Genetic Testing and Liquid Biopsy for Prostate Cancer

Humana

Medical Coverage Policy

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Disclaimer

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 prostate cancer. Testing may be appropriate for affected individuals as well as asymptomatic family members at increased risk for cancer. This type of testing may also be referred to as **germline genetic testing**.

Somatic tumor genetic testing identifies mutations in cancer cells by testing the tumor specimen. Tumor testing differs from germline testing. Germline testing is performed to determine an inherited risk of disease and these mutations are present in genes at birth. With tumor testing, genetic alterations occur after birth and throughout the lifetime. Tumor testing may be done to determine diagnostic,

therapeutic or prognostic significance. Sometimes somatic tumor testing detects germline variants.

Confirmatory (dedicated) germline genetic testing may be performed when a pathogenic or likely pathogenic variant (mutation) has been identified through somatic tumor genetic testing.

Homologous recombination repair (HRR) germline and somatic tumor genetic testing analyzes HRR genes, which are involved in the repair of damaged DNA, to detect variants that can inhibit the ability of these genes to repair DNA.

Immunohistochemistry (IHC) and microsatellite instability (MSI) testing may be performed to analyze prostate tumor tissue samples to determine if there are mutations in the mismatch repair (MMR) genes. Mutations in these genes are associated with an increased risk of developing a number of cancers.

Liquid biopsy refers broadly to laboratory testing on a body fluid sample, typically blood, to analyze the presence of cancer cells released from a tumor that are circulating or fragments of DNA from tumor cells in the fluid. These tests have been suggested to manage treatment, assist in drug selection, determine prognosis as well as therapy response and be used as a minimally invasive alternative to tumor biopsy. The test may have the potential to diagnose cancer at an early stage. Liquid biopsy may identify two main biomarkers in individuals with cancer: circulating cell-free DNA (cfDNA), also known as circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs). cfDNA are DNA fragments from a tumor that circulate in the blood or body fluid of an individual who has cancer.

Mitomic Prostate Cancer Core Test [PCMT]) is a molecular test that analyzes mitochondrial DNA (mDNA) to detect variants in tumor tissue of individuals with a negative prostate biopsy in whom prostate cancer continues to be suspected. (**Refer to Coverage Limitations section**)

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 individuals with a personal and/or family history of more than one hereditary condition or syndrome. 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.

ProstaVysion is a genetic test that purportedly provides information regarding prognosis of prostate cancer. The test analyzes three markers associated with prostate cancer: DNA methylation of *HOXD3*, *ERG* gene fusion/translocation and loss of the tumor suppressor gene, *PTEN*. Positive results of all three markers (triple-positive) indicates a poor prognosis. (**Refer to Coverage Limitations section**)

Tumor mutation burden (TMB) testing is a next-generation sequencing (NGS) test that examines tumor tissue to detect the number of variants in the DNA of the tumor. Tumors with a high number of mutations (TMB-high or TMB-H) are more likely to respond to certain types of immunotherapy.

For information regarding **genetic testing for the following**, please refer to Genetic Testing Medical Coverage Policy:

- DNA banking or preservation
- General population screening
- Individual 17 years of age or younger for adult-onset conditions
- Interpretation and reporting for molecular pathology procedure
- Polygenic risk score (PRS) and single nucleotide polymorphisms (SNPs)
- Repeat germline or somatic genetic testing
- Retrieved archival tissue

Humana recognizes that the field of genetic testing is rapidly changing and that other tests may become available.

Coverage Determination

Any state mandates for genetic testing and liquid biopsy for prostate cancer take precedence over this medical coverage policy.

Genetic testing may be excluded by contract. Please consult the member's individual contract regarding Plan coverage.

Apply General Criteria for Genetic and Pharmacogenomics Tests when disease- or gene-specific criteria are not available on a medical coverage policy. For information

regarding **general criteria for genetic tests**, please refer to Genetic Testing Medical Coverage Policy.

