Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

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DESCRIPTION

Various genetic and protein biomarkers associated with prostate cancer may potentially improve the specificity of testing and diminish the probability of unnecessary biopsies. This evidence review addresses these types of tests for prostate cancer risk assessment and diagnosis.

In 2022, it is estimated that 268,490 individuals will be diagnosed with prostate cancer and there will be an estimated 34,500 deaths. Prostate cancer is a complex, heterogeneous disease, ranging from microscopic tumors unlikely to be life-threatening to aggressive tumors that can metastasize, leading to morbidity or death. Early localized disease can usually be cured with surgery and radiotherapy, although active surveillance may be adopted in individuals whose cancer is unlikely to cause major health problems during their lifespan or for whom the treatment might be dangerous. In individuals with

inoperable or metastatic disease, treatment consists of hormonal therapy and possibly chemotherapy. The lifetime risk of being diagnosed with prostate cancer for individuals in the United States is approximately 16%, while the risk of dying of prostate cancer is 3%. African American individuals have the highest prostate cancer risk in the United States; the incidence of prostate cancer is about 60% higher and the mortality rate is more than 2 to 3 times greater than that of Caucasian individuals. Autopsy results have suggested that about 30% of individuals aged 55 and 60% of individuals age 80 who die of other causes have incidental prostate cancer, indicating that many cases of cancer are unlikely to pose a threat during an individual's life expectancy.

The most widely used grading scheme for prostate cancer is the Gleason system which has been compressed into grading groups:

Grade Group	**Gleason Score**	**Gleason Pattern**
1	≤ 6	≤ 3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

Numerous genetic alterations associated with development or progression of prostate cancer have been described, with the potential for the use of these molecular markers to improve the selection process of individuals who should undergo biopsy or rebiopsy after an initial negative biopsy.

For assessing future prostate cancer risk, numerous studies have demonstrated the association of many genetic and protein biomarker tests and prostate cancer. Commercially available tests include but are not limited to the following:

Test	**Description**
4Kscore Test (kallikrein markers) (OPKO Lab)	a blood test that measures 4 biomarkers (PSA, free PSA, intact PSA and hK2 [human Kallikrein-2]), which are combined into an algorithm with a patient's age, optional digital rectal exam, and any prior biopsy history to give the physician a personal risk of aggressive prostate cancer to decide whether a patient should proceed to prostate biopsy or repeat prostate biopsy.
APIFINY (Armune BioScience)	Measures eight prostate cancer specific biomarkers (autoantibodies) ARF 6, NKX3-1, 5-UTR-BMI1, CEP 164, 3-UTR-Ropporin, Desmocollin, AURKAIP-

	1, CSNK2A2. These biomarkers (autoantibodies) are produced and replicated (amplified) by the immune system in response to the presence of prostate cancer cells. The autoantibodies are stable and, because of their amplifications, are likely to be abundant and easy to detect, especially with small tumors characteristics of early-stage cancers. APIFINY should be used in combination with other accepted methods of patient management. In men with elevated PSA, APIFINY is designed to aid in the assessment of risk for prostate cancer and in the selection of patients for biopsy. APIFINY test process is performed in part using a qualitative immunoassay technique and in part using flow cytometry. The laboratory data generated by these methodologies are then subjected to a proprietary algorithmic analysis that generates a cancer risk score. APIFINY does not rely on PSA values.
ConfirmMDx (MDxHealth)	Measures hypermethylation of 3 genes (GSTP1, APC, RASSF1) in a negative prostate biopsy to determine whether a patient should undergo repeat biopsy.
ExoDx Prostate (IntelliScore)/ExosomeDx Prostate (IntelliScore) (Exosome Diagnostics, Inc):	Non-digital rectal exam (DRE) urine based liquid biopsy test that predicts the presence of high grade (Gleason score $\geq$ 7) prostate cancer for men 50 years of age and older with a PSA 2-10 ng/mL presenting for an initial biopsy. A "rule out" test ExoDx Prostate (IntelliScore) is designed to more accurately predict whether a patient presenting for an initial biopsy does not have a high- grade prostate cancer and, thus could potentially avoid an initial biopsy and instead continue to be monitored. Using a proprietary algorithm that combines the relative weighted expression of the three gene signature, the test assigns an individual risk score for patients ranging

	from 0 to 100. A score > 15.6 is associated with an increased likelihood of high- grade prostate cancer on a subsequent biopsy. Physicians can utilize the score in conjunction with the other standard of care prognostic information to determine whether to proceed with a tissue biopsy.
MI-Prostate Score (University of Michigan MLabs)	Urine test looks for the T2-ERG fusion (TMPRSS2: ERG) as well as another marker, PCA3. This is combined with the PSA measure to produce a risk assessment for prostate cancer. The test also predicts risk for having an aggressive tumor, helping doctors and patients make decisions about whether to wait and monitor test levels or pursue immediate biopsy. This can also be utilized in individuals who had a prior negative biopsy to determine if repeat biopsy should be performed.
PanGia Prostate (Genetics Institute of America)	Is a urine test that uses a device with binding pockets for small molecules, proteins, and cells. Results are uploaded to the cloud and a machine learning algorithm compares the results with a signature from patients who have had a positive biopsy and patients who have had a negative prostate biopsy. The report includes a diagnosis with the level of confidence in the diagnosis. This test is for physicians considering prostate biopsy to help prostate cancer decision making. Men with a PanGIA Prostate score below 40 have a NuTec signature consistent with men who were confirmed negative after prostate biopsy. Men with a PanGIA Prostate score above 80 have a NuTec signature consistent with men who were confirmed positive after prostate biopsy.
Progensa PCA3 Assay (Gen-Probe now Hologic)/PCA3 tests (ARUP Laboratories; Mayo Medical Laboratories; LabCorp)	Urine test that measures the concentration of PCA3 mRNA and prostate-specific antigen (PSA) and calculates a ratio of PCA3 molecules to PSA molecules

	(PCA3 Score) in post-digital rectal exam (DRE) first catch male urine specimen. Progensa PCA3 Assay is indicated for use in conjunction with other risk indicators to aid in patient management in the "at risk" population of men 50 years of age or older who have had 1 or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on the current standard of care.
Prostate Core Mitomics Test (Mitomics (formerly Genesis Genomics):	Measures mitochondrial DNA mutations in a negative prostate biopsy to determine whether a patient should undergo repeat biopsy.
Prostate Health Index (PHI) (Beckman Coulter)	Is considered a PSA derivative or isoform and is used to evaluate the probability of prostate cancer diagnosis, it combines measurements of % free PSA, tPSA (total PSA) and pro2PSA into a single numerical score (phi score). This score gives more accurate information about what an elevated PSA level might mean and the probability of finding prostate cancer with a biopsy.
SelectMDx for Prostate Cancer (MDxHealth)	Helps identify patients at increased risk for aggressive disease, thereby aiding in the selection of men for prostate biopsy. SelectMDx for Prostate Cancer is a reverse transcription PCR (RT-PCR) assay performed on post-DRE (digital rectal examination), first void urine specimen from patients with clinical risk factors for prostate cancer, who are being considered for biopsy. The test measures the mRNA levels of the DLX1 and HOXC6 biomarkers, using KLK3 expression as internal reference, to aid in patient selection for prostate biopsy. Higher expression levels of DLX1 and HOXC6 mRNA are associated with an increased probability for high grade (Gleason Score (GS) $\geq$ 7) prostate cancer.

TMPRSS Fusion Genes	TMPRSS2 is an androgen-regulated transmembrane serine protease that is preferentially expressed in normal prostate tissue. In prostate cancer, it may be fused to an ETS (E26 transformation-specific) family transcription factor (ERG, ETV1, ETV4, or ETV5), which modulates transcription of target genes involved in cell growth, transformation, and apoptosis. The result of gene fusion with an ETS transcription gene is that the androgen-responsive promoter of TMPRSS2 upregulates expression of the ETS gene, suggesting a mechanism for neoplastic transformation. Fusion genes may be detected in tissue, serum, and urine. TMPRSS2-ERG gene rearrangements have been reported in 50% or more of primary prostate cancer samples. Attention has been directed at using post-DRE urine samples to look for fusion genes as markers of prostate cancer.

Genetic and Protein Biomarker Testing for Selection of an Individual for Prostate Biopsy

Clinical Context and Test Purpose
The purpose of genetic and protein biomarker testing for prostate cancer is to inform the selection of an individual who should undergo initial biopsy or repeat biopsy. Conventional decision- making tools for identifying individuals for prostate biopsy include digital rectal exam (DRE), serum prostate specific antigen (PSA), and patient risk factors such as age, race, and family history of prostate cancer.

DRE has relatively low interrater agreement among urologists, with estimated sensitivity, specificity, and positive predictive value (PPV) for diagnosis of prostate cancer of 59%, 94% and 28%, respectively. DRE might have a higher PPV in the setting of elevated PSA.

The risk of prostate cancer increases with increasing PSA; an estimated 15% of individuals with a PSA level of 4 ng/mL or less and normal DRE, 30% to 35% of individuals with PSA level between 4 and 10 ng/mL, and more than 67% of individuals with PSA level greater than 10 ng/mL will have biopsy detectable prostate cancer. Use of PSA levels in screening has improved detection of prostate cancer. The European

Randomized Study of Screening for Prostate Cancer (ERSPC) and Goteborg prostate screening trials demonstrated that biennial PSA screening reduces the risk of being diagnosed with metastatic prostate cancer.

However, elevated PSA levels are not specific to prostate cancer; levels can be elevated due to infection, inflammation, trauma, or ejaculation. In addition, there are no clear cutoffs for cancer positivity with PSA. Using a common PSA level cutoff of 4.0 ng/mL, the American Cancer Society (ACS) systematically reviewed the literature and calculated pooled estimates of elevated PSA sensitivity of 21% for detecting any prostate cancer and 5% for detecting high-grade cancers with estimated specificity of 91%.

PSA screening in the general population is controversial. In 2018, the U.S. Preventive Services Task Force updated their recommendation against PSA-based screening for individuals ages 55-69 and individuals aged 70 and older (C recommendation/D recommendation), while guidelines published by American Cancer Society (ACS) and the American Urological Association (AUA) endorsed consideration of PSA screening based on age, other risk factors, estimated life expectancy and shared decision making.

