Genetic Testing for Hereditary Breast, Ovarian, Pancreatic and Prostate Cancer

INDEPENDENT CARE HEALTH PLAN

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Medicare Advantage Medical Coverage Policy

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Related Documents

Please refer to CMS website for the most current applicable CMS Online Manual System (IOMs)/National Coverage Determination (NCD)/ Local Coverage Determination (LCD)/Local Coverage Article (LCA)/ Transmittals.

Type	Title	ID Number	Jurisdiction Medicare Administrative Contractors (MACs)	Applicable States/Territories
NCD	Next Generation Sequencing NGS)	90.2		
LCD	MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer MolDX: Molecular Diagnostic Tests (MDT) MolDX: Repeat Germline Testing	L39040 L36807 L38429	J5, J8 - Wisconsin Physicians Service Insurance Corporation	IA, IN, KS, MI, MO, NE
LCD	Molecular Pathology Procedures	L35000	J6, JK - National Government Services, Inc.	CT, IL, ME, MA, MN, NH, NY, RI, VT, WI
LCD	MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer MolDX: Molecular Diagnostic Tests (MDT) MolDX: Repeat Germline Testing	L39017 L36021 L38288	J15 - CGS Administrators, LLC	KY, OH
LCD LCA	MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer MolDX: Molecular Diagnostic Tests (MDT) Billing and Coding: MolDX: Germline testing for use of PARP inhibitors MolDX: Repeat Germline Testing	L38972 L35160 A55294 L38351	JE - Noridian Healthcare Solutions, LLC	CA, HI, NV, American Samoa, Guam, Northern Mariana Islands
	MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer	L38974	JF - Noridian Healthcare Solutions, LLC	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY

LCD LCA	MolDX: Molecular Diagnostic Tests (MDT) Billing and Coding: MolDX: Germline testing for use of PARP inhibitors MolDX: Repeat Germline Testing	L36256 A55295 L38353		
LCD	Biomarkers Overview BRCA1 and BRCA2 Genetic Testing	L35062 L36715	JH, JL - Novitas Solutions, Inc.	AR, CO, DE, LA, MD, MS, NJ, NM, OK, PA, TX, D.C.
LCD	MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer MolDX: Molecular Diagnostic Tests (MDT) MolDX: Repeat Germline Testing	L38966 L35025 L38274	JJ, JM - Palmetto GBA	AL, GA, NC, SC, TN, VA, WV
LCD	BRCA1 and BRCA2 Genetic Testing	L36499	JN - First Coast Service Options, Inc. (Part A/B MAC)	FL, PR, U.S. VI

Description

Genetic testing is a laboratory method that is performed to analyze an individual's deoxyribonucleic acid (DNA) to detect gene variants (mutations) associated with inherited conditions including hereditary cancer such as breast, ovarian (including fallopian tube and peritoneal), pancreatic and prostate. Testing may be appropriate for an affected individual. This type of testing may also be referred to as germline genetic testing. Additional inherited cancers include Li-Fraumeni syndrome (LFS) and PTEN hamartoma tumor syndrome/Cowden syndrome. Both are rare, inherited conditions that are associated with increased risk of many types of cancer.

Multigene (or expanded) panels analyze a broad set of genes simultaneously (as opposed to single gene testing that searches for variants in one specific gene) and have been proposed to evaluate the DNA of an individual with a personal and/or family history of more than one hereditary condition or syndrome or hereditary conditions/syndromes associated with more than one gene. Panels often include medically actionable genes but may also include those with unclear medical management. Targeted (or focused) multigene panels analyze a limited number of genes targeted to a specific condition.

Coverage Determination

iCare follows the CMS requirements that only allows coverage and payment for services that are reasonable and necessary for the diagnosis and treatment of illness or injury or to improve the functioning of a malformed body member except as specifically allowed by Medicare.

Genetic tests must demonstrate clinical utility, analytical and clinical validity and fulfill the CMS "reasonable and necessary" criteria. Analytic validity (test accurately identifies the gene variant), clinical validity (test identifies or predicts the clinically defined disorder) and clinical utility (test measurably improves clinical outcomes) of the genetic test is supported by 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. The test must be ordered by a physician who is treating the beneficiary and the results will be used in the management of a beneficiary's specific medical problem.

