OptimaHealth
A Service of Sentara

Gene Expression Profiling and Protein Biomarkers for Prostate Cancer

Policy Number: AHS – M2166 – Gene Expression Profiling and Protein Biomarkers for Prostate Cancer	Prior Policy Name and Number, as applicable: AHS – M2166 – Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management
Policy Revision Date: 03/09/2022	

I. Policy Description

Prostate cancer is characterized by malignancy which originates in the small walnut-shaped gland in men that produces the seminal fluid. 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 (Benedettini et al., 2008; Taplin & Smith, 2022).

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 (Steiling & Christenson, 2021). 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 (Blume-Jensen et al., 2015; Ross et al., 2021).

II. Related Policies

Policy Number	Policy Title
AHS-G2007	Prostate Biopsies
AHS-G2008	Prostate Specific Antigen (PSA) Testing
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 Section VII of this policy document.

1) The one-time use of Prolaris®, Oncotype DX®, OR Decipher® tumor-based assays to guide management of prostate cancer **MEETS COVERAGE CRITERIA** in individuals with low-risk or favorable intermediate-risk disease, as defined by the National Comprehensive Cancer Network (NCCN) (see Note 1), only if **ALL** of the following criteria have been met:

   a) Needle biopsy with localized adenocarcinoma of prostate with no clinical evidence of metastasis or lymph node involvement; AND

   b) No presence of significant co-morbidities, including advanced age, to suggest individual has an estimated life expectancy of less than 10 years

2) The one-time use of Prolaris® or Decipher® tumor-based assays to guide management of prostate cancer **MEETS COVERAGE CRITERIA** in individuals with unfavorable intermediate-risk and high-risk disease, as defined by the NCCN (see Note 1), only if **ALL** of the following criteria have been met:

   a) Needle biopsy with localized adenocarcinoma of prostate with no clinical evidence of metastasis or lymph node involvement; AND

   b) No presence of significant co-morbidities, including advanced age, to suggest individual has an estimated life expectancy of less than 10 years

3) The one-time use of the ExoDx (EPI) biomarker test prior to initial biopsy **MEETS COVERAGE CRITERIA** in individuals with a prostate only if **ALL** of the following criteria have been met:

   a) Moderately elevated prostate-specific antigen (PSA) levels for one of the following:

      i) For individuals ages 50 – 75 years, PSA levels between 3 – 10 ng/mL

      ii) For individuals over the age of 75, PSA levels between 4 – 10 ng/mL

   b) No other relative indication for prostate biopsy including ANY of the following:

      i) Digital rectal examination (DRE) suspicious for cancer

      ii) Persistently elevated PSA

      iii) Positive multiparametric magnetic resonance imaging (MRI), if performed

      iv) Ethnicity at higher risk for prostate cancer (See Note 2)

      v) First-degree relative with prostate cancer

      vi) Known to have a high-penetrance prostate cancer risk gene(s) per NCCN guidelines (See Note 3)

   c) No other relative contraindication for prostate biopsy including ANY of the following:

i) <10-year life expectancy

ii) Benign disease not ruled out

4) The following tests to assess and/or monitor prostate cancer **DO NOT MEET COVERAGE CRITERIA**:

a) Ki-67 immunohistochemistry

b) Phosphatase and tensin homolog *(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 a patient's illness.

5) The following tests **DO NOT MEET COVERAGE CRITERIA** including but not limited to**:**

a) All other urine testing for gene expression profile and/or protein biomarkers to assess prostate cancer, including SelectMDx.

b) Other screening tests for prostate cancer, including, but not limited to, alpha-methylacyl coenzyme A racemase (AMACR), 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* (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate-specific antigen]) ratio, 4Kscore, Prostate Health Index (PHI), PCA3 score or ConfirmMDx.

c) Other tests using cellular and biologic features of a tumor, including use in predicting risk of recurrence in patients with prostate cancer.

NOTE 1: NCCN Prostate Cancer Initial Risk Stratification and Staging Workup for Clinically Localized Disease (NCCN, 2022)

Risk Group	Clinical/Pathological Features		
Very Low	Has all of the following: · 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: · cT1-cT2a · Grade Group 1 · PSA <10 ng/mL		
Intermediate	Has all of the following: · No high-risk group features		Has all of the following: · 1 IRF

	· No very-high-risk group features · Has one or more intermediate risk factors » cT2b-cT2c » Grade Group 2 or 3 » PSA 10-20 ng/mL	Favorable Intermediate	· Grade Group 1 or 2 · <50% biopsy cores positive
		Unfavorable Intermediate	Has one or more of the following: · 2 or 3 IRFs · Grade Group 3 · ≥50% biopsy cores positive
High	Has no very-high-risk features and has at least one high-risk feature: · cT3a OR · Grade Group 4 or Grade Group 5 OR · PSA >20 ng/mL		
Very High	Has at least one of the following: · T3b-T4 · Primary Gleason pattern 5 · 2 or 3 high-risk features · >4 cores with Grade Group 4 or 5		

NOTE 2: According to the NCCN Prostate Cancer Early Detection guidelines, "African-American men, men with a family history of prostate cancer, and those with a known genetic predisposition represent high-risk groups (NCCN, 2021)."

NOTE 3: 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* (NCCN, 2021).

