Gene-Based Tests for Screening, Detection, and Management of Prostate or Bladder Cancer

Effective: July 1, 2025

Next Review: September 2025
Last Review: June 2025

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

There are a variety of gene-based biomarkers that have been associated with prostate cancer or bladder cancer. These tests have the potential to improve the accuracy of risk prediction, diagnosis, staging, or cancer prognosis.

MEDICAL POLICY CRITERIA

Note: This policy does **not** address tumor tissue or liquid biopsy testing for targeted cancer therapy selection (see Cross References).

Genetic tests for the screening, detection, and management of prostate cancer or bladder cancer are considered **investigational,** including but not limited to the following:

A. Single-nucleotide variants (SNVs) for risk assessment;
B. PCA3 for disease diagnosis;
C. TMPRSS fusion genes for diagnosis and prognosis;
D. Gene hypermethylation for diagnosis and prognosis;
E. Mitochondrial DNA variant testing for diagnosis;

F. Gene expression analysis, including but not limited to Prolaris®, Oncotype DX® Genomic Prostate Score (GPS), SelectMDx™, Decipher® Prostate (Biopsy and RP), and Decipher® Bladder.

G. Exosomal RNA analysis, including but not limited to ExoDx™ and miR-Sentinel™.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Gene Expression-Based Assays for Cancers of Unknown Primary, Genetic Testing, Policy No. 15
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Expanded Molecular Testing of Cancers to Select Targeted Therapies, Genetic Testing, Policy No. 83
4. Circulating Tumor DNA and Circulating Tumor Cells for Management (Liquid Biopsy) of Solid Tumor Cancers, Laboratory, Policy No. 46
5. Protein Biomarkers for Screening, Detection, and/or Management of Prostate Cancer, Laboratory, Policy No. 69
6. Investigational Gene Expression, Biomarker, and Multianalyte Testing, Laboratory, Policy No. 77

BACKGROUND

Prostate cancer and bladder cancer are complex, heterogeneous diseases. Some forms may be indolent and never progress to cause harm, while other metastasize quickly. Current challenges in cancer care are assessing risk; providing early and accurate detection; monitoring low-risk patients undergoing surveillance only; predicting recurrence after initial treatment; detecting recurrence after treatment; and assessing efficacy of treatment for advanced disease.

In response to the need for better biomarkers for risk assessment, diagnosis, and prognosis, a variety of exploratory research is ongoing. Some products of this work have already been translated or are in the process of being translated into commercially available tests, including:

- Single-nucleotide variants (SNVs) for risk assessment
- The Gen-Probe PROGENSA® *PCA3* Assay (*PCA3*) for diagnosis
- TMPRSS fusion genes for diagnosis and prognosis
- Gene hypermethylation for diagnosis and prognosis
- Mitochondrial DNA variant testing for diagnosis
- Gene expression analysis for risk assessment and diagnosis, including Prolaris®, Oncotype DX® Genomic Prostate Score (GPS), Decipher® Prostate, and Decipher® Bladder
- Exosomal RNA-based urine assays ExoDx™ Prostate (Intelliscore) and miR Sentinel™ (miR Sciences) for diagnosis

While studies using these tests generate information that may help elucidate the biologic mechanisms of prostate or bladder cancer and eventually help design treatments, the above-mentioned tests are currently in a developmental phase, without evidence of clinical utility for diagnosis, prognosis, or risk assessment. Many of the tests listed above have not been submitted to the U.S. Food and Drug Administration (FDA) for marketing clearance but, if available, are offered as laboratory-developed tests by Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories.

SNV testing as part of genome-scanning tests with risk assessment for prostate cancer is offered by a variety of laboratories including Navigenics, LabCorp (23andme), and ARUP (deCode) as laboratory-developed tests. The *PCA3* test is offered in the U.S. by reference laboratories including ARUP, Mayo Medical Laboratories, and LabCorp. The reagents used in testing are developed by Gen-Probe. A test for hypermethylation of GSTP1 was available from LabCorp ("Glutathione S-transferase Gene [GSTP1, pi-class] Methylation Assay"); but as of January 2015, this test is no longer offered.

ConfirmMDx is offered from MDxHealth. The tissue-based DNA methylation multigene assay aims to improve stratification of men being considered for repeat prostate biopsy. Hypermethylation of *GSTP1*, *APC*, and *RASSF1* are assessed in core biopsy samples.

SelectMDx™ for Prostate Cancer is also offered from MdxHealth. The reverse transcription PCR (RT-PCR) assay is performed on post-DRE (digital rectal examination), first-void urine specimens 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.
Regulatory Status

One mitochondrial DNA test, Mitomics (Broomfield, CO), is currently available. Mitomics offers the Prostate Core Mitomics Test which measures mitochondrial DNA variants in a negative prostate biopsy to determine whether a patient should undergo repeat biopsy. The test is performed on the initial negative prostate biopsy tissue.

The PROGENSA® *PCA3* Assay was approved by the FDA on February 15, 2012 through the premarket approval process. According to the approval granted by the FDA:[1]

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

The Prolaris®, Oncotype DX® Genomic Prostate Score (GPS), and Decipher® gene expression profiling tests are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In May 2024, the FDA issued a final rule to help ensure the safety and effectiveness of laboratory developed tests (LDTs).[2] FDA argued that many tests need more FDA oversight than the regulatory requirements of CLIA. CLIA standards relate to laboratory operations, but do not address inaccuracies or unreliability of specific tests. Prolaris® is among the 20 case studies in the document cited as needing FDA oversight. The document asserted that patients are potentially receiving inappropriate prostate cancer care because there is no evidence that results from the test meaningfully improve clinical outcomes.

The other tests mentioned in this policy, if available, are offered as laboratory-developed tests under the Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[3] is used to describe variants found

in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance

In general, the evidence for genetic tests related to prostate cancer screening, detection, and management addresses either preliminary clinical associations between genetic tests and disease states or, in some cases, the clinical validity of these tests i.e., the association of the test result with outcomes of interest, expressed in terms of clinical performance characteristics such as sensitivity, specificity, predictive value, and comparisons to current standards using receiver-operating curve (ROC) analysis and/or logistic regression. There is no published evidence demonstrating clinical utility (i.e., a test will change treatment decisions and improve patient important outcomes).

GENE-BASED TESTS IN GENERAL

A 2009 BlueCross BlueShield Association (BCBSA) TEC Special report of recently published studies on gene-based tests (SNVs, *PCA3*, TMPRSS, gene panels, and gene hypermethylation) for prostate cancer risk assessment and diagnosis concluded that, in general, research on these tests is still in a "developmental phase, currently without evidence of clinical utility."[4] This policy was initially based on a 2013 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment which was updated in January 2015 with a literature review through September 30, 2014.[5 6] Full-length publications were sought that described the analytic validity (technical performance), clinical validity (prognostic accuracy), and clinical utility (accurately identifying men experiencing improved health outcomes by avoiding treatment or undergoing more appropriate therapies) of Prolaris, Oncotype DX® GPS, and Decipher® gene expression profiling. The Blue Cross Blue Shield Association Medical Advisory Panel also reviewed the evidence in September 2017.

SINGLE-NUCLEOTIDE VARIANTS (SNVS) FOR PROSTATE CANCER RISK ASSESSMENT AND PROGNOSIS

There have been numerous large observational correlational studies focusing on the association of many different SNVs with prostate cancer, an example of which includes the study by Lindstrom of 10,501 cases of prostate cancer and 10,831 controls, which identified 36 SNVs showing association with prostate cancer risk including two (rs2735893 and rs266849) showing differential association with Gleason grade. Per allele odds ratios ranged from 1.07 to 1.44.[7]

Because the SNVs individually provide relatively modest incremental information on both the occurrence of cancer and its behavior, investigators have begun to explore use of algorithms incorporating information from multiple SNVs to increase the clinical value of testing. Several such recent studies focused on the development of testing algorithms incorporating SNVs.[8-11]

Systematic Reviews

A systematic review of multigene panels for prostate cancer risk assessment was published by Little (2016).[12] The authors included 21 studies that evaluated 18 individual panels. All studies were focused on clinical validity, moderate risk of bias, and had poor discriminative ability for

predicting prostate cancer risk and/or distinguishing between aggressive and latent cancers. The authors noted that the current evidence is insufficient to assess analytic validity, and that "at best the panels assessed would add a small and clinically unimportant improvement" to current factors used for risk stratification, like age and family history. Additionally, they found no evidence on the clinical utility of these panels.

A 2012 AHRQ report on multigene panels in prostate cancer risk assessment, also by Little, reviewed the literature on SNV panel tests for assessing risk of prostate cancer.[13] All of the studies included in the review had poor discriminative ability for predicting risk of prostate cancer, had moderate risk of bias, and none of the panels had been evaluated in routine clinical settings. The conclusions of the review were that the evidence on currently available SNV panels does not permit meaningful assessment of analytic validity, the limited evidence on clinical validity is insufficient to conclude that SNV panels would perform adequately as a screening test and that there is no evidence available on the clinical utility of current panels.

Ishaak (2011) reviewed 11 replication studies involving 30 SNVs (19 in men of African descent and 10 in men with familial prostate cancer).[14] Odds ratios were positively associated with prostate cancer, although the magnitude of association was generally small (range 1.11 to 2.63).

Amin Al Olama (2013) conducted a meta-analysis of four GWASs including 5,953 cases of aggressive prostate cancer (Pca) and 11,463 controls.[15] Authors computed association tests for approximately 2.6 million SNVs and followed up the most significant SNVs by genotyping 49,121 samples in 29 studies through the international PRACTICAL and BPC3 consortia. The authors confirmed the association of a Pca susceptibility locus, rs11672691 on chromosome 19, but also showed an association with aggressive Pca (odds ratio [OR] 1.12, 95% confidence interval [CI] 1.03 to 1.21, $p=1.4 \times 10^{-8}$). The authors concluded their report described a genetic variant which is associated with aggressive Pca, and which is a type of Pca associated with a poorer prognosis.

Nonrandomized Studies

A pilot study by Castro (2016) tested the use of a 71-SNV panel in 100 men with a family history of prostate cancer.[16] These men underwent a prostate biopsy regardless of PSA level, and 25 were diagnosed with prostate cancer. Age and PSA level were significantly associated with a cancer diagnosis, but the SNV risk score was not. While this study might not have been adequately powered to detect such an association, there was a clear relationship seen for age and PSA level (p=0.00004 and 0.00037, respectively).

Kader (2012) evaluated a panel of 33 SNVs associated with prostate cancer in 1,654 men.[17] Genetic score was a significant ($p<0.001$) independent predictor of prostate cancer (OR 1.72, 95% CI 1.44 to 2.09) after adjustment for clinical variables and family history. Addition of genetic markers to the classification of prostate cancer risk resulted in 33% of men reclassified into a different risk quartile. Approximately half of these (n=267) were downgraded to a lower risk quartile and the other half (n=265) were upgraded into a higher risk quartile. The net reclassification benefit was 10% (p=0.002). The authors concluded that with the additional information of genetic score the same number of cancers could be detected by using 15% fewer biopsies. However, this study includes a limited sample size and there is no clear indication of how clinical management changed when patients were reclassified into lower risk groups.

Ren (2013) calculated genetic scores for various combinations of 29 Pca risk-associated SNVs in 667 consecutive patients that underwent prostate biopsy.[18] Performance of these genetic scores for discriminating prostate biopsy outcomes were compared using the area under a receiver operating characteristic curve (AUC). The discriminative performance of genetic score derived from a panel of all 29 SNVs (24 previous and five new) was similar to that derived from the 24 previously established SNVs, the AUCs of which were 0.60 and 0.61, respectively (p=0.72). Authors concluded that genetic score based on Pca risk-associated SNVs implicated to date is a significant predictor of biopsy outcome.

Tsuchiya (2013) identified 14 SNVs in six genes (*XRCC4*, *PMS1*, *GATA3*, *IL13*, *CASP8*, and *IGF1*) that were statistically associated with cancer-specific survival.[19] Using a subset of six SNVs, three subgroups of men with prostate cancer were defined by the number of SNV's present (0 to 1, 2 to 3, or 4 to 6). Median cancer-specific survival in these subgroups was 13.3, 7.0, and 3.8 years, respectively (log-rank test, p<0.001).