The utility of PSA screening depends on whether screening can lead to management changes that improve net health outcome. Results from the National Health Services supported Prostate Testing for Cancer and Treatment Trial (2016) demonstrated no difference in 10- year prostate cancer mortality rates between the treatment strategies of active monitoring, radical prostatectomy, and external beam radiotherapy in clinically localized prostate cancer detected by PSA testing.

Existing screening tools have led to unnecessary prostate biopsies. More than 1 million prostate biopsies are performed each year in the United States, with a resulting cancer diagnosis in 20% to 30% of individuals. About one-third of individuals who undergo prostate biopsy experience transient pain, fever, bleeding, and urinary difficulties. Serious biopsy risks, such as bleeding or infection requiring hospitalization, are rare with estimates of rates ranging from less than 1% to 3%.

Given the risk, discomfort, and burden of biopsy and low diagnostic yield, there is a need for noninvasive tests that distinguish potentially aggressive tumors that should be referred for biopsy from clinically insignificant localized tumors or other prostatic conditions that do not need biopsy with the goal of avoiding low yield biopsy.

Populations

The relevant population of interest are individuals for whom an initial prostate biopsy is being considered because of clinical symptoms or elevated PSA or individuals for whom a rebiopsy is being considered because the results of an initial prostate biopsy were negative or equivocal and other clinical symptoms remain suspicious (elevated PSA).

Comparators
Standard clinical examination for determining who goes to biopsy might include DRE, review of history of PSA values, along with consideration of risk factors such as age, race, and family history. The ratio of free or unbound PSA to total PSA is lower in individuals who have prostate cancer than in those who do not. A percent free PSA (%fPSA) cutoff of 25% has been shown to have sensitivity and specificity of 95% and 20%, respectively, for individuals with total PSA values between 4.0 ng/mL and 10.0 ng/mL.

The best way to combine all the risk information to determine who should go to biopsy is not standardized. Risk algorithms have been developed that incorporate clinical risk factors into a risk score or probability. Two examples are the Prostate Cancer Prevention Trial (PCPT) predictive model and the Rotterdam Prostate Cancer risk calculator (also known as the European Research Screening Prostate Cancer Risk Calculator 4 (ERSPC-RC). The American Urological Association (AUA) and the Society of Abdominal Radiology's prostate cancer disease-focused panel recently recommended that high quality prostate MRI, if available, should be strongly considered in any individuals with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is under evaluation for a possible repeat biopsy.

Outcomes
The beneficial outcome of the test is to avoid a negative biopsy for prostate cancer. A harmful outcome is failure to undergo a biopsy that would be positive for prostate cancer, especially when disease is advanced or aggressive. Therefore, the relevant measures of clinical validity are sensitivity and negative predictive value (NPV). The appropriate reference standard is biopsy, though prostate biopsy is an imperfect diagnostic tool. Biopsies can miss cancers and repeat biopsies are sometimes needed to confirm the diagnosis. Detection rates vary by method used for biopsy and patient characteristics, with published estimates between 10% and 28% for a second biopsy and 5% and 10% for a third biopsy.

Timing
The timeframe of interest for calculating performance characteristics is time to biopsy result. Individuals who forgo biopsy based on test results could miss or delay diagnosis of cancer. Longer follow-up would be necessary to determine effects on overall survival.

Setting
Initial screening using PSA levels and DRE may be performed in the primary care setting with referral to specialty (urologist) care for suspicious findings and biopsy. Clinical practice on screening methods and frequency varies widely.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome of care can be improved if individuals receive correct therapy, or more effective therapy, or avoid unnecessary testing.

Based on the current National Comprehensive Cancer Network (NCCN) guideline Prostate Cancer Early Detection Version 1.2022, when a patient meets the standards for biopsy, sometimes the patients and physicians wish to further define the probability of cancer before proceeding to biopsy with its associated risks. Several biomarker tests have been developed with the goals of refining patient selection for biopsies, decreasing unnecessary biopsies, and increasing the specificity of cancer detection, without missing a substantial number of higher grade (Grade Group $\geq$ 2) cancers. These tests may be especially useful in individuals with PSA levels between 3 and 10 ng/mL. NCCN also notes that biomarkers that improve the specificity of detection are not recommended as first-line screening tests, rather for use in those individuals who wish to further define the probability of high-grade cancer.

Review of Evidence

4Kscore Test
The 4Kscore test (OPKO Lab) is a blood test that generates a risk score estimating the probability of finding high-grade prostate cancer (defined as a Gleason Score $\geq$ 7) if a prostate biopsy were performed. The intended use of the test is to aid in the decision of whether or not to proceed with a prostate biopsy or repeat prostate biopsy. A kallikrein is a subgroup of enzymes that cleaves peptide bonds in proteins. The intact prostate-specific antigen (iPSA) and human kallikrein 2 (hK2) tests are immunoassays that employ distinct mouse monoclonal antibodies. The score combines the measurement of 4 prostate-specific kallikreins (total prostate specific antigen (tPSA), free PSA (fPSA), intact PSA (iPSA), and human kallikrein 2 (hK2)), with an algorithm including patient age, digital rectal exam (DRE), and prior prostate biopsy history.

The manufacturer's website states that the ideal patient for the 4Kscrore is one whose other test results are equivocal. The test is not intended for patients with a previous diagnosis of prostate cancer, who have had a digital rectal examination (DRE) in the previous 4 days of this test, who have received 5-alpha reductase inhibitor therapy in the previous 6 months (such as Avodart [dutasteride] or Proscar [finasteride]), or has undergone within the previous 6 months any procedure or therapy to treat symptomatic benign prostatic hypertrophy (BPH) or any invasive urologic procedure that may be associated with a secondary PSA elevation.

Based on the 4Kscore Test U.S. validation study, prostate biopsy should be considered in most men with a 4kscore result of 7.5% or higher. Reference ranges are as follows:

- Low risk: 4Kscore result < 7.5%
- Intermediate Risk: 4Kscore result 7.5%-19%

- High Risk: 4Kscore result ≥ 20%

A prospective multi-institutional U.S. trial of 1012 patients showed that 4Kscore results have a high discrimination value (area under the curve (AUC), 0.82). In this study, using a threshold biopsy of ≥ 15% risk allowed for 591 biopsies to be avoided (58%), while 183 high-grade tumors were detected, and 48 high grade tumors (4.7% of the 1012 participants) were missed. When 4Kscore was examined in 6129 men in another prospective study, the AUC was also 0.82 (95% CI, 0.80-0.84). Using a 6% risk of high-grade cancer cutoff, 428 of 1000 men could avoid biopsy, with 119 of 133 high grade cancers detected and 14 of 133 missed. A multi-center clinical utility study found a 65% reduction in prostate biopsies with use of 4Kscore test. In addition, a correlation between 4Kscore risk category and Gleason score was seen ($P < .01$). A meta-analysis that included 12 clinical validation studies (11,134 patients) led to a calculated pooled AUC for discrimination of prostate cancer with Gleason score of ≥ 7 of 0.81 (fixed effects 95% CI, 0.80-0.83).

Based on the NCCN 2A recommendation, the NCCN panel consensus is that the 4Kscore test 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.

Summary of Evidence
Based on review of the peer reviewed medical literature the 4Kscore test has shown a high discrimination value and the results change management decisions, in a multi-center clinical utility study found a 65% reduction in prostate biopsies with use of 4Kscore test. The use of 4Kscore biomarker test is supported in the published professional society current guideline National Comprehensive Cancer Network (NCCN) Prostate Cancer Early Detection 1.2022 as a 2A recommendation. The NCCN panel consensus is that the 4Kscore test can be considered for patients prior to biopsy and for with a negative biopsy who are thought to be at higher risk for clinically significant prostate cancer. The evidence is sufficient to determine the technology results in a meaningful improvement in net health outcome as indicated by the NCCN panel consensus.

APIFINY
APIFINY technology is based on the measurement of eight prostate cancer specific biomarkers (autoantibodies) ARF 6, NKX3-1, 5-UTR-BMI1, CEP 164, 3-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2. These biomarkers (autoantibodies) are produced and replicated (amplified) by the immune system in response to the presence of prostate cancer cells. The biomarkers (autoantibodies) are stable and, because of their amplifications are likely to be abundant and easy to detect, especially during the early stages of cancer.

Given the complexity of cancer risk assessment, obtaining additional information may provide insight to better inform important clinical decisions such as an initial or repeat biopsy:

- APIFINY may be used in individuals who have an elevated PSA (> 2.5 ng/ml) and are considering a prostate biopsy.
- APIFINY may aid in the assessment of prostate cancer risk.
- APIFNY test results aid in making decisions regarding the right monitoring or cancer detection program.

Statistical analysis shows there is an interdependence among the biomarkers (autoantibodies).

Three of the biomarkers are associated with androgen-response regulation, and four are related to cellular structural integrity. The eighth biomarker has been implicated in prostate cancer progression and a variety of cellular functions ranging from cellular signaling for numerous protein kinases to regulating cell cycle and cell division. The APIFINY test process is performed in part using a qualitative immunoassay technique and in part using flow cytometry. The laboratory data generated by these methodologies are then subjected to a proprietary algorithmic analysis that generates a cancer risk score. APIFINY score reporting was designed to optimize the identification of individuals at lower risk. Individuals with a lower risk APIFINY score may be placed on a routine clinical monitoring program (i.e., semi-annual, or annual check-up) with other accepted methods to assess the ongoing risk of prostate cancer. Individuals with higher APIFINY scores may require a more specific risk-assessment plan, which may include biopsy. Scores below 59 are considered lower relative risk, scores at or above 59 have a higher relative risk of prostate cancer.

Summary of Evidence
The evidence on APIFINY is preliminary. Two studies have been done, a biomarker selection/algorithm development study and a clinical validation study. 519 samples were used in the biomarker selection/algorithm development study and 259 different samples were used in the clinical validation study. Although the studies are promising research has not yet been completed in determining the effects of age, race, or other factors on the APIFINY score. Further studies are needed to determine the effects of demographics such as age, race, or other factors on the APIFINY score and for clinical utility. Clinical utility of APIFINY test is uncertain, currently there is no evidence that the use of APIFINY tests can change patient management in ways that improve outcomes. The current NCCN guideline 1.2022 Prostate Cancer Early Detection does not discuss or indicate the use of the APIFINY test within this guideline. The evidence is insufficient to determine the effects of this technology on net health outcomes.