GERMLINE GENETIC TESTING

Germline Genetic Testing – Core Genes: *ATM, BRCA1, BRCA2, CHEK2, MLH1, MSH2, MSH6, PMS2* and *PALB2* - Affected Individual
Humana members may be eligible under the Plan for **germline single gene testing or targeted multigene panel of 50 or fewer genes (81479, 81445) that includes the core genes for prostate cancer susceptibility** that includes the core genes when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Personal history of prostate cancer; **AND**
  - Any of the following prostate cancer characteristics diagnosed at any age:
    - Metastatic by biopsy and/or radiography; **OR**
    - Regional (node-positive); **OR**
    - Intermediate-risk with intraductal or cribriform histology; **OR**
    - High-risk localized; **OR**
    - Very-high-risk localized; **OR**
  - Personal history of any of the following cancers:
    - Biliary tract; **OR**
    - Breast (includes invasive or ductal carcinoma in situ [DCIS]); **OR**
    - Colorectal; **OR**
    - Gastric; **OR**
    - Exocrine pancreatic; **OR**
    - Glioblastoma; **OR**
    - Melanoma; **OR**
    - Pancreatic; **OR**
    - Small intestinal; **OR**
    - Upper tract urothelial; **OR**

- Ashkenazi Jewish ancestry*; **OR**

- Father or brother diagnosed with prostate cancer (any grade) before 60 years of age; **OR**

- One or more first-, second- or third-degree relatives diagnosed with any of the following cancers:
  - Breast (includes invasive or DCIS) at 50 years of age or younger; **OR**
  - Colorectal at 50 years of age or younger; **OR**
  - Endometrial at 50 years of age or younger; **OR**
  - Exocrine pancreatic at any age; **OR**
  - Male breast at any age; **OR**
  - Ovarian at any age; **OR**
  - Prostate with any of the following characteristics:
    - Metastatic by biopsy and/or radiography at any age; **OR**
    - Regional (node-positive) at any age; **OR**
    - Intermediate-risk with intraductal or cribriform histology; **OR**
    - High-risk localized; **OR**
    - Very-high-risk localized; **OR**

- Two or more first-, second- or third-degree relatives, on the same side of the family, diagnosed at any age with:
  - Breast cancer (includes invasive or DCIS); **OR**
  - Prostate cancer (any grade); **OR**

- Three or more first- or second-degree relatives, on the same side of the family, diagnosed with any of the following Lynch syndrome-related cancers:
  - Biliary tract; **OR**
  - Colorectal; **OR**
  - Endometrial; **OR**
  - Exocrine pancreatic; **OR**
  - Gastric; **OR**
  - Glioblastoma; **OR**
  - Ovarian; **OR**

- Small intestinal cancer; **OR**
- Upper tract urothelial

Germline Genetic Testing – Core Genes: *ATM, BRCA1, BRCA2, CHEK2, MLH1, MSH2, MSH6, PMS2* and *PALB2* – Unaffected Individual

Humana members may be eligible under the Plan for **germline single gene testing or targeted multigene panel of 50 or fewer genes (81479, 81445) that includes the core genes for prostate cancer** that includes the core genes when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested is unaffected; **AND**
  - Ashkenazi Jewish ancestry*****; **OR**
  - One or more first-, second- or third-degree relatives with any of the following cancers:
    - Breast (includes invasive or DCIS) at 50 years of age or younger; **OR**
    - Colorectal at 50 years of age or younger; **OR**
    - Endometrial at 50 years of age or younger; **OR**
    - Exocrine pancreatic at any age; **OR**
    - Male breast at any age; **OR**
    - Ovarian at any age; **OR**
    - Prostate with any of the following characteristics:
      - Metastatic by biopsy and/or radiography at any age; **OR**
      - Regional (node-positive) at any age; **OR**
      - Intermediate-risk with intraductal or cribriform histology; **OR**
      - High-risk localized; **OR**
      - Very-high-risk localized; **OR**
  - Received a negative known familial variant (KFV) genetic test result but family history indicates high risk for hereditary prostate cancer; **OR**

- Two or more first-, second- or third-degree relatives, on the same side of the family with the following at any age:
  - Breast cancer (includes invasive or DCIS); **OR**
  - Prostate cancer (any grade)

Germline Genetic Testing – *ATM, BRCA1, BRCA2, CHEK2, MLH1, MSH2, MSH6, PMS2* and *PALB2* – Known Familial Pathogenic or Likely Pathogenic Variant

Humana members may be eligible under the Plan for **prostate cancer KFV genetic testing** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested has an affected first-, second- or third-degree relative with a pathogenic or likely pathogenic variant in *ATM, BRCA1, BRCA2, CHEK2, MLH1, MSH2, MSH6, PMS2* or *PALB2* genes (test known KFV).