Section Summary

Numerous studies have demonstrated the association of many gene panels and SNVs with prostate cancer. These studies, in early stages of development, have shown a modest degree of association with future risk for prostate cancer. The clinical utility of these tests is uncertain; there is no evidence that information obtained from gene panels or SNV testing can be used to change clinical management in ways that will improve outcomes.

PCA3 FOR PROSTATE CANCER DIAGNOSIS

PCA3 is overexpressed in prostate cancer and *PCA3* mRNA can be detected in urine samples collected after prostate massage. When normalized using PSA to account for the amount of prostate cells released into the urine (*PCA3* Score), the test has been proposed for use in discriminating between patients with eventual benign findings on (first or second) biopsies from those with malignant biopsy results. In particular, the test may be especially helpful at identifying patients with elevated PSA levels but negative first biopsy results who need a follow-up biopsy.

Systematic Reviews

A meta-analysis by Lee (2020) compared *PCA3* in urine or prostatic fluid to prostate biopsy results using data from 54 case-control and cohort studies.[20] Of the 17.575 total patients, 4,034 had a diagnosis of prostate cancer. Using a *PCA3* cutoff of 35, the pooled sensitivity and specificity were 0.71 (95% CI 0.67 to 0.74) and 0.68 (95% CI 0.63 to 0.74), respectively. Study heterogeneity, I^2, was 81.1 for sensitivity and 96.4 for specificity. The AUC was 0.75 (95% CI 0.71 to 0.79).

Qin (2020) published a meta-analysis on the diagnostic accuracy of *PCA3* measurement that included 65 retrospective case-control studies published between 2003 and 2018.[21] There were a total of 8,139 cases and 14,116 controls. Of these, 22,255 had a *PCA3* test, including 5,065 cases. All but two of the studies used urine levels of *PCA3*. The reported pooled sensitivity and specificity were 0.68 (95% CI 0.64 to 0.72) and 0.72 (95% CI 0.68 to 0.75), respectively, and the AUC was 0.76 (95% CI 0.72 to 0.79), but it was not clear what cutoff values were used for these calculations.

A systematic review and meta-analysis by Rodríguez (2020) focused on urine *PCA3* measurement in patients that had not yet undergone prostate biopsy.[22] Nine studies met the

inclusion criteria and of these, five that used 35 as a cutoff value were included in the meta-analysis. The pooled sensitivity was 0.69 (95% CI 0.61 to 0.75, I^2= 0%), and the pooled specificity was 0.65 (95% CI 0.55 to 0.73, I^2= 0%). The AUC was 0.73 (95% CI 0.67 to 0.80). The authors noted that the bias assessment identified an unclear risk of bias related to study flow and timing for most studies.

Cui (2016) reported on results of a systematic review that searched PubMed and EMBASE for case-control or cohort studies of the PROGENSA® PCA3 test.[23] Quality was assessed using the QUADAS tool. Pooled estimates were calculated using random-effects models and summarized ROCs when evidence of threshold effect was detected. The review included 46 studies with over 12,000 men. The quality of the selected studies was rated as moderate to high. The most common *PCA3* cutoff for categorizing low and high risk was 35; 25 studies had a *PCA3* cutoff of 35. Most were performed in the United States and Europe; five were conducted in Asia. The estimates of AUC were lower for studies including men having repeated (0.68, 95% CI 0.67 to 0.70) vs initial (0.80, 95% CI 0.78 to 0.82) biopsies. AUC values were 0.74 (95% CI 0.73 to 0.76) for studies with a cutoff value of 35 and 0.77 (95% CI 0.75 to 0.79) for studies with a cutoff value not equal to 35, although the group with varying cutoff (≠35) had a greater range and more variable performance estimates

Nicholson (2015) published a health technology assessment on behalf of the National Health Service in England and Wales.[24] Publications from 2000 to May 2014 were included in a systematic review. Participants were men suspected of having prostate cancer for whom the results of an initial prostate biopsy were negative or equivocal; and a *PCA3* score or phi in combination with existing standard tests, multiparametric magnetic resonance imaging (MRI) and clinical judgement were evaluated for analytic validity and clinical validity. Overall, six studies met inclusion for the analytical validity review; and fifteen studies met inclusion for the clinical validity review. The authors found issues regarding the precision of the *PCA3* assay measurements, and insufficient evidence to identify useful clinical thresholds.

In 2013, the Agency for Healthcare Quality and Research (AHRQ) published a comparative effectiveness review entitled, "*PCA3* Testing for the Diagnosis and Management of Prostate Cancer."[25] Literature was searched and updated through May 15, 2012. Forty-three studies were included; all were rated poor quality. In their conclusion, the authors stated, "For diagnostic accuracy, there was a low strength of evidence that *PCA3* had better diagnostic accuracy for positive biopsy results than [serum] total PSA elevations, but insufficient evidence that this led to improved intermediate or long-term health outcomes." This finding appeared to apply to both initial and repeat biopsies. Evidence was insufficient to assess the use of *PCA3* in treatment decision-making for men with positive biopsy.

In a 2012 systematic review, authors discuss the potential use of genetic markers to better define groups of men at high risk of developing prostate cancer, to improve screening techniques, discriminate indolent versus aggressive disease, and improve therapeutic strategies in patients with advanced disease.[26] Genetic tests for *PCA3* and *TMPRSS2-ERG* genes were included. Authors concluded that most markers have not been prospectively validated for providing useful prognostic or predictive information or improvement upon clinicopathologic parameters already in use.

A meta-analysis by Ruiz-Aragon (2010) reviewed 14 studies of *PCA3* for use in predicting prostate biopsy results.[27] Sensitivity of testing ranged from 47% to 82% and specificity from 56% to 89%. Global results provided a sensitivity of 85% (CI 84 to 87) and a specificity of 96%

(CI 96 to 97). No publications on how this information affected decision making or either short- of long-term outcomes has been published.

Randomized Controlled Trials

In 2014, the National Cancer Institute conducted a prospective trial to validate the diagnostic use of *PCA3* to complement PSA-based detection of prostate cancer.[28] The target population included men who had been screened for prostate cancer, primarily with a PSA test, some of whom had undergone a previous prostate biopsy. The study included 859 men from 11 centers in the United States. The primary study endpoint was the diagnosis of prostate cancer on biopsy and the secondary study endpoint was diagnosis of high-grade prostate cancer, defined as a Gleason score greater than 6. The primary analyses, including *PCA3* thresholds, were determined a priori, and statistical power was based on independent analyses of prevalidation data from similar cohorts. Of the men in the study, 562 were presenting for their initial prostate biopsy. Positive predictive value was 80% (95% CI 72% to 86%), and using a *PCA3* score of more than 60, diagnostic sensitivity and specificity of *PCA3* was 0.42 (95% CI 0.36 to 0.48) and 0.91 (95% CI 0.87 to 0.94), respectively. For patients who underwent a repeat biopsy, the negative predictive value (NPV) was 88% (95% CI, 81% to 93%), and by using a *PCA3* score of less than 20, sensitivity and specificity were 0.76 (95% CI 0.64 to 0.86) and 0.52 (95% CI 0.45 to 0.58), respectively. For the detection of high-grade cancer, *PCA3* performance in combination with Prostate Cancer Prevention Trial's (PCPT) risk calculator was improved by the addition of *PCA3* to the PCPT risk calculator factors with an AUC improvement of 0.74 to 0.78 for initial biopsy and 0.74 to 0.79 on repeat biopsy ($p \leq 0.003$).

Nonrandomized Studies

Several studies published between 2013 and 2018 reported positive associations between *PCA3* levels and prostate cancer diagnosis.[29-37] Predictive value was increased when *PCA3* testing was combined with PSA level and other clinical information.[37-40] Other groups reported moderate diagnostic accuracy of *PCA3* testing. Among men with PSA level greater than 3 ng/mL, AUC of *PCA3* was 0.74.[41] Conversely, in men with *PCA3* scores of 100 or greater, positive predictive value was 39%.[42] In a multicenter study of 647 men, sensitivity and specificity were 67% and 72%, respectively; AUC was 0.742.[43] Three studies compared *PCA3* to multiparametric MRI; MRI was more accurate than *PCA3,*[44 45] but the combination was better than either alone.[46] PCA3 has also been associated with the risk of Gleason grade re-classification in a study of 90 men receiving 5α-reductase inhibitor therapy during active surveillance.[47]

Clinical utility studies using assay results for decision-making for initial biopsy, repeat biopsy, or treatment have not been reported. One group reported potential reductions in unnecessary biopsies of 48 to 52% with attendant increases in missed prostate cancers of 6 to 15% using either a *PCA3*-based nomogram[48] or *PCA3* level corrected for prostate volume (*PCA3* density).[49] Although both studies were prospective, neither assessed utility of the test for clinical decision-making because all patients underwent biopsy, and recurrence or survival outcomes were not evaluated. Another group evaluated the estimated long-term impact of using the *PCA3* score to guide the decision to recommend a repeat biopsy for men with elevated PSA levels.[50] Their models suggested that using a *PCA3* score threshold of 25 would result in 55.4% reduction in repeat biopsies for a base-case patient, while reducing the 10-year survival by 0.93%. However, these estimates have not been validated in real patient populations.

Section Summary

Studies of *PCA3* as a diagnostic test for prostate cancer reported sensitivities and specificities in the moderate range. In general, these studies are preliminary and report on clinical performance characteristics in different populations and with various assay cutoff values, reflecting the lack of standardization in performance and interpretation of *PCA3* results. Several studies have reported a modest incremental improvement in diagnostic accuracy when *PCA3* was tested in combination with PSA level and other clinical findings. The clinical utility of this test is uncertain, as there is insufficient evidence that the use of *PCA3* can be used to change management in ways that improve outcomes.

TMPRSS FUSION GENES

TMPRSS2 fusion gene detection has been studied for prognostic value (e.g., to identify aggressive disease or to predict disease recurrence). In prostate cancer, it may be fused to an ETS family transcription factor (*ERG*, *ETV1*, *ETV4*, or *ETV5*), which modulates transcription of target genes involved in cell growth, transformation, and apoptosis (*TMPRSS2:ERG*). 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, or urine.

Systematic Review

Yao (2014) published a systematic review with meta-analysis of *TMPRSS2:ERG* for the detection of prostate cancer.[51] Literature was searched and 32 articles were identified. Pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were 47% (95% CI 46 to 49), 93% (95% CI 92 to 94), 8.9 (95% CI 5.7 to 14.1), and 0.49 (95% CI 0.43 to 0.55), respectively. Statistical heterogeneity was high (I^2>85%). It was unclear whether studies in screening populations were pooled with enriched patient samples, e.g., elevated PSA and/or biopsy-negative. There also was variability in the type of tissue samples analyzed (urine, prostatic secretions, biopsy or surgical specimens); the type of *TMPRSS2:ERG* assays used (fluorescence in situ hybridization [FISH], immunohistochemistry [IHC], real-time reverse transcriptase polymerase chain reaction [RT-PCR], and transcription-mediated amplification); and in *TMPRSS2:ERG* threshold cutoff values.

Nonrandomized Studies

Tosoian (2021) 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.[52] 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 (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.

Leyton (2014) investigated the predictive value of *PCA3* and *TMPRSS*2 as individual biomarkers and as part of a panel in a prospective, multicenter study of 443 men.[53] *TMPRSS*2 was found to be highly specific (93%) for predicting clinically significant prostate cancer on

biopsy. Because of this high specificity, the authors suggested that re-biopsy or MRI be performed in *TMPRSS2:ERG*-positive patients who do not have prostate cancer detected on initial biopsy. The authors stated that if *PCA3* in combination with *TMPRSS*2 data had been used to select men for prostate biopsy, 35% of biopsies could have been avoided. However, the clinical utility of this test is uncertain, as there are no studies that report the test leads to changes in management that result in improved health outcomes.

