Healthy Blue

Medical Policy

Subject:	Gene Expression Profiling and Genomic Biomarker Tests for Prostate Cancer		
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Description/Scope

This document addresses gene expression and genomic biomarker tests for the screening, detection and management of prostate cancer. Gene expression profiles measure the activity of multiple genes (examples include the Prolaris® test [Myriad Genetics, Salt Lake City, Utah], Decipher® Prostate Cancer Classifier [Decipher Biosciences, San Diego, CA], and the Oncotype DX® Genomic Prostate Score [Genomic Health, Redwood City, CA]); genomic biomarker tests include, but are not limited to, assessment of gene hypermethylation, multi-gene expression profiles, prostate cancer antigen gene-3 (PCA3 [formerly known as DD3]), ribonucleic acid (RNA), and TMPRSS fusion genes.

Note: Please see the following related document(s) for additional information:

- CG-GENE-14 Gene Mutation Testing for Cancer Susceptibility and Management
- GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling
- LAB.00015 Detection of Circulating Tumor Cells

Position Statement

Investigational and Not Medically Necessary:

Gene expression profiling and genomic biomarker tests as a technique for prostate cancer screening, detection and management are considered **investigational and not medically necessary** for all indications**.**

Rationale

There has been a variety of research surrounding gene expression profiling and genomic biomarker tests for the screening, detection and management of prostate cancer. Currently there is a lack of evidence to support the clinical utility of these tests as techniques for prostate cancer diagnosis, prognosis, or management.

Gene Expression Profiling

Because no single gene biomarker has been found that is both highly sensitive and highly specific for diagnosing and managing prostate cancer, particularly in men already known to have elevated PSA levels, some investigators are combining several markers into a single diagnostic panel. Gene expression profiles measure the activity of multiple genes, generally through assessment of mRNA. Commercially available gene expression profiles for prostate cancer management include a cell cycle progression (CCP) score or Prolaris test, a 46 gene based panel; Decipher Prostate Cancer Classifier, a 22-gene expression panel test that produces a Genomic Classifier (GC)

score; and the Oncotype DX Genomic Prostate Score, a 17 gene biopsy-based test that produces a Genomic Prostate Score (GPS).

In 2012, Cuzick and colleagues investigated the CCP score as a predictor of prostate cancer outcomes. In their series, 776 men had been diagnosed with prostate cancer and needle biopsies were available from 527 of them. Of these, 349 (79%) produced a CCP score. Total ribonucleic acid (RNA) was extracted from specimens and the CCP score was calculated from expression levels of 31 genes. In univariate analysis (n=349), the hazard ratio (HR) for death from prostate cancer was 2.02 (95% confidence interval [CI], 1.62, 2.53; p<10[-9]) for a one-unit increase in CCP score. The CCP score was only weakly correlated with standard prognostic factors and in a multivariate analysis, CCP score dominated (HR for one-unit increase=1.65, 95% CI [1.31, 0.09], p=3 × 10[-5]), with Gleason score (p=5 × 10[-4]) and prostate-specific antigen (PSA) (p=0.017) providing additional contributions. Study limitations included a lack of availability of specimens for follow-up. The authors stated that the most obvious clinical use of the CCP score is to help identify low-risk men who can be safely managed by surveillance. However, since deaths from prostate cancer are rare in this group, a larger cohort is needed to fully demonstrate the value of the CCP score in identifying those at low-risk.

Additional evaluations of the CCP score have been performed (Bishoff, 2014; Cooperberg, 2013; Crawford, 2014; Cuzick, 2011; Cuzick, 2012b; Freedland, 2013; Shore, 2013). However, none of these studies demonstrated that choices made on the basis of the test lead to improved outcomes compared to choices made using Gleason score and PSA, and all authors indicated a need for additional validation.

The Decipher Prostate Cancer Classifier is a whole-transcriptome microarray assay that uses prostate needle biopsy or radical prostatectomy specimens to measure the expression of the 22 genes that produce the GC score. Researchers have investigated it as a predictor of the 5-year risk of clinical metastases and prostate-specific mortality for individuals considering active surveillance after initial prostate cancer diagnosis or considering radiation after radical prostatectomy (Gore, 2019).

Much of the research investigating the Decipher Prostate Cancer Classifier are studies with retrospective designs. In 2017, Spratt and colleagues released the results of a meta-analysis to evaluate the Decipher Prostate Cancer Classifier as a prognostic tool for risk of metastases in individuals with prostate cancer postprostatectomy. The systematic literature search yielded 5 studies with 975 total participants; however, to avoid bias in the estimation of the hazard ratios (HR), 120 (12.3%) participants were not randomly selected from the case-cohort studies and were excluded from the primary end point analysis, which was to determine performance of the Decipher Prostate Cancer Classifier using individual participant data (n=855) to predict time to metastases on multivariable analyses. The results of the meta-analysis showed individuals categorized as low, intermediate, and high risk by the Decipher Prostate Cancer Classifier had a 5-year cumulative incidence of metastasis of 2.4%, 5.8%, and 15.2%, respectively (p<0.001). In addition, the investigators evaluated the 10-year rate, which was 5.5%, 15.0% and 26.7%, respectively (p<0.001). The Decipher Prostate Cancer Classifier's ability to predict time to metastases was also evaluated through pooling of study-specific HRs from all 5 studies, which was the secondary endpoint. As with the primary endpoint, the Decipher Prostate Cancer Classifier was significantly associated with time to metastasis in the secondary endpoint analysis (HR, 1.52; 95% CI, 1.39 to 1.67). While this is a meta-analysis with significant results, there are several limitations. The 5 studies included in the meta-analysis had a retrospective design. Also, there was no data on whether including the Decipher Prostate Cancer Classifier in risk stratification helped to change

treatment decisions. Adding to the limitations of this study were factors that were not accounted for, but could have impacted the results, such as participant comorbidities and variations in treatments.
Michalopoulos and colleagues (2014) published a prospective study with the aim to investigate the effect of the Decipher Prostate Cancer Classifier on urologists' adjuvant treatment decisions when caring for high-risk individuals. Fifteen urologists in community practices were included in the study. Participants provided treatment recommendations via an electronic data collection tool prior to receiving the Decipher Prostate Cancer Classifier test results and again after receiving the test results. Tests ordered for 146 individuals were included in the study. After review of the test results, it was found that urologists revised their treatment recommendations for 30.8% (95% CI=23–39%) of individuals. For those individuals that initially had a recommendation for observation (n=102), 18 (17.6%) were changed to a recommendation of adjuvant treatment after review of the Decipher Prostate Cancer Classifier test results. There were 17 (42.5%) individuals who initially had a recommendation of adjuvant therapy that was changed to observation following review of the test results. "Although the number of patients receiving recommendations for treatment was unaffected by the availability of the GC test report, the genomic information provided by GC test results significantly influenced which patients were recommended adjuvant treatment ($p<0.001$)" (Michalopoulos, 2014). With the data being submitted via an electronic data collection tool rather than medical charts, the reported treatment may have varied from the actual treatment. Furthermore, treatment decisions may have been influenced by those receiving the treatment and this was not captured in the analysis. These factors may limit the applicability of the results.