IV. Table of Terminology

Term	Definition
AACU	American Association of Clinical Urologists
ADT	Androgen deprivation therapy
AMACR	Alpha-methylacyl coenzyme A racemase
APC	*Adenomatous polyposis coli* gene
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	*ATM serine/threonine kinase gene*
AUA	American Urological Association
AUC	Area under the curve
BCR	Biochemical recurrence

BRCA1	*Breast cancer gene 1*
BRCA2	*Breast cancer gene 2*
CAPRA	Cancer of the prostate risk assessment
CCP	Cell-cycle progression
CCR	Cell-cycle risk
CDK12	*Cyclin dependent kinase 12 gene*
CDx	Companion diagnostic
CHEK2	*Checkpoint kinase 2 gene*
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
DLX1	*Distal-less homeobox 1 gene*
DRE	Digital rectal examination
DX	Diagnosis
EAU	European Association of Urology
EBRT	External beam radiation therapy
EDTA	Ethylenediaminetetraacetic acid
EPI	ExoDx Prostate (IntelliScore)
ERG	*ETS Transcription Factor ERG*
ESMO	European Society for Medical Oncology
ESTRO	European Society for Radiotherapy and Oncology
ESUR	European Society of Urogenital Radiology
ETS	E-twenty-six
FANCA	*Fanconi anemia complementation group A gene*
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence *in situ* hybridization
GEC	Gene/genomic expression classifiers
GPS	Genomic prostate score
GSTP1	*Glutathione S-transferase pi 1 gene*
HGPC	High-grade prostate cancer
hK2	Human kallikrein-2
HOXB13	*Homeobox B13 gene*
HOXC6	*Homeobox C6 gene*
HT	Hormonal therapy
IHC	Immunohistochemistry
indels	Insertion and deletion alterations
IRF	Intermediate-risk factor
KLK3	*Kallikrein related peptidase 3 gene*
LDTs	Laboratory-developed tests
LUGPA	Large Urology Group Practice Association
mCRPC	Metastatic castration-resistant prostate cancer

MLH1	*MutL homolog 1 gene*
MRI	Magnetic resonance imaging
MSH2	*MutS homolog 2 gene*
MSH6	*MutS homolog 6 gene*
NBN	*Nibrin gene*
NCCN	National Comprehensive Cancer Network
NPV	Negative predictive value
PALB2	*Partner and localizer of BRCA2 gene*
PARP	Poly (ADP-ribose) polymerase
PC	Prostate cancer
PCa	Prostate cancer
PCA3	Prostate cancer gene 3
PCA3/KLK3	Prostate cancer antigen 3 [non-protein coding]/Kallikrein-related peptidase 3 [Prostate-specific antigen]
PCR	Polymerase chain reaction
PCRMP	Prostate Cancer Risk Management Programme
PHE	Public Health England
PHI	Prostate health index
PLA	Proprietary laboratory analyses
PPCA	Proveri Prostate Cancer Assay
PPV	Positive predictive value
PSA	Prostate specific antigen
PTEN	*Phosphatase and tensin homolog gene*
QALY	Quality adjusted life-years
RAD51D	*RAD51 Paralog D gene*
RASSF1	*Ras association domain family 1 gene*
RNA	Ribonucleic acid
RP	Radical prostatectomy
RT	Radiation therapy
RT-PCR	Reverse transcription-polymerase chain reaction
SIOG	International Society of Geriatric Oncology
SOC	Standard of care practices
SPDEF	*SAM pointed domain containing ETS transcription factor gene*
SSED	Summary of safety and effectiveness data
SUO	Society of Urologic Oncology
TMPRSS2: ERG	*Transmembrane protease serine 2: v-ets erythroblastosis virus E26 oncogene homolog fusion gene*
TP53	*Tumor protein 53 gene*
TRUS biopsy	Transrectal ultrasound guided biopsy

V. Scientific Background

Prostate cancer (PCa) is the most common cancer in American men and the second leading cause of death in men over 65 (Balducci et al., 1997; Tabayoyong & Abouassaly, 2015). In 2021, the American Cancer Society estimates that approximately 248,530 new prostate cancer diagnoses

and approximately 34,130 prostate cancer deaths will occur; although, the 5-year survival rate between 2007-2013 was 99%. About one man in eight will be diagnosed with prostate cancer during his lifetime in the United States (ACS, 2021; Siegel et al., 2018).

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 men aged 55 or older and approximately 60 percent of men by age 80 (Bell et al., 2015). These data suggest that prostate cancer often grows so slowly that most men die of other causes before the disease becomes clinically advanced (Hoffman, 2021).

Prostate cancer survival is related to many factors, especially the extent of tumor at the time of diagnosis. The five-year relative survival among men with cancer localized to the prostate or with regional spread is 100%, compared with 31% among those diagnosed with distant metastases (Hoffman, 2021). 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 (Song et al., 2018). While several types of biomarker tests exist, the NCCN specifically recommends Prolaris, Oncotype DX Prostate, Decipher, and ProMark as tumor-based molecular assays to consider during initial risk stratification (NCCN, 2022). Ki-67 and PTEN are also listed in NCCN guidelines, but are not recommended (NCCN, 2022).

Proprietary Testing, Clinical Utility, and Analytical Validity

Hu et al. (2018) evaluated the utility of three genomic expression classifiers (GEC), including Decipher, Oncotype, 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 men with favorable risk of cancer who undergo GEC testing, one additional patient may have their disease initially managed with AS (Hu et al., 2018)."

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 0 to 10, 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 0-10 is used. Each unit increase represents a doubling of risk of biochemical recurrence (BCR) (Alford et al., 2017).

CCP 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 (Cuzick et al., 2015).

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% (Hu et al., 2018; Lin et al., 2018). 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) (Carneiro et al., 2018).

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 men 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 (Tward et al., 2020).

Oncotype DX

Oncotype DX 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 Oncotype DX only tests 12 genes, with 5 reference genes (compared to 31 and 15, respectively, for Prolaris). 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) (Cullen et al., 2015).

Cullen et al. (2015) found that the GPS score correlated well with BCR. The researchers noted that OncoType DX 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 (Alford et al., 2017; Cullen et al., 2015; Davis, 2014; NCCN, 2022). Oncotype DX was recently validated in a group of men 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) men (Murphy et al., 2020).