ConfirmMDx
ConfirmMDx measures the methylation levels using quantitative methylation PCR of 3 genes (GSTP1, APC, RASSF1) associated with prostate cancer. ConfirmMDx is intended for use in patients with high-risk factors such as elevated/rising prostate specific antigen (PSA) or abnormal digital rectal examination (DRE), with a negative or non-malignant abnormal histopathology finding (e.g., atypical cell or high-grade prostate intraepithelial neoplasia [HGPIN]) in the previous biopsy and is being considered for repeat biopsy.

Several case/control studies in archived biopsy core tissue blocks demonstrated the sensitivity, specificity, and high negative predictive value (NPV) of this biomarker to predict cancer detection in a repeat biopsy procedure. Single biopsy cores, using a little as 20 microns from formalin-fixed, paraffin embedded (FFPE) tissue blocks or sections cut from blocks fixed on glass slides are used in this assay.

The European MATLOC study blindly tested this assay in archived tissue from 498 men with negative biopsies who had repeat biopsies within 30 months. The NPV was 90% (95% CI, 87%-93%). In multivariate analysis, ConfirmMDx was predictive of patient outcome (OR, 3.17; 95% CI, 1.81-5.53). A similar validation study was performed in the United States using archived tissue from 350 men when negative biopsies who had repeat biopsies within 24 months. The NPV was 83% (95% CI, 85%-91%), and the test was again found to be predictive of outcomes on multivariate analysis (OR, 2.69; 95% CI, 1.60-4.51).

Based on the current National Comprehensive Cancer Network (NCCN) guideline for Prostate Cancer Early Detection 1.2022, the 2A recommendation from the panel states the following: "The panel believes that ConfirmMDx can be considered as an option for individuals contemplating repeat biopsy, because the assay may identify individuals at higher risk of prostate cancer diagnosis on repeat biopsy. The assay is approved for limited coverage by MoIDX for the reduction of unnecessary repeat biopsies."

Summary of Evidence
Based on the review of the peer reviewed medical literature and the current NCCN guideline Prostate Cancer Early Detection 1.2022 the use of ConfirmMDx biomarker test is supported and should be considered for individuals who have had at least one prior negative biopsy and are thought to be at high risk or prostate cancer diagnosis on repeat biopsy. The evidence is sufficient to determine the technology results in a meaningful improvement in net health outcome as indicated by the NCCN panel recommendation.

ExoDx Prostate (IntelliScore)
ExoDx Prostate (IntelliScore), also called EPI, is a non-digital rectal exam (DRE) urine based liquid biopsy test that proposes to discriminate Gleason Grade $\geq$ 2 prostate cancer from Grade Group 1 and benign disease at initial biopsy for individuals 50 years of age and older with a PSA 2-10 ng/mL. A "rule out" test ExoDx Prostate (IntelliScore) is designed to more accurately predict whether a patient presenting for an initial biopsy does not have a high-grade prostate cancer and, thus could potentially avoid an initial biopsy and instead continue to be monitored. Using a proprietary algorithm that combines the relative weighted expression of the three gene signature, the test assigns an individual risk score for patients ranging from 0 to 100. A score > 15.6 is associated with an increased likelihood of high-grade prostate cancer on biopsy. Physicians can utilize the score in conjunction with the other standard of care prognostic information to determine whether to proceed with a tissue biopsy.

In 2020, Tutrone et. al., reported on a trial that evaluated the effect of ExoDx Prostate (IntelliScore) (EPI) test on the decision to biopsy for high grade prostate cancer (HGPC). This multicenter, prospective, blinded randomized controlled clinical utility trial enrolled 1094 patients with 72 urologists from 24 urology practices. Patients were considered for prostate biopsy at enrollment based on standard clinical criteria. All patients had an EPI test; however, patients were randomized into EPI versus control arms where only the EPI arm received results for their biopsy decision. In the EPI arm (N = 458), 93 patients received negative EPI scores of which 63% were recommended to defer biopsy by the urologist and 74% ultimately deferred. In contrast, 87% of patients with positive EPI scores were recommended to undergo biopsy with a 72% compliance rate to the urologist's recommendation. This led to detection of 30% more HGPC compared to the control arm, and we 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. The primary reason not to comply with EPI results was rising PSA. The authors concluded this is the first on a prostate cancer biomarker utility study with a blinded control arm. The study demonstrates that the EPI test influences the overall decision to defer or proceed with a biopsy and improves patient stratification

In 2018, McKiernan et. al. report on the second validation of a prospective, two-cohort, adaptive clinical implementation, and utility study of the ExoDx Prostate (IntelliScore) (EPI) urine exosome gene expression assay comparing EPI results with biopsy outcomes. Eligible participants had not been diagnosed with prostate cancer (PCa), were aged ≥ 50 years with a PSA 2-10 ng/mL and scheduled for their initial prostate needle biopsy. After completion of cohort 1, a clinical implementation document (i.e., CarePath) was developed for utilizing the EPI score in a second phase patient cohort, where the biopsy decision is uncertain. In a total of 503 patients, with median age of 64 years, median PSA 5.4ng/ml, 14% African American, 70% Caucasian, 53% positive biopsy rate (22% GG1, 17% GG2, and 15% ≥ GG3), EPI was superior to an optimized model of standard clinical parameters with an area under the curve (AUC) 0.70 versus 0.62, respectively, comparable with previously published results (n=519 patients, EPI AUC 0.71). Validated cut-point 15.6 would avoid 26% of unnecessary prostate biopsies and 20% of total biopsies, with negative predictive value (NPV) 89% and missing 7% of ≥GG2 PCa. Alternative cut-point 20 would avoid 40% of unnecessary biopsies and 31% of total biopsies, with NPV 89% and missing 11% of ≥GG2 PCa. The clinical investigators reached consensus recommending use of the 15.6 cut-point for phase II. Outcome of the decision impact cohort in phase II will be reported separately. The authors concluded, EPI is a noninvasive, easy-to-use, gene expression urine assay, which has now been successfully validated in over 1000 patients across two prospective validation trials to stratify risk of ≥GG2 from GG1 cancer and benign disease. The test improves identification of patients with higher grade disease and would reduce the total number of unnecessary biopsies.

The authors of the above study also included the following patient summary: It is challenging to predict which men are likely to have high-grade prostate cancer (PCa) at initial biopsy with prostate-specific antigen 2-10ng/ml. This study further demonstrates

that the ExoDx Prostate (IntelliScore) test can predict ≥GG2 PCa at initial biopsy and defer unnecessary biopsies better than existing risk calculator's and standard clinical data.

McKiernan et. al. (2016) studied the performance of novel urine exosome gene expression assay (the ExoDx Prostate IntelliScore urine exosome assay) plus standard of care (SOC) (i.e., prostate specific antigen (PSA) level, age, race, and family history) versus SOC alone for discriminating between Gleason score 7 and 6 and benign disease on initial biopsy. In training, using reverse transcriptase polymerase chain reaction (PCR), they compared the urine exosome gene expression assay with biopsy outcomes in 499 patients with prostate-specific antigen (PSA) level of 2 to 20 ng/mL. The main outcomes and measures were evaluating the assay using the area under receiver operating characteristic curve (AUC) in discrimination of GS7 or greater from GS6 and benign disease on initial biopsy. In 255 men in the training target population (median age 62 years and median PSA level 5.0 ng/mL, and initial biopsy), the urine exosome gene expression assay plus SOC was associated with improved discrimination between Gleason score 7 or greater and Gleason score 6 and benign disease. Area under the curve (AUC) 0.77 (95% CI, 0.71-0.83) versus SOC ACU 0.66 (95% CI, 0.58-0.72) (P<.001) Independent validation in 519 patient's urine exosome gene expression assay plus SOC AUC 0.73 (95% CI, 0.68-0.77) compared to SOC AUC 0.63 (95% CI, 0.58-0.68) (P<.001). Using a predefined cut point, 138 of 519 (27%) biopsies would have been avoided, missing only 5% of patients with dominant pattern for high- risk Gleason score 7 disease. The authors concluded, this urine exosome gene expression assay is a noninvasive, urinary 3-gene expression assay that discriminates high grade (>GS7) from low-grade (GS6) cancer and benign disease. In this study, the urine exosome gene expression assay was associated with improved identification of patients with higher grade prostate cancer among men with elevated PSA levels and could reduce the total number of unnecessary biopsies.

The current NCCN Guideline Version 1.2022 Prostate Cancer Early Detection, includes the following regarding this test:

ExoDx Prostate (IntelliScore), also called EPI, evaluates a urine-based 3 gene exosome expression assay utilizing PCA3 and ERG (V-ets erythroblastosis virus E26 oncogene homologs) RNA from urine, normalized to SPDEF (SAM pointed domain-containing ETS transcription factor). The background for these markers is supported by a number of studies, but the application to exosome detection is unique. This gene panel proposes to discriminate Grade Group ≥ 2 prostate cancer from Grade Group 1 and benign disease at initial biopsy. The population for which use of the assay was intended includes patients older than 50 years with no prior biopsy and a PSA value between 2 and 10 ng/mL.

In a recent study by McKiernan et. al., estimates of the AUC were similar in the training (0.74) and validation (0.71) cohorts for the assay, with significant improvements when the test was added to standard of care variables alone. Applying a cutoff value from the training cohort to serve as a threshold for biopsy in the validation cohort decreased the need for biopsy by 27% (138 of 519) while missing 8% (12 of 148) of Grade Group ≥ 2

cancers. The investigators propose the assay as a secondary or reflex test for risk stratification in conjunction with PSA screening. In the McKiernan study, the algorithm was validated in a test set of 255 patients and then validated in the extended screening validation cohort of 519 patients. The majority of exclusions were for urine volume > 49 mL, assay failure, and application outside the intended use population.

A second independent validation study was a 2-phase adaptive clinical utility study that included 503 biopsy-naive patients with PSA levels between 2 and 10 ng/mL and compared EPI and biopsy results. In the first phase of this study, the AUC was 0.70 for predicting Grade Group $\geq$ 2 cancer by EPI. Using the validated cut-point 15.6, the test has an NPV of 89%, reducing total biopsies by 20% and missing 7% of Grade Group $\geq$ 2 cancer. The second phase of this trial will be reported in the future.