Whelan (2014) compared two multivariate models to assess up-staging in 216 patients meeting National Comprehensive Cancer Network (NCCN) criteria for active surveillance.[54] One model included *TMPRSS2:ERG* plus serum PSA; the other model included serum PSA, total RNA in expressed prostatic secretion (EPS, collected by milking the urethra after prostatic massage), and total EPS volume. AUCs were similar (0.80, 95% CI 0.75 to 0.85] and 0.79, 95% CI 0.73 to 0.84], respectively). However, the second model was more accurate for detecting patients who were up-staged, or up-staged and up-graded, by NCCN criteria. Specifically, the second model decreased the risk of up-staging in patients with a negative test approximately eight-fold (from 7% to 1%); decreased the risk of up-staging plus up-grading approximately five-fold (from 5% to 1%); and doubled the prevalence of up-staging in the positive test group. In comparison, the *TMPRSS2:ERG* model decreased up-staging 2.4-fold (from 7% to 3%) and decreased upstaging and upgrading approximately three-fold (from 5% to 2%).

A modeling study by Merdan (2015) estimated that using a *TMPRSS2:ERG* score to guide repeat biopsy decisions in men with elevated PSA could avoid 64.7% of these biopsies, but also reduce the 10-year survival rate by 1.4%.[50] These estimations have not been validated in real-world trials.

A number of studies have reported positive associations between *TMPRSS2* fusion gene levels and prostate cancer diagnosis.[33 34 55 56] One study reported a lack of association between *TMPRSS2:ERG* status and biochemical relapse-free rate in 244 men treated with image-guided radiotherapy (IGRT) for prostate cancer.[57] The authors concluded that "*TMPRSS2-ERG* is therefore unlikely to be a predictive factor for IGRT response."

No studies of clinical utility have been published to date; the evidence consists of correlational studies (association between a fusion gene and prostate cancer).[58-61] However, the results of available studies differ as to the accuracy of *TMPRSS2:ERG* in improving the ability to predict prostate cancer, and/or the ability to estimate prognosis for this purpose.

Section Summary

Limited evidence reports that the measurement of *TMPRSS2:ERG* may improve the ability to predict prostate cancer, and/or the ability to estimate prognosis. However, the results of available studies differ as to the accuracy of *TMPRSS2:ERG* for this purpose. In addition, the clinical utility of this test is uncertain.

TMPRSS2:ERG IN COMBINATION WITH *PCA3*

Nonrandomized Studies

Sanda (2017), from the National Cancer Institute Early Detection Research Network, reported separate developmental and validation cohorts for high-grade prostate cancer in men undergoing initial prostate biopsy.[62] For the validation cohort, any of the following was considered a positive result: PSA level greater than 10 ng/mL, urine *TMPRSS2:ERG* score

greater than 8, or urine *PCA3* score greater than 20. The sensitivity and specificity of this combination were reported to be 92.6% and 33.4%, respectively, an increase from the 17% specificity of *PSA* alone without loss of sensitivity. The difference in specificity was statistically significant, with a prespecified one-sided p-value of 0.04 (lower bound of one-sided 95% CI 0.73%).

Tomlins (2011) developed a transcription-mediated amplification assay to measure *TMPRSS2:ERG* fusion transcripts in parallel with *PCA3*.[61] Combining results from these two tests and incorporating them into the multivariate Prostate Cancer Prevention Trial risk calculator improved the identification of patients with clinically significant cancer by Epstein criteria and high-grade cancer on biopsy. Though the study was large (1,312 men at multiple centers), results were confounded by assay modifications during the course of the study, by the use of cross-validation rather than independent validation, and the use of independent training and testing sets. A validation study by the same group evaluated this risk prediction model (termed Mi-Prostate Score or MiPS), which incorporated serum PSA with urine *TMPRSS2:ERG,* and *PCA3*, in a group of 1,244 men presenting for biopsy.[63] They reported that it improved on PSA alone for predicting prostate cancer and high-grade prostate cancer, but did not assess the clinical utility of this risk score.

A study by Feibus (2016) evaluated the clinical use of *PCA3* and *TMPRSS2:ERG* in African-American men undergoing prostate biopsy.[36] This study included 182 African-American and 139 non-African-American patients. They found that *PCA3* and *TMPRSS2:ERG* scores were associated with prostate cancer, and adding *PCA3* to a standard of care plus PSA model improved concordance statistics for the detection of any prostate cancer in both groups. However, *PCA3* score was only predictive of high grade prostate cancer in African-Americans and not in non-African-Americans, while *TMPRSS2:ERG* did not improve these measures in either group.

In a pilot study, Salami (2013) evaluated 45 men using a multivariable algorithm that included serum PSA plus urine *TMPSS2:ERG* and *PCA3* from a post-DRE sample.[64] Samples were collected before prostate biopsy at two centers. For cancer prediction, sensitivity and specificity were 80% and 90%, respectively. AUC was 0.88. Limitations in this study included the small number of patients and authors used a quantitative RT-PCR assay to measure *PCA3* in urine sediment, and evaluation of this model with the commercially available TMA assay of whole urine would help inform broader clinical applicability. Authors concluded a larger validation study could determine whether a multiplex model combining *PCA3*, *TMPRSS2:ERG* and serum PSA can predict aggressive versus indolent prostate cancer than any of these biomarkers alone.

Robert (2013) retrospectively examined tissue levels of *TMPRSS2:ERG* and *PCA3* in 48 men with benign prostatic hypertrophy, 32 men with normal prostate tissue sampled next to prostate cancer, and 48 men with prostate cancer.[65] Sensitivity, specificity, and positive and negative predictive values for the tests in combination were 94%, 98%, 96%, and 96%, respectively. The limitations of the study included that not all samples were confirmed with a diagnosis, there was a lack of urinary data, and the study results are not generalizable to clinical practice.

Section Summary

Concomitant detection of *TMPRSS2:ERG* and *PCA3* may accurately identify men with prostate cancer. However, estimated accuracy varies across the available studies and clinical utility has not been established.

EXODX™ PROSTATE (INTELLISCORE)

McKiernan (2016) conducted a multicenter validation study of urine exosome *PCA3*, *ERG*, and *SPDEF* RNA expression to predict high-grade (Gleason score ≥7) prostate cancer.[66] The study included men age 50 or older with either a suspicious DRE or PSA levels between 2 and 10 who were scheduled for biopsy. The threshold for a positive test, 15.6, was derived from a training set (n=255) separate from the validation set (n=519). The assay improved on the standard of care alone, with an AUC of 0.73 compared with 0.63 for the standard of care ($p<0.001$) and 0.62 for the PCPT risk calculator. The sensitivity and specificity for the test were reported to be 97.44% and 27.68%, respectively.

Tutrone (2020) reported a trial that evaluated the effect of ExoDx™ Prostate test on the decision to biopsy.[67] This multicenter, prospective, blinded RCT was conducted in partnership with CareFirst BlueCross/BlueShield of Maryland and included 1,094 men with a PSA 2 to 10 ng/ml who were considered for prostate biopsy based on clinical criteria. All patients had the test, but only patients randomized to the ExoDx™ Prostate arm received the test results. The primary outcome of the study was to determine if ExoDX™ Prostate could reduce initial biopsies. The secondary endpoint was the successful diagnosis of high-grade prostate cancer. A total of 942 patients (86.1%) had complete data and usable samples. In the ExoDx™ Prostate arm, 93 patients received low-risk test results, and 106 patients (23%) received recommendations to defer biopsy. High risk ExoDx™ Prostate scores led to a recommendation for biopsy in 87% of the 365 ExoDx™ Prostate positive patients. Compliance with a recommendation for biopsy was 72% in the ExoDx™ Prostate arm compared to about 40% in the control arm, leading to increased biopsy rates in the ExoDx™ Prostate arm (58%) compared to controls (39%). In African-American patients, who represented 23% of the patient population, 91% had high risk scores. The study did not meet its primary endpoint. The main effect of the test was to increase biopsies with an increase in the number of at least Grade Group 2 cancers, but there was also an increase in the number of men biopsied who had no cancer or low-grade cancer compared to the control arm. Additional limitations of the study are the inclusion of men with very low PSA (2 ng/ml) and the lack of information on what screening had preceded the referral for biopsy. It is unclear if the standard of care of repeat PSA and percent free PSA were assessed prior to the decision to biopsy, if controls received this standard of care, or if the test was intended as a replacement for repeat PSA and percent free PSA.

Tutrone (2023) reported on a retrospective outcome analysis follow-up study of 2.5 year of the initial 2020 study reported above.[68] Of the original 1,094 cohort, 833 patients had complete follow-up data at 2.5 years. In this analysis, patients returned to routine standard of care after enrollment in the clinical utility trial, and a retrospective outcome analysis was conducted. The average time from ExoDX™ Prostate testing to the first biopsy was significantly longer in the low-risk ExoDX™ Prostate arm (216 days) compared to high-risk ExoDX ™Prostate arm (68.7 days, $p<0.001$) and when compared to low-risk ExoDX™ Prostate patients in the standard of care arm (79.4 days, $p<0.001$). In the ExoDx™ Prostate arm, low-risk patients had significantly fewer biopsies than high-risk patients (44.6% vs. 79.0%, $p<0.001$); in the standard of care arm the decision to defer was independent of ExoDx™ Prostate score and, as a result, did not differ between low-risk and high-risk scores. Patients in both arms with low-risk ExoDx™ Prostate scores had lower rates of high-grade prostate cancer at 2.5 years than high-risk ExoDx™ Prostate score patients (7.9% vs. 26.8%, $p0<0.001$), and the ExoDx™ Prostate arm discovered 21.8% (106 vs. 87) more high-grade prostate cancer than the standard of care arm. Limitations of this interim analysis mimic limitations that were described in the above study; the

study was also retrospective in nature.

GENE HYPERMETHYLATION FOR PROSTATE CANCER DIAGNOSIS AND PROGNOSIS

Nonrandomized Studies

Several studies have reported associations between DNA hypermethylation at various gene loci (*RASSF1A*, *APC*, *GSTP1*, *PTGS2*, *RAR-beta*, *TIG1*, *AOX1*, *C1orf114*, *GAS6*, *HAPLN3*, *KLF8*, and *MOB3B*) and prostate cancer.[28 61 69-79] In contrast, some studies have not found evidence of an association.[80 81] Further, Kachakova (2013) concluded that *HIST1H4K* hypermethylation was more likely due to aging than to prostate carcinogenesis.[82] ConfirmMDx (MDxHealth) is a commercially available test for gene methylation intended to distinguish true- from false-negative prostate biopsies to avoid the need for repeat biopsy in cases of a true negative and to identify men who may need a repeat biopsy. The test measures methylation of the genes *GSTP1*, *APC*, and *RASSF1*.

Three blinded multicenter validation studies of the ConfirmMDx test have been performed. Partin (2014) reported on results of the DOCUMENT study; it evaluated archived, cancer-negative prostate biopsy core tissue samples from 350 men from five U.S. urology centers.[83] All patients underwent repeat biopsy within 24 months. Men with two consecutive negative biopsies were classified as controls and men with a negative biopsy followed by a positive biopsy were classified as cases. Thirty (9%) men were excluded from analysis because of noneligibility (n=2), insufficient DNA (n=1), insufficient biopsy cores (n=23), or detection of adenocarcinoma in the first biopsy based on central pathology review (n=4); 320 men were included in analysis (92 cases, 228 controls). Median age was 62 years (range, not given). Median PSA level was 5.3 ng/mL; 23% of men had PSA levels less than 4 ng/mL and 10% had a PSA level of 10 ng/mL or higher. Sixty percent of men had a normal DRE. Forty-two (13%) of the men were black, 232 (73%) were white, and 13 (4%) were Asian. The ConfirmMDx test, performed on the first biopsy, resulted in a NPV of 88% (95% CI 85% to 91%), sensitivity of 62% (95% CI 51% to 72%), and specificity of 64% (95% CI 57% to 70%). The study was not powered to determine accurately the performance characteristics in a subgroup of black patients, but the estimated sensitivity was 77% (95% CI 46% to 95%), specificity was 66% (95% CI 46% to 82%), and NPV was 93% (85% CI 82% to 97%). Multivariate analysis of potential predictors of cancer on repeat biopsy, corrected for age, PSA, DRE, first biopsy histopathology characteristics, and race, showed that the ConfirmMDx test was the most significant independent predictor of patient outcome (OR 2.69, 95% CI 1.60 to 4.51).