In 2017, Gore and colleagues reported on the PRO-IMPTACT study, which had a prospective, multicenter design and investigated the impact of the Decipher Prostate Cancer Classifier on decision making for adjuvant radiotherapy (ART) of individuals with aggressive pathology or salvage radiotherapy (SRT) of individuals with a rising PSA after undergoing radical prostatectomy. Individuals were not randomized and enrollment was consecutive. There were 159 individuals who enrolled in the ART arm with 150 (94%) of those individuals completing the study. For the SRT arm, there were 125 individuals who enrolled with 114 (91%) of those individuals completing the study. Before the Decipher Prostate Cancer Classifier test was performed, providers submitted a recommended treatment plan and observation was recommended for 89% of individuals considering ART and 58% of individuals considering SRT. This was repeated after the providers received the test results, and investigators found that 18% (95% CI, 12%-25%) of recommended treatment plans changed in the ART arm and 32% (95% CI, 24%-42%) of recommended treatment plans changed in the SRT arm. Also, individuals and providers both participated in the evaluation of decision effectiveness using the Decisional Conflict Scale (DCS) with a significant decrease in decisional conflict found in both the ART and SRT arms ($p<0.001$), and in the provider group ($p<0.001$). There were no significant changes in prostate cancer-specific anxiety for participants as a whole. Gore and colleagues expanded on the analysis of the PRO-IMPTACT study in 2019. There were 18 (7%) participants who were lost to follow-up by 12 months after the first visit. Out of the remaining participants in the ART arm (n=140), 31 (22%) received the recommended treatment plan based on the Decipher Prostate Cancer Classifier results (95% CI, 16%-30%). Out of the remaining participants in the SRT arm (n=106), 25 (24%) received the recommended treatment plan based on the Decipher Prostate Cancer Classifier results (95% CI, 16%-33%). Some limitations noted in this study include possible influence of treatment decisions in the SRT arm due to the time lapse between radical prostatectomy and study enrollment, potential maturation bias affecting treatment plan observations, and nonrandomized study design with lack of control group, which inhibits the ability to conclude that use of the Decipher Prostate Cancer Classifier test improves prostate cancer-specific health outcomes.

In 2019, Berlin and colleagues retrospectively evaluated the performance of the Decipher Prostate Cancer Classifier in a novel cohort of 121 men diagnosed between 2005 and 2011 with intermediate-risk prostate cancer who had been treated with dose-escalated image guided radiation therapy without androgen deprivation therapy. Decipher Prostate Cancer Classifier scores were derived from pre-treatment tumors sampled during diagnostic biopsy. Primary and secondary study endpoints were biochemical failure (PSA nadir + 2 ng/mL) and metastasis occurrence, respectively. By National Comprehensive Cancer Network (NCCN) sub-classification, 33 (27.3%) study participants were classified as having 'favorable' intermediate-risk prostate cancer and 87 (71.9%) were classified as having 'unfavorable' intermediate-risk prostate cancer (defined by NCCN-endorsed sub-classification as any individual with a primary Gleason grade 4, percentage of positive biopsy cores $\geq$ 50% and/or $\geq$ 2 NCCN intermediate risk factors). Decipher Prostate Cancer Classifier scores were elevated in 3 'favorable' cases and low in 60 'unfavorable' cases. Elevated Decipher Prostate Cancer Classifier scores were significantly associated with biochemical relapse (hazard ratio [HR]=1.36; 95% CI, 1.09-1.71 per 10% increase; p=0.007) and metastasis (HR=2.05; 95% CI, 1.24-4.24; p=0.004). The Decipher Prostate Cancer Classifier predicted biochemical failure at 5 years (AUC=0.78; 95% CI, 0.59-0.91), and the combined NCCN + Decipher Prostate Cancer Classifier scores model significantly outperformed the NCCN alone model for predicting early-onset metastasis (AUC for 5-year metastasis of 0.89 versus 0.86 [Decipher Prostate Cancer Classifier] versus 0.54 [NCCN alone]). Prospective study of the Decipher Prostate Cancer Classifier's role in predicting disease recurrence in intermediate-risk prostate cancer previously treated with dose-escalated image guided radiation therapy alone is warranted.

In 2020, Marascio and colleagues published outcomes from two prospective registries of individuals with prostate cancer treated between 2014 and 2019 with the aim of determining the impact of Decipher tumor testing on management of prostate cancer post prostatectomy. The clinical utility cohort (n=2002) measured the change in treatment decision-making, captured by pre- and post-Decipher tumor testing treatment recommendations. The substantially smaller clinical benefit cohort (n=102) examined differences in the primary endpoint of early biochemical recovery (BCR) from a single academic institution. BCR was chosen as an endpoint due to its recently identified potential as a surrogate endpoint for distant metastasis and prostate cancer-specific mortality and overall survival. In the clinical utility cohort, Decipher tumor testing changed recommendations for 39% of study participants. In the clinical benefit cohort, 2-year cumulative incidence of PSA recurrence was 3% for those that followed treatment recommendations compared with 22% for those that did not (p=0.004). Authors conclude that the use of Decipher tumor testing substantially altered treatment decision-making, based on the clinical utility cohort, and impacted clinically relevant outcomes at 2-years post prostatectomy, based on the clinical benefit cohort. There is a lack of evidence demonstrating that changed decision-making impacts clinically relevant health outcomes. The likelihood of study bias confounding clinical outcomes in individuals who did not adhere to urologists' recommendations is high. Further study is warranted in a larger, randomized clinical trial demonstrating clinical benefit of Decipher tumor testing commensurate to generally accepted standards of medical practice.

In 2020, Jairath conducted a systematic review and meta-analysis of the available evidence supporting the clinical utility of the Decipher genomic classifier. In total, 42 studies comprised of 30, 407 study participants were included. The Decipher performance data available included localized, post-prostatectomy, nonmetastatic castration-resistant, and metastatic hormone-sensitive prostate cancer retrieved from retrospective studies (n=12,141), prospective registries (n=17,053), and prospective and post hoc randomized trials (n=1213). Authors reported, that from data in 32 studies (n=12,600), the Decipher was independently prognostic for all study endpoints (adverse pathology, biochemical failure, metastasis, and cancer-specific and overall survival) and its use impacted decision-making relative to SOC in 24 studies (n=8543). This meta-analysis combined data from registries, clinical trials underway,

and conference abstracts, in addition to published, peer-reviewed literature. While the conglomerate data appear promising, synthesized data selected from published, peer-reviewed literature would provide a more scientifically rigorous representation of the data, to date, regarding the Decipher's clinical utility and impact on net health outcomes in the prostate cancer setting. The Oncotype DX Genomic Prostate Score is a real time polymerase chain reaction (RT-PCR) assay designed for analysis of prostate core needle biopsies. The assay measures the expression of multiple cancer-related genes which are algorithmically combined to calculate a GPS. It has been investigated as a predictor for risk of recurrence, prostate cancer death, and especially adverse pathology at radical prostatectomy (Bostrom, 2015).

Knezevic and colleagues (2013) studied the analytical performance of the Oncotype DX Genomic Prostate Score. Fixed paraffin-embedded (FPE) needle biopsy samples and FPE prostate cancer samples from radical prostatectomies were obtained and RNA was quantified. The lowest quartile of RNA yields from prostate needle biopsies (six 5 µm sections) was between 19 and 34 ng. Amplification efficiencies, analytical sensitivity, and accuracy of gene assays were measured by diluting RNA samples and analyzing features of the linear regression between RNA expression. Gene assays measured expression over a wide range of inputs (from as low as 0.005 ng to 320 ng). Analytical accuracy had average biases at qPCR inputs representative of samples < 9.7% across all assays while amplification efficiencies were within ± 6% of the median. Assessments of reproducibility and precision were completed by testing 10 prostate cancer RNA samples over multiple instruments, reagent lots, operators, days (precision), and RNA input levels (reproducibility) using parameterized linear mixed models. The standard deviations for analytical precision and reproducibility were 1.86 and 2.11 GPS units (100-unit scale) respectively. The authors concluded that the Oncotype DX Genomic Prostate Score complements traditional clinical and diagnostic features and assists in the discrimination of indolent prostate cancer from aggressive prostate cancer.

In 2014, Klein and colleagues evaluated the GPS for its ability to predict high-grade or high-stage prostate cancer at diagnosis. Gene expression was quantified by reverse transcription-polymerase chain reaction for three studies: a prostatectomy study (n=441), a biopsy study (n=167) and a prospective clinical validation study (n=395). A total of 732 candidate genes were analyzed. Of these, 288 (39%) were reported as being able to predict clinical recurrence and 198 (27%) were predictive of aggressive disease, after adjustments were made. Multiple study limitations reported by the authors were:

- The prostatectomy study analyzed genes by polymerase chain reaction and did not use microarray or next-generation sequencing for a comprehensive expression analysis.
- Localized prostate cancer specimens were the focus to identify genes, associated with aggressive diseases, instead of metastatic samples.
- The validation study included men with biopsy Gleason 3+4 prostate cancer, and in the primary analyses, the definition of high grade was restricted to high grade or primary Gleason pattern 4 or any pattern 5.