The panel believes that EPI can be considered as an option for individuals contemplating initial or repeat biopsy.

Summary of Evidence
It is challenging to predict which individuals are likely to have high-grade prostate cancer (PCa) with prostate-specific antigen (PSA) 2-10ng/ml. Based on review of the peer reviewed medical literature, the limited evidence demonstrates that the ExoDx Prostate (IntelliScore) test can predict ≥ Grade Group 2 Pca (prostate cancer) at initial biopsy and defer unnecessary repeat biopsies better than existing risk calculator's and standard clinical data. NCCN guideline Prostate Cancer Early Detection Version 1.2022 states the following: The panel believes EPI can be considered as an option for individuals contemplating initial biopsy and repeat biopsy. The evidence is sufficient to determine the technology results in a meaningful improvement in net health outcome as indicated by the NCCN panel recommendation.

Prostate Health Index (PHI) (proPSA)
The Prostate Health Index (phi) test (Beckman Coulter) utilizes a calculation that combines the results of 3 blood serum immunoassays (tPSA [total PSA], %fPSA [%free PSA] and proPSA [p2PSA]) into a single numerical result, the “phi score.” This score is calculated in a routine laboratory using Beckman Coulter equipment and software with phi algorithm incorporated in the software. This score gives more accurate information about what an elevated PSA level might mean and the probability of finding prostate cancer with a biopsy.

The phi score has been approved by FDA for distinguishing prostate cancer from benign prostatic conditions in individuals 50 years and older with total PSA (tPSA) readings $\geq$ 4.0 and $\leq$10.0 ng/mL, and with a digital- rectal examination (DRE) findings that are not suspicious for cancer.

In a multicenter study, Prostate Health Index (PHI) was noted to have approximately double the sensitivity of fPSA/tPSA for cancer detection in those with serum PSA concentrations between 2 and 10 ng/mL. In addition, the PHI correlated with cancer

grade and had an area under the curve (AUC) of 0.72 for discrimination of high grade (Gleason ≥ 7) cancer from low grade cancer or negative biopsy. Another prospective cohort study calculated an AUC of 0.815 for the detection of high-grade (Gleason Score ≥ 7*)* prostate cancer. This study determined the optimal cutoff of PHI to be a score of 24, which should lead to 36% of biopsies avoided with approximately 2.5% of high-grade cancers missed. Other studies have also shown that PHI can predict aggressive prostate cancer and has potential clinical utility.

A clinical utility study conducted at 4 large urology group practices showed that use of PHI was in fact associated with a decrease in biopsy procedures performed when compared to historical controls from the same physicians (36.4% vs 60.3%; P < 0.0001). Patients in the study had DRE and PSA values ranging from 4 to 10 ng/mL. Physician survey results showed that PHI results impacted biopsy decisions in 73% of cases.

Based on the NCCN 2A recommendation, the NCCN panel recommends the Prostate Health Index (PHI) test can be considered before initial biopsy in individuals with serum PSA levels of > 3 ng/mL who desire more specificity.

Summary of Evidence
Based on review of the peer reviewed medical literature a clinical utility study showed that use of Prostate Health Index (PHI) was associated with a decrease in biopsy procedures performed when compared to historical controls from the same physicians (36.4% versus 60.3%; P < 0.0001). Patients in the study had DRE and PSA values ranging from 4 to 10 ng/mL. Physician survey results showed that PHI results impacted biopsy decisions in 73% of cases. The use of Prostate Health Index (PHI) (proPSA) biomarker is recommended by the National Comprehensive Cancer Network (NCCN) Prostate Cancer Early Detection 1.2022 as a 2A recommendation. The NCCN panel recommends the Prostate Health Index (PHI) test can be considered before initial biopsy in individuals with serum PSA levels of > 3 ng/mL who desire more specificity. The evidence is sufficient to determine the technology results in a meaningful improvement in net health outcome as indicated by the NCCN panel recommendation.

MyProstate Score (Formerly Mi-Prostate Score [MiPS])
The Mi-Prostate score (MiPS) assay renamed MyProstate Score in 2021 measures total serum PSA and post-DRE urine expression of the T2-ERG fusion (TMPRSS2: ERG) as well as another marker, PCA3. The test also predicts risk for having an aggressive tumor, helping doctors and patients make decisions about whether to wait and monitor test levels or pursue immediate biopsy.

In 2021, Tosoian et. al., reported on a study to establish and validate a threshold for the MyProstateScore test (previously named MiPS) to rule out Gleason Group ≥ 2 prostate cancer. A threshold of ≤ 10 was identified in a training cohort and validated using a combined dataset that included 977 biopsy naive men from the validation study previously reported in Tomlins et al (2016) and 548 biopsy naive men prospectively enrolled as part of an Early Detection Research Network study that did not evaluate the

MyProstateScore. In the overall cohort, sensitivity was 97.0%, specificity was 32.6%, NPV was 97.5%, and PPV was 29.1%. Results were similar in the subgroup of men with PSA between 3 and 10 or with PSA <3 with suspicious DRE.The study authors are co-founders and have equity in LynDx, which has licensed the urine biomarkers evaluated in the study.

In the study by Tomlins et. al. (2016), 80% of the 1244 patients were undergoing initial biopsy due to elevated PSA levels (Table 11). Thresholds were not defined and the AUCs for predicting any cancer using PSA alone, The AUC for MiPS was significantly improved compared with the PCPT risk calculator (p<.001). However, a study by Ankerst et. al. (2019) found that adding *TMPRSS2-ERG* to a PCPT risk calculator plus *PCA3* did not improve the AUC. The online PCPT risk calculator now includes both the *PCA3* and *TMPRSS2-ERG* scores, which will be used for further validation.

In a validation study Sanda et. al. (2017) evaluated the priori primary hypothesis that combined measurement of PCA3 and TMPRSS2: ERG (T2; ERG) RNA in the urine after digital rectal exam (DRE) would improve specificity over measurement of prostate specific antigen alone for detecting cancer with Gleason score of 7 or higher. As a secondary objective, to evaluate the potential effect of such urine RNA testing on health care costs. Prospective, multicenter diagnostic evaluation and validation in academic and community based ambulatory urology clinics. Participants were a referred sample of men presenting for first-time prostate biopsy without pre-existing prostate cancer: 516 eligible participants from among 748 cohort participants in the developmental cohort and 561 eligible participants from 928 in the validation cohort. Urinary PCA3 and T2: ERG RNA measurements were taken before the prostate biopsy. The main outcome and measures, presence of prostate cancer having a Gleason score 7 or higher on prostate biopsy. Pathology testing was blinded to urine assay results. In the developmental cohort, a multiplex decision algorithm was constructed using urine RNA assays to optimize specificity while maintaining 95% sensitivity for predicting aggressive prostate cancer at initial biopsy. Findings were validated in a separate multicenter cohort via prespecified analysis, blinded per prospective-specimen-collection, retrospective-blinded-evaluation (PRoBE) criteria. Cost effects of the urinary testing strategy were evaluated by modeling observed biopsy results and previously reported treatment outcomes. Among the 516 men in the developmental cohort (mean age, 62 years; range, 33-85 years) combining testing of urinary T2: ERG and PCA3 at thresholds that preserved 95% sensitivity for detecting aggressive prostate cancer improved specificity from 18% to 39%. Among the 561 men in the validation cohort (mean age, 62 years; range, 27-86 years), analysis confirmed improvement in specificity (from 17% to 33%; lower bound of 1-sided 95% CI, 0.73%; prespecified 1-sided P = .04), while high sensitivity (93%) was preserved for aggressive prostate cancer detection. Forty-two percent of unnecessary prostate biopsies would have been averted by using the urine assay results to select men for biopsy. Cost analysis suggested that this urinary testing algorithm to restrict prostate biopsy has greater potential cost-benefit in younger men.

NCCN Guideline Version 1.2022 Prostate Cancer Early Detection, includes the following regarding this test: Given the lack of validation of the models/algorithms in independent publications, the unclear behavior in other screened populations, and the lack of clarity regarding the incremental value and cost effectiveness of this assay, the panel cannot recommend the routine use of this test at this time. Longer term follow-up of the cohorts to determine whether missed prostate cancers were ultimately detected is needed. In addition, validation of these tests in other cohorts is needed before they can be accepted as alternatives to (or perhaps preferable to) other tests.

Summary of Evidence
There is no direct evidence that supports the clinical utility of the MyProstate Score (Formerly Mi-Prostate Score [MiPS]) test, and the chain of evidence is incomplete due to the limitations in clinical validity and clinical utility. Per the current NCCN guideline Given the lack of validation of the models/algorithms in independent publications, the unclear behavior in other screened populations, and the lack of clarity regarding the incremental value and cost effectiveness of this assay, the panel cannot recommend the routine use of this test at this time. Longer term follow-up of the cohorts to determine whether missed prostate cancers were ultimately detected is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

PanGia Prostate
PanGia Prostate is a urine test that uses a device with binding pockets for small molecules, proteins, and cells. Results are uploaded to the cloud and a machine learning algorithm compares the results with a signature from patients who have had a positive prostate biopsy and patients who have had a negative prostate biopsy. The report includes a diagnosis with the level of confidence in the diagnosis. This test is for physicians considering prostate biopsy to help prostate cancer decision making. Men with a PanGIA Prostate score below 40 have a NuTec signature consistent with men who were confirmed negative after prostate biopsy. Men with a PanGIA Prostate score above 80 have a NuTec signature consistent with men who were confirmed positive after prostate biopsy.

No studies were identified on PanGia Prostate.

Summary of Evidence
There is no direct evidence that supports the clinical utility of the PanGia Prostate test, and the chain of evidence is incomplete due to the limitations in clinical validity and clinical utility. The current NCCN guideline for Prostate Cancer Early Detection Version 1.2022 does not include or recommend the use of PanGia Prostate in decision making related to prostate biopsies in the early detection of prostate cancer. The evidence is insufficient to determine the effects of the technology on health outcomes.

