

Gene Expression Profiling and Protein Biomarkers for Prostate Cancer

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I. Policy Description

Prostate cancer is characterized by malignancy which originates in the small walnut-shaped gland that produces the seminal fluid in individuals who have a prostate. Heterogeneous in both molecular alterations and progression, clinical course ranges from a microscopic tumor that never becomes clinically significant to aggressive disease that can cause metastases, morbidity, and death.^{1,2}

Gene expression assays quantify specific mRNAs being transcribed to assess the genes that are active in a particular cell or tissue. Analyses of gene expression can be clinically useful for disease classification, diagnosis, prognosis, and tailoring treatment to underlying genetic determinants of pharmacologic response.³ Protein expression-based assays measure the expression of the translation end-product(s) to assess cell-cycle progression. Similar to gene expression assays, protein biomarker-based assays can be clinically useful for disease classification and possible surveillance.^{4,5}

II. Related Policies

Policy Number	Policy Title
AHS-G2007	Prostate Biopsy Specimen Analysis
AHS-G2008	Prostate Specific Antigen (PSA) Testing
AHS-G2054	Liquid Biopsy
AHS-G2124	Serum Tumor Markers for Malignancies

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

- 1) For individuals with low-risk or favorable intermediate-risk disease, as defined by the NCCN (see Note 1), the one-time use of Prolaris®, Genomic Prostate Score®, or Decipher® tumor-based assays to guide the management of prostate cancer **MEETS COVERAGE CRITERIA** when **all** of the following conditions are met:
 - a) When pathological examination showed localized adenocarcinoma of the prostate with no clinical evidence of metastasis or lymph node involvement;
 - b) When the individual has no significant co-morbidities, including advanced age, to suggest they have an estimated life expectancy of less than 10 years.

- 2) For individuals with unfavorable intermediate-risk and high-risk disease, as defined by the NCCN (see Note 1), the one-time use of Prolaris® **or** Decipher® tumor-based assays to guide the management of prostate cancer **MEETS COVERAGE CRITERIA** when **all** of the following conditions are met:
 - a) When pathological examination showed localized adenocarcinoma of the prostate with no clinical evidence of metastasis or lymph node involvement;
 - b) When the individual has no significant co-morbidities, including advanced age, to suggest they have an estimated life expectancy of less than 10 years.

- 3) For individuals for whom there is a potential need for a prostate biopsy, the one-time use of the ExoDx Prostate (IntelliScore) (EPI) biomarker test (either once prior to initial biopsy or once prior to repeat biopsy) **MEETS COVERAGE CRITERIA** when **all** of the following conditions are met:
 - a) The individual has confirmed (see Note 2), moderately elevated PSA levels:
 - i) For individuals ages 50 – 75 years, PSA levels greater than 3 and less than 10 ng/mL
 - ii) For individuals over the age of 75, PSA levels greater than 4 and less than 10 ng/mL
 - b) The individual has none of the conditions for which a prostate biopsy is already indicated (see Note 3)
 - c) The individual has no other relative contraindication for prostate biopsy (see Note 4).

- 4) For individuals for whom there is a potential need for a prostate biopsy, the one-time use of the 4Kscore test (either once prior to initial biopsy or once prior to repeat biopsy) **MEETS COVERAGE CRITERIA** when **all** of the following conditions are met:
 - a) The individual has confirmed (see Note 2), moderately elevated PSA levels:
 - i) For individuals ages 45 – 75 years, PSA levels greater than 3 and less than 10 ng/mL
 - ii) For individuals over the age of 75, PSA levels greater than 4 and less than 10 ng/mL
 - b) The individual has none of the conditions for which a prostate biopsy is already indicated (see Note 3)
 - c) The individual has no other relative contraindication for prostate biopsy (see Note 4).

- 5) For individuals for whom there is a potential need for a prostate biopsy, the one-time use of the IsoPSA test (either once prior to initial biopsy **or** once prior to repeat biopsy) **MEETS COVERAGE CRITERIA** when **all** of the following conditions are met:
 - a) For individuals 50 years of age or older who have confirmed (see Note 2) PSA levels greater than 4 and less than or equal to 25 ng/mL
 - b) The individual has no other relative contraindication for prostate biopsy (see Note 4).

- 6) For individuals for whom there is a potential need for a prostate biopsy, the one-time use of the Prostate Health Index (either once prior to initial biopsy **or** once prior to repeat biopsy) **MEETS COVERAGE CRITERIA** when **all** of the following conditions are met:
 - a) For individuals 50 years of age or older who have confirmed (see Note 2) PSA levels greater than 4 and less than 10 ng/mL

- b) The individual has none of the conditions for which a prostate biopsy is already indicated (see Note 3)
 - c) The individual has no other relative contraindication for prostate biopsy (see Note 4).
- 7) For the assessment and/or monitoring of prostate cancer, the following tests **DO NOT MEET COVERAGE CRITERIA**:
- a) Ki-67 immunohistochemistry.
 - b) *PTEN* loss.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

- 8) The following tests **DO NOT MEET COVERAGE CRITERIA**:
- a) All other urine testing for gene expression profile and/or protein biomarkers designed to assess prostate cancer.
 - b) Other screening tests for prostate cancer (e.g., alpha-methylacyl coenzyme A racemase [AMACR], ConfirmMDx, early prostate cancer antigen, endoglin, E twenty-six [ETS] gene fusions, human kallikrein 2, analysis of prostatic fluid electrolyte composition, interleukin-6, transforming growth factor-beta 1, *TMPRSS2:ERG* gene fusion, MyProstateScore, gene hypermethylation, *PCA3/KLK3* ratio, *PCA3* score).
 - c) All other tests not described above that use cellular and biologic features of a tumor (e.g., those that are used to predict risk of recurrence in patients with prostate cancer).

NOTES:

Note 1: NCCN Prostate Cancer Initial Risk Stratification and Staging Workup for Clinically Localized Disease.⁶

Risk Group	Clinical/Pathological Features
Very Low	Has all of the following: <ul style="list-style-type: none"> · cT1c; AND · Grade Group 1 · PSA <10 ng/mL · Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core · PSA density <0.15 ng/mL/g
Low	Has all of the following but does not qualify for very low risk: <ul style="list-style-type: none"> · cT1-cT2a · Grade Group 1 · PSA <10 ng/mL
Intermediate	Has all of the following: Has all of the following:

	<ul style="list-style-type: none"> · No high-risk group features · No very-high-risk group features · Has one or more intermediate risk factors <ul style="list-style-type: none"> » cT2b-cT2c » Grade Group 2 or 3 » PSA 10-20 ng/mL 	<ul style="list-style-type: none"> Favorable Intermediate 	<ul style="list-style-type: none"> · 1 IRF · Grade Group 1 or 2 · <50% biopsy cores positive
		<ul style="list-style-type: none"> Unfavorable Intermediate 	<ul style="list-style-type: none"> Has one or more of the following: <ul style="list-style-type: none"> · 2 or 3 IRFs · Grade Group 3 · ≥50% biopsy cores positive
High	<ul style="list-style-type: none"> Has no very-high-risk features and has at least one high-risk feature: <ul style="list-style-type: none"> · cT3a OR · Grade Group 4 or Grade Group 5 OR · PSA >20 ng/mL 		
Very High	<ul style="list-style-type: none"> Has at least one of the following: <ul style="list-style-type: none"> · T3b-T4 · Primary Gleason pattern 5 · 2 or 3 high-risk features · >4 cores with Grade Group 4 or 5 		

Note 2: PSA elevation should be verified after a few weeks under standardized conditions (e.g., no ejaculation, manipulations, and urinary tract infections, no medications such as 5 α -reductase) in the same laboratory or other Clinical Laboratory Improvement Amendments (CLIA) approved laboratory before considering a biopsy.

Note 3: Conditions for which a prostate biopsy is already indicated:

- DRE suspicious for cancer.
- Persistently elevated PSA.
- Positive multiparametric MRI (if performed).
- Ethnicity at higher risk for prostate cancer (see Note 5)
- First-degree relative (see Note 6) with prostate cancer.
- Known to have a high-penetrance prostate cancer risk gene(s) per NCCN guidelines (see Note 7).

Note 4: Relative contraindications for a prostate biopsy:

- A less than 10-year life expectancy
- Benign disease not ruled out

Note 5: According to the NCCN Prostate Cancer Early Detection guidelines, “Black/African American individuals have a significantly higher incidence of prostate cancer, increased prostate cancer mortality, and earlier age of diagnosis compared to white individuals.”⁷

Note 6: First-degree relatives include parents, full siblings, and children of the individual.