Cullen and colleagues (2015) evaluated the association of the GPS with recurrence of prostate cancer after radical prostatectomy and adverse pathology at surgery. A total of 431 biopsies obtained from men treated for NCCN very low-, low-, or intermediate-risk prostate cancer were tested to validate the association. GPS results were obtained in 402 cases (93%). Of these, 62 (15%) men had biochemical recurrence, 5 developed metastasis, and 163 had adverse pathology. Median follow-up was 5.2 years. The authors reported that the GPS predicted time to biochemical recurrence and predicted time to metastasis, however, the event rate was low (n=5). Additionally, it was found to be

associated with adverse pathology. Study limitations included a small number of metastatic events and a limited amount of available biopsy tissue.

Eggener and colleagues (2019) published the results of a multicenter, prospective study that evaluated the GPS as a predictor of adverse pathology in individuals who elected radical prostatectomy (primary outcome). The study enrolled 1200 individuals and of those who enrolled, 114 met inclusion criteria. Participant inclusion criteria consisted of individuals with NCCN very low-, low-, and favorable intermediate-risk prostate cancer who used the GPS results in treatment management decisions, elected radical prostatectomy, and did not have any missing data for evaluation of the primary outcome. A total of 59 physicians from 19 centers who practiced at a center with experience in active surveillance (AS) and annually managed at least 25 newly diagnosed prostate cancer individuals with NCCN very low-, low-, or intermediate-risk disease were chosen to participate in the study. Of the 114 individuals who met inclusion criteria, only 40 (35%) had adverse pathology. Univariable analysis showed the GPS was a significant predictor of adverse pathology (odds ratio per 20 GPS units [OR/20 units]: 2.2; 95% CI, 1.2-4.1; p=0.008). Other variables that resulted in significant prediction of adverse pathology were the biopsy Gleason score (OR: 3.2; 95% CI, 1.2-4.1; p=0.004) and the NCCN Intermediate vs very low risk group (OR: 6.6; 95% CI, 1.1-125.9; p=0.032). The perceived value of the GPS test on physician and participant treatment decisions was also evaluated. "Mean pre-GPS Decisional Conflict Scale score was 27 (95% CI 24-31), which improved significantly after GPS testing to 14 (95% CI 11-17) (p<0.001)" (Eggener, 2019). There are several limitations to this study. Physicians included in the study varied in prostate cancer decision making due to no decision making training or protocol being implemented. Also, biopsy and prostatectomy specimens went through a local review process that did not include central review, which can cause interobserver variability in grading and staging. Furthermore, this was a nonrandomized study with no comparator group.

Other investigators have developed and evaluated new gene expression signatures as predictive tools (Sinnott, 2017; Zhao, 2016). The results suggest the new gene expression signatures provide prognostic information, including risk of dying from prostate cancer and postoperative radiotherapy outcomes; however, the study designs are retrospective, clinical utility is not validated, and the investigators conclude the new gene expression signatures require further evaluation.

Both the American Urological Association (AUA) and NCCN recommend AS for very low-, low-, or intermediate-risk prostate cancer risk groups in the most recent guidelines. While AS is considered the generally accepted standard of medical practice, there have been studies that have investigated AS utilization with and without GPS testing (Canfield, 2018; Eure, 2017; Lynch, 2017). All three studies found AS utilization was higher in groups with GPS testing; however, there were limitations to these studies. Two of the studies used a retrospective design (Canfield, 2018; Lynch, 2017). As the authors note in all three studies, the study definitions of AS may have classified some subjects as receiving AS, but those subjects did not actually receive it. This misclassification may lower the AS utilization with GPS testing reported in the studies.

NCCN guidelines (V1.2023) for prostate cancer include molecular testing as a consideration if life expectancy is greater than or equal to 10 years and criteria for risk groups are met:

- Low
  - T1-T2a AND
  - Gleason ≤6/grade group 1 AND
  - PSA <10ng/mL

- Favorable intermediate
  - T2b-T2c OR
  - Gleason score 3+4=7/grade group 2 OR
  - PSA 10-20ng/mL AND
  - Percentage of positive biopsy cores <50%

NCCN notes that these recommendations are based on lower-level evidence, including retrospective studies and expert consensus.

In 2020, Leapman conducted a larger cohort study which included 92,218 men from a US commercial health plan to determine adoption rates of tissue-based genomic testing for prostate cancer; the median (interquartile range) age at diagnosis was 60 (56-63) years. Overall, the proportion of men who received genomic testing increased from 0.8% in 2012-2013 to 11.3% in 2017-2018. Modeling identified five distinct regional trajectories of genomic testing adoption. Although less than 1% of each group received tissue-based genomic testing at baseline (2012-2013), group 1 (lowest adoption) increased to 4.0% over the course of investigation, while groups 2 (7.8%), 3 (14.6%), and 4 (17.3%) experienced modest growth and group 5 (highest adoption) use increased to 33.8% by study-end, 2017-2018. Study investigators concluded, "…the adoption of commercial tissue-based genomic testing for prostate cancer was highly variable in the US at the regional level and may be associated with contextual measures related to socioeconomic status and patterns of prostate cancer care". Despite the wide availability and use of tissue-based genomic testing for prostate cancer, the lack of adoption as part of SOC pathways and guideline recommendations reflects of the lack of prospective study demonstrating improved long-term, clinically relevant health outcomes.

SelectMDx®

The SelectMDx is a novel 2-gene, urine-based, non-invasive test that targets mRNA overexpressed in aggressive forms of prostate cancer. In administering the test, mRNA levels are measured following digital rectal exam (DRE), and the results are combined with clinical risk factors to determine individualized risk of Gleason score 7 or high-grade prostate cancer histopathology at a subsequent biopsy. The 2-gene test was originally clinically validated for the detection of Gleason score 7 or greater prostate cancer in a prospective multicenter cohort of 386 subjects, including 342 (89%) undergoing initial biopsy and 44 (11%) with prior prostate cancer negative biopsies (Van Neste, 2016).

In 2019, Haese and colleagues sought to optimize and further validate the clinical model for SelectMDx testing in men with serum PSA less than 10 ng/ml who were undergoing initial prostate biopsy. Urine samples were collected from 1955 men across the countries (The Netherlands, France and Germany) prior to an initial prostate biopsy. Enrolled participants were subsequently divided into training (n=805) and validation (n=715) cohorts. SelectMDx results from the validation cohort were then compared with the Prostate Cancer Prevention Trial Risk Calculator (PCPTRC), version 2.0 results. The optimal clinical model included the urinary 2-gene (HOXC6 and DLX1) mRNA levels, age, DRE and PSA density (serum PSA/prostate volume). In the 715 validation cohort subjects with PSA less than 10 ng/ml, the AUC was 0.82 with 89% sensitivity, 53% specificity and 95% negative predictive value (NPV). The PCPTRC AUC was 0.70. Clinical utility and demonstration of net health outcomes remains to be established.

Genomic Biomarker Tests:

Gene hypermethylation for diagnosis and prognosis

The association of a gene hypermethylation marker, GSTP1, with prostate cancer has been investigated. Several studies of GSTP1 hypermethylation using tissue samples reported significant results for identifying prostate cancer with a sensitivity of 92%, a percent specificity of 85%, and an area under curve (AUC) of about 0.9 (Eilers, 2007; Ellinger, 2008). Trock and colleagues (2011) reported on a small (86 subjects) diagnostic exploratory cohort study showing hypermethylation of adenomatous polyposis coli (APC) was associated with a high sensitivity and high specificity for cancer on repeat biopsy. The authors indicated that the potential of APC methylation to reduce unnecessary repeat prostate biopsies needs validation in a larger prospective study. In addition, there was no evidence suggesting how this test should be used to change management. Two other studies did not find significant associations between GSTP1 methylation and prostate cancer recurrence (Henrique, 2007; Woodson, 2006).