Progensa PCA3 Assay
Progensa PCA3 Assay (prostate cancer gene 3) is overexpressed in prostate cancer, this test measures the concentration of PCA3 mRNA and prostate-specific antigen (PSA) and

calculates a ratio of PCA3 molecules to PSA molecules (PCA3 Score) in post-digital rectal exam (DRE) first catch urine specimen. Progensa PCA3 Assay is indicated for use in conjunction with other risk indicators to aid in patient management in the "at risk" population of men 50 years of age or older who have had 1 or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on the current standard of care.

In a prospective multicenter clinical study of 466 men with at least 1 prior negative prostate biopsy, a PCA3 score cutoff of 25 showed a sensitivity of 78%, specificity of 57%, negative predictive value (NPV) of 90%, and PPV of 34%. Men with a score of $\geq$ 25 were 4.6 times more likely to have a positive repeat biopsy than those with a score $<$ 25.

Results were reported from an NCI Early Detection Research Network (EDRN) validation study of the PCA3 urinary assay in 859 men scheduled for a diagnostic prostate biopsy in 11 centers. The primary outcomes reported at a PPV of 80% (95% CI, 72%-86%) in the initial biopsy setting and NPV of 88% (95% CI, 81%-93%) in the repeat biopsy setting. Based on the data, use of PCA3 in the repeat biopsy setting would reduce the number of biopsies by almost half, and 3% of men with a low PCA3 score would have high grade prostate cancer that would be missed. In contrast, the risk of high-grade disease in men without prior biopsy with a low PCA3 is 13%. Thus, the NCCN panel believes that this test is not appropriate to use in the initial biopsy setting.

The Progensa PCA3 assay (Hologic Gen-Probe) has been approved by the FDA to aid in the decision for repeat biopsy in men 50 years or older who have had 1 or more negative prostate biopsies and for whom a repeat biopsy would be recommended based on current standard of care. The Progensa PCA3 assay should not be used for men with atypical small acinar proliferation (ASAP) on their most recent biopsy.

Based on the NCCN 2A recommendation, the NCCN panel recommends that PCA3 may be considered for men who have had a least one prior negative biopsy and are thought to be at a higher risk for clinically significant prostate cancer.

Summary of Evidence
Based on review of the peer reviewed medical literature results reported from an NCI Early Detection Research Network (EDRN) validation study showed the use of PCA3 in the repeat biopsy setting would reduce the number of biopsies by almost half, and 3% of men with a low PCA3 score would have high grade prostate cancer that would be missed. In contrast, the risk of high-grade disease in men without prior biopsy with a low PCA3 is 13%. The National Comprehensive Cancer Network (NCCN) Prostate Cancer Early Detection 1.2022 as a 2A recommendation states "The use of Progensa PCA3 (prostate cancer gene 3) biomarker test is supported in individuals aged 50 years or older with one or more previous negative biopsies to avoid unnecessary repeat biopsies." The evidence is sufficient to determine the technology results in a meaningful improvement in net health outcome as indicated by the NCCN panel recommendation.

Prostate Core Mitomics Test

The Prostate Core Mitomics Test (PCMT; Mitomics; formerly Genesis Genomics) is a proprietary test that is intended to determine whether a patient has prostate cancer, despite a negative prostate biopsy, by analyzing deletions in the mitochondrial DNA by polymerase chain reaction (PCR) to detect "tumor field effect." The test is performed on the initial negative prostate biopsy tissue. According to the company website, a negative PCMT result confirms the results of the negative biopsy (i.e., the patient does not have prostate cancer) and the patient can avoid a second biopsy, but a positive PCMT means the patient is at high risk of undiagnosed prostate cancer. The website also states that physicians should consider using PCMT for patients who have a negative initial biopsy but continue to have elevated PSA, rising PSA, irregular DRE, atypical small acinar proliferation, high-grade prostatic intraepithelial neoplasia, or inconclusive biopsy.

In 2016, Legisi et. al. queried a pathology services database to identify (1) men who had a negative initial prostate biopsy and a negative PCMT (n=644), and (2) men who had a negative initial prostate biopsy and a repeat biopsy (n=823). Of the 644 patients with a negative PCMT, 35 had a repeat biopsy and 5 (14.2%) were false negatives who were found to have cancer on rebiopsy. The number of false negatives of the patients who did not have a repeat biopsy cannot be determined from this study. Of the second group of 823 men who had a repeat biopsy, 132 had a PCMT. Changes in physician decision-making led to earlier detection of prostate cancer by 2.5 months and an increase in cancer detection rates, but this was only observed when men with atypical small acinar proliferation on index biopsy were not included. Interpretation of these results is limited because testing was not random or consecutive.

Summary of Evidence

No studies were found that directly show the effects of using Prostate Core Mitomics Test (PCMT) on clinical outcomes. Given the lack of direct evidence of utility, a chain of evidence would be needed to demonstrate clinical utility. The Prostate Core Mitomics Test (PCMT) has preliminary data on performance characteristics in small validation study, but independent confirmation of clinical validity is needed. The studies did not provide estimates of validity compared to a standard clinical examination. No data is available on long term clinical outcomes. Data on clinical utility is lacking. The current NCCN guideline version 1.2022 Prostate Cancer Early Detection The current NCCN guideline Prostate Cancer Early Detection version 1.2022 does not include or indicate the use of this genetic testing in the detection of prostate cancer. The evidence is insufficient to determine the effects of the technology on health outcomes.

SelectMDx

SelectMDx helps identify individuals at increased risk for aggressive disease, thereby aiding in the selection for prostate biopsy. SelectMDx for prostate cancer is a reverse transcription PCR (RT-PCR) assay performed on post-DRE (digital rectal examination), first void urine specimen from individuals with clinical risk factors for prostate cancer, who are being considered for biopsy. The test measures the mRNA levels of the DLX1 and HOXC6 biomarkers, using KLK3 expression as internal reference, to aid in patient

selection for prostate biopsy. Higher expression levels of DLX1 and HOXC6 mRNA are associated with an increased probability for high grade (Gleason Grade ≥ 2) prostate cancer.

The assay was developed on an initial training set of 519 patients from 2 prospective multicenter studies and was then validated in a separate set of 386 patients from these trials. Using the expression of DLX1 and HOXC6 alone resulted in an AUC of 0.76, a sensitivity of 91%, a specificity of 36%, an NPV of 94%, and a PPV of 27% for the prediction of Gleason score ≥ 7 prostate cancer. When combined with PSA levels, PSAD, DRE results, age and family history in a multimodal model, the overall area under the curve (AUC) was 0.90 in the training set and 0.86 (95% CI, 0.80-0.92) in the validation set. A retrospective observational study compared results of SelectMDx with mpMRI (multi-parametric MRI) results in 172 patients who had mpMRI because of persistent clinical suspicion of prostate cancer or for local staging after positive biopsy. The AUC of SelectMDx for the prediction of mpMRI outcome was 0.83, whereas the AUC for PSA and PCA2 were 0.66 and 0.65, respectively.

A multicenter study used pre-biopsy urine samples from 1955 individuals to validate the assay with a training cohort and validation cohort. The AUC was 0.85, the sensitivity was 93%, the specificity was 47%, and the NPV was 95% for detection of Grade Group ≥ 2 prostate cancer in the 916-patient validation cohort. When only those with PSA levels <10 ng/mL were included, the values were 0.82, 53% and 95% respectively.

NCCN Guideline Version 1.2022 Prostate Cancer Early Detection, includes a change in their recommendation regarding this testing from the prior version in which this test was not recommended by the panel. The current recommendation states the following: "Overall, the panel believes that SelectMDx score is potentially informative in patients who have never undergone biopsy and therefore may be considered in such individuals."

Summary of Evidence
Based on review of the peer reviewed medical literature which includes observational studies, prospective reviews and a multicenter study using pre-biopsy urine samples from 1955 individuals to validate the assay with a training cohort and validation cohort. The AUC was 0.85, the sensitivity was 93%, the specificity was 47%, and the NPV was 95% for detection of Grade Group ≥ 2 prostate cancer in the 916-patient validation cohort. When only those with PSA levels <10 ng/mL were included, the values were 0.82, 53% and 95% respectively. NCCN Version 1.2022 Prostate Cancer Early Detection includes a change in their recommendation regarding this testing from the prior version in which this test was not recommended by the panel. The current 2A recommendation states the following: "Overall, the panel believes that SelectMDx score is potentially informative in patients who have never undergone biopsy and therefore may be considered in such individuals." The evidence is sufficient to determine the technology results in a meaningful improvement in net health outcome as indicated by the NCCN panel recommendation.

TMPRSS Fusion Genes
TMPRSS2 is an androgen-regulated transmembrane serine protease that is preferentially expressed in normal prostate tissue. In prostate cancer, it may be fused to an ETS (E26 transformation-specific) family transcription factor (ERG, ETV1, ETV4, or ETV5), which modulates transcription of target genes involved in cell growth, transformation, and apoptosis. The result of gene fusion with an ETS transcription gene is that the androgen-responsive promoter of TMPRSS2 upregulates expression of the ETS gene, suggesting a mechanism for neoplastic transformation. Fusion genes may be detected in tissue, serum, and urine.

TMPRSS2-ERG gene rearrangements have been reported in 50% or more of primary prostate cancer samples. Although ERG appears to be the most common ETS family transcription factor involved in the development of fusion genes, not all are associated with TMPRSS2. About 6% of observed rearrangements are seen with SLC45A3, and about 5% appear to involve other types of rearrangement. Attention has been directed at using post-DRE urine samples to look for fusion genes as markers of prostate cancer.

Summary of Evidence
Based on review of the peer reviewed medical literature current evidence on the TMPRSS2-ERG fusion genes is insufficient to support its use in the management of prostate cancer. There are currently no studies that directly show the effects of using TMPRSS2-ERG fusion genes on clinical outcomes. The current NCCN guideline Prostate Cancer Early Detection version 1.2022 does not include or indicate the use of this genetic testing in the detection of prostate cancer. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Urological Association (AUA)
In 2013 (reviewed and validity confirmed 2018), the American Urological Association (AUA) published guidelines for the early detection of prostate cancer:

This guideline addresses prostate cancer early detection for the purpose of reducing prostate cancer mortality with the intended user as the urologist. This document does not make a distinction between early detection and screening for prostate cancer. Early detection and screening both imply detection of disease at an early, pre-symptomatic stage when a man would have no reason to seek medical care –an intervention referred to as secondary prevention. In the U.S., early detection is driven by prostate specific antigen (PSA) – based screening followed by prostate biopsy for diagnostic confirmation.