Note 7: According to the NCCN Prostate Cancer Early Detection guidelines, the main high-penetrance cancer risk genes include *BRCA1*, *BRCA2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *HOXB13*, *CHEK2*, *NBN*, *PALB2*, *RAD51D*, and *TP53*.⁷

IV. Table of Terminology

Term	Definition
ADT	Androgen deprivation therapy
AMACR	Alpha-methylacyl coenzyme A racemase
APC	<i>Adenomatous polyposis coli gene</i>
ARSI	Androgen receptor signaling inhibitor
AR-V7	Androgen receptor splice variant-7
AS	Active surveillance
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
ATM	<i>ATM serine/threonine kinase gene</i>
AUA	American Urological Association
AUC	Area under the curve
BCR	Biochemical recurrence
<i>BRCA1</i>	<i>Breast cancer gene 1</i>
<i>BRCA2</i>	<i>Breast cancer gene 2</i>
CAPRA	Cancer of the prostate risk assessment
CCP	Cell-cycle progression
CCR	Cell-cycle risk
<i>CDK12</i>	<i>Cyclin dependent kinase 12 gene</i>
CDx	Companion diagnostic
<i>CHEK2</i>	<i>Checkpoint kinase 2 gene</i>
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CNAs	Copy number alterations
CTCs	Circulating tumor cells
DDR	DNA damage and repair
<i>DLX1</i>	<i>Distal-less homeobox 1 gene</i>
DRE	Digital rectal examination
DX	Diagnosis
EANM	European Association of Nuclear Medicine
EAU	European Association of Urology
EBRT	External beam radiation therapy
EDTA	Ethylenediaminetetraacetic acid
EPI	ExoDx Prostate (IntelliScore)
<i>ERG</i>	<i>ETS Transcription Factor ERG</i>
ESMO	European Society for Medical Oncology
ESTRO	European Society for Radiotherapy and Oncology
ESUR	European Society of Urogenital Radiology
ETS	E-twenty-six
<i>FANCA</i>	<i>Fanconi anemia complementation group A gene</i>
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence <i>in situ</i> hybridization
GEC	Gene/genomic expression classifiers

GPS	Genomic Prostate Score
<i>GSTP1</i>	<i>Glutathione S-transferase pi 1 gene</i>
HGPC	High-grade prostate cancer
hK2	Human kallikrein-2
<i>HOXB13</i>	<i>Homeobox B13 gene</i>
<i>HOXC6</i>	<i>Homeobox C6 gene</i>
HT	Hormonal therapy
IHC	Immunohistochemistry
indels	Insertion and deletion alterations
IRF	Intermediate-risk factor
ISUP	International Society of Urological Pathology
<i>KLK3</i>	<i>Kallikrein related peptidase 3 gene</i>
LDTs	Laboratory-developed tests
mCRPC	Metastatic castration-resistant prostate cancer
<i>MLH1</i>	<i>MutL homolog 1 gene</i>
MRI	Magnetic resonance imaging
<i>MSH2</i>	<i>MutS homolog 2 gene</i>
<i>MSH6</i>	<i>MutS homolog 6 gene</i>
<i>NBN</i>	<i>Nibrin gene</i>
NCCN	National Comprehensive Cancer Network
NPV	Negative predictive value
<i>PALB2</i>	<i>Partner and localizer of BRCA2 gene</i>
PARP	Poly (ADP-ribose) polymerase
PCa	Prostate cancer
PCA3	Prostate cancer gene 3
PPCR	Polymerase chain reaction
PCRMP	Prostate Cancer Risk Management Programme
PHI	Prostate health index
PLA	Proprietary laboratory analyses
PPV	Positive predictive value
PSA	Prostate specific antigen
<i>PTEN</i>	<i>Phosphatase and tensin homolog gene</i>
QALY	Quality adjusted life-years
<i>RAD51D</i>	<i>RAD51 poaralog d gene</i>
<i>RASSF1</i>	<i>Ras association domain family 1 gene</i>
RNA	Ribonucleic acid
RP	Radical prostatectomy
RT	Radiation therapy
RT-PCR	Reverse transcription-polymerase chain reaction
<i>TMPRSS2</i>	<i>Transmembrane serine protease 2</i>
<i>TP53</i>	<i>Tumor protein 53 gene</i>
TRUS	Transrectal ultrasound guided biopsy

V. Scientific Background

Prostate cancer (PCa) is the most common cancer in American individuals who have a prostate and the second leading cause of death in the same group. In 2025, the American Cancer Society estimates that approximately 313,780 new prostate cancer diagnoses and approximately 35,770 prostate cancer deaths will occur; although, the five-year survival rate between 2014-2020 was 97%. About one individual in eight amongst those who have a prostate will be diagnosed with prostate cancer during their lifetime in the United States.^{8,9}

Many cases of prostate cancer do not become clinically evident, as indicated in autopsy studies, where prostate cancer is detected in approximately 30 percent of individuals with a prostate aged 55 or older and approximately 60 percent of individuals with a prostate by age 80.¹⁰ These data suggest that prostate cancer often grows so slowly that most individuals die of other causes before the disease becomes clinically advanced.¹¹

Prostate cancer survival is related to many factors, especially the extent of tumor at the time of diagnosis. The five-year relative survival among individuals with cancer localized to the prostate or with regional spread is 100%, compared with 31% among those diagnosed with distant metastases.¹¹ Gene expression profiling has been proposed as a method of risk stratification for prostate cancer. Several tests evaluating the expression levels of various genes have been produced to be used in conjunction with other tools such as Gleason score and prostate-specific antigen (PSA) assessment. The Gleason score is a scoring system used to categorize a prostate cancer biopsy based on risk assessment.

Tissue-based gene expression classifiers (GEC) are now widely used to assist in prostate cancer prognosis. These tests are RNA-based prognostic biomarkers that analyze a distinct multigene panel to predict cancer progression, from the chance of having the disease to the probability of death at ten years due to prostate cancer. Genomic tests can predict prostate cancer aggressiveness, detect potentially dangerous prostate cancer-related genomic activity, and utilize biopsy samples to deliver prognostic information via immunofluorescence imaging. Additionally, researchers have identified the potential of microRNAs as human prostate cancer biomarkers.¹² While several types of biomarker tests exist, the NCCN specifically recommends Prolaris, Genomic Prostate Score® (GPS) (formerly Oncotype Dx Prostate), and Decipher as tumor-based molecular assays to consider during initial risk stratification.⁶ Ki-67 and PTEN are also listed in NCCN guidelines, but are not recommended.⁶

Proprietary Testing, Clinical Utility, and Analytical Validity

Hu, et al. (2018) evaluated the utility of three genomic expression classifiers (GEC), including Decipher, GPS, and Prolaris. A total of 747 patients underwent GEC testing. The authors found that “Among patients with clinical favorable risk of cancer, the rate of active surveillance (AS) differed significantly among patients with a GEC result above the threshold (46.2%), those with a GEC result below the threshold (75.9%), and those who did not undergo GEC (57.9%).” The authors further estimated that for every nine individuals “with favorable risk of cancer who undergo GEC testing, one additional patient may have their disease initially managed with AS.”¹³

Prolaris

The test “Prolaris” (created by Myriad Genetics) has been used to inform decision making on AS and whether to proceed to a treatment option, such as radiation or surgery. Prolaris is an assessment of the average expression of 31 cell-cycle progression (CCP) genes compared to 15 reference genes. This score

is combined with the patient's age, PSA, percent positive cores, clinical stage, Gleason score, and American Urological Association (AUA) risk category; it is intended to provide a 10-year prostate cancer-specific mortality risk. Scores range from zero to ten, with each unit increase representing a doubling of disease-risk progression. Prolaris may also be used to assess risk post-prostatectomy, and the same scale of zero to ten is used. Each unit increase represents a doubling of risk of biochemical recurrence (BCR).¹⁴

Cell cycle progression expression has been found to correlate with mortality rate of prostate cancer and can provide important pretreatment prognostic information. Cuzick, et al. (2015) found that not only was there a relationship between CCP expression and mortality rate, the increased expression of CCP was predictive of BCR after 10 years. Even after adjusting for factors such as PSA and Gleason score, the CCP was both "highly significant" and "independent" of prostate cancer mortality rate. The authors noted that the CCP score could be created from minimal tumor mass (as little as 0.5 mm), with a 90% success rate with >0.5 mm visible tumor, as well as Prolaris' objective criteria compared to the Gleason score.¹⁵

Prolaris may be used to lower unnecessary treatment by providing a molecular indication of the disease's progression. Radical treatments, such as prostatectomies, are often unnecessary, and there is utility in a biomarker metric than can reliably inform providers of a course of treatment or condition. An AS status is preferable to treatment. Hu, et al. (2018) used data provided by the CCP score (along with two other biomarker tests) to perform risk stratification and assess whether further treatment was needed or if the condition could be managed by active surveillance. Lin, et al. (2018) clearly separated high- and low-risk patients using the CCP score. The study combined the CCP score as well as a clinical assessment from the Cancer of the Prostate Risk Assessment (CAPRA) into a cell-cycle risk (CCR) score. This CCR score was used to select patients for an AS status. The threshold created from both the molecular measures and the clinical measures has the advantage of including higher-risk patients whose clinical features may be lower-risk. Furthermore, the patients that fell below the threshold were found to have a mortality risk of 2.5%, and the probability of survival of patients with scores under the threshold was 100%.^{13,16} Finally, Prolaris has been used by providers to inform clinician decision making. A survey by Carneiro, et al. (2018) found that the course of treatment for prostate cancer patients was influenced by Prolaris' results. About 65% of cases were reported to have shifted in the intended treatment based on the test results, and about 40% were reported to have opted for the AS choice (a "decrease" in treatment).¹⁷

Tward, et al. (2020) studied the ability of CCR to predict prostate cancer metastasis using Prolaris. According to a CCR threshold of 2.112, 29.5% patients were hypothesized to be high risk metastasis (CCR>2.112) and 70.5% were unfavorable intermediate risk patients (CCR < 2.112). Patients were followed five years later to determine if CCR accurately predicted metastasis in those undergoing multimodality therapy (androgen deprivation with surgery) or radiation therapy. According to the results, the CCR score does provide a clinically meaningful different risk of metastasis for patients receiving multimodality therapy or radiation therapy. Multimodality therapy reduced patients' risk of metastasis and treatment benefit can be evaluated as a function of the CCR score. For those with CCR scores below the threshold of 2.112 (27% of high-risk group and 73% of the unfavorable intermediate group), radiation therapy was considered after assessing the difference in the risk of metastasis.¹⁸

Genomic Prostate Score[®] (*GPS*[™]) (formerly Oncotype Dx Prostate) is similar to Prolaris in that it assesses levels of gene expression, should be used for lower-risk patients, and can inform clinicians about the possible course of treatment. The primary difference is that GPS only tests 12 genes, with five reference genes (compared to 31 and 15, respectively, for Prolaris).¹⁹ These expression levels are combined into

an algorithm to produce a genomic prostate score (GPS) of 0-100. This GPS score correlated with prediction of cancer aggression (outcomes such as death or recurrence).²⁰

