Medicare Medical Policy

Genetic Testing: Gene Expression Profile Testing for Breast Cancer

MEDICARE MEDICAL POLICY NUMBER: 48

Effective Date: 5/1/2023

Last Review Date: 4/2023

Next Annual Review: 4/2024

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, Providence Plan Partners, and Ayin Health Solutions 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	Code(s)	Medicare Guidelines
BluePrint (Agendia®; California)	CPT 81479	Local Coverage Articles (LCA): MolDX: BluePrint® Coding and Billing Guidelines (A55115)
Breast Cancer Index (BCI) (bioTheranostics, Inc.; California)	CPT 81518	Local Coverage Determination (LCD): MolDX: Breast Cancer Index℠ Genetic Assay (L37822)
EndoPredict (Myriad®; Utah)	CPT 81522	LCD: MolDX: EndoPredict® Breast Cancer Gene Expression Test (L37311)
MammaPrint or MammaPrint – NGS (Agendia®; California)	CPT 81521, 81523	LCA: MolDX: MammaPrint Coding and Billing Guidelines (A54445)
Oncotype DX Breast (Genomic Health Inc.; California)	CPT 81519	LCA: MolDX: Oncotype DX® Breast Cancer Assay Billing and Coding Guidelines (A54480)
Oncotype DCIS (Genomic Health Inc.; California)	CPT 0045U	LCD: MolDX - Oncotype DX® Breast Cancer for DCIS (Genomic Health™) (L36941)
Prosigna (PAM50) (NanoString Technologies Inc.; Washington)	CPT 81520	LCD: MolDX: Breast Cancer Assay: Prosigna (L36386)
• *DCISionRT® (Prelude Corp., California) (0295U)* • *TargetPrint® (Agendia®; California)* • *BreastOncPx™ (LabCorp; headquartered in North Carolina)* • *BreastPRS™ (Signal Genetics; California)*	Varies	These tests are considered **not medically necessary**, based on Medicare guidelines. *See "Policy Guidelines" below.*

• *Mammostrat® (Clarient Diagnostic Services; California)* • *Insight TNBCtype (Insight Molecular Labs; Tennessee) (0153U)*		
• *Molecular Grade Index (AviaraDx, Inc.)* • *Theralink® Reverse Phase Protein Array (RPPA) (Theralink® Technologies, Inc.) (Code 0249U)*	Varies	Company medical policy for Genetic Testing: Gene Expression Profile Testing for Breast Cancer I. These tests are considered **not medically necessary** for Medicare Plan members based on the Company medical policy. *"Investigational" services are considered not medically necessary for Medicare Plan members. 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

MEDICARE AND MEDICAL NECESSITY

General

In order for a laboratory test to be considered for coverage, Medicare requires the test in question meet all of the following:

- Not be excluded from coverage by statute, regulation, National Coverage Determination, (NCD), or Local Coverage Determination (LCD);
- Be ordered by a physician or practitioner who is treating the beneficiary;
- Provide data that will be directly used in the management of a beneficiary's specific medical problem;
- Be considered medically reasonable and necessary, as required per the Social Security Act, §1862(a)(1)(A).

In addition to the test being medically appropriate for the condition, this also includes performing the services at an appropriate frequency, in accordance with accepted standards of medical practice for the condition.

Medicare Molecular Diagnostics (MolDX) Program

Laboratories performing tests in service areas which have adopted guidelines or coverage determinations made by the Medicare Molecular Diagnostics (MolDX) Program contractor are required to submit a technology assessment (TA) to establish analytical and clinical validity (AV/CV) and clinical utility (CU). Supporting LCDs regarding TA reviews include, but are not limited to, the following:

- Laboratories in CA & NV: LCD for MolDX: Molecular Diagnostic Tests (MDT) (L35160)
- Laboratories in NC, SC, GA, TN, AL, VA, & WV: LCD for MolDX: Molecular Diagnostic Tests (MDT) (L35025)
- Laboratories in AK, ID, OR, WA, UT, AZ, MT, ND, SD, & WY: LCD for MolDX: Molecular Diagnostic Tests (MDT) (L36256)

Coverage or non-coverage determinations made by MolDX are maintained in the DEX™ Diagnostics Exchange registry catalog and are available for public viewing. If a test does not have a coverage determination by the MolDX Program, then AV/CV and CU have **not** been established and the test is considered not medically reasonable and necessary under *SSA §1862(a)(1)(A)* until a MolDX review is complete and coverage is indicated by MolDX or Noridian. Therefore, tests identified in this policy as not meeting this requirement are not medically reasonable or necessary for Medicare under *SSA §1862(a)(1)(A).*

Table 1: Tests relevant to this policy include the following

*This list only applies to tests which do **not** have an LCD or LCA specific to that individual test in the Medicare guideline table above. This list was accurate at the time of publication, but it is subject to change at any time by the Medicare MolDX Program contractor. A "MolDX TA Review Outcome" of "Covered" does not indicate the test is automatically covered. All relevant criteria from the above Medicare references as applicable to the individual test must still be met.*

Proprietary Test Name	Laboratory	MolDX TA Review Outcome (as found in the DEX™ Diagnostics Exchange registry)
DCISionRT® (CPT 0295U)	Prelude Corp. (California)	Not covered
TargetPrint®	Agendia® (California)	Not covered
BreastOncPx™	LabCorp (headquartered in North Carolina)	Not covered
BreastPRS™	Signal Genetics (California)	Not covered
Mammostrat®	Clarient Diagnostic Services (California)	Not covered
Insight TNBCtype (0153U)	Insight Molecular Labs (Tennessee)	Not covered