While the benefits of PSA-based prostate cancer screening have been evaluated in randomized-controlled trials, the literature supporting the efficacy of DRE, PSA derivatives and isoforms (e.g., free PSA, 2proPSA, prostate health index, hK2, PSA velocity or PSA doubling time) and novel urinary markers and biomarkers (e.g., PCA3)

for screening with the goal of reducing prostate cancer mortality provide limited evidence to draw conclusions. While some data suggest use of these secondary screening tools may reduce unnecessary biopsies (i.e. reduce harms) while maintain the ability to detect aggressive prostate cancer (i.e., maintain the benefits of PSA screening), more research is needed to confirm this. However, the likelihood of future population-level screening study using these secondary screening approaches is highly unlikely at least in the near future. Therefore, this document focuses only on the efficacy of PSA screening for the early detection of prostate cancer with the specific intent to reduce prostate cancer mortality and not secondary tests often used after screening to determine the need for a prostate biopsy or a repeat prostate biopsy (e.g., PSA isoforms, PCA3, imaging).

Guideline Statements:

- The Panel recommends against PSA screening in men under age 40 years
    - In this age group there is a low prevalence of clinically detectable prostate cancer, no evidence demonstrating benefit of screening and likely the same harms of screening as in other age groups.
- The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk.
    - For men younger than age 55 years at higher risk, decisions regarding prostate cancer screening should be individualized. Those at higher risk may include men of African American race; and those with a family history of metastatic or lethal adenocarcinomas (e.g., prostate, male and female breast cancer, ovarian and pancreatic) spanning multiple generations, affecting multiple first-degree relatives, and that develop at younger ages.
- For men ages 55 to 69 years the Panel recognizes that the decision to undergo PSA screening involves weighing the benefits of reducing the rate of metastatic prostate cancer and prevention of prostate cancer death against the known potential harms associated with screening and treatment. For this reason, the Panel strongly recommends shared decision-making for men aged 55 to 69 years that are considering PSA screening and proceeding based on a man's values and preferences.
    - The greatest benefit of screening appears to be in men ages 55 to 69 years.
    - Multiple approaches subsequent to PSA test (e.g., urinary and serum biomarkers, imaging, risk calculators) are available for identifying men more likely to harbor a prostate cancer and/or one with an aggressive phenotype. The use of such tools can be considered in men with a suspicious PSA level to inform prostate biopsy decisions.
- To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision making and decided on screening. As compared to annual screening, it is expected that screening intervals of two years preserve the majority of the benefits and reduce over-diagnosis and false positives.
    - Additionally, intervals for rescreening can be individualized by a baseline PSA level.

- The panel does not recommend routine PSA screening in men over age 70 years or any man with less than 10-to-15-year life expectancy.
    - Some men over age 70 -years who are in excellent health may benefit from prostate cancer screening.

National Comprehensive Cancer Network (NCCN)

Prostate Cancer Early Detection Version 1.2022

Biomarker Testing: PSA Derivatives and Other Tests
When the first recommendations for early detection programs for prostate cancer were made, serum tPSA was the only PSA-based test available. PSA derivatives and other assays exist that potentially improve the specificity of testing and thus may diminish the probability of unnecessary biopsies.

When a patient meets the standards for biopsy, sometimes the patient and physician wish to further define the probability of cancer before proceeding to biopsy with is associated risks. Several biomarker tests have been developed with the goals of refining patient selection for biopsies, decreasing unnecessary biopsies, and increasing the specificity of cancer detection, without missing a substantial number of higher grade (Grade group $\geq$2) cancers. These tests may be especially useful in individuals with PSA levels between 3 and 10 ng/mL. Most often, these tests have been used in patients who have had one negative biopsy to determine if repeat biopsy is an appropriate consideration.

The Panel recommends consideration of biomarker tests that have been validated in peer-reviewed, multi-site studies using an independent cohort of patients. These include percent free PSA (%f PSA), which may improve cancer detection and Prostate Health Index (PHI) , SelectMDx, 4Kscore, or ExoDx Prostate Test (EPI), which may further define the probability of Grade Group $\geq$ 2 cancer in patients with PSA levels > 3ng/mL who have not yet had a biopsy. Percent free PSA (%fPSA), PHI, 4Kscore, EPI, PCA3 and ConfirmMDx may also be considered for men who have had at least one prior negative biopsy and are thought to be a higher risk. The extent of validation of these tests across divers populations varies. Results of biomarker assays can be complex and should be interpreted with caution. Referral to specialist should be considered. Multiparametric MRI is also a consideration in these same patients. It is not yet known, with certainty, how biomarker tests can be applied in optimal combination with MRI.

Head-to-head comparisons have been performed for some of these tests, used independently or in combinations in the initial or repeat biopsy settings, but sample sizes were small, and results varied. Therefore, the panel believes that no biomarker test can be recommended over any other at this time. Furthermore, a biomarker assay can be done alone or in addition to multiparametric MRI/refined biopsy techniques. The optimal order of biomarker tests and imaging is unknown; and it remains unclear how to interpret results of multiple tests in individual patients, especially when results are contradictory. However, several recent studies suggest that upfront biomarker testing with conditional

MRI may be an efficient and effective way to assess those with a persistently elevated PSA.

Results of any of these tests, when performed, should be included in discussions between clinician and patient to assist in decisions regarding whether to proceed with biopsy. These other tests are discussed below.

PCA3
PCA3 is a noncoding, prostate tissue specific RNA that is over-expressed in prostate cancer. Current assays quantify PCA3 overexpression in post-DRE urine specimens. PCA3 appears most useful in determine which patients should undergo a repeat biopsy. For example, in a prospective multicenter clinical study of 466 men with at least 1 prior negative prostate biopsy, a PCA3 score cutoff of 25 showed a sensitivity of 78%, specificity of 57%, negative predictive value (NPV) of 90%, and PPV of 34%. Men with a score of $\geq$ 25 were 4.6 times more likely to have a positive repeat biopsy than those with a score < 25.

Results were reported from an NCI Early Detection Research Network (EDRN) validation study of the PCA3 urinary assay in 859 men scheduled for a diagnostic prostate biopsy in 11 centers. The primary outcomes reported at a PPV of 80% (95% CI, 72%-86%) in the initial biopsy setting and NPV of 88% (95% CI, 81%-93%) in the repeat biopsy setting. Based on the data, use of PCA3 in the repeat biopsy setting would reduce the number of biopsies by almost half, and 3% of men with a low PCA3 score would have high-grade prostate cancer that would be missed. In contrast, the risk of high-grade disease in men without prior biopsy with a low PCA3 is 13%. Thus, the panel believes that this test is not appropriate to use in the initial biopsy setting.

The FDA has approved the PCA3 assay to help decide, along with other factors, whether a repeat biopsy in individuals aged 50 years or older with one or more previous negative prostate biopsies is necessary. This assay is recommended in men with previous negative biopsy in order to avoid repeat biopsy by the Molecular Diagnostic Services Program (MOiDX) and is therefore covered by CMS (Centers for Medicare and Medicaid Services) in this setting.

Prostate Health Index (PHI)
The Prostate Health Index (PHI) is a combination of the tPSA, fPSA and proPSA tests. In the multicenter study, it was noted to have approximately double the sensitivity of fPSA/tPSA for cancer detection in those with serum PSA concentrations between 2 and 10 ng/mL. In addition, the PHI correlated with cancer grade and had an area under the curve (AUC) of 0.72 for discrimination of high grade (Grade Group $\geq$2) cancer from low grade cancer or negative biopsy. Another prospective cohort study calculated an AUC of 0.815 for the detection of high-grade (Grade Group $\geq$2*)* prostate cancer. This study determined the optimal cutoff of PHI to be a score of 24, which should lead to 36% of biopsies avoided with approximately 2.5% of high-grade cancers missed. Other studies

have also shown that PHI can predict aggressive prostate cancer and has potential clinical utility.

The PHI was approved by the FDA in 2012 for use in those with serum PSA values between 4 and 10 ng/mL. A clinical utility study conducted at four large urology group practices showed that use of PHI was in fact associated with a decrease in biopsy procedures performed when compared to historical controls from the same physicians (36.4% vs 60.3%; $P < 0.0001$). Patients in the study had a normal DRE and PSA values ranging from 4 to 10 ng/mL. Physician survey results showed that PHI results impacted biopsy decisions in 73% of cases. However, the authors of this study did not report the numbers of high-grade cancers missed, and some have estimated that it may be as high as 30%.

4KScore

The 4Kscore test is another combination test that measures free and tPSA, human kallikrein 2 (hK2), and intact PSA and also considers age, DRE results, and prior biopsy status. This test reports the percent likelihood of finding high-grade (Grade Group ≥ 2) cancer on biopsy. A prospective multi-institutional United States trial of 1012 patients showed that 4Kscore results have a high discrimination value (AUC, 0.82). In this study, using a threshold biopsy of $\geq$ 15% risk allosed for 591 biopsies to be avoided (58%), while 183 high-grade tumors were detected, and 48 high grade tumors (4.7% of the 1012 participants) were missed. When 4Kscore was examined in 6129 partcipants in another prospective study, the AUC was also 0.82 (95% CI, 0.80-0.84). Using a 6% risk of high-grade cancer cutoff, 428 of 1000 men could avoid biopsy, with 119 of 133 high grade cancers detected and 14 of 133 missed. A multi-center clinical utility study found a 65% reduction in prostate biopsies with use of 4Kscore test. In addition, a correlation between 4Kscore risk category and Gleason score was seen ($P < .01$). A meta-analysis that included 12 clinical validation studies (11,134 patients) led to a calculated pooled AUC for discrimination of Grade Group ≥ 2 prostate cancer of 0.81 (fixed effects 95% CI, 0.80-0.83).

The consensus is that the test can be considered for patients prior to biopsy and for those with prior negative biopsy who are thought to be at higher risk for clinically significant prostate cancer. It is important for patients and their urologists to understand, however, that no optimal cut-off threshold has been established for the 4Kscore. If a 4Kscore test is performed, the patient and his urologist should discuss the results to decide whether to proceed with a biopsy.