For jurisdictions with no Medicare guidance for a particular test, iCare will utilize the MolDX program and Technical Assessments for molecular assays as the standard to evaluate clinical utility, analytical and clinical validity in conjunction with adhering to Medicare's reasonable and necessary requirement.

In interpreting or supplementing the criteria above and in order to determine medical necessity consistently, iCare may consider the following criteria:

Multigene Next-Generation Sequencing Panel Testing

Multigene next-generation sequencing (NGS) panel testing will be considered medically reasonable and necessary when the following requirements are met:

- Requirements of NCD 90.2 Section B2 have been met;[29,30] **AND**
- Test is FDA approved/cleared; **AND**
- Analytic validity, clinical validity and clinical utility of the genetic test is supported by the MolDX program; **AND**
- All genes in the panel are relevant to the personal and family history of the individual being tested;[29,30] **AND**
- Criteria #1 and #2 or #3 or #4 or #5 listed below for *BRCA1* and *BRCA2* testing are met;[29,30] **AND**
- Individual also meets criteria for at least one BRCA-related cancer syndrome for which National Comprehensive Cancer Network (NCCN) guidelines (category 1 or 2A recommendations) provide clear testing criteria and management including, but not limited to, *BRCA*-related breast or ovarian cancer syndrome, Li-Fraumeni syndrome, Cowden syndrome or Lynch syndrome[29,30]

***BRCA1* and *BRCA2* Gene Testing**

For **multigene panel testing for *BRCA1* and *BRCA2***, please refer to the Multigene Next-Generation Sequencing Panel Testing Criteria above.

***BRCA1* and *BRCA2* full gene sequencing and deletion/duplication analysis** will be considered medically reasonable and necessary when the following requirements are met (based on NCCN guidelines category 1 or 2A recommendations);[47]

1. Results of testing will be used to benefit the individual tested in terms of potential to guide therapeutic decision making;[47] **AND**

2. Personal history of breast cancer with any of the following:[111]

   - Diagnosed at 50 years of age or younger;[111] **OR**
   - Diagnosed at any age and any of the following:[111]
     - To aid in systemic treatment decisions using PARP inhibitors for metastatic breast cancer;[111] **OR**
     - To aid in adjuvant treatment decisions with olaparib (Lynparza) for high-risk HER2-negative breast cancer;[111] **OR**
     - Triple-negative breast cancer;[111] **OR**
     - Multiple primary breast cancers (synchronous or metachronous);[111] **OR**
     - Lobular breast cancer with personal or family history of diffuse gastric cancer;[111] **OR**
     - Male breast cancer;[111] **OR**
     - Ashkenazi Jewish ancestry; **OR**
     - At least one first-, second- or third-degree relative diagnosed with any of the following:[111]
       - Breast cancer at 50 years of age or younger;[111] **OR**
       - Male breast cancer;[111] **OR**
       - Ovarian cancer;[111] **OR**
       - Pancreatic cancer;[111] **OR**
       - Prostate cancer with metastatic* or high- or very-high-risk group;[111] **OR**

- At least three diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the individual with breast cancer;[111] **OR**

3. Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age;[111] **OR**

4. Personal history of exocrine pancreatic cancer at any age;[111] **OR**

5. Personal history of prostate cancer with any of the following:[111]

   - Metastatic*****;[111] **OR**
   - High- or very-high-risk group;[111] **OR**
   - At least one first-, second- or third-degree relative with any of the following:[111]
     - Breast cancer at 50 years of age or younger;[111] **OR**
     - Triple-negative breast cancer at any age;[111] **OR**
     - Male breast cancer at any age;[111] **OR**
     - Ovarian cancer at any age;[111] **OR**
     - Pancreatic cancer at any age;[111] **OR**
     - Metastatic*****, high-, or very-high-risk group prostate cancer diagnosed at any age;[111] **OR**
     - At least three first-, second- or third-degree relatives on the same side of the family with breast and/or prostate cancer (any grade) including the individual with prostate cancer;[111] **OR**
     - Ashkenazi Jewish ancestry[111]

