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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 (Benedettini et al., 2008; Taplin & Smith, 2024).

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, 2023). 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., 2022).

II. 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®, Oncotype DX 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 between 3 – 10 ng/mL
      ii) For individuals over the age of 75, PSA levels between 4 – 10 ng/mL
   b) The individual has none of the following conditions for which a prostate biopsy is already indicated:
      i) DRE suspicious for cancer.
      ii) Persistently elevated PSA.
      iii) Positive multiparametric MRI, if performed.
      iv) Known to have a high-penetrance prostate cancer risk gene(s) per NCCN guidelines (see Note 3).
   c) The individual has no other relative contraindication for prostate biopsy, including **any** of the following:
      i) A less than 10-year life expectancy.
      ii) Benign disease not ruled out.
4) For individuals with a prostate, 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 or equal to 4 and less than 10 ng/mL.
b) The individual has none of the following conditions for which a prostate biopsy is already indicated:
   i) DRE suspicious for cancer.
   ii) Persistently elevated PSA.
   iii) Positive multiparametric MRI (if performed).
   iv) Ethnicity at higher risk for prostate cancer (see Note 4)
   v) First-degree relative (see Note 5) with prostate cancer.
   vi) Known to have a high-penetrance prostate cancer risk gene(s) per NCCN guidelines (see Note 3).
c) The individual has no other relative contraindication for prostate biopsy, including **any** of the following:
   i) A less than 10-year life expectancy.
   ii) Benign disease not ruled out.

5) For individuals with a prostate, 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, including **any** of the following:
      i) A less than 10-year life expectancy.
      ii) Benign disease not ruled out.

6) 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.

7) 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, Prostate Health Index (PHI), *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

(NCCN, 2024a)

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 · 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	Has all of the following: · 1 IRF · 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: 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 5α-reductase) in the same laboratory or other Clinical Laboratory Improvement Amendments (CLIA) approved laboratory before considering a biopsy.

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, 2024b).
Note 4: 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" (NCCN, 2024b).
Note 5: First-degree relatives include parents, full siblings, and children of the individual.

III. Table of Terminology

Term	Definition
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
EANM	European Association of Nuclear Medicine
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
ISUP	International Society of Urological Pathology
KLK3	*Kallikrein related peptidase 3 gene*
LDTs	Laboratory-developed tests
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
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
PTEN	*Phosphatase and tensin homolog gene*
QALY	Quality adjusted life-years
RAD51D	*RAD51 poaralog 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
TMPRSS2	*Transmembrane serine protease 2*
TP53	*Tumor protein 53 gene*
TRUS	Transrectal ultrasound guided biopsy

IV. 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 2024, the American Cancer Society estimates that approximately 299,010new prostate cancer diagnoses and approximately 35.250prostate cancer deaths will occur; although, the five-year survival rate between 2012-2018 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 (ACS, 2024a, 2024b).

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 (Bell et al., 2015). These data suggest that prostate cancer often grows so slowly that most individuals die of other causes before the disease becomes clinically advanced (Hoffman, 2023).

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 (Hoffman, 2023). 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 Genomic Prostate Score® (GPS™), and Decipher as tumor-based molecular assays to consider during initial risk stratification (NCCN, 2024a). Ki-67 and PTEN are also listed in NCCN guidelines, but are not recommended (NCCN, 2024a).

Proprietary Testing, Clinical Utility, and Analytical Validity

Hu et al. (2018) evaluated the utility of three genomic expression classifiers (GEC), including Decipher, Oncotype Dx, 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" (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 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) (Alford et al., 2017).

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 (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 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 (Tward et al., 2020).

Oncotype DX Genomic Prostate Score® (GPS™) 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 five reference genes (compared to 31 and 15, respectively, for Prolaris)(Exact Sciences, 2021). 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, 2024a). Oncotype DX 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 (Murphy et al., 2020).

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 (Epic Sciences, 2023).