Cullen, et al. (2015) found that the GPS score correlated well with BCR. The researchers noted that GPS is a good predictor of both early and late BCR and is validated for adverse pathology whereas Prolaris is validated for 10-year mortality or BCR after radical prostatectomy.^{6,14,20,21} GPS was recently validated in a group of individuals separated by race, showing that this tool is an independent predictor of adverse pathology with similar predictive accuracy in both African American (n=96) and European American (n=76) populations.²²

AR-V7 Nucleus Detect test

The AR-V7 Nucleus Detect test is available through Epic Sciences. This test evaluates the Androgen Receptor Splice Variant-7 (AR-V7) protein in the nucleus of circulating tumor cells and is intended to identify metastatic castration-resistant prostate cancer patients who will not respond to androgen-receptor targeted therapies.²³

Scher, et al. (2016) examined 161 patients with progressive metastatic castration-resistant prostate cancer (mCRPC) to assess its association with AR-V7. Out of 191 samples (128 pre-ARS inhibitor and 63 pretaxane), the investigators found AR-V7-positive circulating tumor cells in 34 samples, and those samples were found to have worse clinical outcomes and overall survival than those without AR-V7. Scher, et al. (2016) concluded that “the results validate CTC nuclear expression of AR-V7 protein in [individuals] with mCRPC as a treatment-specific biomarker that is associated with superior survival on taxane therapy over ARS-directed therapy in a clinical practice setting.”²⁴

Further, Chen, et al. (2018) studied the overexpression of the nuclear AR-V7 protein in prostate cancer cases. A total of 401 individuals participated in this study. Participants were split into two cohorts: cohort I included those who were high-risk (n=238), and cohort II included those who were not considered high-risk (n=238). Analyses showed that high nuclear AR-V7 protein expression was detected in approximately 30-40% of participants, and a “High baseline expression of nuclear AR-V7 protein was associated with an unfavorable BCR-free survival in the high-risk patient cohort I but not in the unselected consecutive cohort II. Remarkably, AR-V7 was an independent negative prognostic factor in high-risk prostate cancer patients of cohort I who were selected to receive adjuvant treatment.”²⁵

Graf, et al. (2020) studied the clinical utility of AR-V7 as a biomarker for patients with progressing metastatic castration-resistant prostate cancer (mCRPC). The results were used by physicians to make a second line of therapy choice of either an androgen receptor signaling inhibitor (ARSI) or taxane chemotherapy. There were 255 samples of circulating tumor cells (CTCs) tested for AR-V7. Patients with detectable AR-V7 in the CTCs had superior survival with taxane treatment over ARSIs and patients who were AR-V7- negative had superior survival on ARSIs over taxanes. These results showed that individuals who tested AR-V7- positive were more likely to survive longer on taxane chemotherapy. Overall, the authors suggest that the use of AR-V7 CTC test “to inform treatment choice can improve patient outcomes relative to decisions based solely on standard-of-care measures.”²⁶

Decipher

Decipher is a genomic prognostic test that is used to predict cancer outcomes in patients that have undergone a radical prostatectomy (RP), which is the removal of the prostate gland and surrounding tissues. Decipher relies on the expression levels of 22 RNA markers in the RP specimen and is primarily

used to predict likelihood of metastases or mortality. The algorithm score ranges from zero to one, where a higher score corresponds with higher chance of metastasis. This algorithm was shown to have outperformed the traditional assessment of clinical and pathological features in predicting metastasis (0.75 accuracy compared to 0.69) as well as 17 other genetic tests (0.54 to 0.68 accuracy).^{14,27}

Van den Broeck, et al. (2019) aimed to validate the Decipher test in the prediction of distant metastatic recurrence in individuals with high-risk nonmetastatic prostate cancer ten years after the surgery was completed. A total of 298 people participated in this study. Results showed that “the median Decipher scores were higher in the population that developed metastases” suggesting that this study “validates Decipher as a predictor for metastatic recurrence even in patients with high-risk, nonmetastatic PC [prostate cancer] within 10-yr follow-up.”²⁸ Specifically, the data showed that each 10% increase in Decipher score resulted in an increased risk of distant metastatic prostate cancer recurrence.

In a prospective trial by Marascio, et al. (2020), the clinical utility of the Decipher tumor test on postoperative management of prostate cancer post prostatectomy was discussed. There were 3,455 individuals with prostates enrolled in the study and the change in treatment decision-making was recorded. In the cohort, 61% of the patients had high-risk tumors with a two-year prostate cancer reoccurrence. As a result of genome classifier testing, providers’ recommendations changed for 39% of the patients, translating to a number needed to test of three to change one treatment decision. This study demonstrated that genome classifier testing favorably impacts treatment decision making post radical prostatectomy, promoting more post-operative radiotherapy. This translated to improved patient reported quality of life.²⁹

Nguyen, et al. (2023) published a meta-analysis examining the prognostic ability of the Decipher Genomic Classifier for distant metastases, prostate cancer-specific mortality, and overall survival within the context of three randomized phase three high-risk definitive radiation therapy trials. The total cohort consisted of 265 individuals whose median age was 69 years and median pretreatment PSA of 25.8 ng/mL. The authors report that upon meta-analysis, the Decipher Genomic Classifier score was statistically significantly associated with time to distant metastasis, prostate cancer-specific mortality, and overall survival.³⁰

Spratt, et al. (2023) reported on the Decipher Genomic Classifier’s performance in the context of intermediate-risk prostate cancer. Through multivariable analysis of 215 individual samples, it was determined that the test was “independently prognostic for disease progression (subdistribution hazard ratio [sHR], 1.12; 95% confidence interval [CI], 1.00-1.26; P = .04), biochemical failure (sHR, 1.22; 95% CI, 1.10-1.37; P < .001), distant metastasis (sHR, 1.28; 95% CI, 1.06-1.55; P = .01), and prostate cancer-specific mortality (sHR, 1.45; 95% CI, 1.20-1.76; P < .001).” Beyond prognostic utility, the authors argue that the data herein support the predictive value of the Decipher Genomic Classifier for individuals with intermediate risk prostate cancer; among individuals with a test score of intermediate-high, radiation dose-escalation showed greater absolute benefit, with 10-year metastasis-free survival of 75% (95% CI, 55-95) compared with 54% (95% CI, 31-77) for standard dose.³¹

ExoDX Prostate IntelliScore (EPI)

ExoDX is a urinary test that detects the expression level of three genetic biomarkers (ERG, PCA3, and SPDEF).^{32,33} This test integrates the expression levels of these three biomarkers and assigns an individualized risk score to predict the risk of high-grade prostate cancer (Gleason score \geq seven). This test is intended for individuals 50 or over with a PSA level of two to ten ng/mL presenting for an initial

biopsy (prior to a DRE) and as a useful test in the post-biopsy setting for patients thought to be higher risk despite a negative prostate biopsy.^{7,32,33}

McKiernan, et al. (2016) used ExoDx to discriminate between benign prostate cancer (Gleason score 6 and under) and high-risk cancer (Gleason score ≥ 7). The prognostic score was derived from a sample of 499 patients with PSA levels of two to 20 ng/mL; it was then validated in a sample of 1064 patients and evaluated in a population of 255. The test was compared to the standard of care practices (SOC), and the area under the curve (AUC) of the test was 0.77 compared to the SOC's 0.66. An independent validation found the AUC of the test to be 0.73 compared to the SOC's 0.63. The authors calculated that 138 of 519 biopsies (27%) would have been avoided and that the test only missed five percent of patients with high-risk disease.³⁴ Within a second phase of the long-term study, McKiernan and colleagues report that using the EPI validated cut-point of 15.6 results in avoiding 26% of unnecessary prostate biopsies and a 20% decrease in all biopsies. If the EPI cut-point is raised to 20, then 31% of total biopsies would be avoided, including 40% of unnecessary biopsies.³⁵

A study published in 2018 did a cost-effectiveness analysis and comparison of not only ExoDx (EPI), but also Prostate Health Index (PHI), 4Kscore, and SelectMDx to current standard care of care. Using 2017 US dollars for their calculations, the cost and quality adjusted life-years (QALY) for the current standard of care—transrectal ultrasound guided biopsy (TRUS biopsy)—was \$3,863 and 18.0865, respectively. The authors of the study note that EPI, PHI, and SelectMDx cost less than performing TRUS biopsy. They note, “The EPI provided the highest QALY with an incremental cost-effectiveness ratio of \$58,404 per QALY. The use of biomarkers could reduce the number of unnecessary biopsies by 24% to 34% compared to the current standard of care... Using SelectMDx or the EPI following elevated prostate specific antigen but before proceeding to biopsy is a cost-effective strategy in this setting.”³⁶

A randomized, blinded, two-armed clinical utility study was published in 2020 using ExoDx (EPI) in individuals presenting for initial biopsy with PSA values in the intermediate range (two to ten ng/mL). This large study ($n = 1,094$) included 72 urologists from 24 different practices. All patients had an EPI test performed, but the patients were divided into two different groups (control and experimental) where only the experimental group received results prior to their biopsy decision. Of the individuals within the experimental group who received negative EPI scores, 74% deferred biopsy. For individuals within the experimental group who received positive EPI scores, 87% were recommended by their urologists to undergo the biopsy, and ultimately 72% did. As compared to the control arm of the study, there is a 30% increase in the detection of high-grade prostate cancer [HGPC], and the authors “estimate that 49% fewer HGPC were missed due to deferrals compared to standard of care (SOC). Overall, 68% of urologists reported that the EPI test influenced their biopsy decision.”³⁷

McKiernan, et al. (2020) investigated the use of the EPI test in a prospective clinical validation study of 229 individuals who were undergoing repeat biopsy. The EPI test demonstrated an NPV of 92% and results evidenced avoidance of 26% of unnecessary biopsies while missing 2.1% of the incidences of high-grade prostate cancer (a total of five patients).³⁸

4Kscore

4Kscore is intended to assess the risk for “aggressive” prostate cancer. The test incorporates total PSA, free PSA, “intact” PSA, and “hk2” [human kallikrein 2].^{6,39} These biomarkers, along with other patient clinical information (such as age and prior biopsy status) are evaluated by the 4Kscore algorithm, which

generates a risk score for aggressive cancer (percent risk of Gleason seven or higher, if a biopsy were to be performed).