OncoType DX AR-V7 Nucleus

The OncoType DX AR-V7 Nucleus 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 (OncoType, 2019, 2021).

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 men 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 (Scher et al., 2016)."

Further, Chen et al. (2018) studied the overexpression of the nuclear AR-V7 protein in prostate cancer cases. A total of 401 men 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 (Chen et al., 2018)."

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. 255 samples of circulating tumor cells (CTCs) were

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 men 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 (Graf et al., 2020).”

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 likeliness of metastases or mortality. The algorithm score ranges from 0 to 1, 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) (Alford et al., 2017; Dalela et al., 2016).

Van den Broeck et al. (2019) aimed to validate the Decipher test in the prediction of distant metastatic recurrence in men with high-risk nonmetastatic prostate cancer 10 years after the surgery was completed. A total of 298 men 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 (Van den Broeck et al., 2019).” 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. 3,455 males were 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 (Marascio et al., 2020).

ExoDX Prostate (IntelliScore)

ExoDX is a urinary test that detects the expression level of three genetic biomarkers (ERG, PCA3, and SPDEF) (AMA, 2019; ExoSome, 2019, 2021). 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 ≥7). This test is intended for men 50 or over with a PSA level of 2-10 ng/mL presenting for an initial biopsy (prior to a DRE) (ExoSome, 2019, 2021).

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 2-20 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 5% of patients with high-risk disease (McKiernan et al., 2016). 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 (McKiernan et al., 2018).

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 (Sathianathen Niranjan et al., 2018)."

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 (2 – 10 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 (Tutrone et al., 2020)."

ConfirmMDX

ConfirmMDX uses methylation-specific polymerase chain reaction (PCR) to identify whether a patient with a previously negative prostate biopsy should undergo a repeat biopsy. This test identifies methylation of three genes (*GSTP1*, *APC*, and *RASSF1*) (MDx, 2018a; MDx_Health, 2020a). This test has been evaluated by Van Neste, Partin, et al. (2016) and was found to have a negative predictive value (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 positive predictive value (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 (Van Neste, Partin, et al., 2016). 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 6 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" (MDx, 2018b; MDx_Health, 2020b). Van Neste, Hendriks, 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 (Van Neste, Hendriks, et al., 2016). 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 (Shore, 2018).

Proveri

Proveri evaluates 114 diagnostic biomarkers and 15 prognostic biomarkers to assess prostate cancer. The diagnostic biomarkers were validated with 364 samples (243 tumor samples, 121 control) and assessed at a sensitivity of 88% and specificity of 98% (97% accuracy). The prognostic biomarkers were validated with 49 samples (40 relapse patients, 9 with indolent disease) and were calculated to have a sensitivity of 88%, a specificity of 80% and were 87% accurate (Proveri, 2013). This test has since been discontinued.

Progensa PCA3

Progensa *PCA3* is an FDA-approved assay that examines the concentration of the prostate cancer gene 3 (*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 men 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 men with atypical small acinar proliferation on their most recent biopsy (Hologic, 2017). 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 (Gittelman et al., 2013).

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 were 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" (Matuszczak et al., 2021; Rodríguez & García-Perdomo, 2020).

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 1-100. This score represents individualized risk. Blume-Jensen et al. (2015) narrowed down the 8 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 0-1) 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 (Alford et al., 2017; Blume-Jensen et al., 2015).

4kScore

4kScore, from OPKO, is intended to assess the risk for "aggressive" prostate cancer. The test incorporates total PSA, free PSA, "intact" PSA, and "hk2" [human kallikrein 2] (NCCN, 2022; OPKO, 2021). These biomarkers, along with other patient clinical information (such as age and prior biopsy status) are evaluated by the OPKO 4kScore Algorithm. Finally, the test provides a risk assessment for aggressive cancer (%risk of Gleason 7 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 (Zappala et al., 2017).

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. 50 of the 144 patients underwent biopsy based on the test results. 22 of the 50 patients (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 (Wysock et al., 2020).

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 men with a higher total PSA and p2PSA and a lower fPSA have a higher risk of presenting with

prostate cancer (Couñago et al., 2020). PHI is clinically used to reduce the number of unnecessary biopsies in men 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 (Duffy, 2020).

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 (Jia et al., 2020)."

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 4-10 ng/mL range” in a observational study at several large urology group practices. They found that there was a “significant reduction in biopsy procedures performed” in men 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 (Matuszczak et al., 2021; White et al., 2018)

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 (NCCN, 2022).

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 (NCCN, 2022; Ross et al., 2021). 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 (Ross et al., 2021).

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 (NCCN, 2022; Ross et al., 2021). 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.

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: Decipher, Oncotype DX Prostate, 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 progression after RP or EBRT [external beam radiation therapy], and likelihood of developing metastasis after RP or salvage radiotherapy (NCCN, 2022)." 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 somatic mutations in any gene that has clinical implications if also identified in germline (eg, *BRCA2*, *BRCA1*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PMS2)* (NCCN, 2022)." The NCCN noted that somatic tumor testing of the aforementioned genes has potential for early use of platinum chemotherapy, use of PARP inhibitors, or eligibility for clinical trials. Lastly, they recommend that men with regional disease, metastatic castration-resistant disease, or castration-naïve metastatic disease should additionally consider tumor testing for microsatellite instability or mismatch repair deficiency. The NCCN also specifically does not recommend either Ki-67 or *PTEN* testing (NCCN, 2022).