6. A pathogenic or likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline;[111] **OR**

7. Personal history of breast, ovarian, pancreatic or prostate cancer and any blood relative with a pathogenic or likely pathogenic variant in the *BRCA1* or *BRCA2* gene[111]

*****Biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence only.[111]

TP53 **Gene Testing for Li-Fraumeni Syndrome**

For **multigene panel testing for Li-Fraumeni syndrome**, please refer to the Multigene Next-Generation Sequencing Panel Testing Criteria

***TP53* full gene sequencing and deletion/duplication analysis** will be considered medically reasonable and necessary for Li-Fraumeni syndrome (LFS) when the following requirements are met (based on NCCN guidelines category 1 or 2A recommendations);[111]

- Individual to be tested meets classic LFS criteria, as demonstrated by the presence of **ALL** of the following:
    - Diagnosed with a sarcoma before 45 years of age; **AND**
    - First-degree relative diagnosed with cancer before 45 years of age; **AND**
    - An additional first-, or second-degree relative, on the same side of the family, diagnosed with cancer before 45 years of age or diagnosed with a sarcoma at any age; **OR**
- Individual to be tested meets Chompret criteria as demonstrated by the presence of at least 1 of the following:
    - Diagnosed with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, central nervous system [CNS] tumor, breast cancer, adrenocortical carcinoma) before 46 years of age, **AND** at least one first- or second-degree relative with any of the previously mentioned cancers (other than breast cancer if the proband has breast cancer) before 56 years of age or with multiple primaries at any age; **OR**
    - Diagnosed with multiple tumors (except multiple breast tumors), 2 of which belong to LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma) with the initial cancer occurring before 46 years of age; **OR**
    - Diagnosed with adrenocortical carcinoma or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype at any age of onset, regardless of the family history; **OR**
    - Diagnosed with breast cancer before 31 years of age; **OR**
- Individual to be tested diagnosed with pediatric hypodiploid acute lymphoblastic leukemia; **OR**
- Individual to be tested is affected and has a blood relative with a pathogenic or likely pathogenic variant in the *TP53* gene; **OR**
- Individual with cancer with a pathogenic or likely pathogenic *TP53* variant identified on tumor-only genomic testing and any of the following:
    - Individual meets at least one of the other LFS testing criterion above after reevaluation of personal and family history; **OR**

- Individual diagnosed at less than 30 years of age with any cancer; **OR**

- Individual presenting with a clinical scenario not meeting these criteria but warrants germline evaluation per clinician discretion

PTEN Gene Testing for PTEN Hamartoma Tumor Syndrome/Cowden Syndrome

For **multigene panel testing for PTEN hamartoma tumor syndrome/Cowden syndrome**, please refer to the Multigene Next-Generation Sequencing Panel Testing Criteria.

***PTEN* full gene sequencing and deletion/duplication analysis** will be considered medically reasonable and necessary for PHTS/CS (PHTS) when the following requirements are met (based on NCCN guidelines category 1 or 2A recommendations);[111]

- Individual to be tested does **NOT** meet PHTS Clinical Diagnostic Criteria and has a personal history of any of the following:

  - Adult Lhermitte-Duclos disease (cerebellar tumors); **OR**

  - Autism spectrum disorder and macrocephaly; **OR**

  - 4 or more minor PHTS/CS Testing Criteria; **OR**

  - 1 major and 3 or more minor PHTS/CS Testing Criteria (If an individual has 2 or more major criteria, such as breast cancer and nonmedullary thyroid cancer, but does not have macrocephaly, one of the major criteria may be included as 1 of the 3 minor criteria to meet testing criteria); **OR**

  - 3 or more major PHTS/CS Testing Criteria without macrocephaly; **OR**

  - 2 or more biopsy-proven trichilemmomas; **OR**

  - 2 or more major PHTS/CS Testing Criteria (one must be macrocephaly); **OR**

- Individual to be tested has a personal history of Bannayan-Ryile-Ruvalcaba syndrome (BRRS); **OR**
- Individual to be tested meets PHTS Clinical Diagnostic Criteria as demonstrated by:

  - 3 major criteria of the PHTS Clinical Diagnostic Criteria (one must include macrocephaly, Lhermitte-Duclos disease or gastrointestinal [GI] hamartomas); **OR**

