDaR (**WITHOUT** Active Cancer)* *According to LCD L38814, an individual is considered "without active cancer" when "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."	XIII. **RaDaR** may be considered **medically necessary** for individuals **without** active *HPV-negative head and neck squamous cell carcinoma* (HNSCC) when all of the following are met (based on LCD L38814 and LCA A58454)[15]. A. Testing is performed within the appropriate timeframes (See Table 2)[14,16-20]; **and** B. Personal history of cancer with no evidence of active cancer; **and** C. One of the following: 1. Personal history of HR positive, HER2 negative advanced (stage II or III) breast cancer[21]; **or** 2. Personal history of locally advanced HPV-negative H&N SCC[15]. **NOTE:** These criteria for RaDaR testing are based on LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (L38814) and the companion billing and coding article (A58454).

*Oncodetect (Exact Sciences) – **Initial** Testing (**WITH** Active Cancer*)* *__Active cancer__ is defined by L38814 as clinical, radiographical, or other biological evidence that tumor cells remain post treatment and the patient is subjected to therapeutic interventions for cancer.	XIV. The **Oncodetect** testing **bundle** may be considered **medically necessary** for initial testing of individuals **with** active advanced colorectal cancer to aid in the diagnosis of disease progression, recurrence, or relapse (based on LCD L38814 and LCA A58454). **NOTE:** These criteria for initial Oncodetect testing are based on LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (~~L38816~~ L38814) and the companion billing and coding article (~~A58456~~ A58454), and are directed at the Oncodetect Bespoke Assay Design + Plasma Test **Bundle**.
*Oncodetect – **Repeat or Subsequent** Testing (**WITH** Active Cancer)*	XV. **Repeat** Oncodetect testing for individuals **WITH active** cancer (as defined by L38814) may be considered **medically necessary** when the member meets **both** of the following (A **and** B) (based on LCD L38814 and LCA A58454): A. Member has advanced colorectal cancer (stages II, III or IV); **and** B. There is clinical evidence of *a priori* change in genetic content (LCD L38814 and NCD 90.2 both allow for repeat NGS testing when clinical evidence of a priori change in genetic content is present, such as development of resistance to a targeted therapy). **NOTE:** These criteria for initial Oncodetect testing are based on LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (L38814) and the companion billing and coding article (A58454), and are directed at the Oncodetect Plasma Test **Bundle**.
*Oncodetect – **Initial** Testing (**WITHOUT** Active Cancer)* *According to LCD L38814, an individual is considered "without active cancer" when "there is no clinical, radiographical, or other biological evidence that tumor	XVI. **Initial Oncodetect** testing may be considered **medically necessary** for individuals **without** active advanced colorectal cancer (stages II, III or IV) to aid in the diagnosis of disease progression, recurrence, or relapse (based on LCD L38814 and LCA A58454). **NOTE:** These criteria for initial Oncodetect testing are based on LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (~~L38816~~ L38814) and the companion billing and coding article (~~A58456~~ A58454), and are directed at the Oncodetect Bespoke Assay Design + **single** Plasma Test.

cells remain post treatment and subsequently the patient is no longer being subjected to therapeutic interventions for cancer."	
*Oncodetect – **Repeat** Testing (**WITHOUT** Active Cancer)*	XVII. **Repeat** Oncodetect testing for individuals **WITHOUT** active cancer (i.e., there is no clinical, radiographical, or other biological evidence that tumor cells remain post treatment and the patient is no longer being subjected to therapeutic interventions for cancer") may be considered **medically necessary** when the member meets **all** of the following (based on LCD L38814 and LCA A54554): A. Member has a personal history of advanced colorectal cancer (stages II, III or IV)[4]; **and** B. Testing is performed within the appropriate timeframes for the applicable cancer type (See Table 2 for MRD testing schedules). **NOTE:** These criteria for repeat or subsequent Oncodetect testing are based on LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (L38814) and the companion billing and coding article (A58454), and are directed at the Oncodetect **single** Plasma Test.
*Pathlight Recurrence Monitoring Bespoke Assay Design + single Plasma Test (SAGA Diagnostics [North Carolina]) – **Initial** Testing (**WITHOUT** Active Cancer)* *According to LCD L38779, an individual is considered "without active cancer" when "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	XVIII. **Initial** MRD testing with **Pathlight Recurrence Monitoring Bespoke Assay** may be considered **medically necessary** for individuals **with a personal history of** (meaning *not active*) advanced breast cancer (stages II, III or IV) to aid in the diagnosis of disease progression, recurrence, or relapse (based on LCD L38779 and LCA A58376). **NOTE:** These criteria for initial Pathlight Recurrence Monitoring Bespoke Assay Design + single Plasma testing are based on the LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (L38779) and the companion billing and coding article (A58376), and are directed at the Pathlight Recurrence Monitoring Bespoke Assay Design + single Plasma test. According to the DEX® Diagnostics Exchange Registry, this test may also be referred to as "Pathlight **Fingerprint**."

