Genetic and Molecular Testing for Inherited Cancer Risk

MEDICARE MEDICAL POLICY NUMBER: 443

Effective Date: 9/1/2025

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Next Annual Review: 8/2026

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.

Notes:

- **The list of genetic tests addressed in this policy is not all-inclusive.**
- **In compliance with Medicare guidelines, some LCDs and LCAs used may be for service areas outside of the Company's primary service area, based on where the performing laboratory is located.**
- Other Plan Medicare Medical Policies may be available for specific tests or indications. See Cross References section for medical policies which may apply to specific conditions. *If a test is not found in this policy, see separate genetic testing policies to confirm coverage resources are not provided in another location.*
- Due to the rapidly changing field of genetic testing, panel names, genes included, and coding may change subsequent to the last update of this policy.
- CMS guidance is also subject to change at any time. Therefore, while lists of covered or non-covered tests were accurate at the time of publication, they are subject to change at any time by a Medicare contractor.

Medical Policy Quick Links

- Criteria III: Known Familial Variant (KFV) Analysis
- Criteria IV-VI: Non-Covered Testing

- Policy Guidelines
  - Table 2 – Medicare Contractors and Jurisdictions
- Clinical Practice Guidelines
- CPT and HCPCS Codes

MEDICARE COVERAGE POLICIES USED TO DEVELOP CRITERIA

IMPORTANT: The Medicare coverage policies found in **Table 1**, in addition to Medicare coverage manuals and statutory regulations, were used in the development of this Medicare medical policy and criteria.

Table 1: Medicare Coverage Policies

MAC	JURISDICTION	COVERAGE POLICIES
NCDs	National (all service areas)	• NCD for Next Generation Sequencing (NGS) (90.2)
Noridian J-F	AK, ID, OR, WA, UT, AZ, MT, ND, SD, and WY	• LCD for MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer (L38974) and LCA (A58681) • LCA for Billing and Coding: MolDX: Germline testing for use of PARP inhibitors (A55295) • LCD for MolDX: Repeat Germline Testing (L38353) • LCD for MolDX: Molecular Diagnostic Tests (MDT) (L36256)
Noridian J-E	CA, HI, NV	• LCD for MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer (L38972) and LCA (A58679) • LCA for Billing and Coding: MolDX: Germline testing for use of PARP inhibitors (A55294) • LCD for MolDX: Repeat Germline Testing (L38351) • LCD for MolDX: Molecular Diagnostic Tests (MDT) (L35160)
Palmetto J-J, J-M	VA, WV, NC, SC, GA, TN, and AL	• LCD for MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer (L38966) and LCA (A58652) • LCA for Billing and Coding: MolDX: Germline testing for use of PARP inhibitors (A54338) • LCD for MolDX: Repeat Germline Testing (L38274)

		• LCD for MolDX: Molecular Diagnostic Tests (MDT) (L35025)
CGS J-15	KY and OH	• LCD for MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer (L39017) and LCA (A58734) • LCD for Billing and Coding: MolDX: Germline testing for use of PARP inhibitors (A54689) • LCD for MolDX: Repeat Germline Testing (L38288) • LCD for MolDX: Molecular Diagnostic Tests (MDT) (L36021)
WPS J-5, J-8	IA, KS, MO, NE, IN, and MI	• LCD for MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer (L39040) and LCA (A58756) • LCD for Billing and Coding: MolDX: Germline testing for use of PARP inhibitors (A55224) • LCD for MolDX: Repeat Germline Testing (L38429) • LCD for MolDX: Molecular Diagnostic Tests (MDT) (L36807)
NGS J-6, J-K	IL, MN, WI, CT, NY, ME, MA, NH, RI, and VT	• LCD for Molecular Pathology Procedures (L35000) • LCA for Billing and Coding: Molecular Pathology Procedures (A56199) The LCD L35000 requires clinical utility and analytical validity be established, but it doesn't address all tests by name specifically. For panels, this LCD also states, "testing would be covered ONLY for the number of genes or test that are reasonable and necessary to obtain necessary information for therapeutic decision making." In the absence of specific guidance in these LCDs, the Plan will make coverage decisions using the criteria in this policy. This may include non-coverage of panel tests which include biomarkers that do not have proven clinical validity/utility.
Novitas J-H, J-L	CO, NM, OK, TX, AR, LA, MS, DE, MD, NJ, PA and DC	• LCD for Biomarkers for Oncology (L35396) • LCD for Biomarkers Overview (L35062) • LCD for BRCA1 and BRCA2 Genetic Testing (L36715) The LCD L35062 requires clinical utility and analytical validity be established, but it doesn't address all tests by name specifically. Additionally, for multi-biomarker panel test, the LCD L35396 requires evidence to support how "each requested biomarker can be individually contributory." In the absence of specific guidance in these LCDs, the Plan will make coverage decisions using the criteria in this policy. This may include non-coverage of panel tests which include biomarkers that do not have proven clinical validity/utility.

First Coast J-N	FL	• LCD for Molecular Pathology Procedures (L34519) • LCA for Billing and Coding: Molecular Pathology and Genetic Testing (A58918) • LCD for BRCA1 and BRCA2 Genetic Testing (L36499) The LCD L34519 requires tests to undergo evaluation to establish clinical utility and analytical validity, based on published peer reviewed medical literature, or be FDA-approved, in order to be eligible for coverage. However, it doesn't address all tests by name specifically. For panels, this LCD also states, "testing would be covered ONLY for the number of genes or test that are reasonable and necessary to establish a diagnosis." In the absence of specific guidance in these LCDs, the Plan will make coverage decisions using the criteria in this policy. This may include non-coverage of panel tests which include biomarkers that do not have proven clinical validity/utility.

IMPORTANT – PLEASE READ BEFORE APPLYING COVERAGE CRITERIA BELOW

A large number of Commercial-available molecular diagnostic tests (MDT) or laboratory developed tests (LDT) are subject to LCD guidelines. Such Medicare coverage policies are noted in Table 1 above and should be referenced whenever possible. However, NCD 90.2 and the available LCDs **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 medical necessity consistently for all Plan Medicare Advantage members**. These coverage policies do not provide specific coverage guidance for clinical indications or risk factors of hereditary cancer. In addition, these coverage policies do not provide guidance for many hereditary cancer types or National Comprehensive Cancer Network (NCCN) recommendations, nor do they provide specific criteria around when many tests may be considered reasonable and necessary. Therefore, if a determination cannot be made based on available CMS guidance noted in Table 1 because such criteria are not fully established, **the Plan may use the following to interpret or supplement available Medicare NCDs and LCDs criteria to establish medical necessity**.

*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 are based on peer-reviewed evidence and clinical practice guidelines (e.g., National Comprehensive Cancer Network [NCCN]), and they evaluate how testing is 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, due to 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]

General Coverage Criteria

When a determination cannot be made based solely on CMS guidance (see Table 1) because the criteria are not fully established (i.e., the test is not called out specifically by name within the NCD or LCD, relevant NCCN guidelines are not provided, etc.), the following criteria are used.