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" (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 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" (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. 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" (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 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) (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 individuals with high-risk nonmetastatic prostate cancer 10 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" (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. 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 (Marascio et al., 2020).

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 (Nguyen et al., 2023).

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 (Spratt et al., 2023).

ExoDX Prostate IntelliScore (EPI)

ExoDX is a urinary test that detects the expression level of three genetic biomarkers (ERG, PCA3, and SPDEF) (ExoSome, 2024a, 2024b). 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 ≥ 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(ExoSome, 2024a, 2024b; NCCN, 2024b).

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 (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 (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" (Tutrone et al., 2020).

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) (McKiernan et al., 2020).

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] (NCCN, 2024a; OPKO, 2021). 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" (Zappala et al., 2017).

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) (Parekh et al., 2015; Punnen et al., 2018).

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 (Wysock et al., 2020).

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 (MDxHealth, 2023a). This test has been evaluated by Van Neste, Partin, 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 (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 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" (MDxHealth, 2023b). 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).

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] ≥ 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 ≥ 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 (Hologic, 2024). 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 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" (Matuszczak et al., 2021; Rodríguez & García-Perdomo, 2020).

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 ≥ 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 (Alford et al., 2017; Blume-Jensen et al., 2015).

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 (Couñago et al., 2020). 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 (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 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 (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, 2024a).

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, 2024a; Ross et al., 2022). 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., 2022).

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, 2024a; Ross et al., 2022). 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 (ArteraAI, 2024; Hannah Clarke, 2024).

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 (Esteva et al., 2022).

V. 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 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" (NCCN, 2024a). 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 (e.g.,

BRCA2, *BRCA1*, *ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, PMS2)"* (NCCN, 2024a). 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 individuals 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, 2024a).

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, 2024a, 2024b):

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 Prostate	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 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 further define risk. Lower percent-free PSA and/or higher PSA density are associated with a greater risk of high-grade prostate cancer. The probability of high-grade cancer (Gleason score ≥ 3+4, Grade Group two or higher) may be further defined utilizing the Prostate Health Index (PHI), SelectMDx, 4Kscore, and ExoDx Prostate Test, MyProstateScore (MPS), and IsoPSA. 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" (NCCN, 2024b).

The NCCN notes that "Tests that improve specificity in the post-biopsy setting—including percent-free PSA, 4Kscore, PHI, PCA3, ConfirmMDx, ExoDx Prostate Test, MPS, and IsoPSA—should be considered in patients thought to be higher risk despite a negative prostate biopsy" (NCCN, 2024b).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 individuals 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 individuals contemplating initial or repeat biopsy because the assay may identify individuals at higher risk of prostate cancer diagnosis on repeat biopsy." IsoPSA and MyProstrateScore "can be considered for patients prior to 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" (NCCN, 2024b).

The NCCN also lists ArteraAI Prostate Cancer in "Table 2: Risk Stratification, Selected Advanced Tools for Localized Prostate Cancer." The category of the listing is "AI Pathology" and it is listed as "predictive" and "prognostic" for "biochemical recurrence," "distant metastases," and "prostate cancer specific mortality" with a IB category for predictive and IB for prognostic (IB meaning: "Prospective clinical trial(s) using archived samples with design that accommodates tumor marker utility, ≥1 validation study available with consistent results"), it also falls under "**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate."(NCCN, 2024a).

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., 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 (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" (Eggener et al., 2020).

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 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" (Eggener et al., 2020).

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 Oncotype Dx, 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" (Mottet et al., 2023).

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 (Parker et al., 2020).

VI. 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. For the most up-to-date Medicaid policies and coverage, 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.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VIII. Evidence-based Scientific References

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IX. Policy History

Action Date	Action
June 01, 2023	Policy created
December 03, 2024	Policy approved by Medical Directors
December 20, 2024	Policy approved at UMC
February 01, 2025	Policy effective date following notification period