therapeutic interventions for cancer."	
*NeXT Personal MRD Testing – Initial Testing (Personalis, Inc. [California]) – **Initial** Testing (**WITHOUT** Active Cancer)* *Includes:* • *NeXT Personal DX Breast MRD Recurrence Monitoring Test: WGS Assay Design + Plasma Initial Test* • *NeXT Personal NSCLC: WGS Assay Design + Plasma Initial Test* *According to LCD L38814, an individual is considered "without active cancer" when "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."	XIX. **Initial** MRD testing with the **NeXT Personal Breast MRD** test may be considered **medically necessary** for individuals **with a personal history of** (meaning *not active*) advanced breast cancer (stages II, III or IV) to aid in the diagnosis of disease progression, recurrence, or relapse (based on LCD L38814 and LCA A58454). XX. **Initial** MRD testing with the **NeXT Personal NSCLC MRD** test may be considered **medically necessary** for individuals **with a personal history** (meaning *not active*) of non-small cell lung cancer (NSCLC) to aid in the diagnosis of disease progression, recurrence, or relapse (based on LCD L38814 and LCA A58454). **NOTE:** These criteria for initial NeXT Personal Breast ***or*** NSCLC MRD testing are based on the LCD for *MolDX: Minimal Residual Disease Testing for Cancer* (L38814) and the companion billing and coding article (A58454).

NeXT Personal Single Plasma Test (Personalis, Inc. [California]) ***OR*** *Pathlight Recurrence Monitoring Single Plasma Test (SAGA Diagnostics; [North Carolina])* – ***REPEAT** Testing (**WITHOUT** Active Cancer*)*	XXI.	**Repeat** MRD testing with either NeXT Personal MRD or Pathlight Recurrence Monitoring for individuals **WITHOUT** active cancer (i.e., there is no clinical, radiographical, or other biological evidence that tumor cells remain post treatment and the patient is no longer being subjected to therapeutic interventions for cancer") may be considered **medically necessary** when the member meets **all** of the following (based on LCD L38814 and LCA A58454): A. Member has a **personal history** of one of the following (1 or 2): 1. advanced breast cancer (stages II, III or IV)[4]; **or** 2. NSCLC; **and** B. Testing is performed within the appropriate timeframes for the applicable cancer type (See Table 2 for MRD testing schedules). **NOTE:** These criteria for repeat or subsequent testing using either NeXT Personal MRD or Pathlight Recurrence Monitoring are based on respective jurisdictional LCDs for *MolDX: Minimal Residual Disease Testing for Cancer* (L38814 and L38779) and their respective companion billing and coding articles (A58454 and A58376), and are directed at the NeXT Personal **Single** Plasma test and Pathlight Recurrence Monitoring **Single** Plasma test. According to the DEX® Diagnostics Exchange Registry, this test may also be referred to as "Pathlight **Monitor**."

*Not Covered MRD Tests - **Solid Tumor Cancers***	XXII.	The above solid tumor cancer MRD tests (i.e., Signatera, NavDx, Guardant360 Response, Guardant Reveal, or RaDaR) are considered **not medically necessary** when the applicable LCD ~~L38816~~ L38814 and LCA A58454 test criteria are not met.
(Limited to MolDX service areas only – for non-MolDX service areas [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], see below)	XXIII.	Other solid tumor cancer MRD tests which do not meet MRD LCD and LCA criteria for solid tumor cancers[22-31] are also considered **not medically necessary**. Specifically, these tests do not have FDA approval or clearance, nor have they completed a technical assessment (TA) by the MolDX Program contractor to evaluate that analytical validity, clinical validity, and clinical utility criteria are met to establish coverage under Medicare. Non-covered tests include, but are not limited to, the following: A. Guardant Reveal Advanced Cancer Therapy Monitoring Bundle (Guardant Health) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry. B. Haystack MRD™ Baseline (0560U) (Quest Diagnostics) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry. C. Haystack MRD™ Monitoring (0561U) (Quest Diagnostics) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry. D. Invitae Personalized Cancer Monitoring (PCM) Tissue Profiling and MRD Baseline Assay (0306U) (Invitae Corp.; California) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry. E. Invitae Personalized Cancer Monitoring (PCM) MRD Monitoring (0307U) (Invitae Corp.; California) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry. F. UroAmp MRD (0467U) (Convergent Genomics, Inc.; California) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry. G. PredicineBEACON Baseline (0641U) and PredicineBEACON MRD (0642U) (Predicine, Inc.; California) - Tests are not FDA approved or cleared, **and** neither test has successfully completed the MolDX technical assessment requirement. H. Plasma Detect Genome MRD – Baseline (0646U) and Plasma Detect Genome MRD – Monitoring (0647U) (LabCorp; North Carolina) – Tests are not FDA approved or cleared, **and** both are listed as "not covered" in MolDX® DEX® Registry.