Zappala, et al. (2017) performed a meta-analysis of 4kScore validation studies. A total of 12 studies encompassing 11134 patients were included, and the pooled area under curve (AUC) for the test to “discriminate for high-grade PCa [prostate cancer] was found to be 0.81.”⁴⁰

Two key prospective and blinded investigations were completed in 2015 and 2018, attempting to validate 4Kscore in a total of 937 patients, defined as the “intended use” population. The test demonstrated an overall sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of 96.9%, 27.4%, 95.9%, and 33.7%, respectively. These metrics showed little variation between African American and non-African American individuals, with the exception of PPV (46.7% compared to 28.1%, respectively).^{41,42}

Wysock, et al. (2020) compared the performance of 4K score to SelectMDx in detecting prostate cancer in 114 patients who received both tests. These tests were analyzed to provide guidance on whether to perform biopsy. Based on the results, the two scores lead to different biopsy recommendations. A total of 50 out of 144 patients underwent biopsy based on the test results. Of the 50 patients, 22 (44%) were found to have clinically significant prostate cancer. In addition, the specificity of 4K score was significantly greater compared to SelectMDx while sensitivity was similar. The area under the curve for 4K score was 0.830 and SelectMDx was 0.672. The authors state that “the 4Kscore when combined with magnetic resonance imaging was superior to the SelectMDx” in detecting prostate cancer.⁴³

Mi, et al. (2021) completed a meta-analysis to help inform the diagnostic accuracy of 4Kscore in detecting high-grade prostate cancer, covering a total of nine studies and 1,689 patients. The investigators reported a pooled sensitivity, specificity, and AUC of 0.90 (95%CI: 0.86-0.92), 0.44 (95%CI: 0.36-0.52), and 0.81 (95%CI: 0.77-0.84), respectively, and concluded that “4Kscore can be used as a model for the diagnosis of high-grade CaP [prostate cancer]. However, we detected significant heterogeneity among studies that was not explained by subgroup or meta-regression analysis, thus lowering our confidence in these results.”

Further validation of the test will be useful; however, to date, 4Kscore has demonstrated relatively high sensitivity and AUC compared to other molecular testing for the assessment of high-grade prostate cancer risk.

ConfirmMDX

ConfirmMDX uses methylation-specific polymerase chain reaction (PCR) to identify methylation of three genes (*GSTP1*, *APC*, and *RASSF1*), and determine whether a patient with a previously negative prostate biopsy should undergo a repeat biopsy.⁴⁵ This test has been evaluated by Van Neste, et al. (2016) and was found to have an NPV of 96% for high-grade prostate cancer. A total of 7899 prostate core biopsies from 803 patients were assessed, and the NPV of finding low levels of DNA methylation was 89.2% for all cancers. The PPV of the genetic assay was found to be 28.2% (for detection of any cancer on a repeat biopsy), and this was calculated to be “significantly higher” than the PPV of standard of care practices. The final algorithm was optimized to a maximum of 0.742 AUC.⁴⁶ Wojno, et al. (2014) evaluated the utility of this test and found that out of 138 patients that the test had been performed on, only six with a negative result had undergone a repeat biopsy.

SelectMDX

SelectMDX evaluates two mRNA cancer-related biomarkers (HOXC6 and DLX1 with *KLK3* as a reference gene) to assist a clinician in deciding to continue routine screening or to order a prostate biopsy. This test is considered a “non-invasive urine test” and reports a binary result of “increased risk” or “very low risk.”⁴⁸ Van Neste, et al. (2016) evaluated this test at a 0.90 AUC in a validation cohort. The authors concluded that the mRNA signature was one of the most significant components of the validation results.⁴⁹ Shore (2018) assessed the effect of SelectMDX results on clinical decision making, and found that out of 253 patients that SelectMDX evaluated as “negative,” only 12% underwent a biopsy.⁵⁰

IsoPSA®

IsoPSA® is a blood test indicated for use in individuals with a prostate who are over 50 years of age with elevated PSA, to help inform the likelihood of having high-grade prostate cancer. Utilizing a proprietary, 2-phase aqueous polymer and salt mixture, PSA isoforms separate between the two aqueous phases, where the discriminatory power between benign and cancerous clinical phenotypes purportedly resides primarily in the top phase. The PSA isoform content in the top layer is then measured with conventional, FDA-approved PSA ELISA immunoassays, and a single numerical score (IsoPSA Index) that is either above or below an established cutoff is generated, providing a binary positive or negative result.

The clinical validity of IsoPSA® was demonstrated in several studies. Stovsky, et al. (2019) performed a multicenter, prospective validation in 271 individuals scheduled for prostate biopsy, and found that the test yielded an area under the receiver operating characteristic curve of 0.784 for high grade cancer. Klein, et al. (2022) completed an additional multicenter study of 888 individuals scheduled for prostate biopsy and found similar results, establishing an AUC of 0.783 for IsoPSA®. These investigators further reported a sensitivity, specificity, NPV, and PPV of 0.902, 0.455, 0.893, and 0.477, respectively.

To investigate the clinical utility of IsoPSA®, Scovell, et al. (2022) performed a “real-world” observational study engaging 38 providers across the Cleveland Clinic health system. The authors examined whether an IsoPSA® result changed the number of biopsy and magnetic resonance imaging recommendations for a cohort of 734 individuals with total serum prostate specific antigen [PSA] \geq four and $<$ 100 ng/ml and no history of prostate cancer. The authors determined that “IsoPSA testing resulted in a 55% (284 vs 638) net reduction in recommendations for prostate biopsy” for those “with total PSA \geq four ng/ml.”

ProgenSA PCA3

ProgenSA PCA3 is an FDA-approved assay that examines the concentration of the prostate cancer gene three (*PCA3*) and compares it to the amount of prostate-specific antigen RNA. This test is intended for assistance in decision making for a repeat biopsy in individuals with a prostate who are 50 years or older, and a *PCA3* score under 25 was associated with a decreased likelihood of a positive biopsy. However, the manufacturer states this test should not be used for those with atypical small acinar proliferation on their most recent biopsy.⁵⁴ A total of 466 samples were provided, and 102 of these samples were evaluated to require a repeat biopsy. This assay was evaluated at a 77.5% sensitivity, a 57.1% specificity, a 33.6% positive predictive value, and a 90.0% negative predictive value.⁵⁵

Rodríguez and García-Perdomo (2020) performed a systematic review and meta-analysis of the diagnostic accuracy of PCA3 prior to a patient’s first prostate biopsy. They found that with a cutoff of 35, the sensitivity of the diagnostic tests was 0.69 (95% confidence interval 0.61-0.75), specificity was 0.65 (95% confidence interval 0.553-0.733), the diagnostic odds ratio was 4.244 (95% confidence interval

3.487-5.166), and the AUC was 0.734 (95% confidence interval 0.674-0.805). This study suggests that there may be a greater clinical utility with 35 as the cutoff as opposed to the 25 approved by the FDA, and ultimately urinary PCA3 can “be used as a guide for directing the performance of the first prostate biopsy and decreasing unnecessary biopsies.”^{56,57}

MyProstateScore

MyProstateScore is a panel that measures urinary prostate cancer antigen three (PCA3), urinary TMPRSS2:ERG gene fusion (T2:ERG), and serum PSA, to predict the likelihood of prostate cancer in biopsy-naïve patients. Validating the test in a cohort of 1225 patients, Tomlins, et al. (2016) found that MyProstateScore was superior to PSA alone, yielding an AUC of 0.693 (compared to 0.585 for PSA). Tosoian, et al. (2021) aimed to validate an optimal MyProstateScore threshold for ruling out clinically significant (grade group \geq two) cancer, finding that a threshold of 10 resulted in 97% sensitivity and 98% NPV. The investigators further concluded that use of the test could have prevented about one out of three of the biopsies that patients received.