Summary

Many Medicare contractors (MACs) have adopted guidelines developed and published by the Molecular Diagnostic Services (MolDX) Program for their service area. As called out within relevant LCDs for these service areas (L36256, L35160, L35025, L36807, L36021), genetic and molecular tests performed within a MolDX service area are required to undergo a technical assessment (TA) review by the MolDX Medicare Contractor, Palmetto GBA. These TA reviews assess clinical utility and analytical validity (CU/AV) to ensure the tests meets requirements for Medicare coverage. The outcome of these TA reviews is maintained in the DEX™ Diagnostics Exchange registry catalog. When possible, the coverage outcome is included within this medical policy to assist with coverage decision-making.

- Tests listed as "not covered" in this registry have had the CU/AV reviewed and were determined to be not medically reasonable or necessary for Medicare under *Social Security Act, §1862(a)(1)(A).*
- Tests not listed at all 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), based on the requirements found in the LCDs noted above.
- Tests listed as "covered" in this registry have completed the required TA review and have been determined to be potentially medically reasonable or necessary for Medicare under *§1862(a)(1)(A)*; however, applicable NCD, LCD, and LCA criteria must still be met, and the member must have signs/symptoms of a relevant disease or condition.

Non-MolDX Service Areas and Coverage in the Absence of a Specific Medicare Policy Guideline

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.

LCDs and LCAs for each of the above service areas require clinical utility and analytical validity to be established, but most tests are not called out by name specifically. Additionally, for multi-biomarker panel test, each requested biomarker needs to be individually contributory to the member's treatment. In the absence of specific guidance in these LCDs, the PHP Company policies for genetic tests provide a peer review of medical literature to evaluate clinical utility/analytical validity. When the biomarkers included in a test do not have proven clinical validity/utility, the test is not medically reasonable or necessary under Social Security Act, §1862(a)(1)(A) for Medicare members.

The Company 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. In the absence of Medicare coverage policies (e.g., manual, national coverage determination [NCD], local coverage determination [LCD], article [LCA], etc.), Medicare regulatory guidelines do allow Medicare Advantage Organizations (MAOs) to make their own coverage determinations, as long as the MAO applies an objective, evidence-based process, based on authoritative evidence. *(Medicare Managed Care Manual, Ch. 4, §90.5)*

Following an evidence-based assessment of current peer-reviewed medical literature, the Company may consider certain medical services or technologies to be "investigational." The term "investigational" is not limited to devices or technologies which have not received the appropriate governmental regulatory approval (e.g., U.S. Food and Drug Administration [FDA]), but rather may also mean the procedure,

device, or technology does not meet all of the Company's technology assessment criteria, as detailed within the Company policy for *Definition: Experimental/Investigational* (MP5).

For Medicare, 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)*. Thus, services which lack scientific evidence regarding safety and efficacy because they are investigational are "not medically reasonable or necessary" for Medicare Plan members. *(Medicare Claims Processing Manual, Ch. 23, §30 A)*

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

See associated local coverage articles (LCAs) for additional coding and billing guidance:

- LCA for Coding Article for MolDX: Breast Cancer Index™ (BCI) Gene Expression Test (A56335)
- LCA for Billing and Coding: MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™) (A57620)
- LCA for Billing and Coding: MolDX: Breast Cancer Assay: Prosigna (A57364)
- LCA for Billing and Coding: MolDX: EndoPredict® Breast Cancer Gene Expression Test (A57608)

FREQUENCY

Testing must be performed at an appropriate frequency, as determined by the above Medicare references, as well as established clinical edits (e.g., National Correct Coding Initiative [NCCI] edits) which may be in place.

CODES*		
CPT	0045U	Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score *(Used to report the Oncotype DCIS test)*
	0153U	Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement *(Used to report the Insight TNBCtype, by Insight Molecular Labs; Tennessee)*

	0249U	Oncology (breast), semiquantitative analysis of 32 phosphoproteins and protein analytes, includes laser capture microdissection, with algorithmic analysis and interpretative report *(Used to report the Theralink® Reverse Phase Protein Array (RPPA) test)*
	0295U	Oncology (breast ductal carcinoma in situ), protein expression profiling by immunohistochemistry of 7 proteins (COX2, FOXA1, HER2, Ki-67, p16, PR, SIAH2), with 4 clinicopathologic factors (size, age, margin status, palpability), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a recurrence risk score *(Used to report the DCISionRT® test)*
	81479	Unlisted molecular pathology procedure
	81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy *(Used to report the Breast Cancer Index (BCI) test)*
	81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score *(Used to report the Oncotype DX Breast test)*
	81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score *(Used to report the Prosigna (PAM50) test)*
	81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis *(Used to report the MammaPrint test)*
	81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score *(Used to report the EndoPredict test)*
	81523	Oncology (breast), mRNA, next-generation sequencing gene expression profiling of 70 content genes and 31 housekeeping genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk to distant metastasis *(Used to report the MammaPrint test if performed by next generation sequencing [NGS])*
	81599	Unlisted multi-analyte with algorithmic analysis
	84999	Unlisted chemistry 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)
5/2023	Annual review; added 0153U