Laboratory Analysis for Prostate Cancer

Humana

Medical Coverage Policy

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Disclaimer

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Description

Laboratory analysis for prostate cancer may include a variety of methodologies including, but may not be limited to:

- Gene expression profiling (GEP)
- Genetic testing for prostate cancer prognosis
- Germline genetic testing
- Liquid biopsy
- Multianalyte assays with algorithmic analyses (MAAAs)
- Somatic (tumor) genetic testing
- Tumor marker testing

Measurement of prostate-specific antigen (PSA) is considered the gold standard for prostate cancer screening and management; however, only a biopsy of the prostate gland can establish a prostate cancer diagnosis. While these biopsies are the primary method for diagnosing prostate cancer, studies have shown that biopsies fail to identify prostate cancer in some men. As a result, several laboratory tests have been developed to assist with clinical decision making regarding initial or repeat prostate biopsy.

GEP is a laboratory test that measures the activity, or expression, of ribonucleic acid (RNA) of hundreds to thousands of genes at one time to give an overall picture of gene activity. GEP tests are typically performed on tumor tissue but may also be performed on other specimens such as blood. These tests often use microarray technology though other methodologies are also possible. GEP tests are used to determine prognosis, refine risk stratification and/or optimize treatment regimens and have been proposed for prostate cancer.

GEP tests differ from genetic tests. Genetic testing, also known as germline mutation testing, analyzes an individual's deoxyribonucleic acid (DNA) and can identify genetic mutations to determine inherited risk of disease. An individual's germline DNA is constant and identical in all body tissue types. RNA activity is measured by gene expression analysis. It is dynamic and responds to cellular environmental signals. Mutation analysis of tumor tissue determines DNA mutations that have been acquired over an individual's lifetime. These DNA changes are present only in the tissue sampled, are not usually representative of an individual's germline DNA and are not inheritable.

The following GEP assays are clinically available for prostate cancer:

- ConfirmMDx for Prostate Cancer is a tumor- (or tissue-) based epigenetic test. An epigenetic test analyzes the tissue next to (or adjacent to) a nearby cancer focus such as prostate cancer. This tissue can contain DNA molecular changes such as methylation. Cancer cells from a biopsy sample may not be detectable; however, methylation changes associated with the cancer may be identified through a technique referred to as methylation-specific polymerase chain reaction (PCR). The ConfirmMDx assay assesses the DNA methylation status of three genes associated with prostate cancer (ie, *GSTP1, APC, RASSF1*). The assay has been proposed to assist men who may be at high risk for cancer recurrence and are

considering a repeat prostate biopsy when the first biopsy result is negative. The test is performed on a formalin-fixed, paraffin-embedded (FFPE) sample. **(Refer to Coverage Limitations section)**

- Decipher Prostate Biopsy and Decipher Prostate RP are tumor- (or tissue-) based tests suggested for prognosis and treatment of prostate cancer. These tests use oligonucleotide microarrays that measure 22 RNA expression biomarkers (ie, *LASP1*, *IQGAP3*, *NFIB*, *S1PR4*, *THBS2, AN07, PCDH7, MYBPC1, EPPK1, TSBP, PBX1, NUSAP1, ZWILCH, UBE2C, CAMK2N1, RABGAP1, PCAT-32, GLYATL1P4/PCAT-80, TNF RSF19* plus three additional coding and noncoding genomic markers) extracted from a FFPE specimen. The Decipher Prostate Biopsy assay has been purported to determine prognosis for individuals diagnosed with prostate cancer by biopsy presenting with a low-, intermediate- or high-risk biopsy result. Decipher Prostate RP has been proposed for determining prognosis and treatment options for individuals following radical prostatectomy (RP). **(Refer to Coverage Limitations section)**

- Oncotype DX Genomic Prostate Score (GPS) is a tumor- (tissue-) based genomic test proposed for use for newly diagnosed prostate cancer to predict high grade disease in men under surveillance or as a prognostic following RP. The test utilizes quantitative reverse transcription polymerase chain reaction (RT-PCR) in which RNA is extracted to measure gene expression from prostate FFPE tissue. The assay analyzes 17 cancer genes (12 genes associated with prostate cancer plus five reference genes). The following genes are included: *AZGP1, FAM13C, KLK2, SRD5A2, FLNC, GSN, GSTM2, TPM2, BGN, COL1A1, SFRPA, TPX2, ARF1, ATPSE, CLTC, GPS1, PGK1*. **(Refer to Coverage Limitations section)**

- Prolaris Prostate Cancer (including Prolaris Biopsy Test and Prolaris Post-Prostatecomy Test) is a tumor- (tissue-) based RT-PCR test that evaluates gene expression from FFPE for any man diagnosed with prostate cancer. A Prolaris Score (also known as cell cycle progression [CCP] score) is then provided and is a measure of cancer aggressiveness. Prolaris evaluates 46 genes (31 cell cycle genes and 15 housekeeping genes). The following genes are included in the analysis: *FOXM1, CDC20, CDKN3, CDC2, KIF11, KIAA0101, NUSAP1, CENPF, ASPM, BUB1B, RRM2, DLGAP5, BIRC5, KIF20A, PLK1, TOP2A, TK1, PBK, ASF1B, C18orf24, RAD54L, PTTG1, CDCA3, MCM10, PRC1, DTL, CEP55, RAD51, CENPM, CDCA8, ORC6L, RPL38, UBA52, PSMC1, RPL4, RPL37, RPS29, SLC25A3, CLTC, TXNL1,*