ConfirmMDx

ConfirmMDx is a tissue based, multiplex epigenetic assay that aims to improve the stratification of individuals being considered for repeat prostate biopsy. Hypermethylation of the promotor regions of GSTP1, APC, and RASSF1 are assessed in core biopsy tissue samples. The test, performed in on CLIA-certified laboratory, is not FDA approved.

The European MATLOC study blindly tested this assay in archived tissue from 498 men with negative biopsies who had repeat biopsies within 30 months. The NPV was 90% (95% CI, 87%-93%). In multivariate analysis, ConfirmMDx was predictive of patient outcome (OR, 3.17; 95% CI, 1.81-5.53). A similar validation study was performed in the United States using archived tissue from 350 men when negative biopsies who had repeat biopsies within 24 months. The NPV was 83% (95% CI, 85%-91%), and the test was again found to be predictive of outcomes on multivariate analysis (OR, 2.69; 95% CI, 1.60-4.51).

The panel believes that ConfirmMDx can be considered as an option for individuals contemplating repeat biopsy, because the assay may identify individuals at higher risk of prostate cancer diagnosis on repeat biopsy. This assay is approved for limited coverage by MoIDX for the reduction of unnecessary repeat prostate biopsies.

ExoDx Prostate (IntelliScore)

ExoDx Prostate (IntelliScore), also called EPI, evaluates a urine-based 3 gene exosome expression assay utilizing PCA3 and ERG (V-ets erythroblastosis virus E26 oncogene homologs) RNA from urine, normalized to SPDEF (SAM pointed domain-containing ETS transcription factor). The background for these markers is supported by a number of studies, but the application to exosome detection is unique. This gene panel proposes to discriminate Grade Group $\geq$ 2 prostate cancer from Grade Group 1 and benign disease at initial biopsy. The population for which use of the assay was intended includes patients older than 50 years with no prior biopsy and a PSA value between 2 and 10 ng/mL. In a recent study by McKiernan et. al., estimates of the AUC were similar in the training (0.74) and validation (0.71) cohorts for the assay, with significant improvements when the test was added to standard of care variables alone. Applying a cutoff value from the training cohort to serve as a threshold for biopsy in the validation cohort decreased the need for biopsy by 27% (138 of 519) while missing 8% (12 of 148) of Grade Group $\geq$ 2 cancers. The investigators propose the assay as a secondary or reflex test for risk stratification in conjunction with PSA screening. In the McKiernan study, the algorithm was validated in a test set of 255 patients and then validated in the extended screening validation cohort of 519 patients. The majority of exclusions were for urine volume > 49 mL, assay failure, and application outside the intended use population.

A second independent validation study was a 2-phase adaptive clinical utility study that included 503 biopsy-naive patients with PSA levels between 2 and 10 ng/mL and compared EPI and biopsy results. In the first phase of this study, the AUC was 0.70 for predicting Grade Group $\geq$ 2 cancer by EPI. Using the validated cut-point 15.6, the test has an NPV of 89%, reducing total biopsies by 20% and missing 7% of Grade Group $\geq$ 2 cancer. The second phase of this trial will be reported in the future.

The panel believes that EPI can be considered as an option for men contemplating initial or repeat biopsy.

SelectMDx
SelectMDx is a gene expression assay performed on post-DRE urine that measures DLX1 and HOXC6 expression against KLK3 as internal reference. DLX1 and HOXC6 have been associated with prostate cancer aggressiveness. As with the other assays, SelectMDx is designed to improve the identification of individuals with clinically significant prostate cancer prior to biopsy, thereby reducing the number of unnecessary biopsies.

The assay was developed on an initial training set of 519 patients from two prospective multicenter studies and was then validated in a separate set of 386 patients from these trials. Using the expression of DLX1 and HOXC6 alone resulted in an AUC of 0.76%, a sensitivity of 91%, a specificity of 36%, an NPV 94%, and a PPV of 27% for the prediction of Grade Group $\geq$2 prostate cancer. When the gene expression was combined with PSA levels, PSAD, DRE results, previous negative prostate biopsies, age and family history in a multimodal model, the overall AUC was 0.90 in the training set and 0.86 (95% CI, 0.80-0.92) in the validation set. A retrospective observational study compared results of SelectMDx with multiparametric MRI results in 172 patients who had multiparametric MRI because of persistent clinical suspicion of prostate cancer or for local stating after positive biopsy. The AUC of SelectMDx for the prediction of multiparametric MRI outcome was 0.83, whereas the AUC for PSA and PCA2 were 0.66 and 0.65, respectively.

A multicenter study used pre-biopsy urine samples from 1955 individuals to validate the assay with training cohort and a validation cohort. The AUC was 0.85, the sensitivity was 93%, the specificity was 47%, and the NPV was 95% for detection of Grade Group $\geq$ 2 prostate cancer in the 916-patient validation cohort. When only those with PSA levels <10 ng/mL were included, the values were 0.82, 89%, 53% and 95% respectively.

Overall, the panel believes that SelectMDx score is potentially informative in patients who have never undergone biopsy, and it can therefore be considered in such individuals.

Additional Biomarker Tests
The list of assays with the potential to permit improved detection of Grade Group $\geq$ 2 prostate cancers as an adjuvant to PSA screening is growing rapidly. Below, several of these assays are discussed. Given the lack of validation of the models/algorithms in additional, independent publications, their unclear behavior in other screened populations, and the lack of clarity regarding the incremental value and cost effectiveness of these assays, however, the panel cannot recommend their routine use at this time. Furthermore, potential sources of error in these approaches include undetectable cancers, as high as 25%, in patients with a single negative prostate biopsy. Other significant and unaddressed issues include the well-known upgrading (32%-49%) that occurs in patients with Grade Group 1 cancer at biopsy at the time of pathologic assessment of the surgical specimen. Longer term follow-up of the cohorts to determine whether missed prostate cancers were ultimately detected is needed. In addition, validation of these tests in other

cohorts is needed before they can be accepted as alternatives to (or perhaps preferable) other tests, described above.

Mi-Prostate Score
The Mi-Prostate Score (MiPS) assay measures total serum PSA and post DRE urine expression of PCA3 and the TMPRSS2-ERG fusion gene. Rearrangements of the ERG gene are found in approximately half of prostate cancers. The TMPRTSS2-ERG fusion specifically occurs at high frequency and appears to be an early event in prostate cancer development.

A MiPS validation study included 1244 individuals with planned biopsy (80% with no prior prostate biopsy) in a validation cohort. The AUC for the prediction of any cancer was 0.751 for MiPS, compared with 0.585 for PSA alone. For the prediction of Grade Group $\geq$2 cancer, the AUCs for MiPS and PSA alone were 0.772 and 0.651 respectively.

A multicenter prospective validation study of this assay included 516 participants in a development cohort and 561 participants in a validation cohort. In the validation cohort, use of the test improved specificity for the presence of Grade Group $\geq$2 cancer from 17% to 33%, with the sensitivity at 93%. The authors calculate that 42% of unnecessary biopsies could have been avoided by using the assay in biopsy decisions.

Based on reasons discussed above (*See Additional Biomarker Tests*), the panel considers MiPS to be investigational at the present time but will review additional information as it becomes available.

NCCN Panel Recommendations
The decision to participate in an early detection program for prostate cancer is complex for both the patient and physician. Important factors must be assessed when considering early detection of prostate cancer, including patient age, life expectancy, family history, African ancestry, presence of inherited mutations, and previous early detection test results. Most importantly, the patient and physician need to understand the risks and benefits associated with the early detection and treatment of prostate cancer.

- The panel recommends that multiparametric MRI be performed before biopsy if available. Consideration may be given to biomarkers that improve biopsy specificity such as percent free PSA (%free PSA), 4Kscore, SelectMDx, EXODx Prostate and PHI before biopsy in those with serum PSA levels of > 3 ng/mL who desire more specificity. PHI, %fPSA, 4Kscore, ConfirmMDx and PCA3 are also options in individuals through to be at higher risk despite a negative prostate biopsy.

The goal of NCCN and this Guidelines Panel in updating these algorithms is to assist patients and clinicians in choosing a program of early detection for prostate cancer and in making decision regarding the need for prostate biopsy. Any clinician who uses these guidelines is expected to exercise independent medical judgement in the context of the

individual clinical circumstances to determine the patient's need for prostate biopsy. These guidelines will continue to evolve as the field of prostate cancer advances.

U.S. Preventative Services Task Force (USPSTF)
The U.S. Preventative Services Task Force (USPSTF) published an updated recommendation in 2018 for prostate cancer screening, and the recommendation does not address genetic or protein biomarker testing.

Regulatory Status
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed under the CLIA for high-complexity testing. The following laboratories are certified under the CLIA: BioReference Laboratories and GenPath Diagnostics (subsidiaries of OPKO Health; 4Kscore®), ARUP Laboratories, Mayo Medical Laboratories, LabCorp, BioVantra, others (PCA3 assay), Clinical Research Laboratory (Prostate Core Mitomic Test™), MDx Health (SelectMDx, ConfirMDx), Innovative Diagnostics (phi™), ExoDx® Prostate (Exosome Diagnostics) and PanGia Prostate. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

In February 2012, the Progensa® PCA3 Assay (Gen-Probe; now Hologic) was approved by the Food and Drug Administration (FDA) through the premarket approval process. The Progensa PCA3 Assay has been approved by the FDA to aid in the decision for repeat biopsy in men 50 years or older who have had 1 or more negative prostate biopsies and for whom a repeat biopsy would be recommended based on the current standard of care. The Progensa PCA3 Assay should not be used for men with atypical small acinar proliferation on their most recent biopsy. FDA product code: OYM.

In June 2012, proPSA, a blood test used to calculate the Prostate Health Index (phi; Beckman Coulter) was approved by the Food and Drug Administration (FDA) through the premarket approval process. The phi test is indicated as an aid to distinguish prostate cancer from a benign prostatic condition in men ages 50 and older with prostate-specific antigen levels of 4 to 10 ng/mL and with digital rectal exam findings that are not suspicious. According to the manufacturer, the test reduces the number of prostate biopsies. FDA product code: OYA.