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 (NCCN, 2021, 2022):

Test	Platform	Recommendation
Decipher	Whole-Transcriptome 1.4M RNA expression (46,050 genes and non-coding RNA), oligonucleotide microarray optimized for FFPE tissue	Cover post-biopsy for NCCN very-low-, low-risk, favorable intermediate, and unfavorable 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. Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
KI-67	IHC	Not recommended
Oncotype DX	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 that improve the specificity of screening" for individuals who have had elevated levels of PSA (above 3 ng/mL for those ages 45 – 75 years or 4 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 further define risk. Percent-free PSA may improve cancer detection. The probability of high-grade cancer (Gleason score ≥3+4, Grade Group 2 or higher) may be further defined utilizing the Prostate Health Index (PHI), SelectMDx, 4Kscore, and ExoDx Prostate test. Extent of validation of these tests across diverse populations is variable. It is not known how such tests could be applied in the optimal combination with MRI as yet (NCCN, 2021)." The NCCN notes that these tests- including percent-free PSA, 4Kscore, PHI, PCA3, and ConfirmMDx-improve specificity in the post-biopsy setting and it should be considered in patients who are thought to be at higher risk despite a negative prostate biopsy (NCCN, 2021).

The NCCN panel remarks that 4Kscore "can be considered for patients prior to biopsy and for those with a 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 men contemplating repeat biopsy and is approved for limited coverage by MolDX to reduce unnecessary repeat biopsies. Further, ExoDx *Prostate (IntelliScore)*, also called EPI, "can be considered as an option for men contemplating initial or repeat biopsy (NCCN, 2021)."

American Association of Clinical Urologists Inc.

The AACU recommends use of tissue-based molecular testing to assess risk stratification in prostate cancer treatment decision making. The AACU states pursing germline testing when appropriate is encouraged and support any further research into these tests. The AACU specifically recommends, "Tissue-based molecular testing should be considered for low and favorable intermediate risk men with life expectancy ≥ 10 years." The **Large Urology Group Practice Association (LUGPA)** endorses this position statement by the AACU (AACU, 2018; LUGPA, 2018).

American Society of Clinical Oncology (ASCO)

The ASCO released a guideline stating that they endorsed the non-cryotherapy 2017 joint guidelines from the American Urological Association (AUA)/American Society for Radiation

Oncology (ASTRO)/Society of Urologic Oncology (SUO) (Bekelman et al., 2018).

Guideline 32 stated "tissue based genomic biomarkers have not shown a clear role in active surveillance for localized prostate cancer and are not necessary for follow up." These joint guidelines also state that several genomic assays were validated in the pre-MRI era and that their clinical utility "remains to be established" (Sanda et al., 2018).

The AUA has also noted a "lack of predictive biomarkers to help better personalize therapy" in drug development for prostate cancer patients (AUA, 2018).

In 2019, an ASCO multidisciplinary panel published guidelines on molecular biomarkers in localized prostate cancer. These guidelines are below:

- "Commercially available molecular biomarkers (ie, Oncotype Dx Prostate, 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 (eg, 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 (Eggener et al., 2019)."

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 (Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) when the assay result "is likely to have an impact on patient management. Examples include select men with high-volume low-risk or favorable intermediate-risk prostate cancer who are considering active surveillance or in men 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 (Eggener et al., 2020)."

European Association of Urology (EAU), European Society for Radiotherapy and Oncology (ESTRO), European Society of Urogenital Radiology (ESUR), and the International Society of Geriatric Oncology (SIOG)

The EAU, ESTRO, ESUR and SIOG released joint guidelines on prostate cancer. These guidelines stated that "In asymptomatic men with a prostate-specific antigen level between 2-10ng/mL and a normal digital rectal examination, use one of the following tools for biopsy indication:

- risk-calculator (Strong);
- imaging (Strong);
- an additional serum, urine or tissue-based test (Weak)."

These joint guidelines acknowledged both SelectMDX and ConfirmMDX as tests to select for repeat biopsies, but the guidelines noted SelectMDX as having an "uncertain" role and "probably not cost-effective." No recommendation could be made for the routine application of ConfirmMDX. Prolaris and OncoType DX were also recognized as tests that have been used to evaluate prostate cancer, but no recommendation has been made at this time (EAU, 2021).

In 2021, updated joint guidelines acknowledged five commercially available tests (Oncotype Dx, Prolaris, Decipher, Decipher PORTOS and ProMark). Since the long-term impact of the use of these tests is unproven, 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, such as for instance in men with favourable intermediate-risk PCa who might opt for AS or men with unfavourable intermediate-risk PCa scheduled for RT [radiation therapy] to decide on treatment intensification with hormonal therapy (HT) (EAU, 2021)."

Public Health England (PHE)

PHE notes PCA3 as a "promising urinary RNA biomarker" (PHE, 2016). The source guideline for this information was withdrawn on July 27, 2021.

European Society for Medical Oncology (ESMO)

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 (Parker et al., 2020).

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 http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, please visit the applicable state Medicaid website.

A. Food and Drug Administration (FDA)

The FDA has approved 3tests for evaluation of gene expression profiles of prostate cancer as of February 1, 2021 (FDA, 2021).

On November 6, 2020, the FDA approved FoundationOne CDx, by Foundation Medicine, Inc.

This device is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 311 genes, rearrangements in 3 genes, and copy number alterations in 3 genes. FoundationOne CDx also utilizes circulating cell-free DNA collected in FoundationOne® Liquid CDx Blood Sample Collection Kit to identify patients with non-small cell lung cancer, prostate cancer, ovarian cancer, or breast cancer who may benefit from treatment with the targeted therapies. This test provides tumor mutation profiling of *BRCA1*, *BRCA2*, and ATM alterations for prostate cancer diagnosis (FDA, 2020).

On February 13, 2012, the FDA approved the PROGENSA PCA3 Assay created by Gen-Probe Inc. From the FDA website: "The PROGENSA PCA3 Assay is an in vitro nucleic acid amplification test. The assay measures the concentration of prostate cancer gene 3 (PCA3) and prostate-specific antigen (PSA) RNA molecules and calculates the ratio of PCA3 RNA molecules to PSA RNA molecules (PCA3 Score) in post-digital rectal exam (DRE) first catch male urine specimens. The PROGENSA PCA3 Assay is indicated for use in conjunction with other patient information to aid in the decision for repeat biopsy in men 50 years of age or older who have had one or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on current standard of care, before consideration of PROGENSA PCA3 Assay results" (FDA, 2012).