A study by Waterhouse (2019) was specific to African American men undergoing repeat biopsy within 30 months of a negative index biopsy.[84] Of the 211 patients in the study, 81 had a positive second biopsy (cases), while 130 had negative results (controls). In this population, the ConfirmMDx had a sensitivity of 74.1% and a specificity of 60.0%. For Gleason score ≥7, the sensitivity and specificity were 78% and 53%, respectively.

The MATLOC study, reported by Stewart (2013), tested archived cancer-negative prostate biopsy needle core tissue samples from 498 men from the U.K. and Belgium.[85] Patients underwent repeat biopsy within 30 months; cases had a positive second biopsy while controls had a negative second biopsy. A total of 483 men were included in the analysis (87 cases, 396 controls). The median PSA level was 5.9 ng/mL; 21% of men had PSA levels less than 4 ng/mL and 18% had PSA levels of 10 ng/mL or higher. Seventy-three percent of men had benign DRE. The ConfirmMDx test, performed on the first biopsy, resulted in a NPV of 90% (95% CI 87% to 93%), sensitivity of 68% (95% CI 57% to 77%), and specificity of 64% (95% CI

59% to 69%). Multivariate analysis of potential predictors of cancer on repeat biopsy, corrected for patient age, PSA, DRE, and first biopsy histopathology characteristics, showed that the ConfirmMDx test was the most significant independent predictor of patient outcome (OR 3.17, 95% CI 1.81 to 5.53).

Van Neste (2016) reported on results of combined data from the DOCUMENT and MATLOC studies to investigate whether DNA methylation intensities were associated with high-grade (Gleason score, ≥7) prostate cancer.[86] DNA methylation was the most significant and important predictor of high-grade cancer, resulting in an NPV of 96% (precision not reported).

Wojno (2014) reported on a field observation study in which practicing urologists at five centers used the ConfirmMDx test to evaluate at least 40 men with previous cancer-negative biopsies who were considered at risk for prostate cancer.[87] Centers reported whether patients who had a negative test assay result had undergone a repeat biopsy at the time of the analysis. Median patient follow-up after the assay results were received was nine months. A total of 138 patients were included in the analysis. The median PSA level was 4.7 ng/mL. Repeat biopsies had been performed in six (4.3%) of the 138 men with a negative ConfirmMDx test, in which no cancer was identified.

Aubry (2013) analyzed the expected reduction in biopsies associated with ConfirmMDx use.[88] Using the MATLOC estimates of performance characteristics for ConfirmMDx, the authors estimated that 1,106 biopsies per one million people would be avoided. The study did not include decision analysis comparing the tradeoff in reduction in biopsies and missed cancers.

Section Summary

Studies evaluating the diagnostic accuracy and predictive ability of gene hypermethylation report differing results regarding the accuracy of hypermethylation. These inconsistent results make it difficult to determine whether hypermethylation is a useful parameter for diagnosis and/or prognosis of prostate cancer. Two clinical validation studies have reported on the clinical validity of the ConfirmMDx score in the intended use population. The studies did not provide estimates of validity compared with a standard clinical examination with percent free PSA. No data are available on the long-term clinical outcomes or clinical utility of the test. The indirect chain of evidence is incomplete due to the limitations of evidence on the comparative clinical validity and utility.

MITOCHONDRIAL DNA VARIANT TESTING

Variants in the mitochondrial genome (mtDNA) are emerging as tools for the diagnosis of prostate cancer. A growing body of literature is reporting significant associations between both single nucleotide changes and large-scale deletions in mtDNA and prostate cancer, however, the identified studies are of small to medium sample size and do not address clinical utility. A laboratory developed assay offered by Mitomics (formerly Genesis Genomics), called the Prostate Core Mitomics Test™ (PCMT), is a proprietary test which is intended to determine whether a patient has prostate cancer, despite a negative prostate biopsy, by analyzing deletions in mitochondrial DNA by 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 doesn’t have prostate cancer) and that the patient can avoid a second biopsy, but that a positive PCMT means that the patient is at high risk of undiagnosed prostate cancer. The company website states that the sensitivity of the test is 85% and has a negative predictive value of 92%.

Nonrandomized Studies

A study published by Giorgi (2016) examined the role of the mitochondrial genome in prostate cancer risk in 4,086 prostate cancer cases and 3,698 controls from the Multiethnic Cohort.[89] In this study, 350 mitochondrial SNVs were tested in five racial/ethnic populations: Asian Americans, Africans, Europeans, Latinos, and Native Hawaiians. No significant associations were found.

Legisi (2016) 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).[90] Of the 644 patients with a negative PCMT, 35 had a repeat biopsy and five (14.2%) were false-negatives who were found to have cancer on rebiopsy. The number of false negatives among 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 decisionmaking 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.

Published literature from Genesis Genomics on the use of mitochondrial DNA variants in prostate includes several studies. A 2006 study retrospectively analyzed mitochondrial DNA variants from three tissue types from 24 prostatectomy specimens: prostate cancer, adjacent benign tissue and benign tissue distant to the tumor (defined as tissue from a nondiseased lobe or at least 10 cell diameters from the tumor if in the same lobe).[91] Prostate needle biopsy tissue from 12 individuals referred for biopsy that were histologically benign were used as controls. Results from the prostatectomy tissue analysis showed that 16 of 24 (66.7%) had variants in all three tissue types, 22 of 24 (91.7%) had variants in malignant samples, 19 of 24 (79.2%) in adjacent benign samples and 22 of 24 in distant benign glands. Overall, 273 somatic variants were observed in this sample set. In the control group, seven (58.3%) patients were found to have between one and five alterations, mainly in non-coding regions. The authors concluded that the variants found in the malignant group versus the control group were significantly different and that mitochondrial DNA variants are an indicator of malignant transformation in prostate tissue.

Maki (2008) reported the discovery and characterization of a 3.4-kb mitochondrial genome deletion and its association with prostate cancer[92]. A pilot study analyzed 38 benign biopsy specimens from 22 patients, 41 malignant biopsy specimens from 24 patients and 29 proximal to malignant (PTM) biopsy specimens from 22 patients. All of the patients with malignant biopsies had a subsequent prostatectomy, and the diagnosis of cancer was confirmed. The PTM biopsy samples were negative for cancer and were from the cohort who underwent prostatectomy. A confirmation study used 98 benign biopsy specimens from 22 patients, 75 malignant biopsy specimens from 65 patients, and 123 PTM biopsy specimens from 96 patients. In the confirmation study, patients were required to have at least two successive negative biopsies; the first negative biopsy was used for analyses. For both the pilot and confirmation studies, samples for analysis were selected based upon review of pathology reports. The levels of the variant were measured by quantitative PCR and using PCR cycle threshold data were used to calculate a score for each biopsy sample. In the pilot study, the scores were statistically significant between benign and malignant ($p<0.0001$) and benign and proximal ($p<0.003$) samples. The PTM samples closely resembled the malignant sample, with no statistically significant resolution between their scores ($p<0.833$), to which the authors

attributed as a field cancerization phenomenon. Results from the larger confirmation study were similar. Compared with histopathologic examination of the benign and malignant samples, the sensitivity and specificity were 80% and 71%, respectively, and the area under a ROC curve was 0.83 for the deletion. A blinded, external validation study showed a sensitivity and specificity of 83% and 79% and an AUC of 0.87.

Robinson (2010) assessed the clinical value of the 3.4-kb deletion described in the Maki (2008) study in predicting re-biopsy outcomes[92]. Levels of the deletion were measured by quantitative PCR in prostate biopsies negative for cancer from 101 patients who underwent repeat biopsy within a year and had known outcomes. Of the 101 first biopsies, the diagnosis was normal in eight, atypical and/or had prostatic intraepithelial neoplasia (PIN) in 50 and hyperplasia or inflammation in 43. Using an empirically established cycle threshold cutoff, the lowest cycle threshold as diagnostic of prostate cancer, and the histopathologic diagnosis on second biopsy, the clinical performance of the deletion was calculated. The final data was based on 94 patients, who on second biopsy had 20 malignant and 74 benign diagnoses. The cycle cutoff gave a sensitivity and specificity of 84% and 54%, respectively, with AUC of 0.75. Negative predictive value was 91%.

Section Summary

Studies using the PCMT test for the diagnosis of prostate cancer reported sensitivities and specificities in the moderate range. In general, these studies are preliminary and only report on clinical validity. There is a lack of standardization in methodology and the clinical utility of this test was not addressed.

GENE PANELS

Xiao (2016) reported the development of an eight-gene panel (*PMP22*, *HPN*, *LMTK2*, *FN1*, *EZH2*, *GOLM1*, *PCA3*, *GSTP1*) that distinguished high-grade prostate cancer from indolent prostate cancer with a sensitivity of 93% and NPV of 61%.[93] Validation of this panel is needed.

GENE EXPRESSION ANALYSIS

The Department of Veterans Affairs published a systematic review of genomic classifier testing for prostate cancer in 2023.[94] This evidence review focused on the Decipher, Oncotype DX® GPS, and Prolaris tests, with a focus on three key questions:

1) Among individuals with localized prostate cancer who are considering first-line definitive treatment, does the addition of a tissue-based genomic test to existing clinical risk models impact risk classification?

2) Does tissue-based genomic testing impact the choice of treatment intensity or harms among a) individuals with localized prostate cancer before first-line definitive treatment or b) individuals who have undergone radical prostatectomy?

3) Among patients with localized prostate cancer, what is the prognostic effect of tissue-based genomic tests after adjusting for existing prognostic clinical features on key clinical outcomes (e.g., biochemical recurrence-free survival, metastases-free survival) following definitive treatment?

Regarding their findings, the authors stated:

> "While there was a wide range of impact on risk reclassification reported across studies, there was no clear pattern in these changes across tests. We did find that there was no change in risk classification for a majority of patients apart from a potentially greater rate of reclassification among those at intermediate risk by clinical features. Despite the large proportion of patients without a change, across the identified studies there were still clinically meaningful proportions of included patients who experienced a change in risk assessment that could contribute to important changes in treatment. Of note, most of the data on risk reclassification have been generated with the Oncotype test and were almost exclusively related to risk assessment at the time of initial diagnosis. With respect to the clinical utility of these tests, we found that providers do change their treatment recommendations after receipt of test results in observational studies, although this was not found in the single randomized trial. Evidence around clinical utility was distinct by test type and timeframe such that Oncotype and Prolaris were studied only at initial diagnosis and Decipher only after prostatectomy. Last, we found that these tests do seem to provide additional prognostic information with respect to biochemical recurrence, development of metastatic disease, and prostate-cancer-specific mortality; we have the most certainty of this effect with Decipher compared to the other 2 tests. The value of that additional prognostic information is limited by these findings that largely stem from patients diagnosed and treated prior to the current era of prostate cancer management defined by advanced screening practices as well as evolution in pathologic assessment, staging, and treatment modalities. Of note, we did not find any evidence of acute harms of the tests studied, although there is likely limited harm as the test does not require new tissue acquisition and does not identify or disclose genetic risk applicable to patient family members."

Oncotype DX® Genomic Prostate Score

Clinical Validity

Van Den Eeden (2018) reported on a retrospective study of the Oncotype DX® GPS (previously Oncotype DX® Prostate) using a stratified cohort sampling design including 279 of 6,184 men who were diagnosed with prostate cancer within a registry between 1995 and 2010 and underwent radical prostatectomy (RP) within 12 months of diagnosis, with a median followup of 9.8 years.[95] In an analysis adjusted for NCCN risk classifications, the GPS was associated with BCR-free survival (hazard ratio [HR] 2.1, 95% CI 1.4 to 3.1), distant metastasis (HR 2.3, 95% CI 1.4 to 3.9), and prostate cancer death following RP (HR 2.7, 95% CI 1.5 to 4.8). Ten-year prostate cancer death by GPS score was displayed in a figure stratified by NCCN risk classification, which provides some information on potential reclassification. Ten-year prostate cancer death appears to be close to 0 for men who are NCCN low-risk regardless of GPS score, indicating little useful reclassification of NCCN low-risk men based on GPS. For NCCN intermediate risk, the risk of prostate cancer death ranges from approximately zero for a GPS of less than 40 to close to 40% for a GPS of 100. It is unclear how many men with GPS less than 40 were NCCN favorable intermediate risk.