ProMark

Another test that may have utility is ProMark. It measures the levels of eight proteins through the quantitative immunofluorescence of a biopsy specimen. ProMark is used to predict cancer aggression in patients with a Gleason score of 3+3 or 3+4. The proteins chosen have roles in cell proliferation, signaling, or stress response, and the score is reported from one to 100. This score represents individualized risk. Blume-Jensen, et al. (2015) narrowed down the eight primary protein biomarkers used (down from the 12 proposed by an earlier study) as well as assessed its ability to predict clinical endpoints of favorable and nonfavorable disease. They recommended a cutoff of 0.33 (on a scale of zero to one) for “nonfavorable” pathology (83.6% of patients with favorable disease fell below this cutoff). Conversely, a cutoff of 0.8 was recommended for favorable pathology as 76.9% of patients with nonfavorable pathology were above this cutoff. The authors concluded that this assay provided useful information, especially when differentiating between Gleason scores.^{4,14}

Prostate Health Index

Prostate Health Index (PHI) measures total PSA, fPSA (free non-protein bound PSA), and p2PSA (an isoform of fPSA). Levels of these three proteins are combined and calculated, implying that individuals with a higher total PSA and p2PSA and a lower fPSA have a higher risk of presenting with prostate cancer.⁶⁰ PHI is clinically used to reduce the number of unnecessary biopsies in those with border-line PSA levels, predict biochemical recurrence after radical prostatectomy, and enhance the predictive value of multi-parametric MRI. PHI is not recommended in primary screening for prostate cancer.⁶¹

Jia, et al. (2020) compared the diagnostic value of PCA3 and PHI for detection of prostate cancer at initial biopsy in a meta-analysis of 10,376 patients from 20 studies. The pooled sensitivity for PCA3 and PHI was 0.55 and 0.88, respectively. The pooled specificity for PCA3 and PHI was 0.74 and 0.36. The area under the curve, measuring overall quality of the diagnostic test, was 0.72 for PCA3 and 0.76 for PHI. The combination use of PCA3 and PHI resulted in a higher area under the curve of 0.79. Overall, this study suggests that both PCA3 and PHI show acceptable results and a “combination of these two diagnostic tests may be more helpful than the use of either test alone in prostate cancer management.”⁶²

White, et al. (2018) evaluated the clinical utility of the PHI on “biopsy decision management” among patients with “non-suspicious DRE findings and tPSA in the four to ten ng/mL range” in an observational study at several large urology group practices. They found that there was a “significant reduction in biopsy procedures performed” in individuals receiving a PHI test when comparing to the control group (36.4% biopsy vs 60.3% biopsy), and that the “PHI score impacted physician’s patient management plan in 73% of cases, including biopsy deferrals when the PHI score was low, and decisions to perform biopsies when the PHI score indicated an intermediate or high probability of prostate cancer,” defined as a score greater than or equal to 36. This altogether conveyed the importance of the PHI score in clinical decision making in terms of how to proceed with individual patient circumstances.^{57,63}

Ki-67 and PTEN

Finally, the NCCN specifically recommends *against* two particular tests in assessment of prostate cancer; Ki-67 staining and phosphatase and tensin homolog (*PTEN*) loss.⁶

Ki-67 is a nuclear protein involved in cell cycle proliferation and is intended to provide prognostic information on metastasis and prostate cancer-specific mortality.^{5,6} Ki-67 staining has shown some promising results. However, the primary limitation with these studies is that most active surveillance populations will have a Gleason Score of 6 or less, which is considered “low-risk.” This population will most likely have low Ki-67 levels, clouding its utility in populations trying to decide between immediate and deferred treatment.⁵

PTEN loss is a relatively early event in the course of prostate cancer. *PTEN* is a tumor suppressor gene on chromosome 10q and is involved in cell cycle regulation. *PTEN* is intended to provide prognostic information on prostate cancer-specific mortality, biochemical recurrence, and cancer progression.^{5,6} Data on prognostic value of *PTEN* loss post-treatment have been conflicting. It is possible that active treatments contribute to the disruption of the *PTEN* pathway or the high correlation between *PTEN* loss and clinicopathologic factors. Lotan, et al. (2011) found that when clinicopathologic factors, such as Gleason Score and surgical margin status, were included in their multivariable analysis, *PTEN*’s association with metastasis and prostate cancer-specific mortality decreased significantly.

ArteraAI Prostate Cancer

ArteraAI Prostate Cancer is a multimodal artificial intelligence (MMAI) digital pathology-based post-radical prostatectomy biomarker test that stratifies the risk of metastasis as well as identifies the potential benefits of additional hormone therapy. It is for patients who have been diagnosed with localized prostate cancer who have not yet received radiation therapy (RT) or androgen-deprivation therapy (ADT) before getting a biopsy. The current standard for individuals with intermediate-risk localized prostate cancer includes treatment with ST-ADT in combination with radiation therapy, but a clinical study of the predictive biomarker used in the ArteraAI Prostate test showed that only 34% of patients require radiation therapy. The AI portion of the test “learns” from digital pathology images and clinical data inputs to then predict the likelihood of additional therapy being beneficial, as well provides details as to the prognosis of the patient. Test results do not require tissue, but rather a validated algorithm is used to assess the “digital image” from a patient’s biopsy and clinical data.

The development of the ArteraAI model relied on two trials and utilized clinical data and digital pathology. The 5-year DM area under the curve was 0.83 for ArteraAI, compared with 0.72 for NCCN risk group ($P < .001$). Results show promising risk stratification for hormonal therapy (Results identified 40%

of biochemical recurrence (BCR) patients who benefited from therapy intensification vs. 60% of patients who did not) indicating potential benefits for high-risk patients; this tool is purported to be of use with both newly-diagnosed patients and those that show biochemical recurrence.^{65,66}

Esteva, et al. (2022) performed a study to demonstrate the usage of multimodal deep learning architecture to personalize therapy for prostate cancer by predicting long-term outcomes using clinical data and digital histopathology from prostate biopsies. The models, trained and validated on data from the five phase III randomized trials, outperformed the National Cancer Center Network (NCCN) risk groups in terms of discriminatory performance on all endpoints. The AI-based tool (ArteraAI) provided superior prognostication with a relative improvement over these current risk group tools (based on digital rectal exam, serum prostate-specific antigen (PSA) level, and tumor biopsy grade) of between 9.2% to 14.6% in a held-out validation set.⁶⁷

VI. Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN)

Patients with low or favorable intermediate-risk disease and life expectancy ≥ 10 y may consider the use of the following tumor-based molecular assays during initial risk stratification: Decipher, GPS, and Prolaris. Patients with unfavorable intermediate- and high-risk disease and life expectancy ≥ 10 y may consider the use of Decipher and Prolaris tumor-based molecular assays. Retrospective studies have shown that molecular assays performed on prostate biopsy or RP specimens provide prognostic information independent of NCCN or CAPRA risk groups. These include, but are not limited to, “likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or EBRT, likelihood of adverse pathologic features after radical prostatectomy, and likelihood of developing metastasis after operation, definitive EBRT, or post-recurrence EBRT.”⁶ Furthermore, they note that clinicians may consider testing patients with metastatic prostate cancer and regional prostate cancer for alterations in homologous recombination DNA repair genes *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and *CDK12*; “Post-test genetic counseling is recommended if pathogenic/likely pathogenic variant (mutation) identified in any gene that has clinical implications if also identified in germline (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *PMS2*).”⁶ The NCCN noted that somatic tumor testing of the aforementioned genes has potential for early use of platinum chemotherapy or understanding eligibility for biomarker-directed treatments or clinical trials. Lastly, tumor testing for microsatellite instability or mismatch repair deficiency is recommended in patients with metastatic castration-resistant disease and may be considered in patients with regional or castration-sensitive metastatic prostate cancer. The NCCN also specifically does not recommend either Ki-67 or *PTEN* testing.⁶

The NCCN does include available tissue-based tests for prostate cancer risk stratification/prognosis within their table of possible testing as indicated below. Regarding Decipher testing, NCCN states that Decipher “may be considered to inform adjuvant treatment if adverse events are found after radical prostatectomy and during workup for radical prostatectomy PSA persistence or recurrence.” NCCN discourages repeat molecular tumor analysis:^{6,7}

Test	Platform	Recommendation
Decipher	Whole-Transcriptome 1.4M RNA expression (46,050 genes and non-coding RNA),	Cover post-biopsy for NCCN very-low-, low-risk, favorable intermediate, and unfavorable intermediate risk prostate cancer in patients

	oligonucleotide microarray optimized for FFPE tissue	with at least 10 years life expectancy who have not yet received treatment for prostate cancer and are candidates for active surveillance or definitive therapy. Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
KI-67	IHC	Not recommended
GPS	Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls	Cover post-biopsy for NCCN very-low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not yet received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.
Prolaris	Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls	Cover post-biopsy for NCCN very-low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not yet received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.
PTEN	Fluorescence in situ hybridization or IHC	Not recommended

The NCCN, within the algorithm for the indications for prostate biopsy, says to “consider biomarkers and/or risk calculators that improve the specificity of screening” for individuals who have had elevated levels of PSA (above three ng/mL for those ages 45 – 75 years or four ng/mL or higher for those individuals over the age of 75 years). The NCCN goes on to state, “biomarkers that improve the specificity of detection are not, as yet, mandated as first-line screening tests in conjunction with serum PSA. However, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to more precisely estimate risk... Lower percent-free PSA and/or higher PSA density are associated with a greater risk of high-grade prostate cancer.”

- “Prior to initial biopsy: The probability of high-grade cancer (Grade Group ≥ 2) may be further defined prior to initial biopsy utilizing tools such as the Prostate Health Index (PHI), SelectMDx, 4Kscore, ExoDx Prostate Test, MyProstateScore (MPS), and IsoPSA.
- After initial biopsy: Tests that improve specificity in the post-biopsy setting may be considered in patients thought to be higher risk despite a negative prostate biopsy. Tests to be considered are percent-free PSA, 4Kscore, PHI, PCA3, ConfirmMDx, ExoDx Prostate Test, MPS, and IsoPSA.
- The extent of validation of these tests across diverse populations is variable.
- It is not yet known how such tests could be applied in optimal combination with MRI.”⁷

The NCCN panel remarks that 4Kscore, IsoPSA, and MyProstateScore “can be considered for patients

prior to biopsy and for those with prior negative biopsy who are thought to be at higher risk for clinically significant prostate cancer.” The NCCN further remarks that SelectMDx is “potentially informative” in patients who have never undergone biopsy and can therefore be “considered” in these patients. The NCCN also acknowledged that ConfirmMDx can be considered an option for individuals contemplating repeat biopsy and is approved for limited coverage by MoDX to reduce unnecessary repeat biopsies. Further, ExoDx Prostate (IntelliScore), also called EPI, “can be considered as an option for individuals contemplating initial or repeat biopsy.” Lastly, the PCA3 assay can be used to help “decide, along with other factors, whether a repeat biopsy in individuals aged ≥ 50 years with one or more previous negative prostate biopsies is necessary.”⁷

The NCCN also lists ArteraAI Prostate as an advanced tool in the principles of risk stratification and biomarkers. The category of the listing is “AI Pathology” and it is listed as predictive for short term androgen deprivation therapy and prognostic for distant metastases and prostate cancer specific mortality with a 2A category recommendation (2A meaning: “based upon lower-level evidence, there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate”).⁶

American Society of Clinical Oncology (ASCO)

In 2020, an ASCO multidisciplinary panel published guidelines on molecular biomarkers in localized prostate cancer. These guidelines are below.