On December 19, 2014, the FDA approved the BRACAnalysis CDx™ created by Myriad Genetics. From the FDA website: BRACAnalysis CDx™ is an in vitro diagnostic device intended for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the *BRCA1* and *BRCA2* genes using genomic DNA obtained from whole blood specimens collected in EDTA. Single nucleotide variants and small insertions and deletions (indels) are identified by polymerase chain reaction (PCR) and Sanger sequencing. Large deletions and duplications in *BRCA1* and *BRCA2* are detected using multiplex PCR. Results of the test are used as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants eligible for treatment with Lynparza™ (olaparib). This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108" (FDA, 2014) This test is commonly known as Prolaris.

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.

B. Centers for Medicare & Medicaid Services (CMS)

- L35632 MolDX: ConfirmMDx Epigenetic Molecular Assay: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35632&ver=38&bc=0
- L36665 ProMark® Risk Score: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=36665&ver=19&bc=0

- A56955 Billing and Coding: MolDX: ConfirmMDx Epigenetic Molecular Assay: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=56955&ver=7
- L38292 MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38292&ver=10&bc=0
- A58343 Billing and Coding: MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=58343&ver=11

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 Proprietary test: 4Kscore® Lab/manufacturer: OPKO Health, Inc.
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 Proprietary test: Prolaris® Lab/Manufacturer: Myriad Genetic Laboratories, Inc
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score Proprietary test: Decipher® Prostate Lab/Manufacturer: Biosciences
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 Proprietary test: ConfirmMDx® for prostate cancer Lab/Manufacturer: MDxHealth, Inc
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: Apifiny® 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 Proprietary test: Oncotype DX® Genomic Prostate Score™ Lab/manufacturer: Genomic Health, Inc.
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 Proprietary test: Prostate Cancer Risk Panel Lab/Manufacturer: Mayo Clinic Laboratory
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

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

AACU. (2018). https://aacuweb.org/docs/position-statements/ps_genomic-testing-in-prostate-cancer.aspx

ACS. (2021). *Cancer Facts & Figures 2020*. Retrieved 02/01/2021 from https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf

Alford, A. V., Brito, J. M., Yadav, K. K., Yadav, S. S., Tewari, A. K., & Renzulli, J. (2017). The Use of Biomarkers in Prostate Cancer Screening and Treatment. *Rev Urol*, *19*(4), 221-234. https://doi.org/10.3909/riu0772

AMA. (2019). *CPT® Proprietary Laboratory Analyses (PLA) Codes: Long Descriptors*. https://www.ama-assn.org/system/files/2018-11/cpt-pla-codes-long_0.pdf

AUA. (2018). Castration-Resistant Prostate Cancer (2018). https://www.auanet.org/guidelines/prostate-cancer-castration-resistant-guideline

Balducci, L., Pow-Sang, J., Friedland, J., & Diaz, J. I. (1997). Prostate cancer. *Clin Geriatr Med*, *13*(2), 283-306.

Bekelman, J. E., Rumble, R. B., Chen, R. C., Pisansky, T. M., Finelli, A., Feifer, A., Nguyen, P. L., Loblaw, D. A., Tagawa, S. T., Gillessen, S., Morgan, T. M., Liu, G., Vapiwala, N., Haluschak, J. J., Stephenson, A., Touijer, K., Kungel, T., & Freedland, S. J. (2018). Clinically Localized Prostate Cancer: ASCO Clinical Practice Guideline Endorsement of an American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology Guideline. *Journal of Clinical Oncology*, *36*(32), 3251-3258. https://doi.org/10.1200/JCO.18.00606

Bell, K. J., Del Mar, C., Wright, G., Dickinson, J., & Glasziou, P. (2015). Prevalence of incidental prostate cancer: A systematic review of autopsy studies. *Int J Cancer*, *137*(7), 1749-1757. https://doi.org/10.1002/ijc.29538

Benedettini, E., Nguyen, P., & Loda, M. (2008). The pathogenesis of prostate cancer: from molecular to metabolic alterations. *Diagn Histopathol (Oxf)*, *14*(5), 195-201. https://doi.org/10.1016/j.mpdhp.2008.03.001

Blume-Jensen, P., Berman, D. M., Rimm, D. L., Shipitsin, M., Putzi, M., Nifong, T. P., Small, C., Choudhury, S., Capela, T., Coupal, L., Ernst, C., Hurley, A., Kaprelyants, A., Chang, H., Giladi, E., Nardone, J., Dunyak, J., Loda, M., Klein, E. A., . . . Saad, F. (2015). Development and clinical validation of an in situ biopsy-based multimarker assay for risk stratification in prostate cancer. *Clin Cancer Res*, *21*(11), 2591-2600. https://doi.org/10.1158/1078-0432.Ccr-14-2603

Carneiro, A., Priante Kayano, P., Gomes Barbosa, Á. R., Langer Wroclawski, M., Ko Chen, C., Cavlini, G. C., Reche, G. J., Sanchez-Salas, R., Tobias-Machado, M., Sowalsky, A. G., & Bianco, B. (2018). Are localized prostate cancer biomarkers useful in the clinical practice? *Tumor Biology*, *40*(9), 1010428318799255. https://doi.org/10.1177/1010428318799255

Chen, X., Bernemann, C., Tolkach, Y., Heller, M., Nientiedt, C., Falkenstein, M., Herpel, E., Jenzer, M., Grullich, C., Jager, D., Sultmann, H., Duensing, A., Perner, S., Cronauer, M. V., Stephan, C., Debus, J., Schrader, A. J., Kristiansen, G., Hohenfellner, M., & Duensing, S. (2018). 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*, *36*(4), 161.e119-161.e130. https://doi.org/10.1016/j.urolonc.2017.11.001