Brand (2016) combined studies from Klein (2014) and Cullen (2015) using a patient-specific meta-analysis.[96] The GPS was compared to the CAPRA score, NCCN risk group, and AUA/EAU risk group. The authors tested whether the GPS added predictive value for the likelihood of favorable pathology above the clinical risk assessment tools. The model including the GPS and CAPRA score provided the best risk discrimination; the AUC improved from 0.68 to 0.73 by adding the GPS to CAPRA score. The AUC improved from 0.64 to 0.70 by adding

the GPS to the NCCN risk group. The improvements were reported to be significant but the confidence intervals for AUC were not provided.

Whalen (2016) prospectively evaluated the correlation of GPS with final pathology at RP in a clinical practice setting. Eligible men were 50 years of age and older with more than 10 years of life expectancy, PSA levels of 20 ng/mL or less, stage cT1c-cT2c newly diagnosed, untreated prostate cancer, and who met NCCN classifications as very low risk, low risk, or low-intermediate risk.[97] Men were enrolled from May 2013 to August 2014 at an academic medical center. Genomic Health reclassified patients' cancers as "less favorable," "consistent with," or "more favorable" than what would have been predicted by their NCCN risk group. The primary outcome was adverse pathology at RP defined as any pT3 stage and primary Gleason grade of 4 or any pattern 5. Fifty patients had RP pathology and the reclassification results for these participants are discussed here; 21 (42%) met the definition of adverse pathology. The NCCN risk classification categorized two (4%) patients as very low risk, 34 (68%) as low risk, and 14 (28%) as low-intermediate risk. Twenty-three (46%) of patients were reclassified using GPS. Confidence intervals were not provided.

One publication compiled results of three cohorts, two of which were used for test development, of contemporary (1997 to 2011) patients in a prostatectomy study (n=441; Cleveland Clinic database, 1987 to 2004), a biopsy study (n=167; Cleveland Clinic database, 1998 to 2007), and an independent clinical validation study cohort (n=395; mean age, 58 years; University of California, San Francisco Urologic Oncology Data Base, 1998 to 2011).[98]

A study by Salmasi (2018) examined the ability of the test to predict adverse pathology in 134 patients with NCCN very low, low, or intermediate risk prostate cancer, who had additionally undergone MRI testing.[99] MRI results were reported by both UCLA score and Pi-RADSv2. In contrast to the results of other studies, the PSA and MRI scores in this group were not independent predictors of adverse pathology, while the GPS was (OR 3.3, 95% CI 1.74 to 6.62, p<0.001).

Results from the clinical validation study and prostatectomy study provide information on the potential clinical validity of this test. The cohorts had a mix of low to low-intermediate clinical risk characteristics using National Comprehensive Cancer Network (NCCN) or American Urological Association (AUA) criteria.

The clinical validation study was prospectively designed, used masked review of prostatectomy pathology results, and as such met the REMARK (Reporting Recommendations for Tumor Marker Prognostic Studies) guidelines for biomarker validation.[100] The prostatectomy study used a case-cohort design to select a 1:3 ratio of recurrent to nonrecurrent patients. The prespecified primary endpoint of the validation study was the ability of the GPS to predict the likelihood of favorable pathology in the needle biopsy specimen. Favorable pathology was defined as freedom from high-grade or non-organ-confined disease. In the prostatectomy study, the ability of the GPS to further stratify patients within AUA groupings was related to clinical recurrence-free interval in regression-to-the-mean estimated survival curves.

The validation study results showed that the GPS could refine stratification of patients within specific NCCN criteria groupings, as summarized in Table 1. The proportions in Table 1 were estimated from a plot of GPS versus the percent likelihood of favorable pathology.[101]

Table 1. Reclassification of Prostate Cancer Risk Categories with Oncotype DX® GPS[101]

NCCN Risk Level	Estimated Mean Likelihood of Favorable Tumor Pathology	
	NCCN Criteria, %	GPS + NCCN, % Range
Very low	≈84	63-91
Low	≈76	55-86
Intermediate	≈56	29-75

GPS: Genomic Prostate Score; NCCN: National Comprehensive Cancer Network.

The actual number of patients correctly or incorrectly reclassified between all three categories cannot be ascertained from the data provided. The results suggested that the combination of GPS plus clinical criteria could reclassify patients on an individual basis within established clinical risk categories. However, whether these findings support a conclusion that the GPS could predict the disease-specific survival based solely on the level of pathology in a biopsy specimen is unclear. Moreover, extrapolation of this evidence to a true active surveillance population, for which the majority in the study would be otherwise eligible, is difficult because all patients had elective RP within six months of diagnostic biopsy.

The Klein (2014) prostatectomy study, although used to identify genes to include in the GPS, provided estimates of clinical recurrence rates stratified by AUA criteria (Epstein), compared with rates after further stratification according to the GPS from the validation study. The survival curves for clinical recurrence reached a duration of nearly 18 years based on the dates individuals in the cohort were entered into the database (1987-2004). The reclassifications are summarized in Table 2. The GPS groups are grouped by tertiles defined in the overall study. These data suggest the GPS can reclassify a patient's risk of recurrence based on a specimen obtained at biopsy. However, the findings do not necessarily reflect a clinical scenario of predicting disease progression in untreated patients under active surveillance.

Table 2. Reclassification of Prostate Cancer 10-Year Clinical Recurrence Risk with Oncotype DX® GPS

Overall 10-Year Risk, % (AUA Risk Level)	10-Year Risk, % (GPS Low Group)	10-Year Risk, % (GPS Intermediate Group)	10-Year Risk, % (GPS High Group)
3.4 Low	2.0	3.4	7.0
9.6 (Intermediate)	2.8	5.1	14.3
18.2 (high)	6.2	9.2	28.6

AUA: American Urological Association; GPS: Genomic Prostate Score.

A retrospective cohort study by Cullen (2015) included men with NCCN-defined very low- through intermediate-risk prostate cancer undergoing RP within six-months of diagnosis.[102] The sample was obtained from men enrolled in the Center for Prostate Disease Research longitudinal study at two U.S. military medical centers. A Gleason score of 4 or 5 with non-organ-confined disease was considered adverse pathology. Biopsies were available for 500 (57.9%) of 864 eligible patients; 382 (44.2% of eligible) with both adequate tissue for gene expression analysis and available RP pathology were included in the analysis. Selected patients were older (61.0 years vs. 59.7 years, p=0.013) and had both higher Gleason scores (p<0.001) and NCCN risk classification (29.8% vs 32.9% intermediate, p=0.035). Median follow-up was 5.2 years and biochemical recurrence (BCR) occurred in 62 (15.4%). Adverse

pathology was noted in 163 (34%) men. In an analysis adjusted for baseline characteristics, the GPS was associated with BCR-free survival (HR 2.73 for each 20-point increase, 95% CI 1.84 to 3.96) and adverse pathology following RP (HR 3.23 per 20-point increase, 95% CI 2.17 to 4.97). The GPS improved the C statistic for adverse pathology over NCCN risk alone from 0.63 to 0.72 (CIs not reported). Comparisons with other predictors such as CAPRA or Gleason score alone were not reported. Study implications were limited by the low proportion of eligible men in the analysis and differences between excluded and included men.

Clinical Utility

Decision-impact studies have assessed the potential impact of Oncotype DX® GPS on physicians' and patients' treatment decisions.[103-108] Given the lack of established clinical validity and no reported outcomes, it is uncertain whether any treatment changes were clinically appropriate. With the exception of Carbunaru (2023),[107] other decision-impact studies have indicated that men classified as low-risk by guidelines criteria, and thus meeting guidelines criteria for active surveillance, are more likely to receive active surveillance if they are *tested* with the Oncotype DX® GPS test.[104-106 108] These arguments would suggest that the test may be a useful behavioral modifier. However, a comparison with educational or quality improvement initiatives designed to improve the uptake of active surveillance in low-risk men has not been provided. This is important to consider, since Carbunaru (2023) found that higher GPS scores seemed to shift urologists' preferences from active surveillance to active treatment, but lower scores did not frequently shift preferences from active treatment back to active surveillance.[107] Furthermore, authors' noted that there were times when the urologists' treatment preferences did not align with NCCN recommendations for that patient's risk group (e.g., active surveillance in low-risk men).

Klein (2014) also reported a decision-curve analysis that they have proposed reflects the clinical utility of Oncotype DX® GPS.[101] The analysis investigated the predictive impact of the GPS in combination with the Cancer of the Prostate Risk Assessment (CAPRA) validated tool[109] versus the CAPRA score alone on the net benefit for the outcomes of patients with high-grade disease (Gleason >4+3), high-stage disease, and combined high-grade and high-stage disease. They reported that, over a range of threshold probabilities for implementing treatment, "incorporation of the GPS would be expected to lead to fewer treatments of patients who have favorable pathology at prostatectomy without increasing the number of patients with adverse pathology left untreated." For example, at a threshold risk of 40% (e.g., a man weighing the harms of prostatectomy versus the benefit of active surveillance at 4:6) the test could identify 2 per 100 with high-grade or high-stage disease at a fixed false positive rate compared with using the CAPRA score alone. However, no confidence intervals were presented for the decision curve analysis. Thus, an individual patient could use the findings to assess his balance of benefits and harms (net benefit) when weighing the choice to proceed immediately to curative RP with its attendant adverse sequelae, or to enter an active surveillance program. The latter would have an immediate benefit realized by forgoing RP, but perhaps would be associated with greater downstream risks of disease progression and subsequent therapies.

Section Summary

No direct evidence of clinical utility was found. Klein's decision-curve analyses suggest a potential ability of the combined GPS and CAPRA data to help patients make decisions based on relative risks associated with immediate treatment or deferred treatment (i.e., active

surveillance). This would reflect the clinical utility of the test. However, it is difficult to ascribe possible clinical utility of Oncotype DX® GPS in active surveillance because all patients regardless of clinical criteria elected RP within six months of diagnostic biopsy. Moreover, the validity of using different degrees of tumor pathology as a surrogate for cancer-specific death is unclear. Reports from validation studies lack precision estimates for important variables such as risk estimates for recurrence.

Prolaris®

Analytic Validity

Although there is no reference standard for gene expression profiling tests, other measures of technical performance are relevant and include reproducibility, tissue-sample adequacy, potential batch effects, and test-set bias. Warf (2015) evaluated the precision of the Cell Cycle Progression (CCP) score using six formalin-fixed, paraffin-embedded (FFPE) biopsy (three replicate scores) and 12 FFPE RP (four to six replicate scores) specimens.[110] Overall precision was estimated from replicate samples, intended to reflect combined variation from tissue dissection through gene expression. Across replicate samples, the standard deviation of the CCP score was 0.1 (95% CI 0.98 to 0.13). After eight weeks of sample storage, results were similar. In 2013, Myriad Genetics reported 95.3% of samples were adequate to produce a CCP score.[111]

Clinical Validity: Needle Biopsy, Conservative Management

In 2016, results of a systematic review and meta-analysis supported by the manufacturer were reported.[112] Published and unpublished studies of prognostic validity or clinical utility of CCP testing were eligible for inclusion. Seven published studies were identified; five were clinical validity studies. Two are reviewed in the following paragraphs and the remaining validity studies will be reviewed in a subsequent section on post-RP management. The two “utility” studies are discussed in the following section. Two validity studies reported outcomes for disease-specific mortality[113 114] but of the two, only the Cuzick (2012)[113] included newly diagnosed patients, so the pooled outcome is not of relevance in this section.

The more recent study by Cuzick (2015) examined three U.K. cancer registries from 1990 to 2003 to identify men with prostate cancer who were conservatively managed following needle biopsy, with follow-up through December 2012. Men were excluded if they had undergone RP or radiation therapy within six months of diagnosis.[111] A combination of the CCP and Cancer of the Prostate Risk Assessment (CAPRA) scores (called the combined clinical cell cycle risk [CCR] score) was used to predict prostate cancer death. There were 989 men who fit eligibility criteria; CCP scores were calculable for 761 (77%) and combined CCP and clinical variables were available for 585 (59%). Median age at diagnosis was 70.8 years and median follow-up was 9.5 years. The prostate cancer mortality rate was 17% (n=100), with 29% (n=168) dying from competing causes. Higher CCP scores were associated with increased 10-year risk of prostate cancer mortality: 7% (CCP score <0), 15% (CCP score 0 to 1), 36% (CCP score 1 to 2), 59% (CCP score >2). A one-unit increase in CCP was associated with a crude HR for death of 2.08 (95% CI 1.76 to 2.46) and when adjusted for CAPRA score yielded a HR of 1.76 (95% CI 1.47 to 2.14). For the combined CAPRA/CCP score, the HR for 10-year prostate cancer mortality increased to 2.17 (95% CI 1.83 to 2.57). The c-statistic for the CAPRA score was 0.74; adding the CCP score increased the C statistic to 0.78 (no confidence intervals for the AUC were reported). Treatment changes after six months were documented in only part of one of the three cohorts; at 24 months, 45% of the men in this cohort had undergone radiotherapy

or prostatectomy. Therefore, the potential effect of treatment changes on prognostic estimates is uncertain.