- “Commercially available molecular biomarkers (i.e., GPS, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended.”
- “Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered.”
- “The Expert Panel recommends consideration of a commercially available molecular biomarker (e.g., Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered.”
- In individuals “with newly diagnosed prostate cancer who are eligible for active surveillance, both genomics and MRI intend to identify clinically significant cancers. The Expert Panel endorses their use only in situations in which the result, when considered as a whole with routine clinical factors, is likely to have an impact on patient management.”⁶⁸

In 2020, an ASCO panel published guidelines on the use of molecular biomarkers in localized prostate cancer. In concordance with the 2018 and 2019, ASCO recommends the use of commercially available tests (GPS, Prolaris, Decipher, and ProMark) when the assay result “is likely to have an impact on patient management. Examples include select individuals with high-volume low-risk or favorable intermediate-risk prostate cancer who are considering active surveillance or in individuals with high-risk features for treatment intensification. While testing may influence management decisions, there is no high-level evidence that the results from these panels will improve quality of life or cancer-specific outcomes.”⁶⁸

European Association of Urology (EAU), European Association of Nuclear Medicine (EANM), European Society for Radiotherapy and Oncology (ESTRO), European Society of Urogenital Radiology

(ESUR), International Society of Urological Pathology (ISUP), and the International Society of Geriatric Oncology (SIOG)

In 2023, the EAU, EANM, ESTRO, ESUR, ISUP and SIOG released joint guidelines on prostate cancer. These guidelines state that asymptomatic individuals with a prostate-specific antigen level between three and ten ng/mL and a normal digital rectal examination, use one of the following tools for biopsy indication:

- “Risk-calculator, provided it is correctly calibrated to the population prevalence(strong);
- magnetic resonance imaging of the prostate (strong).
- An additional serum, urine biomarker test (weak).”

These joint guidelines acknowledged PHI, ProgenSA *PCA3*, and SelectMDX as tests used to select for repeat biopsies but stated that “given the limited available data and the fact that the role of MRI in tumour detection was not accounted for, no recommendation can be made regarding the routine application of ConfirmMDX, in particular in light of current use of MRI before biopsy.” They also noted that the “clinically added value of SelectMDX in the era of upfront MRI and targeted biopsies remains unclear.”

Other tests recognized as having use in the evaluation of prostate cancer included GPS, Prolaris, Decipher, Decipher PORTOS and Promark. These five commercially available tests have “extensive validation in large retrospective studies and evidence that their tests results might actually impact clinical decision-taking.” However, “since the long-term impact of the use of these commercially available tests on oncological outcome remains unproven and prospective trials are largely lacking, the Panel concluded that these tests should not be offered routinely but only in subsets of patients where the test result provides clinically actionable information.” They provide the examples of an individual with favorable intermediate-risk PCa who decides to continue with active surveillance or an individual with unfavorable intermediate-risk PCa who opts for radiotherapy (RT) to consider treatment intensification with hormonal therapy.”⁶⁹

European Society for Medical Oncology (ESMO)

European Society for Medical Oncology (ESMO) provided recommendations on the use of precision medicine in providing prognostic information for prostate cancer. These are the following recommendations provided:

- ESMO does not recommend the use of AR-V7 testing, stating that the test is of limited value in therapy selection.
- Other tissue-based molecular assays may be used on conjunction with clinicopathological factors to make treatment decision.
- Germline testing for *BRCA2* and other DDR [DNA damage and repair] genes is recommended in patients with a family history of cancer and should be considered in patients with metastatic cancer.⁷⁰

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to

make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, please visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)
81479	Unlisted molecular pathology procedure
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.
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
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score
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
84153	Prostate specific antigen (PSA); total
84154	Prostate specific antigen (PSA); free
86316	Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549), each
0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score Proprietary test: ExoDx® Prostate (IntelliScore) Lab/manufacturer: Exosome Diagnostics, Inc.
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 Proprietary test: Apify® Lab/Manufacturer: Armune BioScience, Inc.
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

CPT	Code Description
	Proprietary test: Genomic Prostate Score® (GPS) Test Lab/manufacturer: MDxHealth, Inc
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 Proprietary test: MyProstateScore Lab/Manufacturer: Lynx DX
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 Proprietary test: PanGIA Prostate Lab/Manufacturer: Genetics Institute of America/Entopsis, LLC
0339U	Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following digital rectal examination, algorithm reported as probability of high-grade cancer Proprietary test: SelectMDx® for Prostate Cancer Lab/Manufacturer: MDxHealth®, Inc
0359U	Oncology (prostate cancer), analysis of all prostate-specific antigen (PSA) structural isoforms by phase separation and immunoassay, plasma, algorithm reports risk of cancer Proprietary test: IsoPSA® Lab/Manufacturer: Cleveland Diagnostics, Inc
0403U	Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch urine, algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer Proprietary test: MyProstateScore 2.0 Lab/Manufacturer: LynxDX
0424U	Oncology (prostate), exosome- based analysis of 53 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as no molecular evidence, low-, moderate- or elevated-risk of prostate cancer. Proprietary test: miR Sentinel™ Prostate Cancer Test Lab/Manufacturer: miR Scientific®, LLC
0433U	Oncology (prostate), 5 DNA regulatory markers by quantitative PCR, whole blood, algorithm, including prostate-specific antigen, reported as likelihood of cancer. Proprietary test: EpiSwitch® Prostate Screening Test (PSE) Lab/Manufacturer: Oxford BioDynamics PLC
0495U	Oncology (prostate), analysis of circulating plasma proteins (tPSA, fPSA, KLK2, PSP94, and GDF15), germline polygenic risk score (60 variants), clinical information (age, family history of prostate cancer, prior negative prostate biopsy), algorithm reported as risk of likelihood of detecting clinically significant prostate cancer Proprietary test: Stockholm3 Lab/Manufacturer: BioAgilytix Diagnostics
0497U	Oncology (prostate), mRNA geneexpression profiling by real-time RT-PCR of 6 genes (FOX M1, MCM3, MTUS1, TTC21B, ALAS1, and PPP2CA), utilizing formalin-fixed

CPT	Code Description
	paraffin-embedded (FFPE) tissue, algorithm reported as a risk score for prostate cancer Proprietary test: OncoAssure™ Prostate Lab/Manufacturer: DiaCarta, Inc
0534U	Oncology (prostate), microRNA, single-nucleotide polymorphisms (SNPs) analysis by RT-PCR of 32 variants, using buccal swab, algorithm reported as a risk score Proprietary test: PROSTOXTM ultra Lab/Manufacturer: MiraDx, Inc
0550U	Oncology (prostate), enzyme-linked immunosorbent assays (ELISA) for total prostate-specific antigen (PSA) and free PSA, serum, combined with age, previous negative prostate biopsy status, digital rectal examination findings, prostate volume, and image and data reporting of the prostate, algorithm reported as a risk score for the presence of high-grade prostate cancer Proprietary Test: ClarityDx Prostate Lab/Manufacturer: Protean BioDiagnostics
0572U	Oncology (prostate), high- throughput telomere length quantification by FISH, whole blood, diagnostic algorithm Proprietary Test: ProstAV® Lab/Manufacturer: Life Length

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

1. Taplin M-E, Smith JA. Clinical presentation and diagnosis of prostate cancer. Updated March 22, 2024. <https://www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-prostate-cancer>
2. Benedettini E, Nguyen P, Loda M. The pathogenesis of prostate cancer: from molecular to metabolic alterations. *Diagn Histopathol (Oxf)*. May 2008;14(5):195-201. doi:10.1016/j.mpdhp.2008.03.001
3. Steiling K, Christenson S. Tools for genetics and genomics: Gene expression profiling. Updated May 1, 2025. <https://www.uptodate.com/contents/tools-for-genetics-and-genomics-gene-expression-profiling>
4. Blume-Jensen P, Berman DM, Rimm DL, et al. Development and clinical validation of an in situ biopsy-based multimarker assay for risk stratification in prostate cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research*. Jun 1 2015;21(11):2591-600. doi:10.1158/1078-0432.Ccr-14-2603
5. Ross AE, D'Amico AV, Freedland SJ. Molecular prognostic tests for prostate cancer. Updated November 26, 2024. <https://www.uptodate.com/contents/molecular-prognostic-tests-for-prostate-cancer>
6. NCCN. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Version 1.2025 — December 4, 2024 https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
7. NCCN. Prostate Cancer Early Detection Version Version 1.2025 — March 11, 2025. https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf
8. ACS. Key Statistics for Prostate Cancer. Updated May 30, 2025. <https://www.cancer.org/cancer/types/prostate-cancer/about/key-statistics.html>