I. Medicare Advantage plans must follow Medicare rules for coverage of medically necessary services. Medicare rules and regulations can be found in multiple references, including the national coverage determination (NCD) 90.2 and local coverage determinations (LCDs) L38974, L38972, L38966, L39017, L39040, L35000, L35396, L35062, L36715, L34519, and L36499, representing all service areas and jurisdictions. According to Medicare coverage policy guidelines, genetic **multigene panel** testing for **hereditary cancer syndromes** may be considered **medically necessary** when **all** of the following criteria are met (A-C):

A. The test has been **ordered by a treating qualified healthcare provider** (e.g., the provider who furnishes a consultation or treats a member for a specific medical problem) and documentation in the medical record supports how the ordering provider plans to promptly use the test results to manage that condition for the member[3,4]; **and**

B. The **patient** meets **all** of the following (1-4)[5-16]:
1. Has a cancer diagnosis or personal history of cancer; **and**
2. Has **both** a clinical indication* **and** a risk factor† for hereditary cancer as determined by National Comprehensive Cancer Network (NCCN) guidelines *(clinical indications and risk factors vary by cancer type. Examples include early age diagnosis, multiple affected generations, clinical features indicative of a hereditary cancer, multiple cancer types in a single individual, multiple blood relatives on same side of family with same or similar types of cancer, etc. The list below can be used to find clinical indications and risk factors for some cancer types, but is **not** an all-inclusive list):*
   i. Hereditary Breast, Ovarian, Pancreatic, or Prostate Cancers
   ii. Colorectal, Endometrial and Gastric Cancers

* Clinical indication = sign, symptom, lab test result, medical condition, or a combination of these indications, that leads to the recommendation of a treatment, laboratory test, or procedure for a hereditary disease or condition. (Source: 2020 Decision Memo for NCD 90.2)
† Risk factor = variable associated with an increased risk of a disease, such as age, sex, or family history of disease. (Source: 2020 Decision Memo for NCD 90.2)

3. Has **not** been previously tested with the same germline genetic content *(if the member **has** been previously tested with the same germline content, see Criterion IV below).*
4. Has no known pathogenic or likely pathogenic (P/LP) variant in the family *(if a P/LP variant **has** been detected in an affected family member, see Criterion III below)*; **and**

C. The **test** meets analytical and clinical validity standards and demonstrates clinical utility at a level that meets Medicare medically reasonable and necessary requirements, as determined by **one** of the following (1 or 2)[‡]:

1. MolDX Program approved technical assessment, as determined by viewing the DEX Diagnostics Exchange Registry *(a **publicly available database** of genetic and molecular tests which have been evaluated by the MolDX Program Contractor, with their respective coverage outcomes).*[17,18] *As of the most recent policy review, the following tests **meet** this requirement. This is **not** an all-inclusive list*; **or**
   i. **BRCAplus (0129U)** (Ambry Genetics; California)
   ii. **BRCAplus-Expanded** (Ambry Genetics; California)
   iii. **CancerNext** (Ambry Genetics; California)
   iv. **CancerNext 37 +RNAInsight™** (Ambry Genetics; California)
   v. **CancerNext 37 DNA Only** (Ambry Genetics; California)
   vi. **CancerNext-Expanded** (Ambry Genetics; California)
   vii. **CancerNext-Expanded +RNAinsight™** (Ambry Genetics; California)
   viii. **CancerNext +RNAinsight™** (Ambry Genetics; California)
   ix. **ColoNext** (Ambry Genetics; California)
   x. **ColoNext +RNAinsight™** (Ambry Genetics; California)
   xi. **CustomNext-Cancer Panel (aka CN-Cancer Panel)** (Ambry Genetics: California)
   xii. **Riskguard™ Hereditary Cancer Test** (Exact Sciences)
   xiii. **Invitae Common Hereditary Cancers Panel** (LabCorp; California)
   xiv. **Invitae Common Hereditary Cancers + RNA Panel** (LabCorp; California)
   xv. **Invitae Hereditary Breast Cancer STAT Panel** (LabCorp; California)
   xvi. **Invitae Hereditary Nervous System/Brain Cancer** (LabCorp; California)
   xvii. **Invitae Hereditary Thyroid Cancer Panel** (LabCorp; California)
   xviii. **Invitae Lynch Syndrome Panel** (LabCorp; California)
   xix. **Invitae Multi-Cancer Panel** (LabCorp; California)
   xx. **Invitae Multi-Cancer + RNA Panel** (LabCorp; California)
   xxi. **Invitae Pancreatic Hereditary Cancer Panel** (LabCorp; California)

[‡] **Criteria I.C is based on** Palmetto GBA MolDX Manual.

xxii. **myRisk® Hereditary Cancer** (Myriad; Utah) - The myRisk® Hereditary Cancer *Update* test is addressed separately below when performed alone.
xxiii. **VistaSeq Breast and Gyn Cancer Profile** (LabCorp / Integrated Genetics / Integrated Oncology)
xxiv. **VistaSeq Breast Cancer Profile** (LabCorp / Integrated Genetics / Integrated Oncology)
xxv. **VistaSeq Colorectal Cancer Profile** (LabCorp / Integrated Genetics / Integrated Oncology)
xxvi. **VistaSeq Hereditary Cancer Panel** (LabCorp / Integrated Genetics / Integrated Oncology)
xxvii. **VistaSeq High/Moderate Risk Breast Cancer Profile** (LabCorp / Integrated Genetics / Integrated Oncology)

2. FDA approval/clearance **when** the test is performed within FDA labeling indications. *As of the most recent policy review, the following tests **meet** this requirement, but it may not be an all-inclusive list*:
   i. **BRACAnalysis CDx®** (Myriad; Utah) *(NOTE: This test may be performed with or without the myRisk® Hereditary Cancer Update test as a combination or reflex test. Both the CDx test alone and the CDx/myrisk Update combination meet LCD requirements. For **testing for use of PARP inhibitors** apply LCA A55295.)*

II. Medicare Advantage plans must follow Medicare rules for coverage of medically necessary services. According to Medicare rules and regulations found in coverage manuals, MolDX Program Manual, NCD 90.2, and LCDs L38974, L38972, L38966, L39017, L39040, L35000, L35396, L35062, L36715, L34519, and L36499, genetic **single gene** testing for **hereditary cancer syndromes** may be considered **medically necessary** when **both** of the following criteria are met (A or B):

A. BRCA1 and/or BRCA2 testing is performed in one of the following states and meets the relevant LCD criteria (1 or 2):
   1. Testing performed in CO, NM, OK, TX, AR, LA, MS, DE, MD, NJ, PA and DC: Novitas LCD for BRCA1 and BRCA2 Genetic Testing (L36715)
   2. Testing performed in FL: LCD for BRCA1 and BRCA2 Genetic Testing (L36499). **OR**

B. All of the following requirements are met (1-3):
   1. Criteria I.A and I.B above are met[5-16]:
   2. The single gene to be tested is the **only gene or variant** considered to be reasonable and necessary for a cancer type (the same "clinical indications/risk factors" table above can be used to find which conditions may only have a single gene as a high-penetrance susceptibility gene for that cancer type);
   3. The **test** meets analytical and clinical validity standards and demonstrates clinical utility at a level that meets Medicare reasonable and necessary requirements, determined by **one** of the following (i or ii):
      i. MolDX Program approved technical assessment as determined by viewing the DEX Diagnostics Exchange Registry *(a **publicly available database** of genetic and molecular tests which have been evaluated by the MolDX Program Contractor, with their respective coverage outcomes)*[17,18]; **or**

ii. FDA approval/clearance **when** the test is performed within FDA labeling indications.