MRD TESTING FOR HEMATOLOGIC CANCERS		
*ClonoSeq Assay B-Cell **Set** (81479) (Adaptive Biotechnologies; Washington) (**WITH** Active Cancer)*	XXIV.	ClonoSeq® testing for individuals **WITH** active cancer (as defined by L38814) may be considered **medically necessary** when **all** of the following are met (based on L38814 and A58996): A. Patient has a diagnosis of **one** of the following: 1. Acute lymphoblastic leukemia (ALL); **or** 2. Multiple myeloma (MM); **or** 3. Chronic lymphocytic leukemia (CLL); **or** 4. Diffuse Large B-Cell Lymphoma (DLBCL); **or** 5. Mantle Cell Lymphoma; **and** B. Patient intends on being treated for said cancer or is currently being treated; **and** C. Either: 1. The patient has not been previously tested with the same test; **or** 2. There is clinical evidence of *a priori* change in genetic content (e.g., development of resistance to a targeted therapy).
*ClonoSeq B-Cell **Single** Assay (0364U) (Adaptive Biotechnologies; Washington) (**WITHOUT** active cancer)* *According to LCD L38814, an individual is considered "without active cancer" when "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	XXV.	ClonoSeq® testing for individuals **WITHOUT** active cancer may be considered **medically necessary** when all of the following are met (based on L38814 and A58996): A. Patient has a personal history of **one** of the following (see LCA A58997 for ICD-10 codes): 1. Acute lymphoblastic leukemia (ALL); **or** 2. Multiple myeloma (MM); **or** 3. Chronic lymphocytic leukemia (CLL); **or** 4. Diffuse Large B-Cell Lymphoma (DLBCL); **or** 5. Mantle Cell Lymphoma.

therapeutic interventions for cancer."		
Not Covered MRD Tests - ***Hematologic Cancers***	XXVI.	The above hematologic cancer MRD test (ClonoSeq) is considered **not medically necessary** when the applicable LCD L38814 and LCA A58996 test criteria are not met.
(Limited to MolDX service areas only – for non-MolDX service areas [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], see below)	XXVII.	The following hematologic cancer MRD tests do **not** meet MRD LCD and LCA criteria for hematologic cancers[22-26,32-36]. Specifically, these tests do not have FDA approval or clearance, nor have they completed a technical assessment (TA) by the MolDX Program contractor to evaluate that analytical validity, clinical validity, and clinical utility criteria are met to establish coverage under Medicare. Therefore, the following tests are considered **not medically necessary**: A. NPM1 MRD Assay by NGS (0049U) (Laboratory for Personalized Molecular Medicine, or LabPMM LLC; California) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry. B. MyMRD® NGS Panel test (0171U) (Laboratory for Personalized Molecular Medicine, or LabPMM LLC; California) - Test is not FDA approved or cleared, **and** has not been reviewed and approved by the MolDX® Program. C. FusionMRD™ Baseline (0644U) and FusionMRD™ Monitoring (0645U) (Pairidex®; Missouri) - Tests are not FDA approved or cleared, **and** neither test has successfully completed the MolDX technical assessment requirement.

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 certain MRD tests to be non-covered (see LCA A58917), they do **not** have an LCD with general 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.
- ***NOTE:*** *The summary of evidence, as well as the list of citations/references used in the development of the Company's internal coverage criteria, are publicly available and can be found using the Company medical policy link below [CFR § 422.101(6)(ii)(A) and (B)].*

MRD Tests Performed in Non-MolDX Service Areas (FL, CO, NM, OK, TX, AR, LA, MS, DE, MD, NJ, PA, IL, MN, WI, CT, NY, ME, MA, NH, RI, and VT) *Examples Include:* *HPV-SEQ Test (CPT 0470U) (Sysmex Inostics, Inc., Maryland)*	XXVIII. Company medical policy for Next Generation Sequencing for Minimal Residual Disease Detection A. These services may be considered **medically necessary** for Medicare when the Company medical policy criteria are met. B. 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.[37]

The MolDX Program was developed by Palmetto GBA in 2011. The MolDX Contractor performs the following functions[37,38]:

- 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	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.

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, or Clonoality (ID) test. This provides a one-time baseline summary that identifies the dominant DNA sequences related specifically to an individual's specific cancer.*
- Part 2 is a bundle of assays that track those changes in the tumor over time. *This is the ClonoSEQ MRD or Tracking assessment. Once dominant cancer DNA sequence(s) are identified, the patient is tested periodically to monitor the cancer using these Tracking (MRD) Reports.*

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 test is reported with 0364U and it 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 test completed the required technical assessment review, and may now be covered when LCD criteria are met as of 1/29/2025.

- **ClonoSEQ® (with no additional words in the title)** is for T-cells. *This is also listed in the DEX™ Exchange Registry as **non-covered***.

Signatera

The Signatera test also consists of two components:

- Part 1 – **Tumor tissue** testing: This component identifies the DNA fingerprint associated with a specific tumor, personalized to an individual member, obtained via comprehensive genomic profile (CGP) assay and an initial plasma test to obtain a baseline.
- Part 2 – Periodic **plasma** testing: This component consists of a series of assays that either:
    - Track changes in the tumor over time (aka, **response to therapy**) ***or***
    - Identify molecular **recurrence or progression** before there is clinical, biological, or radiographical evidence of recurrence or progression (aka, surveillance purposes).