9. ACS. Survival Rates for Prostate Cancer. Updated January 16, 2025. <https://www.cancer.org/cancer/types/prostate-cancer/detection-diagnosis-staging/survival-rates.html>
10. Bell KJ, Del Mar C, Wright G, Dickinson J, Glasziou P. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. *International journal of cancer*. Oct 01 2015;137(7):1749-57. doi:10.1002/ijc.29538
11. Hoffman R. Screening for prostate cancer. Updated June 3, 2024. <https://www.uptodate.com/contents/screening-for-prostate-cancer>
12. Song CJ, Chen H, Chen LZ, Ru GM, Guo JJ, Ding QN. The potential of microRNAs as human prostate cancer biomarkers: A meta-analysis of related studies. *J Cell Biochem*. Mar 2018;119(3):2763-2786. doi:10.1002/jcb.26445
13. Hu JC, Tosoian JJ, Qi J, et al. Clinical Utility of Gene Expression Classifiers in Men With Newly Diagnosed Prostate Cancer. 2018;(2):1-15. doi:10.1200/po.18.00163
14. Alford AV, Brito JM, Yadav KK, Yadav SS, Tewari AK, Renzulli J. The Use of Biomarkers in Prostate Cancer Screening and Treatment. *Reviews in urology*. 2017;19(4):221-234. doi:10.3909/riu0772
15. Cuzick J, Stone S, Fisher G, et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. *British journal of cancer*. Jul 28 2015;113(3):382-9. doi:10.1038/bjc.2015.223
16. Lin DW, Crawford ED, Keane T, et al. Identification of men with low-risk biopsy-confirmed prostate cancer as candidates for active surveillance. *Urologic Oncology: Seminars and Original Investigations*. 2018/06/01/ 2018;36(6):310.e7-310.e13. doi:10.1016/j.urolonc.2018.03.011
17. Carneiro A, Priante Kayano P, Gomes Barbosa ÁR, et al. Are localized prostate cancer biomarkers useful in the clinical practice? *Tumor Biology*. 2018/09/01 2018;40(9):1010428318799255. doi:10.1177/1010428318799255
18. Tward JD, Schlomm T, Bardot S, et al. Ability of the combined clinical cell-cycle risk score to identify patients that benefit from multi versus single modality therapy in NCCN intermediate and high-risk prostate cancer. *Journal of Clinical Oncology*. 2020;38(6_suppl):346-346. doi:10.1200/JCO.2020.38.6_suppl.346
19. Exact Sciences. A Tailored Report for Clinically Low Risk Prostate Cancer Patients https://d2ft3j3kbsqj8w.cloudfront.net/-/media/Project/PrecisionOncology/PrecisionOncology/OIQ-Reports/Prostate/GPS-Interactive-Report-Tool/GPSRE_GPS_Annotated_Report-2-Page_M_US_GPS_00374.pdf?rev=50c0c67b355241178c9deba9609ded65
20. Cullen J, Rosner IL, Brand TC, et al. A Biopsy-based 17-gene Genomic Prostate Score Predicts Recurrence After Radical Prostatectomy and Adverse Surgical Pathology in a Racially Diverse Population of Men with Clinically Low- and Intermediate-risk Prostate Cancer. *European urology*. Jul 2015;68(1):123-31. doi:10.1016/j.eururo.2014.11.030
21. Davis JW. Novel commercially available genomic tests for prostate cancer: a roadmap to understanding their clinical impact. *BJU International*. 2014/09/01 2014;114(3):320-322. doi:10.1111/bju.12695
22. Murphy AB, Carbuñaru S, Nettey OS, et al. A 17-Gene Panel Genomic Prostate Score has Similar Predictive Accuracy for Adverse Pathology at Radical Prostatectomy in African American and European American Men. *Urology*. Apr 8 2020;doi:10.1016/j.urology.2020.01.052
23. Epic Sciences. AR-V7 by Epic Sciences. <https://www.epicsciences.com/ar-v7-test/>
24. Scher HI, Lu D, Schreiber NA, et al. Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate CancerAR-V7 Expression in Circulating Tumor Cells and Castration-Resistant Prostate Cancer OutcomesAR-V7

- Expression in Circulating Tumor Cells and Castration-Resistant Prostate Cancer Outcomes. *JAMA Oncology*. 2016;2(11):1441-1449. doi:10.1001/jamaoncol.2016.1828
25. Chen X, Bernemann C, Tolkach Y, et al. Overexpression of nuclear AR-V7 protein in primary prostate cancer is an independent negative prognostic marker in men with high-risk disease receiving adjuvant therapy. *Urol Oncol*. Apr 2018;36(4):161.e19-161.e30. doi:10.1016/j.urolonc.2017.11.001
 26. Graf RP, Hullings M, Barnett ES, Carbone E, Dittamore R, Scher HI. Clinical Utility of the Nuclear-localized AR-V7 Biomarker in Circulating Tumor Cells in Improving Physician Treatment Choice in Castration-resistant Prostate Cancer. *European urology*. 2020/02/01/ 2020;77(2):170-177. doi:10.1016/j.eururo.2019.08.020
 27. Dalela D, Løppenbergs B, Sood A, Sammon J, Abdollah F. Contemporary Role of the Decipher® Test in Prostate Cancer Management: Current Practice and Future Perspectives. *Reviews in urology*. 2016;18(1):1-9.
 28. Van den Broeck T, Moris L, Gevaert T, et al. Validation of the Decipher Test for Predicting Distant Metastatic Recurrence in Men with High-risk Nonmetastatic Prostate Cancer 10 Years After Surgery. *Eur Urol Oncol*. Sep 2019;2(5):589-596. doi:10.1016/j.euo.2018.12.007
 29. Marascio J, Spratt DE, Zhang J, et al. Prospective study to define the clinical utility and benefit of Decipher testing in men following prostatectomy. *Prostate Cancer and Prostatic Diseases*. 2020/06/01 2020;23(2):295-302. doi:10.1038/s41391-019-0185-7
 30. Nguyen PL, Huang HR, Spratt DE, et al. Analysis of a Biopsy-Based Genomic Classifier in High-Risk Prostate Cancer: Meta-Analysis of the NRG Oncology/Radiation Therapy Oncology Group 9202, 9413, and 9902 Phase 3 Randomized Trials. *Int J Radiat Oncol Biol Phys*. Jul 1 2023;116(3):521-529. doi:10.1016/j.ijrobp.2022.12.035
 31. Spratt DE, Liu VYT, Michalski J, et al. Genomic Classifier Performance in Intermediate-Risk Prostate Cancer: Results From NRG Oncology/RTOG 0126 Randomized Phase 3 Trial. *International Journal of Radiation Oncology, Biology, Physics*. 2023;117(2):370-377. doi:10.1016/j.ijrobp.2023.04.010
 32. ExoSome. ExoDx™ Prostate Test. <http://www.exosomedx.com/physicians/exodx-prostate-test>
 33. ExoSome. Prostate Cancer. <http://www.exosomedx.com/prostate-cancer-0>
 34. McKiernan J, Donovan MJ, O'Neill V, et al. A Novel Urine Exosome Gene Expression Assay to Predict High-grade Prostate Cancer at Initial Biopsy Urine Exosome Signature to Predict High-Grade Prostate Cancer Urine Exosome Signature to Predict High-Grade Prostate Cancer. *JAMA Oncology*. 2016;2(7):882-889. doi:10.1001/jamaoncol.2016.0097
 35. McKiernan J, Donovan MJ, Margolis E, et al. A Prospective Adaptive Utility Trial to Validate Performance of a Novel Urine Exosome Gene Expression Assay to Predict High-grade Prostate Cancer in Patients with Prostate-specific Antigen 2-10ng/ml at Initial Biopsy. *European urology*. Dec 2018;74(6):731-738. doi:10.1016/j.eururo.2018.08.019
 36. Sathianathan Niranjana J, Kuntz Karen M, Alarid-Escudero F, et al. Incorporating Biomarkers into the Primary Prostate Biopsy Setting: A Cost-Effectiveness Analysis. *Journal of Urology*. 2018/12/01 2018;200(6):1215-1220. doi:10.1016/j.juro.2018.06.016
 37. Tutrone R, Donovan MJ, Torkler P, et al. Clinical utility of the exosome based ExoDx Prostate(IntelliScore) EPI test in men presenting for initial Biopsy with a PSA 2-10 ng/mL. *Prostate Cancer Prostatic Dis*. May 7 2020;doi:10.1038/s41391-020-0237-z
 38. McKiernan J, Noerholm M, Tadigotla V, et al. A urine-based Exosomal gene expression test stratifies risk of high-grade prostate Cancer in men with prior negative prostate biopsy undergoing repeat biopsy. *BMC Urol*. Sep 1 2020;20(1):138. doi:10.1186/s12894-020-00712-4
 39. OPKO Health Receives U.S. FDA Approval for the 4Kscore® Test. December 8, 2021, 2021. <https://www.opko.com/news-media/press-releases/detail/454/opko-health-receives-u-s-fda-approval-for-the-4kscore>