Lin (2018) validated a CCR cutoff of 0.8 using a subset of 585 conservatively managed men from the Cuzick (2015) cohort.[115] Of the 585 men, 60 had CCR scores of 0.8 or less. Among the 284 men who were at low- or intermediate-risk by NCCN criteria, 59 had CCR scores of 0.8 or less. The text reports that the estimated 10-year prostate cancer mortality risk was 2.7% for men with CCR scores below the threshold and 3.3% (95% CI 1.9% to 5.7%) at the threshold in the full cohort, and 2.3% below the threshold and 2.9% (95% CI 1.3% to 6.7%) at the threshold in the cohort that excluded high-risk men. However, the Kaplan-Meier curves show an estimated prostate cancer mortality at 10 years of 0% for men with CCR of 0.8 or less in both cohorts. The Kaplan-Meier curve estimated prostate cancer mortality at 10 years for men with CCR greater than 0.8 was 20% in the full cohort and 9% in the cohort excluding high-risk men.

Tward (2021) reported the association of the CCR score with 10-year metastais and progression in men with unfavorable intermediate- or high-risk prostate cancer. However, this study did not meet inclusion criteria for this review because it did not provide survival outcomes.[116]

The Cuzick (2012) study examined the prognostic value of Prolaris® for prostate cancer death in a conservatively managed needle biopsy cohort.[113] Cell cycle expression data were read blind to all other data. Patients were identified from six cancer registries in Great Britain and were included if they had clinically localized prostate cancer diagnosed by needle biopsy between 1990 through 1996; were younger than 76 years at diagnosis; had a baseline PSA measurement; and were conservatively managed. Potentially eligible patients who underwent RP, died, showed evidence of metastatic disease within six months of diagnosis, or received hormone therapy before diagnostic biopsy were excluded. The original biopsy specimens were retrieved and centrally reviewed by a panel of expert urologic pathologists to confirm the diagnosis and, where necessary, to reassign Gleason scores.44 Of 776 patients diagnosed by needle biopsy and for which a sample was available to review histology, needle biopsies were retrieved for 527 (68%), 442 (84%) of which had adequate material to assay. From the 442 samples, 349 (79%) produced a CCP score and had complete baseline and follow-up information, representing 45% of 776 patients initially identified. The median follow-up time was 11.8 years. Ninety deaths from prostate cancer occurred within 2799 person-years.

The primary, unadjusted analysis found a one-unit increase in CCP score associated with a two-fold increase (HR 2.02, 95% CI 1.62 to 2.53) in the risk of dying from prostate cancer. In a multivariate model including CCP, Gleason score, and PSA level, the adjusted HR for a one-unit increase in CCP score was 1.65 (95% CI 1.31 to 2.09). However, changes in HRs may not reflect meaningful changes in absolute risk. It appears that there might be a large change in risk for scores below 2 compared with above 2, but no CIs are reported so it is impossible to draw conclusions. Measures that would suggest improved discriminatory ability (e.g., AUC or reclassification) compared with an existing nomogram were not reported. The authors did not provide evidence that the test could correctly reclassify men initially at high risk to lower risk to avoid overtreatment, or conversely, correctly reclassify those initially at low risk to high risk to avoid undertreatment.

Table 3. Univariate and Multivariate Associations between CCP and Death from Prostate Cancer in the Cuzick 2012 and 2015 Validation Studies

Study (year)	N	Unadjusted	Multivariate
		Hazard Ratio (95% CI) for 1-unit increase in CCP	Hazard Ratio (95% CI) for 1-unit increase in CCP
Cuzick (2012)[113]	349	2.02 (1.62 to 2.53)	1.65 (1.31 to 2.09)[a]
Cuzick (2015)[111]	585	2.08 (1.76 to 2.46)	1.76 (1.47 to 2.14)[b]

CI: confidence interval
CCP: cell cycle pression
[a.] adjusted for Gleason score and prostate-specific cancer level
[b] adjusted for Cancer of the Prostate Risk Assessment

In summary, Table 3 displays the association between CCP score adjusted for CAPRA and Table 4 shows the risk of death by groups of CCP score. The CCR score is most relevant as it appears in the sample report provided by the manufacturer. Table 3 demonstrates an association between CCP and risk of death on the relative scale but does not necessarily indicate that there is a difference in absolute risk that would be meaningful for clinical decision making. Table 4 displays the estimated absolute risk of death for the CCP score but notably absent are CIs which would help in interpretation. However, given the data provided, several concerns arise. Even the lowest risk group shown in Cuzick (2012)[113] has a 10-year death rate of 20%, which may be explained by the population characteristics (i.e., not PSA screen-selected, a third with Gleason >7 and half with PSA >25); however, a death rate of 20% is unlikely to be low enough to forgo immediate treatment.

Table 4 does not include the death rates by CCR score; however, the predicted 10-year prostate cancer death rates by CCR score were provided in a figure in Cuzick (2015).[111] The predicted 10-year risk for CAPRA alone compared with CCR was provided in a dot plot. The authors stated that CCR identified 11 men with a CAPRA score of 2 (indicating an estimated 10-year mortality rate of 4%) who "had a higher risk" based on CCR score. From the dot plot, it appears that for these 11 men, the 10-year mortality rate estimated by CCR score ranged from just greater than 4% to about 8%. The authors also indicated that for 31 men with CAPRA of 3 (corresponding to a 10-year risk of death rate of 5.7%) the risk as estimated by CCR was less than 4.0%, from the plot the CCR estimated risk appears to range from about 2.5% to 4% for those 31 men. It is not clear that either of these reclassifications would change estimated mortality enough to alter treatment decisions.

Table 4. Kaplan-Meier Estimates of Prostate Cancer Death at 10 Years According to CCP Score Groupings in the Cuzick Validation Studies

	Cuzick (2012)[113]		Cuzick (2015)[111]	
CCP Score	N	10-Year Death Rate (%)[a]	N	10-Year Death Rate (%)[a]
≤ 0	36	19.3	194	7
0 to ≤ 1	133	19.8	251	15
1 to ≤ 2	114	21.1	110	36
2 < CCP ≤ 3	50	48.2	30[b]	59
> 3	16	74.9		

CCP: cell cycle progression
[a] Confidence intervals not reported
[b] Grouped CCP scores >2

Clinical Validity: Posttreatment (RP and external beam radiation therapy)

Five studies have reported clinical validity in the post-RP management setting. Four of these studies –Cuzick (2011),[114] Cooperberg (2013),[98] Bishoff (2014), and Swanson (2021)[117] reported on post-RP patients. Koch et al (2016) reported on post-RP patients with BCR. Freedland et al (2013) reported on post-RT patients but is included in this section for completeness.

Swanson (2021) published a reanalysis of 360 patients from the cohort first reported in Cuzick (2011).[117] After a median follow-up of 16 years, 163 (45%) of the cohort developed BCR, 41 (11%) developed metastatic disease, and 33 (9%) died from prostate cancer. The CCR score (a combination of CAPRA-S and the CCP molecular score) was prognostic of prostate cancer death, but the estimate was imprecise (HR per unit score 3.40, 95% CI 1.52 to 7.59). The study authors illustrated the added value of CCR for predicting disease-specific mortality by comparing predicted risk using CCR to risk predicted by a CAPRA-S-only model in a Kaplan-Meier curve; however, precision estimates were not presented.

Bishoff (2014) examined the prognostic ability of the CCP score in three cohorts: Martini Clinic (n=283, simulated biopsies from FFPE RP specimen), Durham Veterans Affairs Medical Center (n=176, diagnostic biopsies) and Intermountain Healthcare (n=123, diagnostic biopsies).[118] The combined analysis included all 582 patients. Gleason scores were 7 or lower in 93% of men. In the combined cohorts, a unit increase in the CCP score increased the adjusted HR for BCR by 1.47 (95% CI 1.23 to 1.76). Metastatic events (n=12) were too few to draw conclusions. Although the CCP score was associated with increased risk of BCR, the analyses do not allow examining whether the CCP score provides improved discrimination over clinicopathologic variables.

In Myriad-funded study, Freedland (2013) evaluated the CCP score's ability to predict biochemical recurrence (BCR) in a cohort of men treated with external beam radiation therapy (EBRT).[119] The CCP score was derived retrospectively from diagnostic biopsy specimens of men diagnosed with prostate cancer from 1991 to 2006 (n=141). The primary outcome assessed was time from EBRT to BCR. In a multivariable analysis with Gleason score, PSA, percent positive cores, and androgen deprivation therapy, the HR was 2.11 for a one-unit increase in CCP score (equivalent to a doubling of gene expression) (p=0.034), indicating that CCP provides prognostic information that is not provided by standard clinical parameters. At 10 years post-EBRT, the CCP score was associated with prostate cancer specific mortality (p=0.013). The limitations of this study include small size of the cohort, small number of treatment failures (only 19 patients [13%] had BCR), and short follow-up time. The authors conceded that "definitive conclusions regarding time dependency will require additional studies".

Cooperberg (2013) sought to evaluate the CCP score in a RP cohort and the incremental improvement over the Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score for predicting BCR employing a prospective-retrospective design (conforming to a PRoBE study design).[98] A prognostic model was developed from the RP cohort described by Cuzick (2011).[114] The validation cohort was obtained from patients identified from the University of California, San Francisco (UCSF) Urologic Oncology Database. Tissue sufficient to obtain a CCP score was available for 413 men (69% of the 600 eligible samples). Both UCSF and Myriad Genetics performed statistical analyses. In the validation cohort, 95% had Gleason scores of 7 or lower, 16% of samples had positive margins, 4% had seminal vesicle invasion, and 23% had extracapsular extension. BCR occurred in 82 men (19.9%). The unadjusted HR for BCR increased by 2.1 (95% CI 1.6 to 2.9) per unit increase in CCP score. A predictive

model for the combined CCP/CAPRA-S developed in the Cuzick (2011)[114] RP cohort applied to the UCSF cohort obtained an AUC for BCR with CAPRA-S alone of 0.73 increasing to 0.77 for the combined CCP/CAPRA-S.

Cuzick (2011) examined the potential use of the Prolaris® CCP test combined with a clinical score following RP, using a retrospective cohort and the prospective-retrospective design for archived samples.[114] The study also included a cohort of men with localized prostate cancer detected from specimens obtained during transurethral resection of the prostate, which is not a population of interest here, and so has not been described. Men conservatively managed post RP between 1985 and 1995 were identified from a tumor registry (n=366 with CCP scores, Scott and White Clinic, in Texas). The primary endpoint was time to biochemical recurrence (BCR) and the secondary end point was prostate cancer death. Myriad Genetics assessed CCP scores blindly. The median age of patients was 68 years and the median follow-up 9.4 years. Gleason scores were 7 or lower in 96%, but margins were positive in 68%. Cancers were clinically staged as T3 in 34%; following RP, 64% was judged pathologic stage T3. CCP score was associated with BCR (adjusted HR 1.77, 95% CI 1.40 to 2.22). Analyses of prostate cancer deaths in the RP cohort were problematic, owing to only 12 (3%) deaths. The clinical score included PSA, stage, positive surgical margins, and Gleason score. The model was optimized using stepwise variable selection (e.g., a development model). The AUC for BCR within five years in the RP cohort was 0.825 for the clinical score and 0.842 for the combined clinical/CCP score. The discriminatory ability of the clinical score is of note. Although the CCP increased the AUC by 2%, whether that improvement might be clinically useful is unclear lacking reclassification or examination of net benefit.