Known Familial Variant (KFV) Analysis

III. Medicare Advantage plans must follow Medicare rules for coverage of medically necessary services. According to Medicare rules and regulations found in LCDs L38974, L38972, L38966, L39017, L39040, L36715, and L36499, **known familial variant (KFV) testing** for hereditary cancer, may be considered **medically necessary** when **both** of the following criteria are met (A **and** B):

A. The **member** meets **all** of the following (1-3)[6-10,14,16]:
1. Has a cancer diagnosis or personal history of cancer; **and**
2. Has an affected first-, second-, and third-degree relatives with a pathogenic or likely pathogenic variant (known familial variant) associated with a cancer as determined by clinical practice guidelines; **and**
3. Testing is limited to the known familial variant (KFV).

B. The **test** meets analytical and clinical validity standards **and** demonstrates clinical utility at a level that meets Medicare reasonable and necessary requirements, as determined by **one** of the following (A or B):
1. MolDX Program approved technical assessment, as determined by viewing the DEX Diagnostics Exchange Registry *(a **publicly available database** of genetic and molecular tests which have been evaluated by the MolDX Program Contractor, with their respective coverage outcomes)*[17,18]; **or**
2. FDA approval/clearance and the test is performed within FDA labeling indications.

Non-Covered Testing

IV. Medicare Advantage plans must follow Medicare rules for coverage of medically necessary services. According to Medicare rules and regulations found in LCDs L38353, L35351, L38274, L38288, L38429, L35000, L35396, L35062, L36715, and L36499, repeat **germline (hereditary) testing** (e.g., single gene or panel tests for hereditary cancer syndromes or cancer predisposition, inherited disorders, and pharmacogenomics/cytochrome P450 testing) is considered **not medically necessary**[13,14,15,19-23]. The germline sequence of an individual does not change over time and repeated testing of the same genetic information does not provide new clinical information. (*This non-coverage of repeat germline testing does **not** apply to repeat testing performed for somatic [acquired] cancer conditions. While somatic alterations are constantly occurring during the life of an individual, the germline sequence of an individual does not change over time. Situations where repeat testing may be medically indicated include clinical scenarios where repeat testing of somatically-acquired mutations [e.g., pre- and post- therapy] may be required to inform appropriate therapeutic decision-making, and are addressed in separate Medicare medical policies.)*

V. Medicare Advantage plans must follow Medicare rules for coverage of medically necessary services. According to Medicare rules and regulations found in Medicare manuals, as well as the MolDX Program Manual and LCDs L38974, L38972, L38966, L39017, L39040, L38353, L35351, L38274, L38288, L38429, L35000, L35396, L35062, L36715, and L36499, genetic testing will be considered **not medically necessary** for any of the following scenarios, **for all jurisdictions and service areas**. Medicare non-coverage does not mean the noted tests or testing situations may not provide valid or useful information. It only means they do not meet Medicare's benefit or medical necessity requirements to be eligible for Medicare coverage. The Policy Guidelines section below provides detailed information regarding these Medicare coverage policies, regulatory language, and statutory coverage requirements. [5-23]:

A. Criterion I.A above are not met (i.e., the test was not ordered by a physician who is treating the member).
B. The **member** does **not** meet clinical coverage Criterion I.B above (e.g., member does **not** have a cancer diagnosis or a personal history of cancer, does **not** have either a clinical indication or a risk factor for hereditary cancer, **has** been previously tested with the same germline content, etc.).[5-16] This includes testing requested due to family history when the member does not personally have signs/symptoms of disease relevant to the requested test. While some NCCN guidelines and even the U.S. Preventive Services Task Force may recommend testing for unaffected individuals, this does not dictate Medicare coverage. Medicare does **not** allow testing based on family history alone. Testing in these situations is considered screening and thus is not medically necessary under *Title XVIII of the Social Security Act, Section 1862(a)(1)(A).*[17,18,24]
C. The **test** requested does **not** meet coverage Criterion I.C above. As of the most recent policy review, tests which do **not** meet analytical and clinical validity standards or clinical utility requirements for Medicare coverage include, but are not limited to, the following[17,18]:
    i. **Breast/Gyn Cancer Panel** (GeneDx, Maryland) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry.
    ii. **BRCA1/2 +RNAinsight™** (Ambry Genetics; California) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry.
    iii. **+RNAinsight™ for BRCA1/2 (0138U)** (Ambry Genetics; California) - Test is not FDA approved or cleared, **and** has not been reviewed and approved by the MolDX® Program.
    iv. **RNAinsight™ for CancerNext®** (0134U) (Ambry Genetics; California) – Test is not FDA approved or cleared, **and** has not been reviewed and approved by the MolDX® Program.
        1. NOTE: This RNAInsight™ test is an add-on option for certain Ambry tests. RNAInsight™ for CancerNext® is performed alone, when CancerNext has been performed *previously*. When CancerNext +RNAInsight™ are performed together, this is known as "CancerNext +RNAInsight, and is addressed separately.

v. **CNGnome™** (PerkinElmer Genomics; Pennsylvania) - Test is not FDA approved or cleared, **and** has not been reviewed and approved by the MolDX® Program.

vi. **Colorectal Cancer Panel** (GeneDx, Maryland) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry.

vii. **COLARIS AP®** (Myriad; Utah) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry.

viii. **COLARISPLUS** (Ambry Genetics; California) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry.

ix. **COLARIS PLUS** + myRisk Update (Myriad; Utah) - Test is not FDA approved or cleared, **and** this test combination is listed as "not covered" in MolDX® DEX® Registry.

x. **ColoSeq** (UW Dept of Laboratory Medicine and Pathology; Washington) - Test is not FDA approved or cleared, **and** has not been reviewed and approved by the MolDX® Program. In addition, the LCD L38974 states that tests covered by Noridian Healthcare Solutions at the time the LCD was initially published were **not** exempt from the required MolDX TA review process. It adds, "Tests that are currently covered and have not undergone a TA by MolDX® will be non-covered unless complete documents to perform a TA are submitted in a timely manner." Therefore, while ColoSeq may possibly have been covered by Medicare ***in the past***, it does not meet current coverage criteria based on the Medicare resources that are available.

xi. **GeneticsNow™ Comprehensive Germline Panel** (0474U) (GoPath Diagnostics, Inc. Illinois and Arizona) - Test is not FDA approved or cleared, and has not been reviewed and approved by the MolDX® Program. *(**NOTE**: Test is not listed in the DEX® Registry under GoPath Diagnostics, but other tests are listed for this laboratory, under multiple locations – one location in Arizona and the other location in Illinois. Clinical utility and clinical and analytical validity are **not** established by either service area.)*

xii. **Invitae BRCA1/2 Panel** (Labcorp; California) – Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry.

xiii. **Invitae Cancer Screen** (Labcorp; California) – Test is not FDA approved or cleared, **and** has not been reviewed and approved by the MolDX® Program.

xiv. **myRisk® Hereditary Cancer *Update*** (Myriad; Utah) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry.