  - 2 major and 3 minor criteria of the PHTS Clinical Diagnostic Criteria; **OR**

- Individual to be tested is affected and has a blood relative with a pathogenic or likely pathogenic variant in the *PTEN* gene; **OR**

- *PTEN* pathogenic or likely pathogenic variant detected by tumor genomic testing on any tumor type in the absence of germline analysis

The use of the criteria in this Medicare Advantage Medical Coverage Policy provides clinical benefits highly likely to outweigh any clinical harms. Services that do not meet the criteria above are not medically necessary and thus do not provide a clinical benefit. Medically unnecessary services carry risks of adverse outcomes and may interfere with the pursuit of other treatments which have demonstrated efficacy.

Coverage Limitations

US Government Publishing Office. Electronic code of federal regulations: part 411 – 42 CFR § 411.15 - Particular services excluded from coverage

The following tests may not be considered a benefit (statutory exclusion):[116]

- Tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law; **OR**
- Tests that confirm a diagnosis or known information; **OR**
- Tests to determine risk for developing a disease or condition; **OR**
- Tests performed to measure the quality of a process; **OR**
- Tests without diagnosis specific indications; **OR**
- Tests identified as investigational by available literature and/or the literature supplied by the developer and are not a part of a clinical trial

These treatments and services fall within the Medicare program's statutory exclusion that prohibits payment for items and services that have not been demonstrated to be reasonable and necessary for the diagnosis and treatment of illness or injury (§1862(a)(1) of the Act). Other services/items fall within the Medicare program's statutory exclusion at 1862(a)(12), which prohibits payment.

The following items will not be considered medically reasonable and necessary:

- Any laboratory test that investigates the same germline genetic content, for the same genetic information, that has already been tested in the same individual[42,43,44,45,46]
- Deletion/duplication analysis is obtained as part of the sequencing procedure but submitted as an independent analysis

- Genetic tests that have not demonstrated clinical utility, analytical and clinical validity via the MolDX Program
- Multigene panel if only a single gene on the panel is considered reasonable and necessary
- Multigene panel with genes that are not relevant to the individual's personal and family history
- Multigene panel used to confirm a variant(s) detected by somatic tumor testing that can be confirmed by a test targeted to that specific variant(s)[32,33,34,35,36]
- Multigene panel used to identify a KFV that could be identified with a test targeted to that specific variant[32,33,34,35,36]
- Previous test performed for the same genetic content[32,33,34,35,36]
- Repeat germline testing (testing is limited to once-in-a-lifetime)[42,43,44,45,46]

A review of the current medical literature shows that the evidence is insufficient to determine that these services are standard medical treatments. There remains an absence of randomized, blinded clinical studies examining benefit and long-term clinical outcomes establishing the value of these services in clinical management.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)	
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)	
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	
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	
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis	
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant	
81323	PTEN (phosphatase and tensin homolog) (eg, 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	
81404	Molecular pathology procedure, Level 5 (eg, 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 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)	
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)	
81408	Molecular pathology procedure, Level 9 (eg, 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); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53	
81433	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11	
81479	Unlisted molecular pathology procedure	
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])	
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])	
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)	

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)	
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)	
0133U	Hereditary prostate cancer-related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure)	
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)	
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)	
0136U	ATM (ataxia telangiectasia mutated) (eg, ataxia telangiectasia) mRNA sequence analysis (List separately in addition to code for primary procedure)	
0137U	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)	
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)	
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	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		

HCPCS Code(s)	Description	Comments
No code(s) identified		

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Appendix

Appendix A
Family Relationships

Degree of Relationship	Relative of the Individual to be Tested
First-degree	Child, full-sibling, parent
Second-degree	Aunt, uncle, grandchild, grandparent, nephew, niece, half-sibling
Third-degree	First cousin, great aunt, great-uncle, great-grandchild, great-grandparent, half-aunt, half-uncle

Appendix B
Initial Risk Stratification and Staging Workup for Clinically Localized Disease[114]

Risk Group	Clinical/Pathologic Features
Very-low	All of the following: • cT1c; **AND** • Grade Group 1; **AND** • PSA less than 10 ng/mL; **AND** • Fewer than three prostate biopsy fragments/cores positive, 50% or less cancer in each fragment/core; **AND** • PSA density less than 0.15 ng/mL/g
Low	All of the following (but does not qualify for very-low-risk): • cT1-cT2a; **AND**