Couñago, F., López-Campos, F., Díaz-Gavela, A. A., Almagro, E., Fenández-Pascual, E., Henríquez, I., Lozano, R., Linares Espinós, E., Gómez-Iturriaga, A., de Velasco, G., Quintana Franco, L. M., Rodríguez-Melcón, I., López-Torrecilla, J., Spratt, D. E., Guerrero, L. L., Martínez-Salamanca, J. I., & Del Cerro, E. (2020). Clinical Applications of Molecular Biomarkers in Prostate Cancer. *Cancers (Basel)*, *12*(6). https://doi.org/10.3390/cancers12061550

Cullen, J., Rosner, I. L., Brand, T. C., Zhang, N., Tsiatis, A. C., Moncur, J., Ali, A., Chen, Y., Knezevic, D., Maddala, T., Lawrence, H. J., Febbo, P. G., Srivastava, S., Sesterhenn, I. A., & McLeod, D. G. (2015). 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. *Eur Urol*, *68*(1), 123-131. https://doi.org/10.1016/j.eururo.2014.11.030

Cuzick, J., Stone, S., Fisher, G., Yang, Z. H., North, B. V., Berney, D. M., Beltran, L., Greenberg, D., Moller, H., Reid, J. E., Gutin, A., Lanchbury, J. S., Brawer, M., & Scardino, P. (2015). Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. *Br J Cancer*, *113*(3), 382-389. https://doi.org/10.1038/bjc.2015.223

Dalela, D., Löppenberg, B., Sood, A., Sammon, J., & Abdollah, F. (2016). Contemporary Role of the Decipher® Test in Prostate Cancer Management: Current Practice and Future Perspectives. *Rev Urol*, *18*(1), 1-9.

Davis, J. W. (2014). Novel commercially available genomic tests for prostate cancer: a roadmap to understanding their clinical impact. *BJU International*, *114*(3), 320-322. https://doi.org/10.1111/bju.12695

Duffy, M. J. (2020). Biomarkers for prostate cancer: prostate-specific antigen and beyond. *Clin Chem Lab Med*, *58*(3), 326-339. https://doi.org/10.1515/cclm-2019-0693

EAU. (2021). EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2021. https://uroweb.org/guideline/prostate-cancer/#11

Eggener, S. E., Rumble, R. B., Armstrong, A. J., Morgan, T. M., Crispino, T., Cornford, P., van der Kwast, T., Grignon, D. J., Rai, A. J., Agarwal, N., Klein, E. A., Den, R. B., & Beltran, H. (2019). Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline. *J Clin Oncol*, Jco1902768. https://doi.org/10.1200/jco.19.02768

Eggener, S. E., Rumble, R. B., & Beltran, H. (2020). Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline Summary. *JCO Oncology Practice*, *16*(6), 340-343. https://doi.org/10.1200/jop.19.00752

ExoSome. (2019). *Prostate Cancer*. http://www.exosomedx.com/prostate-cancer-0

ExoSome. (2021). *ExoDx™ Prostate Test*. Retrieved 2/8/21 from http://www.exosomedx.com/physicians/exodx-prostate-test

FDA. (2012). *PROGENSA PCA3 ASSAY*. https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100033B.pdf

FDA. (2014). *BRACANALYSIS CDX*. https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140020B.pdf

FDA. (2020). FoundationOne Liquid CDx. https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=455653

FDA. (2021). https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm

Gittelman, M. C., Hertzman, B., Bailen, J., Williams, T., Koziol, I., Henderson, R. J., Efros, M., Bidair, M., & Ward, J. F. (2013). 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*, *190*(1), 64-69. https://doi.org/10.1016/j.juro.2013.02.018

Graf, R. P., Hullings, M., Barnett, E. S., Carbone, E., Dittamore, R., & Scher, H. I. (2020). Clinical Utility of the Nuclear-localized AR-V7 Biomarker in Circulating Tumor Cells in Improving Physician Treatment Choice in Castration-resistant Prostate Cancer. *Eur Urol*, *77*(2), 170-177. https://doi.org/https://doi.org/10.1016/j.eururo.2019.08.020

Hoffman, R. (2021, 07/01/2021). *Screening for prostate cancer*. https://www.uptodate.com/contents/screening-for-prostate-cancer

Hologic. (2017). *LEARN ABOUT PCA3*. http://www.pca3.org/learn-about-pca3

Hu, J. C., Tosoian, J. J., Qi, J., Kaye, D., Johnson, A., Linsell, S., Montie, J. E., Ghani, K. R., Miller, D. C., Wojno, K., Burks, F. N., Spratt, D. E., & Morgan, T. M. (2018). Clinical Utility of Gene Expression Classifiers in Men With Newly Diagnosed Prostate Cancer. (2), 1-15. https://doi.org/10.1200/po.18.00163

Jia, W., Wu, B., Shao, Y., Cao, X., & Wang, D. (2020). 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*, *n/a*(n/a). https://doi.org/https://doi.org/10.1111/iju.14464

Lin, D. W., Crawford, E. D., Keane, T., Evans, B., Reid, J., Rajamani, S., Brown, K., Gutin, A., Tward, J., Scardino, P., Brawer, M., Stone, S., & Cuzick, J. (2018). Identification of men with low-risk biopsy-confirmed prostate cancer as candidates for active surveillance. *Urologic Oncology: Seminars and Original Investigations*, *36*(6), 310.e317-310.e313. https://doi.org/https://doi.org/10.1016/j.urolonc.2018.03.011