RaDaR

According to the MolDX DEX Registry:

- The **RaDaR Breast 1 Plasma Recurrence** test (aka, RaDaR Breast Personalized MRD Plasma Test) is used in patients who previously were diagnosed with breast cancer but presently **do not** have evidence of active disease. It involves one plasma test (post development of the personalized assay).
- The **RaDaR HNSCC Initial Residual** test (aka, RaDaR MRD Whole Exome Design & Personalized MRD Plasma Test) is used in patients who previously were diagnosed with head and neck squamous cell carcinoma but presently **do not** have evidence of active disease. As a "bundle," it involves development of the personalized assay **and** one plasma test (meaning these **cannot** be billed individually).
- The **RaDaR HNSCC Subsequent Residual** test (aka, RaDaR HNSCC Personalized MRD Plasma Test) is used in patients who previously were diagnosed with head and neck squamous cell carcinoma but presently **do not** have evidence of active disease. It involves This test involves one plasma test (post development of the personalized assay) and is limited to up to six times per year.
- The **RaDaR HNSCC Initial & Subseq Bundle Residual** test (aka, RaDaR MRD Whole Exome Design & Personalized MRD Plasma Test Bundle) is used in patients who **have** head and neck squamous cell carcinoma and have not completed therapy. It involves development of the personalized assay and up to six plasma tests (meaning these cannot be billed individually).

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.

SUMMARY AND SOURCES OF EVIDENCE

BACKGROUND

This policy is based on several LCDs and LCAs, which read as follows:

> "MRD testing often requires 2 types of assays to be performed as part of the service. First, a sample is taken from tumor diagnostic material to establish a baseline (solid and/or liquid) tumor signature as defined by the test methodology. This is followed by a series of assays run on a minimally invasive specimen (i.e., liquid biopsy or bone marrow aspirate) to detect the presence or recurrence of tumor, based on the measured biomarkers, expression, or other analytes over various timepoints. Other approaches are also acceptable, based on the validity

established for the individual test comprising the service. This series of assays comprises a single test when the patient is known to have cancer.

"When the patient is NOT known to have cancer (specifically when 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), a second kind of test may exist wherein a single timepoint may constitute a single test. In such patients, the frequency of MRD testing is in accordance with national or society guidelines or recommendations."

Therefore, Medicare criteria state that in some clinical situations, these services are intended to be performed as serial assays, but should only be billed one time.

However, Medicare criteria provided in these LCDs and LCAs are not considered "fully established," as specific testing frequencies or testing schedules are not provided, and the timeline of MRD testing in connection with the provision ICI therapy is also not addressed. Therefore, the Plan uses additional, evidence-based guidelines to supplement the Medicare coverage policies and support coverage decisions regarding testing schedules and ICI therapy.

SUMMARY OF EVIDENCE

Testing Schedules

Medicare coverage policies for MRD testing state testing schedules are to be set in accordance with national or society guidelines or recommendations, and are based on the validity established for a test, for the given indication/cancer type, **not** to exceed more than once in a month (30-day period).

However, these criteria are not considered "fully established," as specific testing frequencies or testing schedules are not provided. Therefore, the Plan uses additional criteria to supplement the LCD and LCA to ensure consistent coverage decisions. Table 2 below provides the testing schedule used by the Plan for different cancer types.

Table 2: MRD Testing Schedule

Cancer Type	Testing Schedule
Colorectal[39-41]	• Years 1 and 2: every 3-6 months • Years 3-5: every 6 months
Breast[40,42,43]	• Years 1-5: every 3-12 months • Year 5 and beyond: annually
Head/Neck[44]	• Year 1: every 1-3 months • Year 2: every 2-6 months • Years 3-5: every 4-8 months • Year 5 and beyond: annually
Non-Small Cell Lung[40,45,46]	• Years 1-3: every 3-6 months • Years 4 and 5: every 6-12 months
Bladder[47]	*(See Appendix I for non-muscle invasive bladder cancer risk stratification)*

	Low risk: • Year 1: at 3 and 12 months • Years 2-5: annually **Intermediate risk:** • Year 1: at 3, 6 and 12 months • Year 2: every 6 months • Years 3-5: annually **High risk:** • Years 1 and 2: every 3 months • Years 3-5: every 6 months • Years 5-10: annually
Ovarian[48]	• Years 1-2: every 2-4 months • Years 3 and 4: every 3-6 months • Year 5 and beyond: annually
Fallopian Tube[48]	
Peritoneal (Primary)[48]	
Anal Cancer[49]	• Years 1-3: every 6-12 months

Colon/Colorectal Cancer

NCCN guidelines do **not** currently recommend ctDNA testing for surveillance of colon cancer.[41] However, since Medicare allows MRD testing using plasma/blood samples under Medicare policy, the plan will apply similar testing frequencies noted for other surveillance procedures.