PSMA1, RPL8, MMADHC, RPL13A/LOC728658, PPP2CA, MRFAP1. **(Refer to Coverage Limitations section)**

Multigene panel testing has also been proposed to determine an individual's risk for prostate cancer. Multigene panels are a type of genetic test to identify mutations in several genes simultaneously (as opposed to single gene testing that searches for a mutation in one specific gene). Targeted multigene panels have also been proposed for analysis of prostate cancer. These types of panels, also referred to as focused panels, include a limited number of genes with known or suspected associations with a disease such as prostate cancer. **(Refer to Coverage Limitations section)**

Commercially available multigene panels for hereditary prostate cancer include, but may not be limited to:

- Invitae Prostate Cancer Panel
- Prostate Cancer Comprehensive Panel
- Prostate Cancer Focus Panel
- ProstateNext

Paired DNA and RNA genetic testing (ie, +RNA Insight) is a genetic test that analyzes both DNA and RNA to supposedly identify individuals at risk for inherited cancers, including hereditary prostate cancer. **(Refer to Coverage Limitations section)**

The terminology, *paired*, may also be used to refer to confirmatory germline genetic testing performed following somatic (tumor) testing. Confirmatory germline testing paired with somatic testing differs from paired DNA and RNA testing (ie, +Insight RNA). For information regarding **paired confirmatory germline testing following somatic (tumor) testing**, please refer to somatic (tumor) testing below.

For information regarding **genetic testing for inherited susceptibility**, please refer to the following Medical Coverage Policies:

- Genetic Testing for Breast, Ovarian and Pancreatic Cancer Susceptibility
- Genetic Testing for Cancer Susceptibility
- Genetic Testing for Colorectal Cancer Susceptibility

Polygenic risk score (PRS) (ie, AmbryScore for Prostate Cancer) is a laboratory method using single nucleotide polymorphisms (SNPs) that have been purportedly associated with prostate cancer risk. The test is added to certain multigene panels to provide an assessment of prostate cancer. **(Refer to Coverage Limitations section)**

Genetic testing may also be performed to determine prognosis and guide treatment decisions. Examples include, but may not be limited to:

- *ERG* fusion and *PTEN* prognostic, tumor-based (or tissue-based) genetic panel (ie, ProstaVysion) to analyze *ERG* and *PTEN* genes supposedly associated with prostate cancer. **(Refer to Coverage Limitations section)**

- Mitochondrial DNA (mDNA) variant testing (ie, Mitomic Prostate Cancer Core Test [PCMT]) is a molecular test used in men with a negative prostate biopsy in whom prostate cancer continues to be suspected. This test analyzes a particular large-scale mDNA deletion mutation proposed as a known variant in prostate cancer cells. The test is performed on tissue obtained during prostate biopsy. **(Refer to Coverage Limitations section)**

- *PTEN* gene testing has been proposed for determining prognosis in men with prostate cancer. **(Refer to Coverage Limitations section)**

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, *MLH1, MSH2, MSH6* and *PMS2*. Mutations in these genes are associated with an increased risk of developing Lynch syndrome, which is linked to an elevated risk of several cancers such as colorectal and endometrial cancer.

Tumor mutations in may result in tumor MSI and deficient mismatch repair (dMMR). MSI testing can identify a defective MMR gene and IHC testing detects the presence or absence of protein products of the MMR genes. A missing protein suggests a gene mutation. Many solid tumors, including prostate cancer, can exhibit high levels of MSI (referred to as microsatellite instability-high or MSI-H) or dMMR. The presence of a tumor that is MSI-H or dMMR may indicate eligibility for clinical

trials or for treatment with Keytruda (pembrolizumab) for castration-resistant prostate cancer (CRPC). **(Refer to Coverage Limitations section)**

For information regarding **IHC/MSI testing for Lynch syndrome**, please refer Genetic Testing for Colorectal Cancer Susceptibility Medical Coverage Policy.

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

Liquid biopsy is a test performed usually on blood samples but may be performed on other body fluid samples such as urine. It purportedly analyzes the presence of cancer cells released from a tumor that are circulating or fragments of DNA from tumor cells in the fluid. ExoDx Prostate Test, Oncotype DX AR-V7 Nucleus Detect Test and SelectMDx for Prostate Cancer are examples of liquid biopsy tests for prostate cancer. **(Refer to Coverage Limitations section)**

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. The following genes associated with prostate cancer have been proposed: *ATM, BRCA1, BRCA2, CDK12, CHEK2, FANCA, PALB2, PTEN* and *RAD51D*. When performing tumor testing, germline cancer predisposition may be discovered or a clinically actionable variation in the germline may be missed. Therefore, confirmatory germline genetic testing (which may also be referred to as paired testing) should be performed to validate tumor testing results. Currently, most laboratories offer tumor testing only (ie, without confirmatory germline genetic testing). Please note that confirmatory germline testing paired with somatic testing differs from paired DNA and RNA testing (ie, +Insight RNA). For information regarding **paired DNA and RNA testing**, please refer to paired DNA and RNA genetic testing (ie, +RNA Insight) above.