The Confirm MDx (MDx Health, Irvine, CA) is a multiplex polymerase chain reaction (PCR) assay measuring DNA methylation of three biomarkers associated with prostate cancer: GSTP1, APC and RASSF1. It is used to predict the results of repeat prostate biopsy after an initial negative biopsy. Van Neste and colleagues (2012) explored the use of an epigenetic, multiplex polymerase approach to GSTP1, APC and RASSF1 testing and compared it to individual, singleplex assays of the biomarkers. The authors found that the multiplex assay approach was similar to the individual singleplex approach, but had the advantage of use with smaller tissue volumes and therefore could be used on older tissues with small quantities and poorer quality DNA.

PCA3 for disease detection

PCA3, a prostate cancer antigen gene, has been investigated as a possible additional tool in the detection of prostate cancer. The PCA3 gene (formerly known as DD3) is markedly upregulated in cancerous prostate cells and is not expressed, or expressed only at very low levels in normal or hyperplastic prostatic tissue. The identification of the PCA gene relies on detection of the overexpression of the associated messenger ribonucleic acid (mRNA) in blood or urine after a digital rectal examination.

A prospective, multicenter European study (Haese, 2008) evaluated the clinical utility of PCA3 urine assay in men scheduled for repeat prostate biopsies. All of the participants had previously had one or two negative prostate biopsies. Urine samples were collected after a digital rectal exam (DRE) and prior to the biopsy procedure. Simultaneously, blood samples were obtained and utilized to determine total and free PSA levels. Using a PCA3 assay, the urine samples were processed to quantify PCA3 and PSA messenger ribonucleic acid (mRNA) concentrations. Sensitivity and specificity were determined by comparing the PCA3 score to the biopsy results. Out of 470 participants, 467 urine samples had sufficient concentrations of both PCA3 and PSA mRNA to calculate the PCA3 score. Conclusive biopsy results were obtained in 463 men out of the 467. A total of 128 men (28%) had cancer diagnosed by the repeat biopsy. Participants with a positive biopsy had statistically significant higher age, higher total PSA, suspicious DRE and a higher mean PCA3 score compared to the participants with negative biopsy results. While this and other studies found that an optimal PCA3 score of 35 would optimize the balance between sensitivity and specificity, using this cutoff score would still result in missing 21% of cancers even though 67% of unnecessary biopsies would have been avoided. Conversely, using a lower cutoff score of 20 would miss only 9% of cancers while avoiding only 44% of unnecessary biopsies. Thus the authors agree that even though the score had

greater diagnostic accuracy than free PSA percentage in this study, further studies are needed to better delineate its role in the diagnosis and management of prostate cancer.

Wang and colleagues (2009) evaluated the ability of the PCA3 with the PSA to detect prostate cancer. From September 2006 to December 2007, urine samples were collected in a urology outpatient clinic following digital rectal exam from 187 men before ultrasound-guided 12-core prostate biopsy. Urine PCA3/PSA mRNA ratio scores were assessed within 1 month and serum PSA within 6 months of biopsy. Overall, 87/187 (46.5%) biopsies were positive for cancer. Sensitivity and specificity of PCA3 score greater than or equal to 35 for positive biopsy were 52.9% and 80.0%; positive and negative predictive values were 69.7% and 66.1%. Study limitations include that study cohorts consisted only of pre-screened individuals undergoing biopsy for an elevated PSA. The authors concluded:

> To date, there is no definitive evidence demonstrating that PCA3 prognosticates for lethal prostate cancer, and in the absence of such evidence, these biomarkers may only contribute to the continued over-diagnosis of prostate cancer.

Roobol and colleagues (2010) investigated the performance characteristics of PCA3 and compared this to the PSA. A total of 721 men between the ages of 63-75 were screened for prostate cancer from September 2007 to February 2009. Both PCA3 scores and serum PSA levels were measured. Men with a PSA greater than or equal to 3.0 ng/ml or a PCA3 score greater than or equal to 10 underwent a DRE, transrectal ultrasounds, and biopsy. It was noted that the correlation between PSA and PCA3 was poor. The authors concluded that the value of PCA3 for improving detection in the low PSA ranges and after previous negative biopsies was hampered by small numbers, is unclear and needs to be further explored.

A meta-analysis by Ruiz-Aragon and Marquez-Pelaez (2010) reviewed 14 studies of PCA3 for use in predicting prostate biopsy results. Sensitivity of testing ranged from 46.9% to 82.3% and specificity from 56.3% to 89%. Global results provided a sensitivity of 85% (CI, 84 to 87) and a specificity of 96% (CI, 96 to 97).

Tosian and colleagues (2010) reported on a short-term prospective cohort study evaluating PCA3 in relation to outcomes in an active surveillance program involving 294 subjects. PCA3 did not appear to distinguish subjects with stable disease from those developing more aggressive features.

In an industry sponsored study, Aubin and colleagues (2010) evaluated the PCA3 alone and with covariates as an indicator of concurrent and future prostate biopsy results in men with increased serum prostate specific antigen and previous negative prostate biopsy results. In a sub-study of the placebo arm of the REDUCE trial, a prostate cancer risk reduction study, urine PCA3 scores were obtained before year 2 and year 4 biopsies from subjects in the placebo arm of the trial. The men had moderately increased serum prostate specific antigen results and negative biopsy at baseline. PCA3 scores were measurable from 1072 of 1140 subjects (94% informative rate). PCA3 scores were associated with positive biopsy rate ($p<0.0001$) and correlated with biopsy Gleason score ($p=0.0017$). PCA3 at year 2 was a predictor of year 4 biopsy results (AUC 0.634, $p=0.0002$). Additionally, serum prostate specific antigen and free prostate specific antigen were not found to be predictive ($p=0.3281$ and 0.6782, respectively). The authors concluded that their results confirm that PCA3 can be used in combination with other clinical information to help guide prostate biopsy decisions.

Van Poppel and colleagues (2012) evaluated the relationship between PCA3 and prostate cancer significance in two European multi-centre open-label prospective studies with a total enrollment of 1009 men. The authors reported that the association between the PCA3 score and prostate cancer aggressiveness needs further evaluation.

A prospective, community based clinical trial (Crawford, 2012) evaluated the PCA3 score before any biopsy. Samples were obtained from 1962 men with increased serum prostate specific antigen (greater than 2.5 ng/ml) with or without abnormal digital rectal examination before transrectal prostate needle biopsy from 50 urology practices in the United States. Study samples consisting of urinary PCA3 and biopsies were analyzed by a single laboratory. A total of 1913 urine samples (97.5%) were adequate for PCA3 testing. Of 802 cases diagnosed with prostate cancer, 222 had high grade prostatic intraepithelial neoplasia or atypical small acinar proliferation and were suspicious for cancer, and 889 cases were benign. The traditional PCA3 cutoff of 35 reduced the number of false-positives from 1089 to 249, a 77.1% reduction. However, false negatives increased from 17 to 413. Lowering the PCA3 cutoff to 10 reduced the number of false-positives 35.4% and false-negatives only increased 5.6%. Clinical utility of the PCA3 has yet to be defined and further study is needed.

In 2013, Goode and colleagues evaluated the value of the PCA3 urine assay in predicting prostate cancer. Both PSA and PCA3 levels were taken from 456 men with no known personal history of prostate cancer prior to prostate biopsy. A total of 289 men underwent an initial prostate biopsy and 167 had a repeat prostate biopsy. PSA and PCA3 levels were compared to the prostate biopsy results. Analyzed data demonstrated that PCA3 scores were independent of prostate volume and PSA level. PCA3 scores were higher in men with prostate cancer confirmed by biopsy compared to those with negative biopsy results. In logistic regression, PCA3 showed a higher area under the curve (AUC) than PSA with this difference persisting at examination of the initial biopsy subgroup. However, PCA3 was not as helpful in the repeat biopsy subgroup. The authors stated:

> Further studies are needed to determine the appropriate use of PCA-3 in counseling patients at higher risk of prostate cancer. The use of PCA3 in men with previous negative biopsies is another area of interest. More studies are also needed to determine the influence of pre-neoplastic conditions on PCA-3 score and the correlation between PCA-3 score and cancer aggressiveness and prognosis.