While the American Cancer Society (ACS) doesn't specifically call out MRD testing, they do recommend serial blood tests for tumor markers, such as carcinoembryonic antigen (CES) testing, at a frequency of every 3 to 6 months for the first couple of years after treatment, then every 6 months or so for the next few years.[39]

Note that NCCN guidelines do **not** recommend routine CES monitoring beyond 5 years.[41]

Breast Cancer

Surveillance and follow-up for breast cancer includes physical exams and breast imaging. NCCN and ASC guidelines do **not** currently recommend blood tests as part of standard follow-up for most women who've been treated for breast cancer.[42,43] However, since Medicare allows MRD testing using plasma/blood samples under Medicare policy, the plan will apply testing frequencies noted for other surveillance procedures.

For invasive breast cancer, NCCN guidelines recommend history and physical examination 1-4 times per year as deemed clinically appropriate by the treating physician for the first 5 years, then annually after that. For ductal carcinoma in situ (DCIS), NCCI guidelines recommend history and examination every 6-

12 months for the first 5 years, then annually after that. For both breast cancers, NCCN recommends the first mammogram 6-12 months after breast-conserving therapy (BCT).[43]

Head and Neck Cancers

HPV-driven oropharyngeal cancers are a type of cancer of the back of the throat, including the tonsils and base of the tongue. They are caused by high-risk types of the human papillomavirus (HPV), most commonly HPV-16. This type of cancer is a distinct disease from oropharyngeal cancer caused by tobacco and alcohol.

According to NCCN guidelines for head and neck cancers, "The majority of recurrences after treatment of head and neck cancer occur in the first 2 years. Surveillance can be challenging because of altered anatomy and/or fibrosis from surgery, radiation, and/or chemotherapy. There are no consensus guidelines on the frequency and modality of routine post-treatment imaging in the asymptomatic patient. Practice varies widely across institutions." In addition, NCCN guidelines do **not** currently include blood tests in the follow-up recommendations for head and neck cancers. However, since Medicare allows this testing under Medicare policy, the plan will apply the same frequencies found in NCCN "Follow-up Recommendations" for head and neck cancers to MRD tests.[44]

NCCN follow-up recommendations for head and neck cancers include history and physical examination every 1-3 months for the first year, then every 2-6 months for year 2, and every 4-8 months for years 3-5. Beyond 5 years, follow-up exams are recommended every 12 months.[44]

Non-Small Cell Lung Cancer (NSCLC)

Surveillance and follow-up for non-small cell lung cancer (NSCLC) includes physical examinations and imaging, such as chest computed tomography (CT).[46] NCCN and American Society of Clinical Oncology (ASCO) guidelines do **not** currently recommend circulating biomarkers as part of a surveillance strategy for detection of recurrence.[45,46] However, since Medicare allows MRD testing under Medicare policy, the plan will apply testing frequencies noted for other surveillance services.

NCCN guidelines recommend history and physical examination every 3-6 months for the first 3 years, then every 6 months for the following 2 years.[46]

Bladder Cancer

NCCN guidelines do not currently include blood tests in the follow-up plans for low-risk, intermediate risk, or high-risk bladder cancer. However, since Medicare allows this testing under Medicare policy, the plan will apply the same frequencies for other follow-up services to MRD testing.[47]

Ovarian, Peritoneal, and Fallopian Tube Cancers

NCCN guidelines also recommend physical exams and tumor marker testing as part of the surveillance strategy for individuals with ovarian, peritoneal or fallopian tube cancers. While NCCN guidelines do not specifically call out MRD testing, they do recommend tumor marker testing, such as CA-125 (additional tumor markers may be indicated if CA-125 is initially elevated). Examination is recommended at a

frequency of every 2 to 2 months for the first 2 years after treatment, then every 3-6 months for years 3 and 4, then annually after that.[48]

Anal Cancer

Surveillance and follow-up for anal cancer includes periodic digital rectal exam (DRE), node palpation, and anoscopy. NCCN guidelines do **not** currently recommend circulating biomarkers as part of a surveillance strategy for detection of recurrence. However, since Medicare allows this testing under Medicare policy, the plan will apply the same frequencies for other follow-up services to MRD testing.[49]

NCCN guidelines recommend DRE and inguinal node palpation every 3-6 months for the first 5 years, and anoscopy every 6-12 months for the first 3 years. Since DRE and inguinal node palpation are non-invasive and can be performed quickly during a physical examination, the guidelines for anoscopy are used for MRD testing.

ICI Therapy

By using a 90-day benchmark, the Plan is consistent with pharmacokinetic evidence[9] that suggests ICI activity may persist for up to 60 days following administration. Most ICI drugs have a *half*-life of three to four weeks, meaning *full*-life is approximately 45-60 days. An extra 30-day window is recognized by the Plan to provide additional allowance for individual patient response to ICI therapy and clinical practice variances.