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

- General population screening

- Individual less than 18 years old for adult-onset conditions
- Interpretation and reporting for molecular pathology procedures
- Negative or variant of unknown significance (VUS) testing result in a relative
- Retrieved archival tissue

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

MAAAs are laboratory measurements that use a mathematic formula to analyze multiple markers that may be associated with a particular disease state and are designed to evaluate disease activity or an individual's risk for disease. The laboratory performs an algorithmic analysis using the results of the assays and sometimes other individual information, such as gender and age and converts the information into a numeric score, which is conveyed on a laboratory report. Generally, MAAAs are exclusive (and/or proprietary) to a single laboratory which owns the algorithm. Prostate cancer is analyzed by the following MAAAs:

- 4Kscore measures the blood plasma levels of four different prostate-derived kallikrein proteins (total PSA, free PSA, intact PSA and human kallikrein2 [hK2]) and combines results in an algorithm with age, digital rectal exam (DRE) (nodules, no nodules) and prior biopsy results. The result purports to identify an individual's specific probability for finding a high-grade, Gleason score of seven or higher prostate cancer upon biopsy. **(Refer to Coverage Limitations section)**
- Apifiny is a non-PSA blood test that purportedly measures eight autoantibodies using T7 phage-peptide detection and an algorithm to assess risk for prostate cancer in men that have an elevated PSA level and are considering biopsy. **(Refer to Coverage Limitations section)**
- Mi-Prostate Score (MiPS) is an early detection test for prostate cancer that incorporates three specific markers, *TMPRSS2:ERG* (T2:ERG) gene fusion, prostate cancer antigen-3 (PCA3) and PSA. MiPS is designed to help individuals and their doctors make a decision after PSA testing about whether to monitor PSA levels or pursue a prostate biopsy. **(Refer to Coverage Limitations section)**

- PanGIA Prostate is a multianalyte molecular profiling urine test that uses a proprietary machine learning algorithm to purportedly assist with prostate biopsy decisions. **(Refer to Coverage Limitations section)**

- ProMark Proteomic Prognostic Test is a protein based prognostic test that uses eight biomarkers (ie, DERL1, CUL2, SMAD4, PDSS2, HSPA9, FUS, pS6, YBOX1), quantitative immunofluorescence and digitalized quantitative measurements to evaluate for prostate cancer. **(Refer to Coverage Limitations section)**

- Prostate Cancer Risk Panel is a fluorescence in situ hybridization (FISH) test that aims to assist with determining the probability of a higher prostate tumor grade. The test analyzes the following genes: *ASAP1, HDAC9, CHD1, PTEN*. **(Refer to Coverage Limitations section)**

- Prostate Health Index (PHI) test utilizes a calculation that combines the results of three quantitative blood serum immunoassays (PSA, free PSA and p2PSA) into a single numerical result (PHI score). This score is used to determine the probability of finding prostate cancer with a biopsy. PHI may also be referred to as proPSA. **(Refer to Coverage Limitations section)**

A tumor marker is a substance such as a protein, antibody, antigen or hormone in the body that may indicate the presence of cancer. Generally, these markers are specific to certain types of cancer and can be detected in blood, bodily fluids, stool, tissue and urine samples. The body may produce the marker in response to cancer or the tumor itself may produce the marker. The detection of tumor markers may be used to determine a diagnosis or as an indicator of disease (cancer) progression. It can also be used to document clinical response to treatment. Tumor markers for prostate cancer include, but may not be limited to, the following:

- IsoPSA is a blood based laboratory test that analyzes changes in PSA protein to detect prostate cancer. This test recently received US Food and Drug Administration (FDA) Breakthrough Device Designation. **(Refer to Coverage Limitations section)**

- Prostate cancer antigen 3 (PCA3) is a urine test that measures the levels of PCA3, which is a prostate-specific RNA that is overexpressed in men with prostate cancer. The test is performed on the first urine sample that is collected after a

DRE. Laboratories provide a PCA3 score, which is based on the ratio of PCA3 messenger RNA (mRNA) to PSA mRNA. The score purportedly may assist with determining if a repeat prostate biopsy is expected to be positive or if the individual can avoid an unnecessary repeat biopsy. Progensa PCA3 is an example of an FDA approved PCA3 test. **(Refer to Coverage Limitations section)**

- PSA (KLK3) testing (also referred to as total PSA [tPSA]) is a blood test that measures the amount of PSA present. PSA is a protein made solely by prostate cells. This test is most commonly used to screen for prostate cancer in men without symptoms though it is also one of the first tests for men who are symptomatic for prostate cancer. If PSA levels are high, additional testing might be recommended. PSA is also used for individuals already diagnosed with prostate cancer to stage cancer and to determine if treatment is working. Free PSA may be offered as a reflex test (ordered by a health care provider dependent on the results of PSA testing).