Gittleman and colleagues (2013) evaluated the usefulness of the PROGENSA PCA3 Assay for predicting repeat prostate biopsy outcomes. A total of 466 men scheduled for repeat prostate biopsy who had at least one previous negative biopsy were evaluated at 14 centers in the United States. Prior to transrectal biopsy being performed, blood samples and post-digital rectal exam urine samples were obtained. Urinary PCA3 scores and biopsy outcomes were assessed by logistic regression analysis. Prostate cancer was identified in 21.9% of the men. A PCA3 score cutoff of 25 yielded 77.5% sensitivity, 57.1% specificity, and negative and positive predictive values of 90% and 33.6%, respectively. Multivariable logistic regression indicated that men with a PCA3 score below 25 were 4.58 times less likely to have a positive repeat biopsy than men with a score of 25 or more. The authors concluded that the PCA3 assay supplements serum PSA and other clinical information for more accurately predicting repeat biopsy outcome.

A single center retrospective review (Chevli, 2014) evaluated the predictive value of the PCA3 test. A PCA3 had been obtained from 3073 men prior to initial prostate biopsy sampling of 12 to 14 areas. Data revealed the mean PCA3 was 27.2 and 52.5 respectively for men without and with cancer. Prostate cancer was identified in 1341

(43.6%) men. Upon analysis, PCA3 was found to be significantly associated with prostate cancer and high grade prostate cancer after adjustments were made for prostate specific antigen, free prostate specific antigen, age, family history, abnormal digital rectal examination, prostate volume and body mass index. Using ROC analysis PCA3 outperformed prostate specific antigen in the prediction of prostate cancer but not for high grade prostate cancer. The authors reported that their results suggest that further exploration of the value of PCA3 is warranted.

A validation study of the PCA3 urinary assay (Wei, 2014) enrolled a total of 859 men from 11 centers who were scheduled for a diagnostic prostate biopsy between December 2009 and June 2011. Primary outcomes included a positive predictive value (PPV) of 80% (95% CI, 72% to 86%) in the initial biopsy group, and a NPV of 88% (95% CI, 81% to 93%) in the repeat biopsy group. Limitations of the study included that the findings did not extend to men who had not been prescreened. The authors reported that the addition of PCA3 may decrease morbidity; however, it could also result in some high grade prostate cancers not being detected.

Xue and colleagues (2014) performed a meta-analysis of 13 prospective studies (3245 participants) to evaluate the clinical value of the PCA3 biomarker urine level for the diagnosis of prostate cancer. The pooled sensitivity, specificity, positive likelihood ratio (+LR), negative likelihood ratio (-LR), diagnosis OR and area under the curve (AUC) were 0.62 (95% CI, 0.59-0.65), 0.75 (95% CI, 0.73-0.76), 6.16 (95% CI, 3.39-11.21), 0.50 (95% CI, 0.43-0.59), 5.49 (95% CI, 3.76-8.019) and 0.75 (95% CI, 0.71-0.78), respectively. The authors reported that "pooled data indicated that urine PCA3 test has acceptable sensitivity and specificity in diagnosis of prostate cancer." However, they further noted that the small number of trials and significant heterogeneity across studies made their conclusion conservative.

Cremers and colleagues (2015) evaluated the value of adding the PCA3 urine test to serum PSA in prostate cancer screening for breast cancer early-onset gene (BRCA) mutation carriers. Individuals were enrolled in the IMPACT study, a large international trial on the effectiveness of PSA screening among BRCA mutation carriers. Urinary PCA3 was measured in 191 BRCA1 mutation carriers, 75 BRCA2 mutation carriers, and 308 non-carriers. A total of 23 cases of prostate cancer were diagnosed, 20 cases involved men who had an elevated PSA level in the initial screening round. The authors indicated that there was a lack of evidence demonstrating that PCA3 was a useful additional indicator of prostate biopsies in BRCA mutation carriers because many participants had an elevated PCA3 in the absence of prostate cancer. However, they also indicated that this must be interpreted with caution.

Merola and colleagues (2015) evaluated the clinical utility of the PCA3 test in 407 Italian men with two or more risk factors for prostate cancer and at least a previous negative biopsy. Of the 407 subjects enrolled, 195 were positive for prostate cancer and 114 of them received an accurate staging with evaluation of the Gleason score. In this study, the PCA3 score was correlated to biopsy outcome and the diagnostic and prognostic utility were evaluated. From the 407 biopsies performed after the PCA3 test, 195 (48%) were positive for prostate cancer. The authors reported that their data suggested that the PCA3 test could predict a prostate cancer. However, it was also noted that the choice to enroll only men with a certain risk for prostate cancer or a number of previous biopsies, could drive data towards an easier or less easy association between the result of the PCA3 test and the tumor aggressiveness.

Vlaeminck-Guillem and colleagues (2015) performed a prospective study of all persons referred to a single French urology department between December 2007 and May 2014 for prostate biopsy. A total of 1029 men had a urinary PCA3 test prior to having a prostate biopsy for suspicion of prostate cancer. The median PCA3 score was higher in

those with positive biopsies. At a cutoff of 35, sensitivity was 68%, specificity 71%, positive and negative predictive values 67% and 71%, and 69% accuracy. At a cutoff of 20, approximately half of the ultimately unnecessary biopsies may have been avoided. Of note, the PCA3 score correlated with tumor volume but did not correlate with Gleason score. The authors indicated that a high PCA3 score is not necessarily synonymous with cancer (false positives) and that low or even very low scores are not necessarily synonymous with the absence of cancer (false negatives).

In 2017, Pang and colleagues investigated the predictive value of PCA3-shRNA2 in subjects with and without prostate cancer, whose initial biopsy did not detect cancer. Data and biopsy tissue samples from 2002-2008 were collected on 116 subjects with, and 94 subjects without, an eventual diagnosis of prostate cancer. RNA was extracted from the biopsies. PSA and PCA3-shRNA2 RNA was detected in all samples and PCA3 mRNA in 90% of the samples. When analyzing RNA expression and the eventual diagnosis in each subject, the authors found upregulation of PCA3 (p=0.02) and PCA3-shRNA2 (p=0.2) in subjects diagnosed with prostate cancer when compared to those without a diagnosis. The authors concluded that the significant association of PCA3 with the detection of prostate cancer could help guide decisions on repeat biopsies for subjects whose initial biopsy did not detect cancer. Some study limitations include possible underpowering of the sample size, small sample size, and retrospective data collection.

The 2013 American Urologic Association guidelines for early detection of prostate cancer, which were confirmed in 2018, include the following information concerning PCA3:

> Novel urinary markers (PCA3), and prostate imaging should be considered secondary tests (not primary screening tests) with potential utility for determining the need for a prostate biopsy, but with unproven benefit as primary screening tests. The Panel recognizes that these tests can be used as adjuncts for informing decisions about the need for a prostate biopsy –or repeat biopsy- after PSA screening, but emphasizes the lack of evidence that these tests will increase the ratio of benefit to harm.

NCCN guidelines (V1.2023) for early detection of prostate cancer report that the PCA3 may be considered for men who have had at least one prior negative biopsy and are thought to be at higher risk. Additionally, the panel indicates that the PCA3 is inappropriate to use in the initial biopsy setting.

The 2018 European Association of Urology (EAU) prostate cancer guidelines state that "currently the main indication for the Progensa test is to determine whether repeat biopsy is needed after an initially negative biopsy, but its clinical effectiveness for this purpose is uncertain."

TMPRSS fusion genes for diagnosis and prognosis

TMPRSS2 fusion gene detection has been investigated as a means to identify aggressive disease or to predict disease recurrence. There is conflicting evidence regarding the association of TMPRSS2 fusion gene detection and biochemical recurrence or survival outcomes of prostate cancer (Demichelis, 2007; Fitzgerald, 2008; Kong, 2019; Mehra, 2007; Nam, 2007a; Nam, 2007b; Wang, 2006; Winnes, 2007). Fusion gene structure is complex and variable, making it a difficult assay target (Clark, 2007; Wang, 2006). As a result, assays have not yet been standardized; once they are, larger studies will be needed to determine clinical utility.