Future Coverage Determinations

It should be noted the MolDX LCDs currently provide coverage of MRD testing, however, they acknowledge limited evidence to support coverage. These LCDs state, "…this coverage decision is based heavily on paradigm for care which was not developed for MRD testing" and "we anticipate future revisions to this coverage decision as the science and standard of care evolves, which may further limit or expand coverage for MRD testing." Therefore, it is possible that Medicare coverage of MRD testing may expand to additional indications, or end altogether.

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.

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 further 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.

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 any cancer (solid tumor or non-solid tumor) therapies.

In August 2025, the FDA granted Breakthrough Device Designation for the Quest Diagnostics Haystack MRD® test for identifying MRD-positive patients with stage II colorectal cancer following curative-intent surgical treatment who may benefit from adjuvant therapy in accordance with therapeutic product labeling. Haystack MRD is used in multiple clinical trials and research studies.

BILLING GUIDELINES AND CODING

GENERAL

Medicare rules say that providers must report services correctly. Providers must report services with the appropriate CPT code and follow Medicare billing guidelines and instructions.

According to the MRD LCAs[27-36], "For patients with cancer, the unit of service for this type of test is 1. Billing should occur at the start of the episode of testing. Regarding the use of NGS-based MRD tests (i.e., ClonoSeq®) in patients with cancer– The service may be performed once per patient per cancer diagnosis, unless there is clinical evidence of *a priori* change in genetic content."

According to these LCAs, typically the term "service" refers to an **entire testing series**, which is by definition going to include multiple timepoints, or tests performed at periodic intervals. Individual timepoint tests may be ordered by the treating physician, but they would be considered part of the test "series." Therefore, while the test itself can be performed and test results provided to the ordering physician, the laboratory is unable to obtain separate reimbursement for it because it is part of the billing that occurred at the start of the episode of testing.

It is possible the Plan may "deny" a claim or prior authorization request for a test that is intended to be included as part of a testing series, even though the test may be clinically indicated and appropriate to perform. In these situations, the Plan is **not** denying ongoing MRD testing, or stating additional timepoints should not be performed or are not clinically appropriate. Rather, the Plan is simply abiding by the published Medicare policy and billing article regarding the expected billing cadence for **payment**.

Note that provider contract language and payment methodology may vary from the LCD and LCA billing and coding instruction.

CODES*		
CPT	0049U	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative *(NPM1 MRD by NGS, by LabPMM LLC; California)*

	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 *(Used to report the MyMRD® NGS Panel test, by the Laboratory for Personalized Molecular Medicine)*
	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 *(Single timepoint of Signatera™ plasma testing for individuals without cancer, as defined by the Noridian LCA, by Natera Inc.; California)*
	0356U	Oncology (oropharyngeal or anal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence *(NavDx®, by Naveris, Inc.; Massachusetts or North Carolina)*
	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® B-Cell Single Assay, by Adaptive Biotechnologies; Washington)*
	0422U	Oncology (pan-solid tumor), analysis of DNA biomarker response to anti-cancer therapy using cell-free circulating DNA, biomarker comparison to a previous baseline pre-treatment cell-free circulating DNA analysis using next-generation sequencing, algorithm reported as a quantitative change from baseline, including specific alterations, if appropriate *(Guardant360 Response™, by Guardant Health, Inc.; 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)*
	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, by Quest Diagnostics)*
	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, by Quest Diagnostics)*

	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™, by Guardant Health; California)*
	0641U	Oncology (minimal residual disease [MRD]), tumor DNA, next-generation sequencing (NGS), using formalin-fixed paraffin-embedded (FFPE) tissue and blood samples, initial (baseline) assessment *(PredicineBEACON Baseline, by Predicine, Inc.; California)*
	0642U	Oncology (minimal residual disease [MRD]), tumor DNA, next-generation sequencing (NGS), whole blood, comparison to previously performed analyses, reported as trend in circulating tumor DNA (ctDNA) level *(PredicineBEACON MRD, by Predicine, Inc.; California)*
	0644U	Oncology (leukemia), minimal residual disease (MRD) detection for rearrangements, blood or bone marrow, personalized assay design and baseline quantification *(FusionMRD™ Baseline, by Pairidex®; Missouri)*
	0645U	Oncology (leukemia), minimal residual disease (MRD) detection for rearrangements, based on digital PCR, blood or bone marrow, reported as not detected or detected with estimated abundance *(FusionMRD™ Monitoring, by Pairidex®; Missouri)*
	0646U	Oncology (molecular residual disease), whole genome sequence analysis, cell-free DNA, whole blood, and formalin-fixed paraffin-embedded (FFPE) tumor tissue DNA, baseline assessment *(Plasma Detect Genome MRD – Baseline, by LabCorp.; North Carolina)*
	0647U	Oncology (molecular residual disease), whole genome sequence analysis, cell-free DNA (cfDNA), whole blood, assessment utilizing patient specific tumor information, reported as negative or percent circulating tumor DNA (ctDNA) *(Plasma Detect Genome MRD – Monitoring, by LabCorp.; North Carolina)*
	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