- PSA slope (eg, NADiA ProsVue) is a blood test that analyzes the rate of change in serum PSA over time following RP. It is also used for prognosis to identify men at risk for prostate cancer recurrence in men who have undergone prostatectomy. **(Refer to Coverage Limitations section)**

Coverage Determination

Any state mandates for genetic testing 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

Humana members may be eligible under the Plan for ***BRCA1*** **and** ***BRCA2*** **germline testing** when the following criteria are met:

- Individual to be tested diagnosed with any of the following:

- Metastatic prostate cancer by biopsy and/or radiography; **OR**
- Prostate cancer with intraductal/cribriform histology; **OR**
- Prostate cancer stratified as high-risk group characterized by one of the following:
  - T3a; **OR**
  - Grade Group 4 or Grade Group 5; **OR**
  - PSA greater than 20 ng/mL; **OR**
- Prostate cancer stratified as very-high-risk group characterized by one of the following:
  - At least two of the following high-risk features:
    - T3a; **OR**
    - Grade Group 4 or Grade Group 5; **OR**
    - PSA greater than 20 ng/mL; **OR**
  - T3b - T4; **OR**
  - Primary Gleason pattern 5; **OR**
  - Greater than four cores with Grade Group 4 or 5; **OR**

- Individual to be tested diagnosed with prostate cancer and any of the following:
  - Ashkenazi Jewish ancestry (for both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial mutation, begin testing with the three Ashkenazi Jewish founder specific mutations. If negative for the three mutations or ancestry also includes non-Ashkenazi Jewish relatives, proceed to *BRCA1* and *BRCA2* genetic testing); **OR**
  - At least one first-, second- or third-degree relative with:
    - Breast cancer (includes invasive or ductal carcinoma in situ [DCIS]) diagnosed before or at age 50 years; **OR**

- Metastatic prostate cancer by biopsy and/or radiography; **OR**
- Ovarian cancer; **OR**
- Pancreatic cancer; **OR**
- Prostate cancer with intraductal/cribriform histology; **OR**

- At least three of the following cancer diagnoses on the same side of the family:
  - Bile duct
  - Breast
  - Colorectal
  - Endometrial
  - Gastric
  - Kidney
  - Melanoma
  - Ovarian
  - Pancreatic
  - Prostate (except clinically localized Grade Group 1)
  - Small bowel
  - Urothelial; **OR**

- At least two first-, second- or third-degree relatives, on the same side of the family, diagnosed with breast cancer (includes invasive or DCIS) or prostate cancer (any grade); **OR**

- Brother, father or at least two first-, second- or third-degree relatives, on the same side of the family, who died from prostate cancer; **OR**

- Brother, father or at least two first-, second- or third-degree relatives, on the same side of the family, with prostate cancer (except clinically localized Grade Group 1) diagnosed at 60 years of age or younger; **OR**

- Individual to be tested has an affected first-, second- or third-degree relative with a pathogenic or likely pathogenic variant in *BRCA1* or *BRCA2* genes (test known familial variant [KVF]); **OR**

- Individual to be tested is unaffected and has a first-degree relative diagnosed with any of the following:

  - Metastatic prostate cancer by biopsy and/or radiography; **OR**

  - Prostate cancer with intraductal/cribriform histology; **OR**

  - Prostate cancer stratified as high-risk group characterized by one of the following:

    - T3a; **OR**
    - Grade Group 4 or Grade Group 5; **OR**
    - PSA greater than 20 ng/mL; **OR**

  - Prostate cancer stratified as very-high-risk group characterized by one of the following:

    - At least two of the following high-risk features:

      - T3a; **OR**
      - Grade Group 4 or Grade Group 5; **OR**
      - PSA greater than 20 ng/mL; **OR**

    - T3b - T4; **OR**
    - Primary Gleason pattern 5; **OR**
    - Greater than four cores with Grade Group 4 or 5

Confirmatory Germline Testing

Humana members may be eligible under the Plan for **confirmatory germline testing** (may also be referred to as paired confirmatory testing)***** of *BRCA1* and/or *BRCA2* when the following criteria are met:

- Performed on a second, independent sample; **AND**

- Potential germline variants in *BRCA1* or *BRCA2* are likely; **AND ANY** of the following:

  - At least three cancers (ie, bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate [except clinically localized Grade Group 1], small bowel or urothelial cancer) diagnosed in a first-, second- or third-degree relative, on the same side of the family, especially for diagnoses at 50 years of age or younger; **OR**

  - Brother, father or multiple family members (ie, at least two) diagnosed with prostate cancer (except clinically localized Grade Group 1) at 60 years of age or younger or who died from prostate cancer; **OR**

  - Somatic (tumor) testing positive for *BRCA1* and/or *BRCA2*

*****Confirmatory germline testing is sometimes referred to as paired confirmatory germline testing. This differs from paired DNA/RNA testing (ie, +RNA Insight). For more information regarding **paired confirmatory testing vs. paired DNA/RNA testing**, please refer to the Description section.