Clinical Utility

One large prospective registry study, funded by Myriad, was recently published that evaluated the impact of the CCP test on treatment decision making for patients newly diagnosed with prostate cancer.[120] Patients (n=1,206) with newly diagnosed prostate adenocarcinoma had the CCP test performed on initial prostate biopsy tissue. Changes in treatment decision making was tracked using the answers provided by physicians in sequential surveys relative to initial therapy recommendations (before cell cycle progression). The CCP test caused a change in actual treatment in 47.8% of patients, 72.1% of which were reductions and 26.9% of which were increases in treatment. For each clinical risk category there was a significant change in treatment modality (intervention vs nonintervention) before vs after CCP testing (p=0.0002). This study did not report any changes in patient-important outcomes, such as biochemical recurrence, cancer-specific survival or long-term survival. Although this study reported a change of management in a modest percentage of patients, there was no evidence that these changes in management lead to clinically important improvements in health outcomes.

A prospective study by Hu (2018) tracked the usage of several genomic classification tests in patients with prostate cancer and correlated the results with treatment decisions.[121] However, this study also did not evaluate clinical outcomes.

Two retrospective survey studies that assessed the potential impact of Prolaris® on physicians' treatment decisions.[122 123] The authors of each study have suggested their findings support the "clinical utility" of the test, based on whether the results would lead to a change in treatment. Although this information may be useful in assessing the potential test uptake by urologists, it does not demonstrate clinical utility in clinical settings. In a decision-curve analysis, Cooperberg[98] found the CAPRA-S score superior to CCP alone (as well as treat-

none or treat-all strategies) in men postprostatectomy. A combined CCP/CAPRA-S predictor appeared only slightly better than CAPRA-S alone for thresholds of approximately 30% or more. For example, at a threshold of 30% (i.e., meaning a man would value the harm-to-benefit of treatment such as radiotherapy as 3:7), the combined CCP/CAPRA-S would detect about two more men per 100 likely to experience BCR if the false-positive rate was fixed. However, the lack of confidence intervals for the decision-curve analysis, together with the small difference, is consistent with an uncertain net benefit obtained by adding CCP to the CAPRA-S score.

Decipher® Prostate Biopsy

Ross (2024) evaluated the Decipher® test in samples from the phase II ENACT trial, which randomized 227 patients with low- or intermediate-risk localized prostate cancer undergoing active surveillance to either 160 mg enzalutamide monotherapy daily or continued active surveillance for a year.[124] The test was run on biopsy samples collected at the trial screening and at one and two years afterward. The Decipher® score at screening (n=95) was not significantly associated with disease progression. When all time-point samples from the active surveillance arm (n=65) were included in the multivariable analysis, there was a significant correlation with progression (HR per 0.1 was 1.17, 95% CI 1.01 to 1.35, p=0.04).

Vince (2021) published a prospective registry study of the Decipher® Biopsy test in a multicenter study that included 855 men who underwent testing between 2015 and 2019.[125] The primary outcomes were time to treatment (TTT) and time to failure (TTF). There were 264 patients that elected for active surveillance and 454 patients that received radical therapy. The Decipher® Biopsy score was associated with shorter TTT and TTF (HR 2.51, 95% CI 1.52 to 4.13, p<0.001, and HR 2.98, 95% CI 1.22 to 7.29, p=0.01, respectively), after adjustment for age, PSA, NCCN risk group, prostate volume, body mass index, and percent positive cores.

Three retrospective cohort studies have been published reporting the clinical validity of Decipher® Biopsy in men with newly diagnosed, localized prostate cancer.

Tosoian (2020) evaluated the performance of the Decipher® GC score in 405 patients with high-risk prostate cancer who underwent RP or radiation therapy (RT) with androgen-deprivation therapy.[126] The GC score was associated with metastasis (HR 1.33 per 0.1-unit increase, 95% CI 1.19 to 1.48, p<0.001), as was a GC high-risk designation (HR 2.95 compared to low-risk, 95% CI 1.79 to 4.87, p<0.001). The authors noted that regression models based on NCCN risk group and CAPRA were improved with the addition of the GC score (NCCN AUC from 0.46 to 0.67, and CAPRA AUC from 0.59 to 0.71).

Berlin (2019) compared NCCN subclassifications with GC scores in 121 patients with intermediate-risk prostate cancer treated with radiation therapy.[127] The primary and secondary endpoints of the study were biochemical failure (PSA antigen nadir +2 ng/mL) and metastasis. GC score performed better than the NCCN classifications for biochemical failure (HR 1.36, 95% CI 1.09 to 1.71, p=0.007) and metastasis (HR 2.05, 95% CI 1.24 to 4.24, p=0.004), and a combination of the two performed better than either alone (AUC 0.89 vs. 0.86 for GC alone, and 0.54 for NCCN classes alone).

A study by Nguyen (2017) included 235 patients who had either RP or first-line radiotherapy (with or without androgen deprivation therapy) between 1987 and 2024, with a median follow-up of six years.[128] After adjusting for treatment and clinical data, the biopsy Decipher® score was associated with five-year metastasis (HR 1.39 per 0.1 unit increase, 95% CI 1.09 to 1.8).

The frequency of metastasis within five years was 4.1%, 7.8%, and 21% for the Decipher® low-, intermediate-, and high-risk groups.

Decipher® Prostate RP

The Decipher® Prostate RP test classifies as low-risk those patients who can delay or defer RT after prostatectomy, or as high-risk those who would potentially benefit from early radiation. The GC is a continuous risk score between 0 and 1, with higher risk scores indicating a greater probability of developing metastasis.

Clinical Validity

The clinical validity of the Decipher® genomic classifier (GC) has been reported in studies to predict metastasis, mortality or BCR after RP in patients with postoperative high-risk features like pathologic stage T2 with positive margins, pathologic stage T3 disease or a rising PSA.[83 129-140] Nearly all studies were retrospective and used registry data or clinical records. The development study was a nested case-control design.[134] Owing to apparent overlap in samples, the number of unique patients in the studies is difficult to ascertain. Many studies were supported by GenomeDx, which offers the Decipher® test; these studies identified multiple authors as company employees.

Four studies,[131-134] including the test (validation) sample from the development study, examined men observed following RP and undergoing adjuvant or salvage radiotherapy. Median follow-up periods ranged from 6.4 to 16.9 years. The distributions of Gleason scores in the studies varied—from 24.3% to 49.3% with 8 or higher and 0.4% to 15.1% with 6 or lower. Extracapsular extension of the tumor ranged from 42.7% and 72.3% of men across of the studies.

Feng (2021) evaluated the Decipher® GC in an industry-sponsored ancillary study that used samples collected from the NRG/RTOG 9601 randomized clinical trial.[141] The trial was designed to assess outcomes for salvage radiotherapy with or without two years of bicalutamide treatment following RP. The primary endpoint of the ancillary study was distant metastasis and secondary outcomes were overall and prostate cancer-specific mortality, and the median follow-up was 13 years. Only 486 of 760 randomized patients (63.8%) had classifier scores generated, and only 352 (46.3%) passed quality control and were included in the analysis. Of these, 148 were classified as GC low (42%), 132 as GC intermediate (38%), and 72 as GC high risk (20%). GC classification was significantly associated with distant metastasis with a rate of 15.3% for high-risk (95% CI 6.9% to 23.7%), 8.7% for intermediate-risk (95% CI 3.7% to 13.6%), and 6.2% for low-risk (95% CI 2.2% to 10.1%, $p = 0.003$). Prostate cancer-specific mortality (high 9.8%, 95% CI 2.9% to 16.8%; intermediate 2.4%, 95% CI 0.0% to 5.0%; low 0.7%, 95% CI 0.0% to 2.0%; $p < 0.001$) and overall survival (high 83.2%, 95% CI 74.4% to 91.9%; intermediate 90.6%, 95% CI 85.5% to 95.7%; low 94.5%, 95% CI 90.7% to 98.2%; $p = 0.013$) were similarly associated with classification. There was no significant interaction between classifier score and hormone treatment effect.

Klein (2016) evaluated the ability of the Decipher® GC to predict metastasis from the prostate needle biopsy diagnostic tumor tissue from 56 men.[136] Median follow-up time was eight years. In that time, eight patients metastasized and three died of PCa. Decipher® plus NCCN model had an improved c-index of 0.88 (95% CI 0.77 to 0.96) compared to NCCN alone (c-index 0.75, 95% CI 0.64 to 0.87). Using the Cox multivariable analysis, Decipher® was the only

significant predictor of metastasis when adjusting for age, preoperative PSA and biopsy Gleason score (HR 1.72 per 10% increase, 95% CI 1.07 to 2.81, p= 0.02).

A study by Freedland (2016) evaluated the Decipher® GC as a predictor or metastasis in a retrospective study of 170 men who received salvage radiation therapy following cancer recurrence after RP.[142] After a median follow-up of 5.7 years, 12% of the patients were diagnosed with metastases. The GC results were associated with metastasis (HR 1.58 for a 0.1 unit increase in GC, 95% CI 1.16 to 2.17, p=0.002) and the c-index for the Decipher® test was 0.85 (95% CI 0.73 to 0.88), compared with 0.63 to 0.65 for the Cancer of the Prostate Risk Assessment Score and Briganti risk models.

Ross (2015) assessed the prognostic accuracy for metastasis through 10 years, excluding men receiving any adjuvant therapy following RP over median follow-up periods of 7.8 and nine years.[143] The investigators reported a 6.5% five-year cumulative incidence of metastases in men with GC scores of 0.45 or lower, compared with 30.3% in those with scores higher than 0.60. The AUCs for development of metastases was 0.76 for the GC. In addition, it was found that combining the GC with the best clinicopathologic tool improve the AUC. The study did not include a “standard” reclassification table, but did report 10-year cumulative incidence of metastases stratified by GC and CAPRA-S. The GC appeared to discriminate within CAPRA-S categories, added little to a score greater than 5.

Den (2015) reported on the use of the Decipher® genomic classifier (GC) to provide prognostic and predictive information into the development of metastases in men receiving post-RP RT (either three-dimensional conformal or IMRT).[129] Genomic classifier scores were calculated from 188 men who were identified within the GenomeDx prostate cancer database with pathologic stage T3 or margin-positive prostate cancer and had received post-RP RT at one of two academic centers between 1990 and 2009. The primary endpoint was metastatic disease (regional or distant) documented on computed tomography or bone scan. Adjuvant versus salvage RT was defined by PSA levels of 0.2 ng/mL or less and more than 0.2 ng/mL before initiation of RT. The clinical characteristics of eligible patients included 72% of men with extraprostatic extension, 35% with seminal vesicle invasion, and 78% with positive surgical margins. Twenty-one percent of patients had a Gleason score of 8 or more. Fifty-one percent of patients received adjuvant RT (89% within 12 months of RP) and overall, patients received RT at a median of five months after RP (range 1 to 160 months). Thirty percent of patients received hormonal therapy with RT. Median follow-up after RP and RT was 10 and 8 years, respectively. Cumulative incidence of metastatic disease at five years after RT for low, average, and high GC scores was 0%, 9%, and 29% (p=0.002). In a multivariate analysis, GC and pre-RP PSA were independent predictors of metastasis (both p<0.01). In the low GC score group (score <0.4) there was no difference in cumulative incidence of metastasis compared with patients who received adjuvant or salvage RT (p=0.79), however, for patients with higher GC scores (≥0.4), the cumulative incidence of metastasis at five years was 6% for patients treated with adjuvant RT compared to 23% treated with salvage RT (p<0.01). The authors concluded that patients with low GC scores are best treated with salvage RT and those with high GC scores with adjuvant RT.

Klein (2014) evaluated whether use of the Decipher® GC test improved accuracy in predicting metastasis within five years following RP (rapid metastasis [RM]).[83] Participants included 169 patients who underwent RP between 1987 and 2008, of which 15 were RM and 154 were non-RM controls. Metastasis developed between 1.7 and 3.3 years (median 2.3 years). Test performance was evaluated both individually and in combination with clinical risk factors. After

adjusting for clinical factors, Decipher® was a significant predictor of RM (OR 1.48, p=0.018). Compared to the Stephenson model, the CAPRA-S, and previously reported biomarkers, Decipher® had the highest concordance index (c-index), with the highest c-index achieved with integration of Decipher® into the Stephenson nomogram.