1. MedlinePlus. What are the risks and limitations of genetic testing. 28 Jul 2021. https://medlineplus.gov/genetics/understanding/testing/riskslimitations/. Accessed 5/20/2026.
2. Testing.com. Genetic testing: benefits, risks and the future. 1 Nov 2023. https://www.testing.com/genetic-testing-benefits-risks-and-future/. Accessed 5/20/2026.
3. Natera, Inc. Signatera indications. https://natera.com. Published 2025.
4. Reinert T, Henriksen TV, Christensen E, et al. Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. *JAMA Oncol.* 2019;5(8):1124-1131.
5. Christensen E, Birkenkamp-Demtroder K, Sethi H, et al. Early detection of metastatic relapse and monitoring of therapeutic efficacy by ultra-deep sequencing of plasma cell-free DNA in patients with urothelial bladder carcinoma. *J Clin Oncol.* 2019;37(18):1547-1557.
6. Hou J, Chapman J, Kalashnikova E, et al. Circulating tumor DNA monitoring for early recurrence detection in epithelial ovarian cancer. *Gynecol Oncol.* 2022;167(2):334-341.
7. Coombes RC, Page K, Salari R, et al. Personalized detection of circulation tumor DNA antedates breast cancer metastatic recurrence. *Clin Cancer Res.* 2019;25(14):4255-4263.
8. Kasi PM, Chakrabarti S, Sawyer S, et al. BESPOKE IO protocol: a multicentre, prospective observational study evaluating the utility of ctDNA in guiding immunotherapy in patients with advanced solid tumours. *BMJ Open.* 2022;12(5):e060342.
9. Liu JC, Y HJ. A review of the pharmacokinetic characteristics of immune checkpoint inhibitors and their clinical impact factors. *Pharmgenomics Pers Med.* 2023:16:29-36.
10. Social Security Administration (SSA). Exclusions from coverage and Medicare as a secondary payer §1395y. https://ssa.gov. Updated April 9, 2025.
11. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature.* 2017;545(7655):446-451.
12. Berger BM, Hanna GJ, Posner MR, et al. Detection of occult recurrent using circulating tumor tissue modified viral HPV DNA among patients treated for HPV-drive oropharyngeal carcinoma. *Clin Cancer Res.* 2022;28(19):4292-4301.
13. Hanna GJ, Roof SA, Jabalee J, et al. Negative predictive value of circulating tumor tissue modified viral (TTMV)-HPV DNA for HPV-driven oropharyngeal cancer surveillance. *Clin Cancer Res.* 2023;29(20):4306-4313.
14. Guardant Health, Inc. Guardant360 Response. https://guardantcomplete.com. Published 2025.
15. Sanz-Garcia E, Xou J, Avery L, et al. Multimodal detection of molecular residual disease in high-risk locally advanced squamous cell carcinoma of the head and neck. *Cell Death Differ.* 2024;31(4):460-468.
16. American Cancer Society (ACS). After colorectal cancer treatment. https://cancer.org. Updated April 29, 2025.
17. American Cancer Society (ACS). Living as a breast cancer survivor. https://cancer.org. Updated January 5, 2022.
18. American Society of Clinical Oncology (ASCO). Lung cancer surveillance after definitive curative-intent therapy: ASCO guideline. https://asco.org. Published December 12, 2019.
19. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Breast cancer. https://nccn.org. Updated May 8, 2026.
20. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Head and neck cancers. https://nccn.org. Updated May 12, 2026.
21. NeoGenomics Inc. Press Release. NeoGenomics announces Medicare coverage for RaDaR Assay for minimal residual disease and recurrence in breast cancer. https://neogenomics.com. Published July 27, 2023.