One small study (n=74) describes the ability of TMPRSS2-ERG fusion genes to predict prostate cancer screening biopsy outcome, and association with high versus low Gleason scores (Clark, 2008). Fusion gene detection improved on PSA plus DRE for predicting the biopsy result (from AUC 0.645 to 0.823) and for predicting Gleason score greater than 7 (from AUC 0.688 to AUC 0.844). These results need further validation in larger studies.

Tomlins and colleagues (2011) developed a transcription mediated amplification assay to measure TMPRSS2: ERG fusion transcript in parallel with PCA3. Combining results from these two tests and incorporating them into the multivariate Prostate Cancer Prevention Trial risk calculator appeared to improve identification of men with clinically significant cancer by Epstein criteria and high-grade cancer on biopsy. While the study was large (1312 men at multiple centers), it was confounded by the fact that the assay was modified during the course of the study and also by the fact that some evaluations were performed using cross-validation rather than independent validation using independent training and testing sets.

In 2018, Eryilmaz and colleagues published a retrospective study with the aim to investigate the significance of T2E expression in prostate cancer recurrence prediction in subjects diagnosed with atypical small acinar proliferation (ASAP). The sample consisted of 76 biopsy materials obtained from 63 subjects. The investigators found that the presence of T2E transcripts in relation to higher AMACR expression significantly associated with risk for developing prostate cancer (p=0.045). It was concluded that the results need further clinical validation with larger sample sizes and various ethnic groups.

Also in 2018, Song and Chen reported on the results of a meta-analysis that evaluated the predictive value of TMPRSS2-ERG fusion in clinical prostate cancer specimens. A literature search between 2005 and 2017 yielded 240 studies. After screening of inclusion criteria [(1) TMPRSS2-ERG fusion status was identified; (2) all cases involved were verified by pathological confirmation for the diagnosis of prostate cancer; (3) sufficient data were reported to calculate the ORs and the 95% CIs; (4) the level of TMPRSS2-ERG was assessed in prostatic tissues or blood or urine samples] and exclusion criteria [(1) the studies were not reviews, letters, commentaries, erratums, and meta-analysis; (2) data for TMPRSS2-ERG fusion gene were not sufficient for extraction; (3) non-English or non-Chinese; (4) data were obtained from non-human samples or human cell lines; (5) duplicate data], 76 of the 240 articles were included in the meta-analysis. The data showed the following:

> TMPRSS2-ERG fusion was associated with T-stage at diagnosis (T3–4 vs. T1–2 OR: 1.40; 95% CI 1.33–1.48) and metastasis (M1 vs. M0 OR: 1.35; 95% CI 1.02–1.78) but not with biochemical recurrence or prostate cancer-specific mortality. Furthermore, the subgroup analysis found that the TMPRSS2-ERG fusion gene was correlated with Gleason (G) scores, and the fusion was common in prostate cancer with G ≤ 7. Additionally, the meta-analysis demonstrated that the fusion was likely to occur in young patients (> 65 vs. ≤ 65 OR: 0.68; 95% CI 0.52–0.89), in patients with high PSA levels (> 10 vs. ≤ 10 OR: 1.30; 95% CI 1.21–1.38), and in patients with peripheral involvement (positive vs. negative OR: 1.17; 95% CI 1.08–1.28), while not associated with tumor volume. Finally, the subgroup analysis of different fusion types demonstrated that the deletion-type fusion was significantly associated with the malignant degree of prostate cancer (pooled OR: 5.67; 95% CI 2.85–11.28). Moreover, the deletion-type was common in Africa patients, followed by Caucasian patients, and no significant difference was observed in the incidence of different fusion types in the Asian population.

While this meta-analysis resulted in some significant results, the authors did not specify the study designs of the included studies, which could impact the applicability of the results. In addition, the results suggest TMPRSS2-ERG fusion gene might be a predictive marker for prostate cancer; however, the results lacked clinical utility.

Exosome Gene Expression Assay

The ExoDx™ Prostate IntelliScore EPI Test (Exosome Diagnostics, Waltham, MA) also known as the EPI test, is a urine based 3-gene exosome expression assay which intended for individuals over aged 50 with no prior biopsy and a PSA value between 2 and 10 ng/mL. The test, which is independent of all clinical features, is proposed as a diagnostic test to discriminate Grade Group ≥ 2 prostate cancer from Grade Group 1 and benign disease at initial biopsy.

A prospective study by McKiernan and colleagues (2016) evaluated the ExoDx test.. The assay measures "exosomal RNA Ct values of ERG, PCA3 and SAM pointed domain-containing Ets transcription factor (SPDEF)" to derive a urine exosome gene expression assay score. The exosome gene expression assay plus standard of care (SOC) (PSA level, age, race, and family history) was compared to SOC alone for differentiating between Gleason score (GS)7 and GS6 and benign disease on initial biopsy. Using reverse-transcriptase PCR, urine exosome gene expression assays were compared to biopsy outcomes in 499 subjects with PSA levels of 2 to 20 ng/mL. The derived prognostic score was then validated in 1064 subjects. Eligible participants included men free of prostate cancer, 50 years or older, scheduled for an initial or repeated prostate needle biopsy due to suspicious digital rectal examination (DRE) findings and/or PSA levels (limit range, 2.0-20.0 ng/mL). In 255 men (median age 62 years and median PSA level 5.0 ng/mL, and initial biopsy), the urine exosome gene expression assay plus SOC was found to be associated with improved discrimination between GS7 or greater and GS6 and benign disease. Independent validation in 519 subjects' urine exosome gene expression assay plus SOC was reported as superior to SOC. The authors concluded the exosome gene expression assay has the potential to reduce the total number of biopsies performed in men with a suspicion of prostate cancer. Study limitations included a lack of central pathology review and the inability to include the DRE and free PSA as part of the SOC variables.

In 2018, McKiernan and colleagues published a prospective adaptive utility trial consisting of a second validation cohort in the evaluation of ExoDx Prostate (IntelliScore) (EPI) compared to SOC (PSA level, age, race, and family history) for distinguishing Group (GG) ≥2 prostate cancer from GG1 prostate cancer and benign disease on initial biopsy. The authors reported on the first of two phases of this study. Phase I consisted of evaluation of the EPI test, which was used for the development of a clinical implementation plan for phase II. A total of 503 men (14% African American, 70% Caucasian) with age greater than 50 years and PSA 2–10 ng/ml scheduled for initial prostate biopsy were included in the study. The data showed EPI had a significantly higher AUC compared to SOC (0.70 versus 0.62, respectively; p=0.0140), which was comparable to previously reported data (n=519; EPI AUC 0.71; McKiernan, 2016). While the EPI cut-point of 15.6 for predicting GG ≥2 prostate cancer demonstrated an NPV of 89% with a sensitivity of 93% and would have avoided 26% (n=90) of unnecessary prostate biopsies, EPI "missed 11 of 158 (7%) ≥grade group (GG)2 cancers of which seven were ≥GG3" (McKiernan, 2018). The EPI cut-point of 15.6 was used to help develop the clinical implementation plan for phase II. A limitation of this study was a lack of central pathology review and clinical utility.

McKiernan and colleagues (2020) published a prospective clinical validation study evaluating the performance of the EPI in ruling out high-grade prostate cancer in individuals with at least one prior negative biopsy (n=229). Individuals underwent EPI testing prior to undergoing 12-core transrectal ultrasound-guided prostate needle biopsy using a standard template. The NPV and sensitivity were 92% (95%CI, 0.81–0.97) 82%, respectively. The results could have avoided 27% of all unnecessary biopsies. Delayed detection would have occurred in 2.01% of individuals with GG3 disease and 1% of individuals with GG3 or higher. Limitations of the study include a lack of central pathology review and the outdated diagnostic techniques which the individuals underwent prior to EPI testing. The study was done prior to the use of multi-parametric imaging prior to a biopsy.