	• Grade Group 1; **AND** • PSA less than 10 ng/mL

Intermediate	All of the following:
	
	• No high-risk group features; **AND**
	• No very-high-risk group features; **AND**
	• Has one or more of the following intermediate risk factors:
	  ○ cT2b-cT2c
	  ○ Grade Group 2 or 3
	  ○ PSA 10-20 ng/mL

High	No very-high-risk features and exactly one of the following high-risk features: • cT3a; **OR** • Grade Group 4 or Grade Group 5; **OR** • PSA more than greater than 20 ng/mL
Very-high	At least one of the following: • cT3b-cT4 • Primary Gleason pattern 5 • Two or three high-risk features • More than four cores with Grade Group 4 or 5

Appendix C
American Joint Committee on Cancer (AJCC) TNM Staging System for Prostate Cancer[114]

Primary tumor (T)	
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)	
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
Note: There is no pathological T1 classification. Note: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.	
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)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease
Note: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.	

Appendix D
AJCC Prognostic Groups[112] (When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available)

Group	T	N	M	PSA (ng/mL)	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 IIA	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	1-4
Stage IIIC	Any	N0	M0	Any	5
Stage IVA	Any	N1	M0	Any	Any
Stage IVB	Any	Any	M1	Any	Any

Appendix E

Definition of Histologic Grade Group[114] (The Gleason system has recently been compressed into Grade Groups)

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

Appendix F

PHTS Clinical Diagnostic Criteria – Clinical diagnosis of PHTS when 3 major criteria (one must include macrocephaly, Lhermitte-Duclos disease or GI hamartomas) or 2 major plus 3 minor criteria are present[111]

Major Criteria	Minor Criteria
• Breast cancer • Endometrial cancer (epithelial) • Follicular thyroid cancer • GI hamartomas (including ganglioneuromas but excluding hyperplastic polyps; at least 3) • Lhermitte-Duclos disease (adult) • Macrocephaly (at least 97th percentile: 58 cm for females, 60cm for males) • Macular pigmentation of glans penis • Multiple mucocutaneous lesions (any of the following):	• Autism spectrum disorder • Colon cancer • Esophageal glycogenic acanthoses (at least three) • Intellectual disability (IQ less than or equal to 75) • Lipomas (at least 3) • Renal cell carcinoma • Testicular lipomatosis • Thyroid cancer (papillary or follicular variant of papillary)

○ Acral keratoses (at least three palmoplantar keratotic pits and/or acral hyperkeratotic papules) ○ Mucocutaenous neuromas (at least three) ○ Multiple oral papillomas (particularly on tongue and gingiva) (at least 3 OR biopsy proven OR dermatologist diagnosed) • Multiple trichilemmomas (at least three and at least one biopsy proven)	• Thyroid structural lesions (eg, adenoma, multinodular goiter) • Vascular anomalies (including multiple intracranial developmental venous anomalies)

Appendix G
PHTS/CS Testing Criteria[111]

Major Criteria	Minor Criteria
• Breast cancer • Endometrial cancer • Follicular thyroid cancer • Macrocephaly (megalocephaly) (at least 97th percentile: 58cm in adult women, 60cm in adult men) • Macular pigmentation of glans penis • Mucocutaneous lesions ○ One biopsy proven trichilemmoma ○ Multifocal or extensive oral mucosal papillomatosis ○ Multiple cutaneous facial papules (often verrucous) ○ Multiple palmoplantar keratosis • Multiple GI hamartomas or ganglioneuromas	• Autism spectrum disorder • Colon cancer • Esophageal glycogenic acanthosis (at least 3) • Intellectual disability (IQ less than or equal to 75) • Lipomas • Papillary or follicular variant of papillary thyroid cancer • Renal cell carcinoma • Single GI hamartoma or ganglioneuroma • Testicular lipomatosis • Thyroid structural lesions (eg, adenoma, nodule[s], goiter) • Vascular anomalies (including multiple intracranial developmental venous anomalies)

Change Summary

- 01/01/2024 New Policy.