1. NOTE: Non-coverage only applies if this "*Update*" test is performed alone. This version is ordered for individuals who have **previously** had either BRACAnalysis CDx, COLARIS, or COLARIS AP testing, when the full myRisk® panel of genes wasn't already performed.

xv. **+RNAinsight™ for ATM (0136U)** (Ambry Genetics; California) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry.

xvi. **+RNAinsight™ for PALB2 (0137U)** (Ambry Genetics; California) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry.

xvii. **VistaSeq Hereditary Cancer Panel without BRCA** (LabCorp / Integrated Genetics / Integrated Oncology) - Test is not FDA approved or cleared, **and** it is listed as "not covered" in MolDX® DEX® Registry.

D. Tests that do not provide the clinician with actionable data for the member (information that will not improve patient outcomes and/or change physician care and treatment of the patient) (this includes at-risk relative testing).[17,18]

E. Tests that confirm a diagnosis or known information;[17,18]

F. Tests to determine risk for developing a disease or condition;[17,18]

G. Tests performed to measure the quality of a process, or tests performed to confirm the sample belongs to a particular member;[17,18]

H. Tests without diagnosis specific indications;[17,18]

I. Carrier testing (tests to determine if they or offspring are potential carriers of a genetic variant). This non-coverage does not mean the testing of family members is not medically warranted; however, the Medicare benefit requires the member to have signs and symptoms of disease. Coverage of molecular testing carrier status of inherited cancer syndromes is considered screening and is statutorily excluded from coverage.[17,18]

J. Tests identified as investigational by all available literature and/or the literature supplied by the developer and are not a part of a clinical trial as determined by LCD, LCA, or the MolDX program (when applicable).[17,18]

K. Genetic test that investigates the same germline genetic content, for the same genetic information, that has already been tested in the same individual.[6-10]

L. Multigene panels which do not contain, at a minimum, all the necessary relevant gene content required for their indicated use to meet clinical utility requirements (it is this criterion which may result in non-coverage by the MolDX Program, mean to avoid unnecessary repeat panel testing with overlapping and duplicative genetic content being analyzed).[6-10]

M. A panel or single gene test used to <u>confirm</u> a variant(s) detected by somatic tumor testing that can be confirmed by a test targeted to that specific variant(s).[6-10]

N. A panel or single gene test used to <u>identify</u> a known familial variant(s) that could be identified with a test targeted to that specific variant(s).[6-10]

O. Multigene panel to analyze a single gene (e.g., using a multigene panel for CDH1 gene analysis for the evaluation of gastric cancer).[6-10].

VI. In general, custom panel tests are considered **not medically necessary**. There is no intended use patient population or diagnosis codes that can be associated with a 'custom' panel, and therefore, the test would not pass a technical assessment[6-10] and would not meet policy criteria for coverage. *(Special consideration may be given to panels requested for unique clinical situations, such as for rare medical conditions and when panel tests are not already commercially available for that condition. This is not expected to be a common occurrence, and all other clinical criteria must still be met.)*

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

Medicare Medical Policies

- Circulating Tumor Cell and DNA Assays for Cancer Management, MP306
- Clinical Trials, Studies and Registries, MP233
- Gene Expression Profile Testing for Breast Cancer, MP48
- Gene Expression Profile Testing for Melanoma, MP253
- Genetic Testing for Myeloproliferative Diseases, MP71
- Genetic Testing for Thyroid Nodules, MP40
- PHA Medicare Medical Policy Development and Application, MP50

Coding Policies

- Laboratory Panel Billing, CP30

The full Company portfolio of Medicare Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

DOCUMENTATION REQUIREMENTS

In order to review for medical necessity, the following documentation **must** be provided. If any of these items are not submitted, the review may be delayed and the decision outcome could be affected:

- CPT and/or HCPCS code(s) billed
- Test name;
  - If the test is a panel test, the name of the panel test;
  - For single gene/variant testing, the name of the gene(s) and/or components of the test;
- Name and location of laboratory that performed or will be performing the test;
- Clinical notes should include the following:
  - Documentation supporting the member was advised what tests were being ordered;
  - Condition or suspected condition;
  - What test results are expected to provide (e.g., make diagnosis, determine medication therapy(ies), etc.);
  - Signs/symptoms/prior test results related to reason for genetic testing;
  - Family history, if applicable;
  - How test results will impact clinical decision making

BACKGROUND

A hereditary cancer syndrome is a disorder in which family members have a higher-than-average risk of developing a certain type or types of cancer. They are caused by inherited genetic variants in certain cancer-related genes. Some family cancer syndromes will present with individuals developing cancer at

an early age or having other noncancer health conditions. Other cancers that appear to "run in families" may not be caused by family cancer syndromes, but rather, are caused by shared environments or habits (e.g., exposure to air pollution or tobacco use may cause the same kind of cancer to develop among family members). All of these factors are collectively referred to as clinical indications or risk factors, and they vary by cancer types.[25]

Genetic testing is performed to detect variants in DNA, RNA, and/or chromosomes. Certain genetic tests can show if an individual has inherited a genetic change that increases their risk of developing cancer. Within the Medicare program, genetic testing may also be referred to as molecular or biomarker testing.

While genetic testing has potential benefits for certain conditions, especially cancer, there are also risks associated with genetic testing. These include emotional, social, or financial consequences. Reasons include what test results may reveal, and the feelings that can arise with such test results (e.g., results revealing information about other family members who were not the intended individual the testing was performed for, etc.). In addition, there are limitations to what genetic and molecular tests can provide regarding an inherited condition. Even if a positive result is received, the test may be unable to determine if a person will ever show symptoms of a disorder, how severe the symptoms will be, or whether the disorder will progress over time. Another limitation of molecular testing is that there may not be treatments or cures available for conditions related to an identified genetic variant or genetic disorder. Therefore, it is very important that any individual who is considering genetic testing understand all aspects of the test results before making a decision. While not a requirement for Medicare coverage in most cases, individuals considering genetic testing may wish to consult with a genetics professional to explain in detail both benefits and risks of testing, as well as any potential and significant limitations of a particular test.[26]

Medicare Coverage Policies

In order for a laboratory service (including genetic and molecular testing) to be considered for coverage, Medicare requires that 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);[27]
- Be ordered by a physician or practitioner who is treating the beneficiary;[3,4]
- Provide data that will be directly used in the management of a beneficiary's specific medical problem;[3,4]
- Be considered medically reasonable and necessary, as required per the Social Security Act, §1862(a)(1)(A). This means the service must be considered reasonable and necessary in the diagnosis or treatment of an illness or injury, or to rule out or confirm a suspected diagnosis because the patient has signs and/or symptoms.[28,29]
    - This also means services deemed not medically necessary for any reason (including lack of safety and efficacy for investigational services) are also non-covered.[30]

In addition to the above general Medicare requirements, under Chapter 13 of the Medicare Program Integrity Manual, Medicare allows contractors to consider a service "reasonable and necessary" when the service is appropriate for the member's condition. This includes appropriateness in duration, frequency, and that the service is furnished in accordance with accepted standards of medical practice for the condition, furnished in a setting appropriate to the medical needs and condition, ordered and furnished by qualified personnel, that the service meets, but does not exceed, the medical need; and is at least as beneficial as an existing and available medically appropriate alternative.[31]

To effectively manage a patient's specific medical problem using genetic or molecular diagnostic testing, the genetic tests performed must be relevant to the medical condition and have established clinical utility and analytical validity for that condition. Therefore, ordering physicians must be familiar with the genetic tests they order to ensure all test result components are clinically actionable.