22. Noridian J-E. Local Coverage Determination (LCD). MolDX: Minimal Residual Disease Testing for Cancer (L38814). Accessed 5/20/2026.
23. Noridian J-F. Local Coverage Determination (LCD). MolDX: Minimal Residual Disease Testing for Cancer (L38816). Accessed 5/20/2026.
24. CGS. Local Coverage Determination (LCD). MolDX: Minimal Residual Disease Testing for Cancer (L38822). Accessed 5/20/2026.
25. Palmetto GBA. Local Coverage Determination (LCD). MolDX: Minimal Residual Disease Testing for Cancer (L38779). Accessed 5/20/2026.
26. Wisconsin Physician Services (WPS). Local Coverage Determination (LCD). MolDX: Minimal Residual Disease Testing for Cancer (L38835). Accessed 5/20/2026.
27. Noridian J-E. Local Coverage Article (LCA). Billing and Coding: MolDX: Minimal Residual Disease Testing for Solid Tumor Cancers (A58454). Accessed 5/20/2026.
28. Noridian J-F. Local Coverage Article (LCA). Billing and Coding: MolDX: Minimal Residual Disease Testing for Solid Tumor Cancers (A58456). Accessed 5/20/2026.
29. CGS. Local Coverage Article (LCA). Billing and Coding: MolDX: Minimal Residual Disease Testing for Solid Tumor Cancers (A58434). Accessed 5/20/2026.
30. Palmetto GBA. Local Coverage Article (LCA). Billing and Coding: MolDX: Minimal Residual Disease Testing for Solid Tumor Cancers (A58376). Accessed 5/20/2026.
31. WPS. Local Coverage Article (LCA). Billing and Coding: MolDX: Minimal Residual Disease Testing for Solid Tumor Cancers (A58468). Accessed 5/20/2026.
32. Noridian J-E. Local Coverage Article (LCA). Billing and Coding: MolDX: Minimal Residual Disease Testing for Hematologic Cancers (A58996). Accessed 5/20/2026.
33. Noridian J-F. Local Coverage Article (LCA). Billing and Coding: MolDX: Minimal Residual Disease Testing for Hematologic Cancers (A58997). Accessed 5/20/2026.
34. CGS. Local Coverage Article (LCA). Billing and Coding: MolDX: Minimal Residual Disease Testing for Hematologic Cancers (A58998). Accessed 5/20/2026.
35. Palmetto GBA. Local Coverage Article (LCA). Billing and Coding: MolDX: Minimal Residual Disease Testing for Hematologic Cancers (A58988). Accessed 5/20/2026.
36. WPS. Local Coverage Article (LCA). Billing and Coding: MolDX: Minimal Residual Disease Testing for Hematologic Cancers (A59004). Accessed 5/20/2026.
37. Palmetto GBA MolDX Manual. Updated Sept. 2025. https://dominoapps.palmettogba.com/palmetto/providers.nsf/Files/MolDX_Manual.pdf/$FILE/MolDX_Manual.pdf. Accessed 5/20/2026.
38. Noridian Healthcare Solutions (Noridian). Molecular Diagnostic Services. Updated July 2025. https://med.noridianmedicare.com/. Accessed 5/20/2026.
39. American Cancer Society (ACS). Living as a Colorectal Cancer Survivor. 2025. https://www.cancer.org/cancer/types/colon-rectal-cancer/after-treatment/living.html. Accessed 5/20/2026.
40. Guardant Health, Inc. Guardant360 Response. https://guardantcomplete.com. Published 2025.
41. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Colon cancer. https://nccn.org. Accessed 5/20/2026.
42. American Cancer Society (ACS). Follow-up Care After Breast Cancer Treatment. 2025. https://www.cancer.org/cancer/types/breast-cancer/living-as-a-breast-cancer-survivor/follow-up-care-after-breast-cancer-treatment.html. Accessed 5/20/2026.
43. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. https://nccn.org. Accessed 5/20/2026.
44. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Head and neck cancers. https://nccn.org. Accessed 5/20/2026.

45. American Society of Clinical Oncology (ASCO). Lung cancer surveillance after definitive curative-intent therapy: ASCO guideline. https://asco.org. Accessed 5/20/2026.
46. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. https://nccn.org. Accessed 5/20/2026.
47. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Bladder cancer. https://nccn.org. Accessed 5/20/2026.
48. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer. https://nccn.org. Accessed 5/20/2026.
49. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Anal Carcinoma. https://nccn.org. Accessed 5/20/2026.

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
3/2025	Interim update. Update coverage status of Guardant Reveal Single Plasma test from “not covered” to “covered”
7/2025	Q3 2025 code updates
8/2025	Interim update. Update coverage for clonoSEQ B-Cell Single test
2/2026	Interim update. Title change, update format, add additional covered MRD tests, as well as MRD testing schedules. (2/14/2026: Replaced multiple MolDX LCDs and LCAs due to Noridian JF consolidation with JE LCD policies)
3/2026	Interim update; clarify Signatera criteria for surveillance testing and add criteria for NavDx and anal cancers
7/2026	Annual review; update coverage for NeXT Personal MRD tests

APPENDICES

Tables provided to assist with coverage determinations and decision-making.

Appendix I: Non-Muscle Invasive Bladder Cancer Risk Stratification[47]

Risk Level	Characteristics
Low	• Papillary urothelial neoplasm of low malignant potential • Low grade urothelial carcinoma o Ta; AND o Less than or equal to 3 cm; AND o Solitary
Intermediate	• Low grade urothelial carcinoma o T1; OR

	o Greater than 3 cm; OR o Multifocal; OR o Recurrence within 1 year • High grade urothelial carcinoma o Ta; AND o Less than or equal to 3 cm; AND o Solitary
High	• High grade urothelial carcinoma o CIS; OR o T1; OR o Greater than 3 cm; OR o Multifocal • Very high risk features (any): o BCG unresponsive o Certain histopathologic subtypes *(Aggressive subtype histologies: micropapillary, plasmacytoid, small cell/neuroendocrine and sarcomatoid histologies (in pure or mixed form with associated urothelial carcinoma)* o Lymphovascular invasion o Prostatic urethral invasion