Somatic (Tumor) Genetic Testing

Humana members may be eligible under the Plan for **somatic (tumor) genetic testing for *BRCA1* and/or *BRCA2*** for individuals diagnosed with metastatic prostate cancer who are under consideration for treatment with Lynparza (olaparib).

For information regarding **Lynparza**, please refer to Lynparza (olaparib) Pharmacy Coverage Policy.

Tumor Markers**

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

- Annual prostate cancer screening in asymptomatic men aged 45 and older; **OR**

- Management (eg, determination of biopsy necessity, monitoring, prognosis, recurrence detection) for individuals diagnosed with prostate cancer

**The General Criteria for Genetic Testing is not used for Coverage Determinations for tumor markers.

Note: The criteria for **PSA testing** are not consistent with the Medicare National Coverage Policy and therefore may not be applicable to Medicare members. Refer to the CMS website for additional information.

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for the following **gene expression profiling tests for prostate cancer** including, but may not be limited to:

- 12-gene mRNA expression assay for prostate cancer; **OR**
- 17-gene expression assay (ie, Oncotype DX Genomic Prostate Score); **OR**
- 22-gene expression assay (ie, Decipher Prostate Biopsy); **OR**
- 46-gene expression assay (ie, Prolaris Prostate Cancer [may also be referred to as cell-cycle progression score, Prolaris Biopsy Test, Prolaris Post-Prostatectomy Test]); **OR**
- Promoter methylation profiling of three genes (*APC, GSTP1, RASSF1*) (ie, ConfirmMDx for Prostate Cancer)

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 for **genetic (germline or somatic) testing** for prostate cancer risk for any genes other than *BRCA1* or *BRCA2* including, but may not be limited to:

- *ATM*
- *BARD1*
- *BRIP1*
- *CDK12*
- *CHEK2*

- *FANCA*
- *FANCL*
- *HOXB13*
- *MLH1, MSH2, MSH6, PMS2* (Lynch syndrome genes)
- *NBN (NBS1)*
- *PALB2*
- *PTEN*
- *RAD51B*
- *RAD51C*
- *RAD51D*
- *RAD54L*

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 to determine prognosis or guide treatment decisions** including, but may not be limited to:

- *ERG* gene fusion and *PTEN* prognostic, tumor- (or tissue-) based genetic panel (ie, ProstaVysion); **OR**

- *PTEN* gene testing; **OR**

- *TMPRSS-ERG* fusion gene testing

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 **liquid biopsy** for prostate cancer including, but may not be limited to:

- Androgen receptor variant 7 (AR-V7) nucleus detection testing (ie, Oncotype DX AR-V7 Nucleus Detect Test); **OR**

- Gene expression profiling by real-time polymerase chain reaction (RT-PCR) of three genes (*ERG, PCA3, SPDEF)* in urine (ie, ExoDx Prostate Test); **OR**

- mRNA urine analysis for prostate cancer related biomarkers (HOXC6 and DLX1) (ie, SelectMDx for Prostate Cancer)

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 **immunohistochemistry (IHC)/microsatellite instability MSI tumor testing for prostate cancer.** These are considered experimental/investigational as they are not identified as widely used and generally accepted for the proposed use as reported in national recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **mitochondrial DNA (mDNA) variant testing** (ie, Mitomic Prostate Core Test [PCMT]) for prostate cancer. This is considered experimental/investigational as it is not identified as widely used and generally accepted for the proposed use as reported in national recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for the following **multianalyte assays with algorithmic analyses (MAAAs) for prostate cancer** including, but may not be limited:

- 4Kscore Test; **OR**

- Autoantibody multiplexed immunoassay and flow cytometry serum prostate cancer test (ie, Apifiny); **OR**

- Multianalyte molecular profiling urine test using machine learning (ie, PanGIA Prostate); **OR**

- ProMark Proteomic Prognostic Test; **OR**

- Prostate Health Index (PHI); **OR**

- Serum based FISH analysis of four genes (*ASAP1, HCAC9, CHD1, PTEN*) (ie, Prostate Cancer Risk Panel); **OR**

- Urine and PSA in serum for *PCA3* and *TMPRSS2-ERG* measurement by RNA amplification and fluorescence-based detection test for prostate cancer (ie, Mi-Prostate Score [MiPS]); OR

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 **germline or somatic multigene panels^ (including targeted panels)** unless **ALL** of the genes in the panel are relevant to the personal and family history of the individual being tested and the individual being tested meets the criteria above. 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 **multigene panels^ for hereditary prostate cancer** unless **ALL** genes in the panel are relevant to the personal and family history of the individual being tested and the individual being tested meets the criteria above. Examples of multigene panels for hereditary prostate cancer include, but may not be limited to:

- Invitae Prostate Cancer Panel; **OR**
- Prostate Cancer Comprehensive Panel; **OR**
- Prostate Cancer Focus Panel; **OR**
- ProstateNext

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.
^^Individual tests within a multigene panel may be medically necessary when the above criteria are met (ie, *BRCA1, BRCA2*).