In 2020, Tutrone and colleagues conducted a blinded, randomized clinical study that enrolled 1094 men. SOC clinical criteria were employed for consideration of prostate biopsy at enrollment. While an EPI test was administered to every study participant, only participants in the "EPI-arm" received results of the test. In the EPI arm (n=458), 93 (20%) study participants received negative EPI scores, 63% of the 93 were recommended to defer biopsy by their urologist and 74% ultimately chose to defer. Of participants with a positive EPI score, 87% were recommended to undergo biopsy, 72% complied with their urologist's recommendation. Overall, in this study, the use of the EPI test results in a 30% higher detection of high-grade prostate cancer relative to the control arm. Investigators estimate that 49% less high-grade prostate cancer diagnoses were missed compared to SOC. Overall, 68% of urologists reported that the EPI test influenced their recommendation for biopsy. The study's primary aim of determining if EPI scores affect decision making was demonstrated. The test's impact on measures of clinical utility, such as the EPI score's effect on net health outcomes, remains to be investigated.

The NCCN CPG for early detection of prostate cancer (V1.2023) notes that biomarkers, including but not limited to ExoDx, may be considered as a method of potentially improving the specificity of detection of high-grade cancer in individuals who may meet the standards for a prostate biopsy or may have had a negative biopsy. These tests are not yet mandated as first-line screening tests to be used in conjunction with PSA testing. EPI testing may have a future role in preventing unnecessary biopsies but published long-term data regarding clinical outcomes is needed.

Other Considerations

The American Society of Clinical Oncology (ASCO) endorsement panel (Chen, 2016) reviewed and endorsed Cancer Care Ontario's guideline on Active Surveillance for the Management of Localized Prostate Cancer. Cancer Care Ontario is a Canadian agency responsible for improving cancer care. ASCO's endorsement of the guideline includes the following recommendations:

- For most patients with low-risk (Gleason score ≤ 6) localized prostate cancer, active surveillance is the recommended disease management strategy.
- Active treatment (radical prostatectomy or radiotherapy) is recommended for most patients with intermediate-risk (Gleason score 7) localized prostate cancer. For select patients with low-volume, intermediate-risk (Gleason 3 + 4 = 7) prostate cancer, active surveillance may be offered.
- The active surveillance protocol should include the following tests:
  - A PSA test every 3-6 months
  - Digital rectal exam at least every year

  - At least a 12-core confirmatory TRUS guided biopsy within 6 to 12 months, and then serial biopsy every 2 to 5 years thereafter or more frequently if clinically warranted. Men with limited life expectancy may transition to watchful waiting and avoid further biopsies.
  - Ancillary radiologic and genomic tests are investigational but may have a role in patients with discordant clinical and/or pathologic findings.
- Those who are reclassified to a higher-risk category (Gleason score ≥ 7) or who have significant increases in tumor volume on subsequent biopsies should be offered active therapy.

The AUA in collaboration with the American Society for Radiation Oncology (ASTRO) and the Society of Urologic Oncology (SUO) (Sanda, 2017) developed guidelines on clinically localized prostate cancer. The guidelines include the following statements:

> Among most low-risk localized prostate cancer patients, tissue based genomic biomarkers have not shown a clear role in the selection of candidates for active surveillance. (Expert Opinion)
>
> Clinicians may consider referral for genetic counseling for patients (and their families) with high-risk localized prostate cancer and a strong family history of specific cancers (e.g., breast, ovarian, pancreatic, other gastrointestinal tumors, lymphoma). (Expert Opinion)
>
> Tissue based genomic biomarkers have not shown a clear role in active surveillance for localized prostate cancer and are not necessary for follow up. (Expert Opinion)

In 2018, ASCO endorsed the AUA/ASTRO/SUO 2017 guideline on clinically localized prostate cancer (Sanda, 2017). This endorsement included the recommendations on genomic biomarkers (Bekelman, 2018).

The ASCO published a guideline in 2020 on molecular biomarkers in localized prostate cancer, which had panel representation from the AUA, College of American Pathologists (CAP), and EAU, and was endorsed by the EAU (Eggener, 2020). The ASCO made the following recommendations:

> Clinical Question 1
> Are there molecular biomarkers to identify patients with prostate cancer who are most likely to benefit from active surveillance?
>
> Recommendation 1.1. Commercially available molecular biomarkers (ie, Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
> Recommendation 1.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).
>
> Clinical Question 2
> Are there molecular biomarkers to diagnose clinically significant prostate cancer?

Recommendation 2.1. Commercially available molecular biomarkers (ie, Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate).
Recommendation 2.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Clinical Question 3
Are there molecular biomarkers to guide the decision of postprostatectomy adjuvant versus salvage radiation?

Recommendation 3.1. The Expert Panel recommends consideration of a commercially available molecular biomarker (eg, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
Recommendation 3.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Clinical Question 4
What are the comparative strengths and weakness of genomics versus magnetic resonance imaging in identifying clinically significant prostate cancer?

Recommendation 4. In men with newly diagnosed prostate cancer eligible for active surveillance, both magnetic resonance imaging and genomics intend to identify clinically significant cancers. The Expert Panel endorses their use only in situations in which the result, when considered with routine clinical factors, is likely to affect management. This may include, for instance, the initial management of men who are potentially eligible for active surveillance, where each of these approaches may provide clinically relevant and actionable information. These tests may provide information independent of routine clinical parameters and independent of one another (Type: Informal consensus; benefits/harms ratio unknown; Evidence quality: Low; Strength of recommendation: Weak).

While this guideline includes the most recent recommendations on molecular biomarkers in localized prostate cancer from the ASCO, the two previously discussed guidelines with a current status of endorsement by the ASCO (Chen, 2016; Bekelman, 2018) contradict the recommendations on molecular biomarkers and their role in AS.

NCCN guidelines (V1.2023) for early detection of prostate cancer include consideration of biomarkers (e.g., ConfirmMDX, MiProstate Score, SelectMDx and PCA3 test,) in the indications for biopsy and the management of

biopsy results recommendations; however, it is noted that biomarkers are not mandated as first-line screening tests in conjunction with serum PSA, and that the results can be complex and should be interpreted with caution.

Summary

At this time, the evidence for gene expression profiling and genomic biomarker tests related to prostate cancer screening, detection, and management does not demonstrate clinical utility. There is a lack of prospective data demonstrating that changes in treatment decisions based on such tests result in improvement in clinically relevant health outcomes such as disease progression, quality of life or overall survival.

Background/Overview

According to the American Cancer Society (ACS) (2020), prostate cancer is the most common form of cancer, other than skin cancer, among men in the United States. It is second only to lung cancer as a cause of cancer-related death among men. In 2022, it is estimated that there will be about 268,490 new cases of prostate cancer diagnosed in the United States and approximately 34,500 deaths from the disease. Screening of prostate cancer generally involves a blood test for a substance in the blood, PSA. Elevated levels of PSA in the blood are known to be associated with the presence of prostate cancer and this test is commonly used in the diagnosis and management of prostate cancer.

The published literature surrounding genomic biomarker tests for the screening, detection and management of prostate cancer initially focused on the technical feasibility of identifying a novel prostate cancer-specific gene, PCA3 gene and its possible function. The PCA3 gene appears to be a non-coding gene, (that is, there is no protein product that can be easily identified with an immunoassay), and thus its identification relies on the detection of the overall expression of the associated mRNA. mRNA is a molecule that results when a cell "reads" a DNA strand. PCA3 testing in clinical practice focuses on the detection of the PCA3-associated mRNA in blood and urine samples following a DRE. PCA3 is therefore a genetic test.

Only PCA3 has been submitted to the U.S. Food and Drug Administration (FDA) for premarket approval. The PROGENSA® PCA3 Assay (Gen-Probe Inc., San Diego, CA) was approved by the FDA on February 15, 2012 through the premarket approval process. According to the FDA, this assay is:

> Indicated for use in conjunction with other patient information to aid in the decision for repeat biopsy in men 50 years of age or older who have had one or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on the current standard of care, before consideration of PROGENSA PCA3 assay results.