Lotan, T. L., Gurel, B., Sutcliffe, S., Esopi, D., Liu, W., Xu, J., Hicks, J. L., Park, B. H., Humphreys, E., Partin, A. W., Han, M., Netto, G. J., Isaacs, W. B., & De Marzo, A. M. (2011). PTEN protein loss by immunostaining: analytic validation and prognostic indicator for a high risk surgical cohort of prostate cancer patients. *Clin Cancer Res*, *17*(20), 6563-6573. https://doi.org/10.1158/1078-0432.Ccr-11-1244

LUGPA. (2018). https://lugpa.org/lugpa-endorses-and-supports-new-cancer-guidelines-from-nccn/

Marascio, J., Spratt, D. E., Zhang, J., Trabulsi, E. J., Le, T., Sedzorme, W. S., Beeler, W. H., Davicioni, E., Dabbas, B., Lin, D. W., Gore, J. L., Bloom, M., Mann, M., Mark, J. R., Calvaresi, A., Godwin, J. L., McCue, P., Hurwitz, M. D., Kelly, W. K., . . . Den, R. B. (2020). Prospective study to define the clinical utility and benefit of Decipher testing in men following prostatectomy. *Prostate Cancer and Prostatic Diseases*, *23*(2), 295-302. https://doi.org/10.1038/s41391-019-0185-7

Matuszczak, M., Schalken, J. A., & Salagierski, M. (2021). Prostate Cancer Liquid Biopsy Biomarkers' Clinical Utility in Diagnosis and Prognosis. *Cancers (Basel)*, *13*(13). https://doi.org/10.3390/cancers13133373

McKiernan, J., Donovan, M. J., Margolis, E., Partin, A., Carter, B., Brown, G., Torkler, P., Noerholm, M., Skog, J., Shore, N., Andriole, G., Thompson, I., & Carroll, P. (2018). 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. *Eur Urol*, *74*(6), 731-738. https://doi.org/10.1016/j.eururo.2018.08.019

McKiernan, J., Donovan, M. J., O'Neill, V., Bentink, S., Noerholm, M., Belzer, S., Skog, J., Kattan, M. W., Partin, A., Andriole, G., Brown, G., Wei, J. T., Thompson, I. M., Jr., & Carroll, P. (2016). A Novel Urine Exosome Gene Expression Assay to Predict High-grade Prostate Cancer at Initial BiopsyUrine Exosome Signature to Predict High-Grade Prostate CancerUrine Exosome Signature to Predict High-Grade Prostate Cancer. *JAMA Oncology*, *2*(7), 882-889. https://doi.org/10.1001/jamaoncol.2016.0097

MDx. (2018a). ConfirmMDx for Prostate Cancer. https://mdxhealth.com/confirmmdx-prostate-cancer

MDx. (2018b). SelectMDx for Prostate Cancer. https://mdxhealth.com/selectmdx-prostate-cancer

MDx_Health. (2020a). ConfirmMDx for Prostate Cancer. https://mdxhealth.com/confirmmdx-physician/#overview

MDx_Health. (2020b). *SelectMDx for Prostate Cancer*. https://mdxhealth.com/selectmdx-physician/

Murphy, A. B., Carbunaru, S., Nettey, O. S., Gornbein, C., Macias, V., Sharifi, R., Kittles, R. A., Yang, X., Kajdacsy-Balla, A., & Gann, P. (2020). 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*. https://doi.org/10.1016/j.urology.2020.01.052

NCCN. (2021, 07/14/2021). *Prostate Cancer Early Detection Version 2.2021*. Retrieved 02/01/2021 from https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf

NCCN. (2022, 01/10/2022). *NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer, Version 3.2022*. Retrieved 2/8/21 from https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

OncoType. (2019). *Leverage the predictive power of the Oncotype DX AR-V7 Nucleus Detect test*. https://www.oncotypeiq.com/en-US/announcements/AR-V7

OncoType. (2021). *Leverage the predictive power of the Oncotype DX AR-V7 Nucleus Detect test*. Retrieved 2/8/21 from https://www.oncotypeiq.com/en-US/announcements/AR-V7

OPKO. (2021). *WHAT IS THE 4KSCORE®?* Retrieved 1/13/21 from https://4kscore.com/what-is-the-4kscore.html

Parker, C., Castro, E., Fizazi, K., Heidenreich, A., Ost, P., Procopio, G., Tombal, B., & Gillessen, S. (2020). Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, *31*(9), 1119-1134. https://doi.org/10.1016/j.annonc.2020.06.011

PHE. (2016). *Prostate cancer risk management programme (PCRMP): benefits and risks of PSA testing*. https://www.gov.uk/government/publications/prostate-cancer-risk-management-programme-psa-test-benefits-and-risks/prostate-cancer-risk-management-programme-pcrmp-benefits-and-risks-of-psa-testing#the-future-of-prostate-cancer-detection

Proveri. (2013). *TECHNOLOGY*. http://www.provericorp.com/technology/

Rodríguez, S. V. M., & García-Perdomo, H. A. (2020). Diagnostic accuracy of prostate cancer antigen 3 (PCA3) prior to first prostate biopsy: A systematic review and meta-analysis. *Can Urol Assoc J*, *14*(5), E214-e219. https://doi.org/10.5489/cuaj.6008

Ross, A. E., D'Amico, A. V., & Freedland, S. J. (2021, 12/08/2021). *Molecular prognostic tests for prostate cancer*. Wolters Kluwer. Retrieved 04/15/2019 from https://www.uptodate.com/contents/molecular-prognostic-tests-for-prostate-cancer

Sanda, M. G., Cadeddu, J. A., Kirkby, E., Chen, R. C., Crispino, T., Fontanarosa, J., Freedland, S. J., Greene, K., Klotz, L. H., Makarov, D. V., Nelson, J. B., Rodrigues, G., Sandler, H. M., Taplin, M. E., & Treadwell, J. R. (2018). Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. *J Urol*, *199*(3), 683-690. https://doi.org/10.1016/j.juro.2017.11.095