As a Medicare Advantage Organization (MAO), the Plan must follow Medicare rules. Medicare rules include the following:

- Items and services that are **not** medically necessary are **not** covered.
- All molecular diagnostic tests (MDT) and laboratory developed tests (LDT) must be ordered by a physician who is treating the patient, and the test results must be used in the management of a specific medical problem.[17,18,28-36]
- Tests must demonstrate analytical validity, clinical validity (AVCV), and clinical utility (CU). Laboratory tests without established clinical utility and/or analytic validity are not eligible for coverage. (MolDX Program Manual, Section 2.2)[17]

The National Coverage Determination (NCD) for *Next Generation Sequencing* (90.2) applies to germline (inherited) cancer tests which meet **all** of the following[5]:

- Test uses next-generation sequencing (NGS) methodology.
- Test performs DNA sequencing to detect genomic mutations.
- Test has FDA approval or clearance as a companion in vitro diagnostic (CDx) test.
- Test is used for ovarian or breast cancer-related indications.

This Medicare coverage policy adds that coverage for genetic tests not otherwise addressed by the NCD is left to local Medicare Administrative Contractor (MAC) discretion. This includes:

- Tests which use a methodology *other than* NGS.
- NGS tests for RNA sequencing and protein analysis.
- NGS tests without FDA approval or clearance as a CDx test.
- NGS tests used for *non-cancer* related indications, or for cancers *other than* breast or ovarian.

MAC coverage criteria for tests which are not subject to the NCD is found in local coverage determinations, or LCDs. However, while these coverage policies provide general coverage criteria for diagnostic testing, not all Medicare coverage polices are considered "fully established," as defined by CMS.[38] *(CFR § 422.101(b)(6)(i)(A))* In these situations, additional criteria to interpret or supplement the Medicare criteria may be used in order to determine medical necessity consistently.

Therefore, when CMS guidance is not fully established for a specific MDT or LDT, the plan will apply the policy criteria found above to determine clinical utility and analytical validity are established and Medicare coverage criteria are met.

For rare medical conditions or for conditions which may not generally apply to the Medicare population, individual consideration may be given to determine medical necessity by utilizing generally accepted standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, specialty society recommendations, and views of physicians practicing in relevant clinical areas to determine medical necessity.

DIAGNOSTIC LABORATORY TEST JURISDICTION

In accordance with Medicare guidelines, LCDs and LCAs for test service areas **outside** of the Company service area may be used. Medicare rules state jurisdiction of claims furnished by an independent laboratory lies with the A/B MAC (B) (aka, Medicare Contractor) serving the area in which the laboratory testing is performed.[39]

Table 2 provides the Medicare Contractor or MAC for each jurisdiction or service area.

Table 2: Medicare Contractors and Jurisdictions

MEDICARE CONTRACTOR (MAC)	JURISDICTION AREA(S)
Noridian Healthcare Solutions, LLC J-F (Noridian J-F)	Alaska (AK) Arizona (AZ) Idaho (ID) Montana (MD) North Dakota (ND) South Dakota (SD) Utah (UT) Washington (WA) Wyoming (WY)
Noridian Healthcare Solutions, LLC J-E (Noridian J-E)	California (CA) Hawaii (HI) Nevada (NV)
Palmetto GBA (Palmetto) J-J and J-M **Palmetto is also the Medicare Molecular Diagnostics (MolDX) Program Contractor*	Alabama (AL) Georgia (GA) Tennessee (TN) North Carolina (NC) South Carolina (SC) Virginia (VA) West Virginia (WV)
CGS Administrators (CGS) J-15	Kentucky (KY) Ohio (OH)
Wisconsin Physicians Service Insurance Corporation (WPS) J-5 and J-8	Iowa (IA) Kansas (KS) Missouri (MO) Nebraska (NE) Indiana (IN) Michigan (MI)
National Government Services (NGS) J-6 and J-K	Illinois (IL) Minnesota (MN) Wisconsin (WI) Connecticut (CT) New York (NY) Maine (ME) Massachusetts (MA) New Hampshire (NH) Rhode Island (RI) Vermont (VT)
Novitas Solutions, Inc. (Novitas) J-H and J-L	Colorado (CO) New Mexico (NM)

	Oklahoma (OK) Texas (TX) Arkansas (AR) Louisiana (LA) Mississippi (MS) Delaware (DE) Maryland (MD) New Jersey (NJ) Pennsylvania (PA) District of Columbia (DC)
First Coast Service Options J-N	Florida (FL)

However, there may be exceptions to this rule.

Exception #1: According to Medicare, while jurisdiction for laboratory services normally lies with the carrier serving the performing laboratory service area, there are situations where a regional or national lab chain jurisdiction (e.g., Quest Diagnostics, LabCorp, etc.) lies with a single carrier.[40] Therefore, tests performed by a national laboratory chain or for laboratories with testing sites in multiple locations, the Plan may use a single LCD or LCA or the plan criteria above as the source of coverage criteria for **all** laboratory locations to ensure consistent coverage outcomes for Plan members.

Exception #2: Another exception to this rule involves "referring laboratory tests." This is when one laboratory sends the sample to another laboratory for processing. Under Medicare rules for referred tests, the location of the **billing** provider determines jurisdiction for claim payment and coverage criteria. Note, also under Medicare rules, only one laboratory is allowed to bill for the services rendered. If the performing laboratory and billing provider both submit a claim, then the performing laboratory's claim is the claim that would adjudicate according to member benefits.[41-43]

PANEL TESTING

According to the MolDX program, a test panel is defined as "A predetermined set of medical tests composed of individual laboratory tests, related by medical condition, specimen type, frequency ordered, methodology or types of components to aid in the diagnosis/treatment of disease."[17]

Genetic panel tests may be used for a number of indications and they may be either be proprietary "off-the-shelf" tests with a set number of genes (subject to change without notice), or they may be custom panel tests with genes selected by the ordering provider or genetic counselor based on a patient's symptoms.

CLINICAL PRACTICE GUIDELINES

CLINICAL INDICATIONS AND RISK FACTORS

Risk factors and clinical indications for hereditary cancer syndromes vary by cancer type. The National Comprehensive Cancer Network (NCCN) has defined criteria for which testing of well-established germline genes is appropriate for a variety of inherited cancers.[6-10] The following tables include common risk factors and clinical indications for specific hereditary cancer types, based on NCCN guidelines.