Humana members may **NOT** be eligible under the Plan for **paired DNA and RNA genetic testing** (ie, +RNA Insight) for prostate cancer. This is considered experimental/investigational as it is not identified as widely used and generally accepted for the proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

(Confirmatory germline testing is sometimes referred to as *paired* confirmatory germline testing. This differs from paired DNA/RNA testing [ie, +RNA Insight]. For more information regarding **paired confirmatory testing vs. paired DNA/RNA testing**, please refer to the Description section).

Humana members may **NOT** be eligible under the Plan for **polygenic risk score (PRS) or single nucleotide polymorphism (SNP) testing** for prostate cancer risk. This is considered experimental/investigational as it is not identified as widely used and generally accepted for the proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **repeat somatic testing** for prostate cancer. This is considered experimental/investigational as it is not identified as widely used and generally accepted for the proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for the following **tumor marker tests for prostate cancer** including, but may not be limited:

- IsoPSA Assay; **OR**
- PCA3 (eg, Progensa PCA3 Assay); **OR**
- PSA slope (ie, NADiA Prosvue)

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.

Background

Additional information about **prostate cancer testing** 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)	**Not Covered if used to report any testing outlined in Coverage Limitations section**
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis	
81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis	
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	

81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)	**Not Covered**
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis	**Not Covered if used to report any testing outlined in Coverage Limitations section**
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant	**Not Covered if used to report any testing outlined in Coverage Limitations section**
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant	**Not Covered if used to report any testing outlined in Coverage Limitations section**
81400	MOLECULAR PATHOLOGY PROCEDURE LEVEL 1	
81479	Unlisted molecular pathology procedure	**Not Covered if used to report any testing outlined in Coverage Limitations section**
81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score	**Not Covered**
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score	**Not Covered**
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score	**Not Covered**

81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy	**Not Covered**
81599	Unlisted multianalyte assay with algorithmic analysis	**Not Covered if used to report any test outlined in Coverage Determination section**
84153	Prostate specific antigen (PSA); total	
84999	Unlisted chemistry procedure	**Not Covered if used to report any test outlined in Coverage Determination section**
86316	Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549), each	**Not Covered if used to report any test outlined in Coverage Determination section**
0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score	**Not Covered**
0011M	Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and urine, algorithms to predict high-grade prostate cancer risk	**Not Covered**
0021U	Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2), multiplexed immunoassay and flow cytometry serum, algorithm reported as risk score	**Not Covered** **Test Obsolete/No Longer Available**
0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score	**Not Covered**
0053U	Oncology (prostate cancer), FISH analysis of 4 genes (ASAP1, HDAC9, CHD1 and PTEN), needle biopsy specimen, algorithm reported as probability of higher tumor grade	**Not Covered**

0113U	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score	**Not Covered**
0133U	Hereditary prostate cancer-related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure)	**Not Covered**
0228U	Oncology (prostate), multianalyte molecular profile by photometric detection of macromolecules adsorbed on nanosponge array slides with machine learning, utilizing first morning voided urine, algorithm reported as likelihood of prostate cancer	**Not Covered** **New Code Effective 01/01/2021**
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
G0103	Prostate cancer screening; prostate specific antigen test (PSA)	

Medical Terms

Algorithmic – Referring to the process or set of rules by which a calculation or process can be carried out; usually referring to calculations that will be done by a computer.

Allele – One version of a gene at a given location (locus) along a chromosome.

Androgen Receptor (AR) Genes – Genes that provide instructions for making the protein androgen receptor. Androgens are hormones and androgen receptors allow the body to respond appropriately to these hormones.

Antibody – A protein produced by the body's immune system when it detects harmful substances (antigens); neutralizes the antigen by binding specifically to it. Also referred to as an immunoglobulin.

Antigen – A toxin or other foreign substance that induces an immune response in the body, especially the production of antibodies.

Ashkenazi Jewish Ancestry – Ancestry traced back to the Jewish communities of Central and Eastern Europe.

Asymptomatic – Having no signs or symptoms of illness or disease.

Autoantibodies – An antibody that an organism produces against any of its own tissues, cells or cell components.

Bile Duct – A large duct that transports bile from the liver to the duodenum.

Biomarker – A biological molecule found in blood, other body fluids or tissues that is a sign of a normal or abnormal process; or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

Biopsy – Removal of a piece of tissue from a living body for a diagnostic study.

Cell Cycle – The series of events that take place in a cell that cause it to divide into two cells.

Chorionic Villus Sampling (CVS) – A prenatal test that can detect genetic and chromosomal abnormalities of a fetus; also known as chorionic villus biopsy.

Chromosome – Thread-like structure of deoxyribonucleic acid (DNA) that carries genes.

Colorectal Cancer – Cancer that occurs in the colon or rectum. Sometimes referred to as colon cancer.

Confirmatory – To establish the certainty or validity of something that is suspected or reported.

Cribriform – Pierced with small holes.

Deoxyribonucleic Acid (DNA) – The molecule that carries genetic information for a living organism.

Deoxyribonucleic Acid (DNA) Methylation – A biochemical process in which a strand of DNA is modified after it is replicated.

Deoxyribonucleic Acid (DNA) Mismatch Repair (MMR) – A system within the cell for correcting errors in DNA that works by detecting and replacing bases in the DNA that are wrongly paired (mismatched base). The system repairs the mismatch.