*****Ashkenazi Jewish ancestry is defined as having one grandparent identified as of Ashkenazi Jewish descent. In the absence of a KVF, testing begins with the three Ashkenazi Jewish founder specific mutations (*BRCA1 185delAG, BRCA1 5382insC* and *BRCA2 6174delT*). If negative, proceed to single gene testing or targeted multigene panel that includes the core genes: *ATM, BRCA1, BRCA2, CHEK2, MLH1, MSH2, MSH6, PMS2* and *PALB2*.

HOMOLOGOUS RECOMBINATION REPAIR (HRR) GENETIC TESTING

HRR Germline and Somatic Tumor Genetic Testing – Core Genes *ATM, BRCA1, BRCA2, CDK12, CHEK2, FANCA, PALB2, RAD51D*

Humana members may be eligible under the Plan for **germline and/or somatic tumor single gene or targeted multigene panel of 50 or fewer genes (81479, 81445) that includes the core genes for HRR for metastatic castration-resistant prostate cancer (mCRPC)** when the following criteria are met:

- Testing performed prior to initiation of treatment with rucaparib (Rubraca); **AND**

- Progression of disease despite prior treatment with abiraterone (Yonsa; Zytiga), enzalutamide (Xtandi), apalutamide (Erleada) or darolutamide (Nubeqa) and a taxane-based chemotherapy (eg, docetaxel [Taxotere]); **OR**

- Testing performed prior to initiation of treatment with olaparib (Lynparza); **AND**

- Progression of disease despite prior treatment with abiraterone or enzalutamide

For information regarding **Erleada, Lynparza, Nubeqa, Rubraca, Xtandi, Yonsa, and Zytiga**, please refer to Erleada (apalutamide), Nubeqa (darolutamide), Lynparza (olaparib), Rubraca (recaparib), Xtandi (enzalutamide), Yonsa (abiraterone acetate) or Zytiga ([abiraterone acetate] and generic abiraterone acetate) Pharmacy Coverage Policies.

SOMATIC TUMOR TESTING

Somatic Tumor Testing for Microsatellite Instability (MSI) and Deficient Mismatch Repair (dMMR) by Immunohistochemistry (IHC)

Humana members by be eligible under the Plan for **somatic tumor testing for MSI and/or dMMR by IHC** when the following criteria are met:

- Metastatic or unresectable prostate cancer; **AND**

- Progression of disease despite prior treatment; **AND**

- Testing performed prior to initiation of treatment with pembrolizumab (Keytruda)

For information regarding **Keytruda**, please refer to Keytruda (pembrolizumab) Pharmacy Coverage Policy.

CONFIRMATORY (DEDICATED) GERMLINE GENETIC TESTING

Confirmatory Germline Genetic Testing - *ATM, BRCA1, BRCA2, CHEK2, MLH1, MSH2, MSH6, PALB2* or *PMS2* Genes

Humana members may be eligible under the Plan for **confirmatory germline genetic testing for prostate cancer** when a pathogenic or likely pathogenic variant has been

identified in the *ATM, BRCA1, BRCA2, CHEK2, MLH1, MSH2, MSH6, PALB2* or *PMS2* genes with somatic tumor genetic testing and germline genetic testing has not been previously conducted.

TUMOR MUTATIONAL BURDEN (TMB) TESTING

TMB Testing

Humana members may be eligible under the Plan for **TMB testing** when the following criteria are met:

- Metastatic or unresectable prostate cancer; **AND**
- Progression of disease despite prior treatment and no alternative treatments available; **AND**

- Testing performed with FDA-approved assay (eg, FoundationOne CDx [0037U]) prior to initiation of treatment with pembrolizumab (Keytruda)

For information regarding **Keytruda**, please refer to Keytruda (pembrolizumab) Pharmacy Coverage Policy.