NOTE: For cancers **not addressed** in the tables below, NCCN guidelines regarding hereditary cancer risk and assessment for that specific cancer type would apply. Some NCCN guidelines and even the U.S. Preventive Services Task Force may recommend testing based on family medical history alone; however, this does not dictate Medicare coverage. Medicare requires a personal history of cancer in order to consider genetic testing for the member to be medically reasonable and necessary. Testing due to family history alone would **not** meet the policy coverage criteria, even if included as a recommendation by NCCN. Testing in this situation is considered screening and is statutorily non-covered by the Medicare Program *(see Criterion V.D).*

Hereditary Breast, Ovarian, Pancreatic, or Prostate Cancers [44]	Criteria
HIGH-PENETRANCE CANCER SUSCEPTIBILITY GENES INCLUDE: ATM, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53	

- The patient has a personal history of breast cancer (including invasive and ductal carcinoma in situ) **and** any one or more of the following: **OR**
  - Diagnosed with breast cancer ≤ 45 years of age; **or**
  - Diagnosed with breast cancer at age 46-50 with **any** of the following:
    - Unknown or limited family history *(A limited family history occurs when a 1st, 2nd and 3rd generation pedigree cannot be obtained **or** when there are too few family members in each generation to reasonably see a pattern of inheritance)*; **or**
    - Multiple primary breast cancers (synchronous or metachronous); **or**
    - 1 or more close blood relative with breast, ovarian, pancreatic, or prostate cancer at any age; **or**
  - Diagnosed with breast cancer ≥ 51 years of age **with** 1 or more close blood relative with any of the following:
    - Breast cancer at age 50 years or younger or male breast cancer at any age
    - Ovarian or pancreatic cancer at any age
    - Metastatic, intraductal/cribriform histology, or high- or very-high risk group prostate cancer (based on NCCN guidelines) at any age
    - ≥3 total diagnoses of breast cancer in patient and/or close blood relatives
    - ≥2 or more close blood relatives with either breast or prostate cancer (any grade) at any age, or
  - Diagnosed with breast cancer at any age **and** any one of the following:
    - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting
    - To aid in adjuvant treatment decisions with olaparib for high-risk, HER-2 negative breast cancer
    - Triple-negative breast cancer
    - Lobular breast cancer with personal or family history of diffuse gastric cancer
    - ≥1 close blood relatives with male breast cancer
    - Ethnicity associated with higher mutation frequency or increased risk of founder mutation (e.g., Ashkenazi Jewish, Norwegian, Dutch, or Icelander descent); **OR**

- The patient has ovarian cancer (includes fallopian tube and primary peritoneal cancers); **OR**

- The patient has male breast cancer; **OR**

- The patient has pancreatic cancer; **OR**

- The patient has metastatic prostate cancer (biopsy-proven and/or with radiologic evidence and includes distant metastases and regional bed or nodes); **OR**

- The patient has prostate cancer **and** any of the following:
  - Metastatic (Stage IVB) or node-positive (Stage IVA) prostate cancer (see Appendix V for stages); **or**
  - Very high-risk or high-risk disease, based on NCCN "Initial Risk Stratification and Staging Workup for Clinically Localized Disease" guidelines (see Appendix III); **or**

- Ashkenazi Jewish ancestry; **or**
- ≥ 1 close blood relative with any of the following:
  - Breast cancer ≤ 50 years of age; **or**
  - Male breast cancer; **or**
  - Ovarian cancer; **or**
  - Pancreatic cancer; **or**
  - Metastatic, node positive, or very high-risk prostate cancer; **or**
  - ≥ 3 close blood relatives with prostate cancer (any grade) and/or breast cancer on the same side of the family including the patient with prostate cancer.

- Personal **and** family history which includes 3 or more of the following diagnoses (can include multiple primary cancers in the same individual):
  - Breast cancer
  - Pancreatic cancer
  - Prostate cancer (Gleason score ≥ 7 or metastatic)
  - Melanoma
  - Sarcoma
  - Adrenocortical carcinoma
  - Brain tumors
  - Leukemia
  - Diffuse gastric cancer
  - Colon cancer
  - Endometrial cancer
  - Thyroid cancer
  - Kidney cancer
  - Dermatological manifestations of Cowden syndrome
  - Macrocephaly
  - Gastrointestinal cancer or hamartomatous polyps of GI tract
  - Ovarian sex chord tumors
  - Testicular sertoli cell tumors
  - Childhood skin pigmentation indicative of Peutz-Jeghers syndrome; or

- A known pathogenic/likely pathogenic variant in a hereditary breast, ovarian, pancreatic, and/or prostate cancer gene detected by tumor profiling on any tumor type in the absence of germline variant analysis. *(In this situation, testing should be limited to the known pathogenic variant. See Criterion III above.)*

- Genetic testing for hereditary breast, ovarian, pancreatic, and/or prostate cancer gene mutation(s) is **not recommended** in patients who have received an allogeneic bone marrow transplant **if only** blood or buccal samples are available. Fibroblast culture is the only acceptable source of DNA for these patients. Per NCCN guidelines, testing from blood and buccal sources may be unreliable due to donor-derived DNA.

NCCN Clinical Practice Guidelines. Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate. CRIT-1, CRIT-2, CRIT-4, CRIT-5, CRIT-6, CRIT-7, and CRIT-8. March 2025.

Colorectal, Endometrial and Gastric Cancers[45]	Criteria
HIGH-PENETRANCE SUSCEPTIBILITY GENES INCLUDE: APC, AXIN2, BMPR1A, BRCA1, BRCA2, CDH1, EPCAM, GREM1, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NTHL1, POLD1, POLE, PMS2, PTEN, RPS20, SMAD4, STK11 (LKB1), and TP53	
Lynch syndrome-related cancers include: colorectal, endometrial, gastric, ovarian, pancreatic, ureter or renal pelvis, brain (usually glioblastoma), small intestinal cancers, sebaceous adenomas and carcinomas, and keratoacanthomas as seen in Muir–Torre syndrome. This includes the following inherited cancer syndromes: ▪ Hereditary Non-Polyposis Colorectal Cancer (HNPCC, also known as Lynch Syndrome). ▪ Polyposis Syndromes. • Adenomatous Polyposis (e.g. Familial Adenomatous Polyposis [FAP]; Attenuated FAP [AFAP]; MUTYH-associated Polyposis [MAP]). • Colonic Adenomatous Polyposis of Unknown Etiology.	

• Peutz-Jeghers Syndrome (PJS)
• Juvenile Polyposis Syndrome (JPS)
• Serrated Polyposis Syndrome (SPS) (previously known as hyperplastic polyposis)

- Personal history of **any** of the following;
  - At least 10 adenomas; **or**
  - At least 2 hamartomatous polyps; **or**
  - At least 5 serrated polyps/lesions proximal to the rectum; **or**
  - ≥ 20 serrated polyps/lesions of any size distributed throughout the large bowel, with ≥5 being proximal to the rectum; **OR**

- Personal history of colorectal, endometrial and gastric cancer **and** any of the following:
  - Meets adenomatous polyposis testing criteria by any of the following:
    - ≥20 cumulative adenomas
    - Known PV in adenomatous polyposis gene in family
    - Multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)
    - Cribriform-morular variant of papillary thyroid cancer
    - Family history of polyposis and family unwilling/unable to have testing
    - Between 10–19 cumulative adenomas, desmoid tumor, hepatoblastoma, unilateral CHRPE, or individual meets criteria for SPS (SPS-1) with at least some adenomas
  - Meets clinical criteria for:
    - JPS by any of the following:
      - ≥5 juvenile polyps of the colon;
      - Multiple juvenile polyps found throughout the GI tract;
      - Any number of juvenile polyps in an individual with a family history of JPS
    - PJS by any of the following:
      - ≥2 histologically confirmed PJS polyps;
      - Any number of PJS polyps detected in an individual who has a family history of PJS in close relative(s);
      - Characteristic mucocutaneous hyperpigmentation in an individual who has a family history of PJS in close relative(s);
      - Any number of PJS polyps in an individual who also has characteristic mucocutaneous pigmentation.
  - Meets hereditary diffuse gastric cancer (HDGC) testing criteria by any of the following:
    - Individual with a known *CDH1* pathogenic variant (PV) in the family;
    - An individual with diffuse gastric cancer (DGC) at any age;
    - ≥2 first- or second-degree relatives with gastric cancer with at ≥ 1 diagnosed at age ≤50 y **or** ≥ 1 confirmed to be DGC at any age.