40. Zappala SM, Scardino PT, Okrongly D, Linder V, Dong Y. Clinical performance of the 4Kscore Test to predict high-grade prostate cancer at biopsy: A meta-analysis of us and European clinical validation study results. *Reviews in urology*. 2017;19(3):149-155. doi:10.3909/riu0776
41. Parekh DJ, Punnen S, Sjoberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. *European urology*. Sep 2015;68(3):464-70. doi:10.1016/j.eururo.2014.10.021
42. Punnen S, Freedland SJ, Polascik TJ, et al. A Multi-Institutional Prospective Trial Confirms Noninvasive Blood Test Maintains Predictive Value in African American Men. *J Urol*. Jun 2018;199(6):1459-1463. doi:10.1016/j.juro.2017.11.113
43. Wysock JS, Becher E, Persily J, Loeb S, Lepor H. Concordance and Performance of 4Kscore and SelectMDx for Informing Decision to Perform Prostate Biopsy and Detection of Prostate Cancer. *Urology*. 2020;141:119-124. doi:10.1016/j.urology.2020.02.032
44. Mi C, Bai L, Yang Y, Duan J, Gao L. 4Kscore diagnostic value in patients with high-grade prostate cancer using cutoff values of 7.5% to 10%: A meta-analysis. *Urol Oncol*. Jun 2021;39(6):366 e1-366 e10. doi:10.1016/j.urolonc.2020.11.001
45. MDxHealth. ConfirmMDx for Prostate Cancer. <https://mdxhealth.com/confirm-mdx-for-physicians/>
46. Van Neste L, Partin AW, Stewart GD, Epstein JI, Harrison DJ, Van Criekinge W. Risk score predicts high-grade prostate cancer in DNA-methylation positive, histopathologically negative biopsies. *The Prostate*. Sep 2016;76(12):1078-87. doi:10.1002/pros.23191
47. Wojno KJ, Costa FJ, Cornell RJ, et al. Reduced Rate of Repeated Prostate Biopsies Observed in ConfirmMDx Clinical Utility Field Study. *American health & drug benefits*. May 2014;7(3):129-34.
48. MDxHealth. SelectMDx for Prostate Cancer. <https://mdxhealth.com/select-mdx-for-physicians/>
49. Van Neste L, Hendriks RJ, Dijkstra S, et al. Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score. *European urology*. Nov 2016;70(5):740-748. doi:10.1016/j.eururo.2016.04.012
50. Shore N. SelectMDx Impacts Prostate Biopsy Decision-making in Routine Clinical Practice. 2018. <https://abstracts.mirrorsmed.org/abstracts/selectmdx-impacts-prostate-biopsy-decision-making-routine-clinical-practice>
51. Stovsky M, Klein EA, Chait A, et al. Clinical Validation of IsoPSA, a Single Parameter, Structure Based Assay for Improved Detection of High Grade Prostate Cancer. *J Urol*. Jun 2019;201(6):1115-1120. doi:10.1097/JU.0000000000000185
52. Klein EA, Partin A, Lotan Y, et al. Clinical validation of IsoPSA, a single parameter, structure-focused assay for improved detection of prostate cancer: A prospective, multicenter study. *Urol Oncol*. Sep 2022;40(9):408 e9-408 e18. doi:10.1016/j.urolonc.2022.06.002
53. Scovell JM, Hettel D, Abouassaly R, et al. IsoPSA® Reduces Provider Recommendations for Biopsy and Magnetic Resonance Imaging in Men with Total Prostate Specific Antigen ≥ 4 ng/ml: A Real-World Observational Clinical Utility Study. 2022;doi:10.1097/UPJ.0000000000000291
54. Hologic. ProgenSA Brochure. <https://stage.hologic.com/sites/default/files/package-insert/ProgenSA%20PCA3%20Physician%20Brochure-USA.pdf>
55. Gittelman MC, Hertzman B, Bailen J, et al. PCA3 molecular urine test as a predictor of repeat prostate biopsy outcome in men with previous negative biopsies: a prospective multicenter clinical study. *J Urol*. Jul 2013;190(1):64-9. doi:10.1016/j.juro.2013.02.018
56. Rodríguez SVM, García-Perdomo HA. Diagnostic accuracy of prostate cancer antigen 3 (PCA3) prior to first prostate biopsy: A systematic review and meta-analysis. *Can Urol Assoc J*. May 2020;14(5):E214-e219. doi:10.5489/cuaj.6008
57. Matuszczak M, Schalken JA, Salagierski M. Prostate Cancer Liquid Biopsy Biomarkers' Clinical Utility in Diagnosis and Prognosis. *Cancers (Basel)*. Jul 5 2021;13(13)doi:10.3390/cancers13133373

58. Tomlins SA, Day JR, Lonigro RJ, et al. Urine TMPRSS2:ERG Plus PCA3 for Individualized Prostate Cancer Risk Assessment. *European urology*. Jul 2016;70(1):45-53. doi:10.1016/j.eururo.2015.04.039
59. Tosoian JJ, Trock BJ, Morgan TM, et al. Use of the MyProstateScore Test to Rule Out Clinically Significant Cancer: Validation of a Straightforward Clinical Testing Approach. *J Urol*. Mar 2021;205(3):732-739. doi:10.1097/JU.0000000000001430
60. Couñago F, López-Campos F, Díaz-Gavela AA, et al. Clinical Applications of Molecular Biomarkers in Prostate Cancer. *Cancers (Basel)*. Jun 12 2020;12(6)doi:10.3390/cancers12061550
61. Duffy MJ. Biomarkers for prostate cancer: prostate-specific antigen and beyond. *Clin Chem Lab Med*. Feb 25 2020;58(3):326-339. doi:10.1515/cclm-2019-0693
62. Jia W, Wu B, Shao Y, Cao X, Wang D. Diagnostic performance of prostate cancer antigen 3 and the Prostate Health Index in detecting overall and clinically significant prostate cancer in men at first biopsy: A meta-analysis. *International Journal of Urology*. 2020;n/a(n/a)doi:10.1111/iju.14464
63. White J, Shenoy BV, Tutrone RF, et al. Clinical utility of the Prostate Health Index (phi) for biopsy decision management in a large group urology practice setting. *Prostate Cancer Prostatic Dis*. Apr 2018;21(1):78-84. doi:10.1038/s41391-017-0008-7
64. Lotan TL, Gurel B, Sutcliffe S, et al. PTEN protein loss by immunostaining: analytic validation and prognostic indicator for a high risk surgical cohort of prostate cancer patients. *Clinical cancer research : an official journal of the American Association for Cancer Research*. Oct 15 2011;17(20):6563-73. doi:10.1158/1078-0432.Ccr-11-1244
65. New Data Validating the First AI-Based Biomarker to Stratify Risk of Metastasis in Radical Prostatectomy Patients with Biochemical Recurrence. May 6, 2024, 2024. <https://www.businesswire.com/news/home/20240506052855/en/New-Data-Validating-the-First-AI-Based-Biomarker-to-Stratify-Risk-of-Metastasis-in-Radical-Prostatectomy-Patients-with-Biochemical-Recurrence>
66. Clarke H. ArteraAI Prostate Test included in NCCN guidelines. Urology Times. Updated March 5, 2024. <https://www.urologytimes.com/view/arteraai-prostate-cancer-test-included-in-nccn-guidelines>
67. Esteva A, Feng J, van der Wal D, et al. Prostate cancer therapy personalization via multi-modal deep learning on randomized phase III clinical trials. *npj Digital Medicine*. 2022/06/08 2022;5(1):71. doi:10.1038/s41746-022-00613-w
68. Eggener SE, Rumble RB, Armstrong AJ, et al. Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline. *J Clin Oncol*. Dec 12 2020:jco1902768. doi:10.1200/jco.19.02768
69. Mottet N, Cornford P, van den Bergh RCN, et al. Guidelines on Prostate Cancer. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2023_2023-06-13-141145.pdf
70. Parker C, Castro E, Fizazi K, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2020;31(9):1119-1134. doi:10.1016/j.annonc.2020.06.011

X. Review/Revision History

Effective Date	Summary
10/15/2025	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: CC1, removed “Oncotype Dx” from name of “Genomic Prostate Score” to match with most up to date test name from MDx Health

	<p>CC3a edited for clarity and consistency</p> <p>CC3, CC4, and CC5, moved conditions for which a prostate biopsy is already indicated into a new Note 3 and relative contraindications for prostate biopsy into a new Note 4.</p> <p>CC4 and CC5, replaced “For individuals with a prostate” with “For individuals for whom there is a potential need for a prostate biopsy” for consistency with CC3</p> <p>New CC6 to allow the use of PHI: “6) For individuals for whom there is a potential need for a prostate biopsy, the one-time use of the Prostate Health Index (either once prior to initial biopsy or once prior to repeat biopsy) MEETS COVERAGE CRITERIA when all of the following conditions are met:</p> <ul style="list-style-type: none"> a) For individuals 50 years of age or older who have confirmed (see Note 2) PSA levels greater than 4 and less than 10 ng/mL b) The individual has none of the conditions for which a prostate biopsy is already indicated (see Note 3) c) The individual has no other relative contraindication for prostate biopsy (see Note 4).” <p>Results in the removal of PHI from former CC7b, now CC8b</p> <p>New notes 3 and 4, results in former Note 3 becoming Note 7. New notes read: “Note 3: Conditions for which a prostate biopsy is already indicated:</p> <ul style="list-style-type: none"> • DRE suspicious for cancer. • Persistently elevated PSA. • Positive multiparametric MRI (if performed). • Ethnicity at higher risk for prostate cancer (see Note 5) • First-degree relative (see Note 6) with prostate cancer. • Known to have a high-penetrance prostate cancer risk gene(s) per NCCN guidelines (see Note 7). <p>Note 4: Relative contraindications for a prostate biopsy:</p> <ul style="list-style-type: none"> • A less than 10-year life expectancy • Benign disease not ruled out” <p>Added CPT code 84153, 84154, 86316; 0572U (effective date 7/1/2025)</p> <p>Removed CPT code 0053U (deleted code; effective date 7/1/2023)</p>
12/01/2024	<p>Reviewed and Updated: Updated background, guidelines, and evidencebased scientific references. Literature review necessitated the following changes in coverage criteria:</p> <p>Updated CC3, changed “prior to initial biopsy” to “(either once prior to initial biopsy or once prior to repeat biopsy)”, now reads: “3) For individuals for whom there is a potential need for a prostate biopsy, the one-time use of the ExoDx Prostate (IntelliScore) (EPI) biomarker test (either once prior to initial biopsy or once prior to repeat biopsy) MEETS COVERAGE CRITERIA when all of the following conditions are met:”</p> <p>Lab test name revised for CPT code 0047U (effective date 7/1/2024)</p> <p>Added CPT code 0113U (effective date 7/1/2024)</p>

12/01/2024	Initial Policy Implementation
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