The FDA summary of safety and effectiveness for the PROGENSA PCA3 warns of the following potential adverse effects of the device on health:

> The risk associated with the PROGENSA PCA3 Assay is a false assay result (i.e., a false positive or false negative result). A false negative result from the PROGENSA PCA3 Assay may defer necessary follow-up procedures (e.g., delay a follow-up prostate biopsy). The associated risk of delaying clinical action is that the cancer may continue to spread leading to an irreversible adverse

condition. Although the test is indicated for use in men for whom a repeat biopsy would be recommended by a urologist based on current standard of care, a false positive result from the PROGENSA PCA3 Assay may lead to more aggressive follow-up procedures (e.g., increased number of cores taken at a subsequent biopsy), which may expose the patient to increased risk. The PROGENSA PCA3 Assay is intended to be used in conjunction with other clinical information; it is not meant to be used as the sole determinant for follow-up procedures. Therefore, the decision in determining appropriate patient management (e.g., the decision for repeat biopsy) must be based on an assessment of multiple risk indicators and not solely on the PROGENSA PCA3 Assay result.

Other tests included in this document are offered as laboratory-developed tests under the Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. In addition to the PCA3, this group of genomic biomarker tests has now evolved to include, but is not limited to, gene hypermethylation, and TMPRSS fusion genes.

Analyses of gene expression has also been investigated as a potentially clinically useful tool for disease classification, diagnosis, prognosis, and tailoring of treatment to underlying genetic determinants of pharmacologic response. Several commercially available tissue-based assays are available, generally purporting to provide prognostic information, including risk of dying from prostate cancer and postoperative radiotherapy outcomes, in men undergoing a prostate biopsy. Decipher Prostate Cancer Classifier is a whole-transcriptome microarray assay that uses prostate needle biopsy or radical prostatectomy specimens to measure the expression of the 22 genes that produce the 'GC score'. The Prolaris test is designed to assess prostate cancer aggressiveness and is designed to classify the cancer's expression of 31 genes based on a cell cycle progression (CCP) test. The Oncotype DX Genomic Prostate Score is a 17 gene biopsy-based, prognostic test that produces a Genomic Prostate Score (GPS); this genomic assay is designed for men with clinically low-risk or favorable intermediate-risk cancer. A urine-based test is also available. The SelectMDx is a novel 2-gene, urine-based, non-invasive test that targets mRNA overexpressed in aggressive forms of prostate cancer, it was originally investigated for the detection of Gleason score 7 or greater prostate cancer.

Definitions

Exosomes: Small, double-lipid membrane vesicles that are secreted from cells and encapsulate a portion of the parent cell cytoplasm. Exosomes shed into biofluids, including blood and urine.

Fusion gene: A hybrid gene created by joining portions of two different genes.

Gene expression profiling: Simultaneous measurement of the activity of multiple genes with the end-goal of establishing a global picture of cellular function.

Genomic biomarker testing: A type of test that is used to determine the presence or absence of a specific biomarker that is associated with a gene(s), genetic function or gene expression.

Messenger ribonucleic acid (mRNA): A molecule that results when a cell "reads" a DNA strand.

Methylation: The attachment of methyl groups to DNA at cytosine bases; correlated with reduced transcription of the gene and thought to be the principal mechanism in X-chromosome inactivation and imprinting.

Screening: The testing of persons, in either the general population or those at high risk, for specific diseases or conditions.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
81313	*PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen])* ratio (eg, prostate cancer)
81479	Unlisted molecular pathology procedure [when specified as gene expression tests such as gene hypermethylation tests or TMPRSS fusion gene tests]
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score Prolaris, Myriad Genetic Laboratories, Inc.
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score Decipher® Prostate, Decipher® Biosciences
81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (*GSTP1*, *APC*, *RASSF1*), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy ConfirmMDx® for Prostate Cancer, MDxHealth, Inc.
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as a prostate cancer gene expression or hypermethylation test]
0011M	Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and urine, algorithms to predict high-grade prostate cancer risk NeoLAB™ Prostate Liquid Biopsy, NeoGenomics Laboratories
0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score ExosomeDx® Prostate (IntelliScore), Exosome Diagnostics, Inc, Exosome Diagnostics, Inc
0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue,

	algorithm reported as a risk score Oncotype DX Genomic Prostate Score, Genomic Health, Inc, Genomic Health, Inc.
0053U	Oncology (prostate cancer), FISH analysis of 4 genes (*ASAP1*, *HDAC9*, *CHD1* and *PTEN*), needle biopsy specimen, algorithm reported as probability of higher tumor grade Prostate Cancer Risk Panel, Mayo Clinic, Laboratory Developed Test
0113U	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score MiPS (Mi-Prostate Score), MLabs, MLabs
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, MDxHealth®, Inc, MDxHealth®, Inc

ICD-10 Diagnosis

All diagnoses

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	02/16/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Rationale and References sections updated.
	09/28/2022	Updated Coding section with 10/01/2022 CPT changes; added 0339U.
Reviewed	02/17/2022	MPTAC review. Rationale, Background, References and Websites sections updated.
Revised	02/11/2021	MPTAC review. Revised Title and Scope to clarify the policy addresses gene expression and genomic biomarker testing only. Clarified INV/NMN criteria

		applies to gene expression and genomic biomarker testing. Updated Rationale, Background/Overview, Coding, References, Websites, and Index sections.
Reviewed	02/20/2020	MPTAC review. Rationale, Background, References, Websites, and Index sections updated.
	12/31/2019	Updated Coding section with 01/01/2020 CPT changes; added 81542.
	10/01/2019	Updated Coding section with 10/01/2019 CPT changes; added 0113U.
Reviewed	03/21/2019	MPTAC review.
Reviewed	03/20/2019	Hematology/Oncology Subcommittee review. Rationale, Background, References, and Websites sections updated.
	12/27/2018	Updated Coding section with 01/01/2019 CPT changes to 0011M descriptor.
Reviewed	05/03/2018	MPTAC review.
Reviewed	05/02/2018	Hematology/Oncology Subcommittee review. Rationale, References, and Websites sections updated. Updated Coding section with 07/01/2018 CPT changes; added 0047U, 0053U.
	02/21/2018	Updated Coding section; added CPT code 0011M.
	12/27/2017	The document header wording updated from "Current Effective Date" to "Publish Date." Coding section updated with 01/01/2018 CPT changes; added codes 81541 and 81551.
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Reviewed	05/03/2017	Hematology/Oncology Subcommittee review. Description, Rationale, Definitions, Index and References sections updated. Updated Coding section with 05/01/2017 CPT changes.
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Reviewed	11/02/2016	Hematology/Oncology Subcommittee review. Rationale, Background and Reference sections updated.
Reviewed	11/05/2015	MPTAC review.
Reviewed	11/04/2015	Hematology/Oncology Subcommittee review. Rationale and Reference sections updated. Updated Coding section with 01/01/2016 HCPCS changes; removed S3721 deleted 12/31/2015; also removed ICD-9 codes.
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Reviewed	05/15/2014	MPTAC review.
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Reviewed	05/08/2013	Hematology/Oncology Subcommittee review. Rationale, Background, Reference and Index sections updated.
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	04/01/2012	Updated Coding section with 04/01/2012 HCPCS changes.

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Reviewed	5/13/2010	MPTAC review.
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Reviewed	05/21/2009	MPTAC review.
Reviewed	05/20/2009	Hematology/Oncology Subcommittee review. Rationale, references and websites updated.
Reviewed	05/15/2008	MPTAC review.
Reviewed	05/14/2008	Hematology/Oncology Subcommittee review. Rationale and background updated. References and websites updated.
	02/21/2008	The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Reviewed	05/17/2007	MPTAC review.
Reviewed	05/16/2007	Hematology/Oncology Subcommittee review. References updated.
Reviewed	03/08/2007	MPTAC review. Classification changed from LAB to GENE.
Reviewed	06/08/2006	MPTAC review. Rationale and references updated.
Reviewed	06/07/2006	Hematology/Oncology Subcommittee review.
	11/21/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Revised	07/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	**Last Review Date**	**Document Number**	**Title**
Anthem, Inc.	07/28/2004	LAB.00010	Gene-Based Tests for Screening, Detection, or Management of Prostate Cancer
WellPoint Health Networks, Inc.	12/02/2004	2.11.20	Gene-Based Tests for Screening, Detection and/or Management of Prostate Cancer