Derivative – A chemical compound that may be produced from another compound of similar structure in one or more steps.

Diagnostic – A symptom or a distinguishing feature serving as supporting evidence in a diagnosis.

Digital Rectal Exam (DRE) – A physical examination of the rectum, the last few inches of the bowel, just above the anus. The doctor uses a gloved and lubricated finger to check for abnormalities of the anus and rectum.

Digitalized – To convert something (eg, data or an image) to digital form.

Ductal carcinoma in situ (DCIS) – Cancer cells that start in the milk ducts of the breast but have not spread into the nearby breast tissue.

Endometrial Cancer – Cancer that begins in the uterus, a pelvic organ where fetal development occurs.

Flow Cytometry – A technique for identifying and sorting cells and their components (such as deoxyribonucleic acid [DNA]) by staining with a fluorescent dye and detecting the fluorescence usually by laser beam illumination.

Fluorescence in situ hybridization (FISH) – Laboratory technique used to detect small deletions or rearrangements in chromosomes.

Formalin-Fixed Paraffin-Embedded (FFPE) – A method for clinical sample preservation and archiving, using a formaldehyde and water solution as the

preservative and paraffin, a waxy substance, as the fixative to stabilize the specimen.

Fusion Gene – A gene made by joining two parts of different genes.

Gastric Cancer – A disease in which malignant (cancer) cells form in the lining of the stomach.

Gleason Score – A system of grading prostate cancer tissue based on how it looks under a microscope. Gleason scores range from two to 10 and indicate how likely it is that a tumor will spread.

Histology – The study of the microscopic structure of tissues.

Hormone – A chemical substance produced in the body which has a specific regulatory effect on the activity of certain cells or a certain organ or organs.

Housekeeping Gene – Any of the genes that are constitutively (a gene that is transcribed continually) expressed at a relatively constant level across many or all known conditions. The terminology housekeeping gene is often used interchangeably with reference gene.

Immunoassay – A technique used to detect the presence or quantity of a substance (as a protein) based on its capacity to act as an antigen.

Immunofluorescence – A technique used with a fluorescence microscope for determining the location of an antigen (or antibody) in tissues by reaction with an antibody (or antigen) labeled with a fluorescent dye.

Immunohistochemical (IHC) Analysis – Laboratory process of detecting an organism in tissues with antibodies.

Intraductal Prostate Cancer – A type of cancer that usually begins in the secretory tissue that lines the prostate and spreads to the ducts within the prostate.

Invasive Breast Cancer – Cancer that has spread from where it began in the breast to surrounding normal tissue.

Kallikrein – A type of protease (an enzyme that breaks down proteins and peptides) that liberates kinins from kininogens.

Keytruda (Pembrolizumab) – A cancer medicine that interferes with the growth and spread of cancer cells in the body. Keytruda is used to treat a variety of types of cancer including, but may not be limited to, melanoma, lung cancer, gastric cancer and renal cell carcinoma. This drug is given only to individuals whose tumor tests positive for PD-L1 or if the tumor has a specific genetic marker.

Kinin – Any group of substances formed in the body tissue in response to injury.

Kininogen – An inactive precursor (a thing that comes before another of the same kind) of a kinin.

Localized Prostate Cancer – Confined to the prostate gland.

Lynch Syndrome – An inherited disorder that increases the risk of many types of cancer, particularly cancer of the colon and rectum. Also known as hereditary nonpolyposis colorectal cancer (HNPCC).

Lynparza (Olaparib) – A cancer medicine that interferes with the growth and spread of cancer cells in the body. Lynparza is used to treat ovarian cancer, fallopian tube cancer, peritoneal cancer, breast cancer and pancreatic cancer in individuals with a certain abnormal inherited gene. It is a PARP inhibitor, a substance that blocks an enzyme in cells called PARP. PARP helps repair deoxyribonucleic acid (DNA) when it becomes damaged. DNA damage may be caused by many things, such as exposure to ultraviolet (UV) light, radiation, certain anticancer drugs, or other substances in the environment. In cancer treatment, blocking PARP may help keep cancer cells from repairing their damaged DNA, causing them to die. PARP inhibitors are a type of targeted therapy.

Machine Learning – An application of artificial intelligence (AI) that provides systems the ability to automatically learn and improve from experience without being explicitly programmed.

Melanoma – A tumor of melanin-forming cells, typically malignant and associated with skin cancer.

Messenger Ribonucleic Acid (mRNA) – The form of RNA in which genetic information transcribed from deoxyribonucleic acid (DNA) as a sequence of bases is transferred to a ribosome.

Metastatic Prostate Cancer – Cancer that originates in the prostate and then spreads to other parts of the body.

Microarray – A laboratory technology to identify changes in genes or gene expression.

Microsatellite Instability Analysis – Laboratory process to detection conditions marked by damaged deoxyribonucleic acid (DNA) due to defects in the normal DNA repair process.