- Personal history of an LS-related cancer **and** any of the following:
  - Diagnosed <50 years old; or
  - A synchronous or metachronous LS-related cancer, regardless of age; **or**
  - 1 first- or second-degree relative with an LS-related cancer diagnosed <50 years old; **or**
  - ≥ 2 first- or second-degree relatives with an LS-related cancer regardless of age; **or**
  - Colorectal, endometrial or gastric cancer at any age with tumor showing evidence of mismatch repair deficiency, either by microsatellite instability (MSI) or loss of MMR protein expression (diagnosed any age); **or**
  - ≥ 5% risk of having an MMR gene pathogenic variant (PV) based on predictive models (e.g., MMRpro [which may require software], $PREMM_5$, or MMRpredict). (Individuals with a personal history of CRC and/or EC with a $PREMM_5$ score of ≥2.5% should be considered for multigene panel test or MGPT.)

- A pathogenic or likely pathogenic variant is identified on tumor genomic testing that has clinical implications *(In this situation, testing should be limited to the known pathogenic variant. See Criterion III above)*; **OR**

- Personal history of LS-related cancer **and** documentation indicates a first-degree relative has a known pathogenic mutation in one of the genes listed above and testing is based on the identified mutation *(In this situation, testing should be limited to the known pathogenic variant. See Criterion III above)*; **OR**

- Genetic testing for *BRAF V600E* or *MLH1* promoter methylation testing may be recommended to rule out a diagnosis of Lynch syndrome in patients with a loss of DNA protein expression of *MLH1* on IHC tumor testing or an MSI-H test result.

NCCN Clinical Practice Guidelines. Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. HRS-1, HRS-2, HRS-3, HGAST-1, POLYP-1, PJS-1, and JPS-1. January 2025.

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

Medicare Coding and Billing References

While not a complete list, please refer to the following local coverage articles (LCAs) for coding and billing assistance:

- Noridian J-F LCA: Billing and Coding: MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer (A58681)
- Noridian J-E LCA: Billing and Coding: MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer (A58679)
- Palmetto LCA: Billing and Coding: MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer (A58652)
- CGS LCA: Billing and Coding: MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer (A58734)
- WPS LCA: Billing and Coding: MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer (A58756)
- NGS LCA: Billing and Coding: Molecular Pathology Procedures (A56199)
- Novitas LCA: Billing and Coding: Biomarkers for Oncology (A52986)
- Novitas LCA: Billing and Coding: Biomarkers Overview (A56541)
- Novitas LCA: Billing and Coding: Molecular Pathology and Genetic Testing (A58917)
- First Coast LCA: Billing and Coding: Molecular Pathology and Genetic Testing (A58918)

BRCA1 and BRCA2 Specific LCAs

- Novitas LCA: Billing and Coding: BRCA1 and BRCA2 Genetic Testing (A56542)
- First Coast LCA: Billing and Coding: BRCA1 and BRCA2 Genetic Testing (A57449)

Appropriate CPT Coding for Panel Tests

Some, but not all, panel tests may have a specific CPT or HCPCS code assigned (81410-81471, 815XX multianalyte assays with algorithmic analyses [MAAA] codes or newly developed proprietary laboratory analyses [PLA] codes). However, many panels may not have a specific code available. **When no single specific CPT or HCPCS code exists for the ENTIRE panel, the provider is required to bill using an unlisted code (e.g., 81479 or 81599).** It is not appropriate for the provider to bill any of the tests in a panel separately as if they were performed individually. This is a misrepresentation of services performed and is not appropriate based on either CPT or CMS guidelines. In a "Healthcare Fraud Prevention Partnership" white paper, the unbundling of claims for lab panels was identified as an area of concern for inappropriate billing.[46]

This also applies to custom NGS panel tests. The practice of stacking multiple Tier I codes is not appropriate coding. The laboratory should submit a single service mapped to the most appropriate code. If no specific panel code exists, then an unlisted code (e.g., 81479) should be used.

If a multianalyte test is performed, it should be billed as a single service. If no specific code exists for that panel, it is not appropriate to bill for the components of that service (this constitutes unbundling) and should be billed with the NOC codes such as 81479, 81599, or 87999, depending on analytes measured.[47-51]

Note: Codes addressed by this policy include, but may not be limited to, the following:

CODES*		
CPT	0101U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [15 genes (sequencing and deletion/duplication), EPCAM and GREM1 (deletion/duplication only) *(ColoNext®, by Ambry Genetics; California)*
	0102U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [17 genes (sequencing and deletion/duplication) *(BreastNext®, by Ambry Genetics; California)*
	0103U	Hereditary ovarian cancer (eg, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [24 genes (sequencing and deletion/duplication); EPCAM (deletion/duplication only) *(OvaNext®, by Ambry Genetics; California)*
	0129U	Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53) *(BRCAplus, by Ambry Genetics; California)*

	0130U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure) (Use 0130U in conjunction with 81435, 0101U) *(RNAinsight™ for ColoNext®, by Ambry Genetics; California)*
	0131U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure) *(RNAinsight™ for BreastNext®, by Ambry Genetics; California)*
	0132U	Hereditary ovarian cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure) (Use 0132U in conjunction with 81162, 81432, 0103U) *(RNAinsight™ for OvaNext®, by Ambry Genetics; California)*
	0133U	Hereditary prostate cancer–related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure) (Use 0133U in conjunction with 81162) *(RNAinsight™ for ProstateNext®, by Ambry Genetics; California)*
	0134U	Hereditary pan cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) (List separately in addition to code for primary procedure) *(RNAinsight™ for CancerNext®, by Ambry Genetics; California)*
	0135U	Hereditary gynecological cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) (List separately in addition to code for primary procedure) (Use 0135U in conjunction with 81162) *(RNAinsight™ for GynPlus®, by Ambry Genetics; California)*
	0136U	ATM (ataxia telangiectasia mutated) (eg, ataxia telangiectasia) mRNA sequence analysis (List separately in addition to code for primary procedure) *(RNAinsight™ for ATM, by Ambry Genetics; California)*
	0137U	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) mRNA sequence analysis (List separately in addition to code for primary procedure) *(RNAinsight™ for PALB2)*
	0138U	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0138U in conjunction with 81162) *(RNAinsight™ for BRCA1/2, by Ambry Genetics; California)*
	0157U	APC (APC regulator of WNT signaling pathway) (eg, familial adenomatosis polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure) *(CustomNext + RNA: APC, by Ambry Genetics; California)*
	0158U	MLH1 (mutL homolog 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) *(CustomNext + RNA: MLH1, by Ambry Genetics; California)*
	0159U	MSH2 (mutS homolog 2) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) *(CustomNext + RNA: MSH2, by Ambry Genetics; California)*
	0160U	MSH6 (mutS homolog 6) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) *(CustomNext + RNA: MSH6, by Ambry Genetics; California)*