Sathianathen Niranjan, J., Kuntz Karen, M., Alarid-Escudero, F., Lawrentschuk Nathan, L., Bolton Damien, M., Murphy Declan, G., Weight Christopher, J., & Konety Badrinath, R. (2018). Incorporating Biomarkers into the Primary Prostate Biopsy Setting: A Cost-Effectiveness Analysis. *Journal of Urology*, *200*(6), 1215-1220. https://doi.org/10.1016/j.juro.2018.06.016

Scher, H. I., Lu, D., Schreiber, N. A., Louw, J., Graf, R. P., Vargas, H. A., Johnson, A., Jendrisak, A., Bambury, R., Danila, D., McLaughlin, B., Wahl, J., Greene, S. B., Heller, G., Marrinucci, D., Fleisher, M., & Dittamore, R. (2016). 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*, *2*(11), 1441-1449. https://doi.org/10.1001/jamaoncol.2016.1828

Shore, N. (2018). SelectMDx Impacts Prostate Biopsy Decision-making in Routine Clinical Practice. https://lab21.com/wp-content/uploads/sites/5/2018/07/SelectMDx-Impacts-Prostate-Biopsy-Decision-making-Read.pdf

Siegel, R. L., Miller, K. D., & Jemal, A. (2018). Cancer statistics, 2018. *CA Cancer J Clin*, *68*(1), 7-30. https://doi.org/10.3322/caac.21442

Song, C. J., Chen, H., Chen, L. Z., Ru, G. M., Guo, J. J., & Ding, Q. N. (2018). The potential of microRNAs as human prostate cancer biomarkers: A meta-analysis of related studies. *J Cell Biochem*, *119*(3), 2763-2786. https://doi.org/10.1002/jcb.26445

Steiling, K., & Christenson, S. (2021, 04/02/2021). *Tools for genetics and genomics: Gene expression profiling*. https://www.uptodate.com/contents/tools-for-genetics-and-genomics-gene-expression-profiling

Tabayoyong, W., & Abouassaly, R. (2015). Prostate Cancer Screening and the Associated Controversy. *Surg Clin North Am*, *95*(5), 1023-1039. https://doi.org/10.1016/j.suc.2015.05.001

Taplin, M.-E., & Smith, J. A. (2022, 01/03/2022). *Clinical presentation and diagnosis of prostate cancer*. https://www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-prostate-cancer

Tutrone, R., Donovan, M. J., Torkler, P., Tadigotla, V., McLain, T., Noerholm, M., Skog, J., & McKiernan, J. (2020). 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*. https://doi.org/10.1038/s41391-020-0237-z

Tward, J. D., Schlomm, T., Bardot, S., Freedland, S. J., Lenz, L., Cohen, T., Stone, S., & Bishoff, J. (2020). 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*, *38*(6_suppl), 346-346. https://doi.org/10.1200/JCO.2020.38.6_suppl.346

Van den Broeck, T., Moris, L., Gevaert, T., Tosco, L., Smeets, E., Fishbane, N., Liu, Y., Helsen, C., Margrave, J., Buerki, C., Davicioni, E., Van Poppel, H., Everaerts, W., Weinmann, S., Den, R., Davis, J., Schaeffer, E., Karnes, R. J., Claessens, F., & Joniau, S. (2019). 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*, *2*(5), 589-596. https://doi.org/10.1016/j.euo.2018.12.007

Van Neste, L., Hendriks, R. J., Dijkstra, S., Trooskens, G., Cornel, E. B., Jannink, S. A., de Jong, H., Hessels, D., Smit, F. P., Melchers, W. J., Leyten, G. H., de Reijke, T. M., Vergunst, H., Kil, P., Knipscheer, B. C., Hulsbergen-van de Kaa, C. A., Mulders, P. F., van Oort, I. M., Van Criekinge, W., & Schalken, J. A. (2016). Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score. *Eur Urol*, *70*(5), 740-748. https://doi.org/10.1016/j.eururo.2016.04.012

Van Neste, L., Partin, A. W., Stewart, G. D., Epstein, J. I., Harrison, D. J., & Van Criekinge, W. (2016). Risk score predicts high-grade prostate cancer in DNA-methylation positive, histopathologically negative biopsies. *Prostate*, *76*(12), 1078-1087. https://doi.org/10.1002/pros.23191

White, J., Shenoy, B. V., Tutrone, R. F., Karsh, L. I., Saltzstein, D. R., Harmon, W. J., Broyles, D. L., Roddy, T. E., Lofaro, L. R., Paoli, C. J., Denham, D., & Reynolds, M. A. (2018). Clinical utility of the Prostate Health Index (phi) for biopsy decision management in a

large group urology practice setting. *Prostate Cancer Prostatic Dis*, *21*(1), 78-84. https://doi.org/10.1038/s41391-017-0008-7

Wojno, K. J., Costa, F. J., Cornell, R. J., Small, J. D., Pasin, E., Van Criekinge, W., Bigley, J. W., & Van Neste, L. (2014). Reduced Rate of Repeated Prostate Biopsies Observed in ConfirmMDx Clinical Utility Field Study. *Am Health Drug Benefits*, *7*(3), 129-134. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24991397/

Wysock, J. S., Becher, E., Persily, J., Loeb, S., & Lepor, H. (2020). Concordance and Performance of 4Kscore and SelectMDx for Informing Decision to Perform Prostate Biopsy and Detection of Prostate Cancer. *Urology*, *141*, 119-124. https://doi.org/10.1016/j.urology.2020.02.032

Zappala, S. M., Scardino, P. T., Okrongly, D., Linder, V., & Dong, Y. (2017). 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. *Rev Urol*, *19*(3), 149-155. https://doi.org/10.3909/riu0776