In December 2021, the Food and Drug Administration (FDA) approved the 4Kscore® Test for use in men aged 45 and older who have not had a prior prostate biopsy or are biopsy negative who have an abnormal age-specific total PSA and/or abnormal DRE. The 4Kscore Test is intended to aid in detection of aggressive prostate cancer (Gleason score $\geq$ 7/Gleason Grade Group $\geq$ 2) for whom a biopsy would be recommended by a urologist, based on current standards of care before consideration of the 4Kscore Test. A 4Kscore < 5.0 is associated with decreased likelihood of a Gleason score $\geq$ 7 on biopsy. Prostate biopsy is required for the diagnosis of cancer. The test is not recommended more than once every 6 months.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policies

- 02.04.57 Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

Medically Necessary

Genetic and Protein Biomarkers

The following prognostic genetic tests may be considered medically necessary for the early detection of prostate cancer when the associated criteria are met:

4Kscore Test (81539 and 0011M)

4Kscore Test may be considered **medically necessary** when **ALL** the following criteria are met:

- The test will be performed prior to an initial prostate biopsy; **OR**
- The individual has had a prior negative prostate biopsy; **and**
- The individual is ≥ 45 years of age; **and**
- Continued clinical suspicion of prostate cancer based on elevation of prostate specific antigen (PSA) > 3 ng/mL, and for whom an initial prostate biopsy or repeat prostate biopsy would be recommended by a urologist based on current standard of care; **and**
- The individual is considered at higher risk for prostate cancer by one or more of the following:
    - Family history of a first degree relative (close blood relative parent, full sibling(s) or children) with prostate cancer diagnosed younger than 65 years; **and/or**
    - African American race; **and/or**
    - Known mutation in a gene associated with increased risk of prostate cancer (e.g., BRCA 1/2, MLH1, MSH2, MHS6, PMS2, EPCAM); **and**
- The individual has not taken 5-alpha reductase inhibitors (5-ARI) within the last 6 months (such as Avodart [dutasteride] or Proscar [finasteride]); **and**
- The individual has not undergone any procedure or therapy to treat symptomatic BPH (benign prostatic hypertrophy) or any invasive urological procedure that may be associated with secondary PSA elevation within the last 6 months; **and**
- The individual has not received a digital rectal exam in the previous 96 hours (4 days) prior to this testing which may be associated with secondary PSA elevation.

ConfirmMDx (81551)

ConfirmMDx may be considered **medically necessary** to reduce an unnecessary repeat biopsy when **ALL** the following criteria are met:

- Age ≥ 45 years of age; **and**
- Prior negative prostate biopsy; **and**
- Prior biopsy histology does not include a cellular atypia suspicious for cancer, but may include the presence of high-grade prostatic intraepithelial neoplasia, proliferative inflammatory atrophy, or glandular inflammation; **and**
- Continued clinical suspicion of prostate cancer based on elevation of prostate specific antigen (PSA) > 3 ng/mL; **and**
- The individual is considered at higher risk for prostate cancer by one or more of the following:
    - Family history of a first degree relative (close blood relative parent, full sibling(s) or children) with prostate cancer diagnosed younger than 65 years; **and/or**
    - Family history of two or more first-degree relatives with prostate cancer diagnosed at any age; **and/or**
    - African descent (including African American and Caribbean of African ancestry); **and/or**
    - Known mutation in a gene associated with increased risk of prostate cancer (e.g., BRCA 1/2, HOXB13 (G84E mutation carriers), MLH1, MSH2, MHS6, PMS2, EPCAM).

ExoDx Prostate (IntelliScore) (0005U)
ExoDx Prostate (IntelliScore) may be considered **medically necessary** when **ALL** the following criteria are met:

- Age ≥ 50 years of age; **and**
- The test will be performed prior to an initial prostate biopsy; **or**
- The individual has had a prior negative prostate biopsy; **and**
- Continued clinical suspicion of prostate cancer based on elevation of prostate specific antigen (PSA) >3 ng/mL, and for whom an initial prostate biopsy or repeat prostate biopsy would be recommended by a urologist based on current standard of care.

PCA3 (Progensa PCA3 assay/Prostate Cancer Gene 3 [PCA3]) (81313)
PCA3 (Progensa PCA3 assay/Prostate Cancer Gene 3 [PCA3] may be considered **medically necessary** to aid in the decision regarding a repeat prostate biopsy when **ALL** the following criteria are met:

- Age ≥ 50 years; **and**
- One or more previous negative prostate biopsies; **and**
- Atypical small acinar proliferation (ASAP) was not identified on the recent biopsy; **and**
- Continued clinical suspicion of prostate cancer based on digital rectal exam (DRE) (the individuals DRE was not performed within 96 hours (4 days) prior to this testing which may be associated with secondary PSA elevation) or elevation of prostate specific antigen (PSA) > 3 ng/mL, and for whom a repeat biopsy would be recommended by a urologist based on current standard of care; **and**

- The individual has not undergone any procedure or therapy to treat symptomatic BPH (benign prostatic hypertrophy) or any invasive urological procedure that may be associated with secondary PSA elevation within the last 6 month.

Prostate Health Index (PHI) (P2PSA) (86316)
Prostate Health Index (PHI) may be considered **medically necessary** when **ALL** the following criteria are met:

- Age ≥ 50 years of age; **and**
- The test will be performed prior to an initial prostate biopsy; **and**
- Continued clinical suspicion of prostate cancer based on elevation of prostate specific antigen (PSA) > 3 ng/mL, and for whom a prostate biopsy would be recommended by a urologist based on current standard of care; **and**
- Digital rectal exam (DRE) findings are not suspicious for prostate cancer.

SelectMDx for Prostate Cancer (0339U)
SelectMDx for Prostate Cancer may be considered **medically necessary** when **ALL** the following criteria are met:

- Age ≥ 50 years of age; **and**
- The test will be performed prior to an initial prostate biopsy; **and**
- Continued clinical suspicion of prostate cancer based on elevation of prostate specific antigen (PSA) > 3 ng/mL, and for whom a prostate biopsy would be recommended by a urologist based on current standard of care; **and**
- Digital rectal exam (DRE) findings are not suspicious for prostate cancer.

Investigational
The following prognostic genetic tests for the early detection of prostate cancer PCA3 (Progensa PCA3 assay/Prostate Cancer Gene 3 [PCA3]), 4Kscore Test, SelectMDx, Prostate Cancer, Health Index (PHI) (pro2PSA), ConfirmMDx or ExoDx Prostate (IntelliScore) not meeting the above criteria is considered **investigational,** there is insufficient evidence to support a conclusion concerning net health outcomes or benefits associated for this testing for all other indications.

Genetic and protein biomarkers for the early detection of prostate cancer, including but not limited to the following, are considered **investigational**:

- APIFINY
- TMPRSS fusion genes
- Prostate Core Mitomics Test (PCMT)/ Mitochondrial DNA mutation testing
- MyProstate Score (formerly known as Mi-Prostate Score [MiPS])
- PanGia Prostate

To date, most of the available studies fail to provide sufficient evidence that the above genetic and protein biomarker testing for the cancer risk assessment and diagnosis of prostate cancer leads to improved net health outcomes or a change in management treatment decisions (i.e., clinical utility). Well - designed randomized controlled trials (RCTs) are needed to determine the clinical utility of these genetic and protein biomarker

tests for the cancer risk assessment and diagnosis of prostate cancer compared to traditional clinical factors/testing to guide medical management and improve clinical outcomes. The NCCN guideline version 1.2022 Prostate Cancer Early Detection states the following: "The panel cannot recommend their routine use at this time. Furthermore, potential sources of errors in these approaches include undetected cancers, as high as 25%." The evidence is insufficient to determine the testing above effects net health outcomes regarding the early detection for prostate cancer and in making decisions regarding the need for prostate biopsy.

Policy Guidelines

Clinically Localized Prostate Cancer AUA/ASTRO/SUO Guideline
Active Surveillance

- Localized prostate cancer patients who elect active surveillance should have accurate disease staging including systematic biopsy with ultrasound or MRI guided imaging. (Clinical Principle)
- Localized prostate cancer patients undergoing active surveillance should have routine surveillance PSA testing and digital rectal exams (DRE). (Strong recommendation)
- Localized prostate cancer patients undergoing active surveillance should be encouraged to have confirmatory biopsy within the initial two years and surveillance biopsies thereafter. (Clinical Principle)
- Clinicians should offer definitive treatment to localized prostate cancer patients undergoing active surveillance who develop adverse reclassification. (Moderate Recommendation)

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81313 PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen] ratio (e.g., prostate cancer)
- 81479 Unlisted molecular pathology procedure (when specified for one of the following: Prostate Core Mitomics Testing (PCMT); or TMPRSS Fusion Genes; or SelectMDx or SelectMDx Prostate Cancer)
- 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 probability score (4Kscore Test)
- 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 (ConfirmMDx)

- 81599 Unlisted multianalyte assay with algorithmic analysis (when specified for one of the following: Prostate Core Mitomics Testing (PCMT); or TMPRSS Fusion Genes; or SelectMDx or SelectMDx Prostate Cancer)
- 86316 Immunoassay for tumor antigen, other antigen, quantitative, (e.g. CA 50, 72-4. 549) each. (Per AUA Coding and Reimbursement Committee this CPT should be used for the calculation of Prostate Health Index (phi) value and immunoassay component pro2PSA)
- 0011M Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and/or urine, algorithms to predict high grade cancer risk (4Kscore Test)
- 0005U Oncology (prostate) gene expression profile by real time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine algorithm reported as risk score (ExoDx Prostate (IntelliScore)/ExosomeDx Prostate (IntelliScore)
- 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 (APIFINY)
- 0113U Oncology (prostate) measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic message, by RNA amplification and fluoresecence-based detection, algorithm reported as risk score (MyProstate Score formerly known as MiPS [Mi-Prostate Score])
- 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 (PanGia Prostate)
- 0339U Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following digital rectal examination, algorithm reported as probability of high-grade cancer (SelectMDx for Prostate Cancer)

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POLICY HISTORY

Date	Reason	Action
June 2022	Annual Review	Policy Revised
June 2021	Annual Review	Policy Revised
June 2020	Annual Review	Policy Renewed
December 2019	Interim Review	Policy Revised

June 2019	Annual Review	Policy Revised
June 2018	Annual Review	Policy Revised
October 2017	Interim Review	Policy Revised
June 2017	Annual Review	Policy Revised
June 2016		Policy Revised and New Policy Created

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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