	0161U	PMS2 (PMS1 homolog 2, mismatch repair system component) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) *(CustomNext + RNA: PMS2, by Ambry Genetics; California)*
	0162U	Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure) *(CustomNext + RNA: Lynch (MLH1, MSH2, MSH6, PMS2), by Ambry Genetics; California)*
	0235U	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions *(Genomic Unity® PTEN Analysis, by Variantyx Inc.; Massachusetts)*
	0238U	Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions *(Genomic Unity® Lynch Syndrome Analysis, by Variantyx Inc.; Massachusetts)*
	0474U	Hereditary pan-cancer (eg, hereditary sarcomas, hereditary endocrine tumors, hereditary neuroendocrine tumors, hereditary cutaneous melanoma), genomic sequence analysis panel of 88 genes with 20 duplications/deletions using next generation sequencing (NGS), Sanger sequencing, blood or saliva, reported as positive or negative for germline variants, each gene *(Used to report the GeneticsNow® Comprehensive Germline Panel test by GoPath Diagnostics, Inc.)*
	81162	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis
	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
	81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
	81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
	81210	BRAF (v-raf murine sarcoma viral oncogene homolog B1) (e.g. Colon Cancer) gene analysis, V600E variant
	81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants

	81215	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
	81216	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
	81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
	81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2 (eg hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81299	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81300	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81307	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence
	81308	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant
	81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81321	PTEN (phosphatase and tensin)(e.g., Cowden Syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
	81322	PTEN (phosphatase and tensin)(e.g., Cowden Syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
	81323	PTEN (phosphatase and tensin)(e.g., Cowden Syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant

	81351	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence
	81352	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
	81353	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant
	81400	Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81402	Molecular pathology procedure, level 3 (e.g.,>10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants 1 exon)
	81403	Molecular pathology procedure, level 4 (e.g. analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons
	81404	Molecular pathology procedure, level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder /triplet repeat by southern blot analysis
	81405	Molecular pathology procedure, level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
	81407	Molecular pathology procedure, level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
	81408	Molecular pathology, level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
	81432	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer, hereditary pancreatic cancer, hereditary prostate cancer); genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
	81435	Hereditary colon cancer-related disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
	81437	Hereditary neuroendocrine tumor-related disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, 5 genes, interrogation for sequence variants and copy number variants
	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis
	84999	Unlisted chemistry procedure

HCPCS		

***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.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
9/2025	New Medicare Advantage medical policy

APPENDICES

Appendix I: Family relationships.[52]

DEGREE	RELATIVE
First	Parents, siblings, children
Second	Grandparents, grandchildren, uncles, aunts, nephews, nieces, half-siblings
Third	Great-grandparents, great-grandchildren, great uncles, great aunts, first cousins
Fourth	Great-great-grandparents, great-great-grandchildren, first cousins once-removed (children of a first cousin)

Appendix II: Examples of hereditary breast cancer risk stratification or assessment tools and their scoring values.[53]

RISK STRATIFICATION TOOL	SIGNIFICANT RISK
Breast Cancer Genetics Referral Screening Tool	Score indicates moderate or high risk
Manchester Scoring System	Score of 15 or higher
Ontario Family History Assessment Tool	Score of 10 or higher

Appendix III: NCCN Guidelines for "Initial Risk Stratification and Staging Workup for Clinically Localized Disease" for prostate cancer.[54]

RISK GROUP	CLINICAL/PATHOLOGIC FEATURES
Very low	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • <3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core *(An ultrasound- or MRI- or DRE-targeted lesion that is biopsied more than once and demonstrates cancer (regardless of percentage core involvement or number of cores involved) can be considered as a single positive core)* • PSA density <0.15 ng/mL/g
Low	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL

Intermediate	Has all of the following:
	• No high-risk group features
	• No very-high-risk group features
	• Has one or more intermediate risk factors (IRFs):
	  ○ cT2b–cT2c
	  ○ Grade Group 2 or 3
	  ○ PSA 10–20 ng/mL

Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (e.g., <6 of 12 cores) *(Percentage of positive cores in the intermediate-risk group is based on biopsies that include systematic biopsies with or without targeted MRI-guided biopsies.)*
Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥50% biopsy cores positive (eg, ≥ 6 of 12 cores) *(Percentage of positive cores in the intermediate-risk group is based on biopsies that include systematic biopsies with or without targeted MRI-guided biopsies.)*
High	Has one or more high-risk features, but does not meet criteria for very high risk: • cT3–cT4 • Grade Group 4 or Grade Group 5 • PSA >20 ng/mL
Very high	Has at least two of the following: • cT3–cT4 • Grade Group 4 or 5 • PSA >40 ng/mL

Appendix IV: American Joint Committee on Cancer (AJCC) TNM Staging System or Prostate Cancer.[54]

CATEGORY	CRITERIA
T Primary Tumor	
Clinical T (cT)	
T CATEGORY	**T CRITERIA**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in 1 or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of 1 side or less
T2b	Tumor involves more than one-half of 1 side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.
Pathological T (pT)	
▪ There is no pathological T1 classification.	
▪ Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.	
T CATEGORY	**T CRITERIA**
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Regional Lymph Nodes (N)	
N CATEGORY	**N CRITERIA**
NX	Regional nodes were not assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)
Distant metastasis (M)	
▪ When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.	
M CATEGORY	**M CRITERIA**
M0	M0
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Appendix V: American Joint Committee on Cancer (AJCC) Prognostic Groups.[54]

GROUP	T	N	M	PSA	GRADE GROUP
Stage I	cT1A-C	N0	M0	Less than 10	1
	cT2a	N0	M0	Less than 10	1
	pT2	N0	M0	Less than 10	1
Stage II	cT1A-C	N0	M0	At least 10 but less than 20	1
	cT2a	N0	M0	At least 10 but less than 20	1
	pT2	N0	M0	At least 10 but less than 20	1
	cT2b	N0	M0	Less than 20	1
	cT2c	N0	M0	Less than 20	1
Stage IIB	T1-2	N0	M0	Less than 20	2
Stage IIC	T1-2	N0	M0	Less than 20	3
	T1-2	N0	M0	Less than 20	4
Stage IIIA	T1-2	N0	M0	At least 20	1-4
Stage IIIB	T3-4	N0	M0	Any	1-5
Stage IIIC	Any	N0	M0	Any	5
Stage IVA	Any	N1	M0	Any	Any
Stage IVB	Any	Any	M1	Any	Any

Appendix VI: Definition of Histologic Grade Group.[54]

GRADE GROUP	GLEASON SCORE	GLEASON PATTERN
1	Less than or equal to 6	Less than or equal to 3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5