Mitochondrial Deoxyribonucleic Acid (mDNA) – Mitochondria are structures within cells that convert the energy from food into a form that cells can use. Each cell contains hundreds to thousands of mitochondria, which are located in the fluid that surrounds the nucleus (the cytoplasm). Although most deoxyribonucleic acid (DNA) is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA.

Molecular – Relating to or consisting of molecules, a group of atoms bonded together, representing the smallest fundamental unit of a chemical compound that can take part in a chemical reaction.

Multiplex – A type of immunoassay that uses magnetic beads to simultaneously measure multiple analytes.

Mutation – Change of the deoxyribonucleic acid (DNA) order (sequence) within a gene or chromosome of an organism resulting in the creation of a new character or trait not found in the parental type.

Nodules – Solid, elevated areas of tissue or fluid inside or under the skin with a diameter greater than 0.5 cm.

Noncoding Deoxyribonucleic Acid (DNA) – DNA sequences that are components of an organism's DNA that do not encode protein sequences.

Oligonucleotide – A short polymer of two to twenty nucleotides, the basic structural unit of nucleic acids (deoxyribonucleic acid [DNA] or ribonucleic acid [RNA]).

Pathogenic – Capable of producing disease.

Phage-Peptide – A laboratory technique for the study of protein to protein, protein to peptide and proteins to deoxyribonucleic acid (DNA) interactions.

Polygenic – Referring to the heredity of complex characters that are determined by a large number of genes, each one usually having a relatively small effect.

Polymerase – An enzyme which brings about the formation of a particular polymer, especially deoxyribonucleic acid (DNA) or ribonucleic acid (RNA).

Polymerase Chain Reaction (PCR) – Laboratory process to detect small amounts of deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) in blood or tissue.

Prenatal – Occurring, existing or performed before birth.

Prognosis – A forecast of the likely course of a disease or ailment.

Proprietary – Owned and legally controlled by a particular company.

Prostate – A firm partly muscular gland surrounding the bladder neck and urethra in the male; produces a viscid secretion that is the fluid part of semen.

Prostatectomy – Surgical removal of the prostate gland.

Protein – Large molecule composed of amino acids; essential components of body tissue.

Proteomics – Large scale study of proteins.

Quantitative – Denoting or expressible as a measurement.

Quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR) – Laboratory technique that is used when the starting material is ribonucleic acid

(RNA). RNA is first transcribed into complementary deoxyribonucleic acid (DNA) by reverse transcriptase from total RNA or messenger RNA (mRNA). This method is used in a variety of applications such as gene expression analysis and genetic testing.

Radical Prostatectomy – A surgical procedure (or operation) to remove the prostate gland and some of the tissue around it.

Radiography – The use of x rays to view a nonuniformly composed material such as the human body. By utilizing the physical properties of the ray, an image can be developed to display areas of different density and composition. An application of this technology is medical imaging to assist in the diagnosis of disease.

Regional Prostate Cancer – Referring to a tumor that has grown through the prostate capsule, either into the seminal vesicles (a pair of glands next to the prostate) or into nearby muscles and organs.

Residual – The quantity remaining after other things have been subtracted.

Ribonucleic Acid (RNA) – A long, single-stranded chain of cells that processes protein.

Ribosome – A minute particle consisting of RNA and associated proteins found in large numbers in the cytoplasm of living cells. They bind mRNA and transfer RNA to synthesize (or combine) polypeptides and proteins.

Serum – The clear yellowish fluid that remains from blood plasma after clotting factors have been removed.

Single Nucleotide Polymorphisms (SNPs) – Gene variants that could indicate predispositions to certain conditions and predict how an individual responds to a medical therapy. Technique in which a ribonucleic acid (RNA) strand is reverse transcribed into its deoxyribonucleic acid (DNA) complement followed by amplification of the resulting DNA using polymerase chain reaction (PCR).

Stratified – To arrange or classify.

Therapeutic – Pertaining to the treatment or curing of a disease, injury or disorder.

Urethra – The duct by which urine is conveyed out of the body from the bladder and which in male vertebrates also conveys semen.

Urothelial Cancer – Cancer that begins in urothelial cells that typically line the urethra, bladder, ureters and renal pelvis. Urothelial cells are also called transitional cells because they cells can change shape and stretch without breaking apart. Also known as transitional cell cancer.

Variant – Alteration (variation) in the normal order (sequence) of a gene.

Variant of Unknown Significance (VUS) – A variation in a genetic sequence whose association with disease risk is unknown.

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Appendix A: Family Relationships

Degree of Relationship	Relative of the Individual to be Tested
First-degree	Child, full-sibling, parent
Second-degree	Aunt, uncle, grandparent, grandchild, niece, nephew, half-sibling
Third-degree	Great-grandparent, great-aunt, great-uncle, first cousin
Affected relative unavailable for genetic testing	Deceased, declines genetic testing or inability to contact

Appendix B: American Joint Committee on Cancer (AJCC) TNM Staging System for Prostate Cancer[69]

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**
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 C: AJCC Prognostic Groups[69] (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	cT1-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	1
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	Any
Stage IVA	Any	N1	M0	Any	Any
Stage IVB	Any	Any	M1	Any	Any

Appendix D: Definition of Histologic Grade Group[69] (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