Coverage Limitations

Humana members may **NOT** be eligible for **genetic testing for prostate cancer** for any indications, genes or tests other than those listed above including, but may not be limited to:

- Any gene other than the core genes listed above for single gene testing or as part of a multigene panel (germline or somatic) including, but may not be limited to:
  - *ATR*
  - *BARD1*
  - *BRAF*
  - *BRIP1*
  - *CHEK1*
  - *ELAC2*
  - *EPCAM*
  - *ERG-PTEN* gene fusion
  - *GEN1*
  - *HOXD3*

- *MSR1*
- *NBN (NBS1)*
- *NKX3-1*
- *PTEN*
- *RAD51B*
- *RAD51C*
- *RAD54L*
- *RNASEL*
- *TMPRSS-ERG* fusion
- *TP53*

- Liquid biopsy (cfDNA and ctDNA) including, but may not be limited to:
  - Androgen receptor variant 7 (AR-V7) nucleus detection testing (such as Oncotype DX AR-V7 Nucleus Detect Test)
  - FoundationOne CDx Liquid (0239U)
  - miR Sentinel
  - SelectMDx for Prostate Cancer
- Mitomic Prostate Core Test [PCMT]) mitochondrial DNA (mDNA) variant testing
- Large multigene panels (51 or more genes) for any indication other than TMB assessment
- ProstaVysion
- TMB assessment performed with a non-FDA-approved test

These are considered experimental/investigational as they are not identified as widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **genetic testing for prostate cancer susceptibility** for the following:

- Individual to be tested is unaffected and an affected first-, second- or third-degree relative is available for genetic testing (if the relative is unavailable for testing, apply disease or gene-specific criteria for the unaffected individual)

- Sequencing, deletion/duplication analysis or large genomic rearrangement analysis (conducted individually, as comprehensive testing or step-wise) for the detection of a KFV without the KFV results of a relative

These are considered **not medically necessary** as defined in the member's individual certificate. Please refer to the member's individual certificate for the specific definition.

Background

Additional information about **prostate cancer** may be found from the following websites:

- American Cancer Society
- National Cancer Institute
- National Library of Medicine

Medical Alternatives

Physician consultation is advised to make an informed decision based on an individual's health needs.

Humana may offer a disease management program for this condition. **The member may call the number on his/her identification card to ask about our programs to help manage his/her care.**

Provider Claims Codes

Any CPT, HCPCS or ICD codes listed on this medical coverage 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	
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis	
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	
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	
81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants	
81403	MOLECULAR PATHOLOGY PROCEDURE LEVEL 4	**Not Covered if used to report any test outlined in Coverage Limitations section**
81406	MOLECULAR PATHOLOGY PROCEDURE LEVEL	**Not Covered if used to report any test outlined in Coverage Limitations section**
81408	MOLECULAR PATHOLOGY PROCEDURE LEVEL 9	

81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed	**Not Covered if used to report any test outlined in Coverage Limitations section**
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed	**Not Covered**
81479	Unlisted molecular pathology procedure	**Not Covered if used to report any test outlined in Coverage Limitations section**
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden	
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations	**Not Covered**
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 A
Pre- and Post-Test Genetic Counseling Criteria

Pre- and post-test genetic counseling performed by any of the following qualified medical professionals
Genetic counselor who is board-certified or board-eligible by the American Board of Medical Genetics and Genomics (ABMGG) or American Board of Genetic Counseling, Inc (ABGC) and is not employed by a commercial genetic testing laboratory; **OR**
Genetic clinical nurse (GCN) or advanced practice nurse in genetics (APNG) who is credentialed by the Genetic Nursing Credentialing Commission (GNCC) or the American of Nurses Credentialing Center (ANCC) and is not employed by a commercial genetic testing laboratory; **OR**
Medical geneticist who is board-certified or board-eligible by ABMGG; **OR**
Treating physician who has evaluated the individual to be tested and has completed a family history of three generations

Appendix B
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 C: Initial Risk Stratification and Staging Workup for Clinically Localized Disease[39]

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 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 D: American Joint Committee on Cancer (AJCC) TNM Staging System for Prostate Cancer[39]

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 one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one 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**
T	Primary tumor
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 E: AJCC Prognostic Groups[39] (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 F: Definition of Histologic Grade Group[39] (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