Karnes (2013) prospectively created a randomly selected subcohort from the same initial 1,010 post-prostatectomy patients in the Cooperberg study.[133] Patients with metastasis at diagnosis or with any prior treatment for prostate cancer were excluded. A randomly-selected subcohort was created, with genomic data was available for 219 patients. Following RP, the rates of biochemical recurrence (BCR) at three years was 35% and metastasis at five years was 6%. Median genomic classifier scores were consistently higher in patients with metastases at last follow-up (mean 6.7 years). Median genomic classifier scores also increased with higher Gleason scores. The authors concluded that the higher net benefit of genomic-based classifiers suggested increased specificity (i.e., lower false positives) compared with clinical-only risk models. Because patients with intermediate risk tumors may progress to advanced disease, the authors recommended further study of genomic classifiers in randomized datasets to determine whether genomic classifier scores from diagnostic biopsy specimens can predict metastasis as well as postoperative specimens. A possible limitation of this study was that nearly 15% of patients were node-positive and 45% received adjuvant therapy. Whether the genomic classifier predicted benefit from local (i.e., radiation) or systemic (e.g., hormone) therapies could not be determined because patients were not randomized to these treatments.

Den (2014) reported that within a Decipher® low-risk group that was treated post-RP with RT, there was no difference in oncologic outcomes (either biochemical failure or metastasis) whether they received adjuvant or salvage RT.[130] For the men classified as high-risk by Decipher, a median four-year PSA-free survival advantage was observed in the patients that received adjuvant versus salvage RT. Of these men classified as high-risk by GC, those who received adjuvant radiation had a 3% cumulative incidence of metastases as compared with 23% incidence of metastasis by eight years in those who delayed treatment and received salvage radiation.

Additional, smaller nonrandomized studies have found associations between GC score and metastatic lymph node involvement[144] and in recurrence after robotic-assisted laparoscopic prostatectomy.[145]

Ross (2016) reported results of a retrospective, comparative study of RT after RP for 422 men with pT3 disease or positive margins.[146] The men were from four cohorts previously described (Karnes [2013], Den [2014], Ross [2016], Freedland [2016]). The four treatment groups were adjuvant RT (n=111), minimal residual disease salvage RT (n=70), salvage RT (n=83), and no RT (n=157). The primary endpoint was metastasis. Thirty-seven men developed metastasis, and the median follow-up was eight years. Both CAPRA-S (HR 1.39, 95% CI 1.18 to 1.62) and Decipher® (HR 1.28, 95% CI 1.08 to 1.52) were independently associated with metastasis in multivariable analysis. There was no evidence that treatment effect was dependent on genomic risk (interaction p=0.16 for CAPRA-S, p=0.39 for Decipher), Men with low CAPRA-S or low Decipher® scores had a low risk of metastatic events regardless of treatment selection and men with high CAPRA-S or Decipher® scores benefitted from adjuvant RT compared to the other treatments.

Clinical Utility

A randomized controlled cluster-crossover trial by Morgan (2024) evaluated the impact of the Decipher® RP test on adjuvant treatment in patients following RP.[147] The trial enrolled 175 patients who had undergone RP within nine months, had pT3-4 disease and/or positive surgical margins, and a PSA of less than 0.1 ng/ml. Medical centers were randomized to sequential three-month intervals of either test-informed care or usual care. At 18 months after RP, there was no significant difference between groups for the proportion of patients receiving adjuvant treatment, though individuals with a high test score were more likely to receive adjuvant treatment (OR 6.9, 95% CI 1.8 to 26, p=0.005) compared with a low score in the test arm. At the time of publication, there were insufficient data to evaluate clinical outcomes related to cancer progression or survival.

Several studies have compared physician's treatment recommendations before and after receiving GC results.[121 148-154] Because the studies did not include information on outcomes and clinical validity has not been established, it is not known whether these treatment decisions represent a clinical improvement in management.

SelectMDx™

Van Neste (2016) evaluated a risk calculator that added *HOXC6* and *DLX1* expression to a clinical risk model that included DRE, PSA density, and previous cancer negative biopsies.[155] A training set in 519 men and an independent validation set in 386 men were assessed. When evaluating the risk model in men who were in the "gray zone" of PSA level between 3 ng/mL and 10 ng/mL, the AUC was significantly higher than a clinical risk model alone, Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) for detection of any cancer or for detection of high-grade cancer. Limitations of this study is the inclusion of men with an abnormal DRE, which was the strongest predictor of prostate cancer in the training set (OR 5.53, 95% CI 2.89 to 10.56) and inclusion of men who were scheduled for either initial or repeat biopsy. The OR for *HOXC6* and *DLX1* expression in this model was 1.68 (95% CI 1.38 to 2.05, p<0.003).

Development and validation studies on a revised risk model that included *HOXC6* and *DLX1* expression along with patient age, DRE, and PSA density in men undergoing initial biopsy was reported by Haese (2019).[156] The new analysis included data from the Dutch patients in the report by Van Neste (2016) along with additional cohorts from France and Germany. In the validation cohort of men with all PSA levels, the AUC was 0.82 with 89% sensitivity and 53% specificity. The PCPTRC AUC was 0.76. Since some clinicians will proceed to biopsy when there is a positive DRE, results were also calculated for patients who had PSA <10 ng/ml and a negative DRE. For this cohort (n=591), the AUC was 0.80 with sensitivity of 84% and specificity of 57%. Comparison with the PCPTRC in this subgroup was not reported.

Lendínez-Cano (2021) published a prospective study of the diagnostic accuracy of the SelectMDx™ test in the detection of high-grade prostate cancer in a cohort of 176 patients with a clinical suspicion of prostate cancer that had not yet undergone biopsy.[157] Of these, 163 patients underwent a multiparametric prostate MRI and had a systematic 12-core trans-rectal biopsy and a targeted biopsy and were included in the analysis. In this group, the SelectMDx™ test had a sensitivity of 76.9% (95% CI 63.2 to 87.5), a specificity of 49.6% (95% CI 39.9 to 59.2), a NPV of 82.09% (95% CI 70.8 to 90.4) NPV, and a positive predictive value (PPV) of 41.67% (95% CI 31.7 to 52.2) for the diagnosis of clinically significant prostate cancer.

A similar prospective study by Hendriks (2021) included 599 biopsy-naïve men with a PSA ≥ 3 ng/ml who underwent multiparametric MRI and systematic transrectal ultrasound-guided biopsy following the SelectMDx™ test.[158] The analysis included comparisons between

SelectMDx™ test and MRI, and evaluation of strategies that included either joint MRI/ SelectMDx™ testing or conditional MRI based on SelectMDx™ results. Using a cut-off value of 2.8, the SelectMDx™ had a specificity of 90% for high-grade cancer, and a NPV of 92% and PPV of 79% for any prostate cancer. The conditional strategy, in which biopsy would only be performed if both the SelectMDx™ and MRI were positive would reduce the number of patients undergoing MRI by 38% (227/599), the number of biopsies by 60% (357/599), at the cost of missing 13% (24/183) of high-grade cancers. The joint strategy (biopsy if either test was positive) detected 98% of high-grade cancers. Decision curve analysis showed the highest net benefit for the MRI only strategy, followed by the conditional strategy at risk thresholds over 10%. Investigators also found that SelectMDx™ test led to a 35% reduction of over-detection of low-grade prostate cancer and could save 38% of MRIs, at the cost of missing 10% of high-grade prostate cancers compared to biopsy for all patients. However, the use of MRI alone in all patients to select for prostate biopsy had the highest net benefit as a prebiopsy stratification tool.

Sari Motlagh (2022) published a systematic review comparing SelectMDx™ to multiparameter MRI for the detection of prostate cancer in patients that were biopsy-naïve or undergoing active surveillance.[159] Seven studies with a total of 1,328 patients were included, most of whom (n=1,241) were biopsy-naïve. Meta-analysis demonstrated a pooled sensitivity and specificity for the SelectMDx™ test was 81% (95% CI 74.6% to 86.2%) and 69.8% (95% CI 51.8% to 83.3%), respectively, with a PPV of 64.7% and NPV of 85%. The MRI testing had a pooled sensitivity and specificity of 80.8% (95% CI 77.5% to 83.7%) and 73.4% (95% CI 62.7% to 81.9%), respectively, and a PPV of 72.4% and NPV of 83.5%. Many of the studies had concerns for risk of bias, based on the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.

DECIPHER® BLADDER

The Decipher® Bladder genomic subtyping classifier (GSC) uses gene expression information to classify muscle-invasive bladder cancer by subtype, which may to help identify patients more likely benefit from neoadjuvant chemotherapy prior to radical cystectomy. The development of the test was described in a study by Seiler (2017), which used the results of whole transcriptome profiling in samples from 343 patients with muscle-invasive bladder cancer prior to chemotherapy to classify tumors into the following subtypes: claudin-low, basal, luminal-infiltrated and luminal.[160] These subtypes were associated with overall survival, with the basal subtype demonstrating the most survival benefit with neoadjuvant chemotherapy compared with surgery alone.

Additional retrospective studies have linked various GSC results with outcomes in patients with bladder cancer,[161 162] but these findings require validation, ideally in prospective studies that evaluate health outcomes in patients managed with and without GSC testing.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

The American Society of Clinical Oncology (ASCO) published guidelines on the use of molecular biomarkers in localized prostate cancer (2020), which included the following recommendations:[163]

- Tissue-based molecular biomarkers (evaluating the sample with the highest volume of the highest Gleason pattern) may improve risk stratification when added to standard clinical parameters, but the Expert Panel endorses their use only in situations in which the assay results, when considered as a whole with routine clinical factors, are likely to affect a clinical decision.
- These assays are not recommended for routine use as they have not been prospectively tested or shown to improve long-term outcomes—for example, quality of life, need for treatment, or survival.

AMERICAN UROLOGICAL ASSOCIATION, SOCIETY OF UROLOGIC ONCOLOGY

In 2023, the American Urological Association (AUA) and the Society of Urologic Oncology (SUO) published updated guidelines on the early detection of prostate cancer.[164] Specific guidance related to diagnosis, risk assessment, and utilization of biomarkers included the following:

- When screening for prostate cancer, clinicians should use PSA as the first screening test. (Strong Recommendation; Evidence Level: Grade A)
- For people with a newly elevated PSA, clinicians should repeat the PSA prior to a secondary biomarker, imaging, or biopsy. (Expert Opinion)
- Clinicians may use digital rectal exam (DRE) alongside PSA to establish risk of clinically significant prostate cancer. (Conditional Recommendation; Evidence Level: Grade C)
- For people undergoing prostate cancer screening, clinicians should not use PSA velocity as the sole indication for a secondary biomarker, imaging, or biopsy. (Strong Recommendation; Evidence Level: Grade B)
- Clinicians may use adjunctive urine or serum markers when further risk stratification would influence the decision regarding whether to proceed with biopsy. (Conditional Recommendation; Evidence Level: Grade C)
- After a negative biopsy, clinicians should not solely use a PSA threshold to decide whether to repeat the biopsy. (Strong Recommendation; Evidence Level: Grade B)
- After a negative biopsy, clinicians may use blood-, urine-, or tissue-based biomarkers selectively for further risk stratification if results are likely to influence the decision regarding repeat biopsy or otherwise substantively change the patient's management. (Conditional Recommendation; Evidence Level: Grade C)
- In patients with multifocal HGPIN (high-grade prostatic intraepithelial neoplasia), clinicians may proceed with additional risk evaluation, guided by PSA/DRE and mpMRI findings. (Expert Opinion)

AMERICAN UROLOGICAL ASSOCIATION, AMERICAN SOCIETY FOR RADIATION ONCOLOGY

The AUA and American Society for Radiation Oncology published guidelines on clinically localized prostate cancer in 2022.[165] The guidelines included the following statements on risk assessment:

1. Clinicians should use clinical T stage, serum PSA, Grade Group (Gleason score), and tumor volume on biopsy to risk stratify patients with newly diagnosed prostate cancer. (Strong recommendation; Evidence level: Grade B)

2. Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion)

3. Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)

EVALUATION OF GENOMIC APPLICATIONS IN PRACTICE AND PREVENTION (EGAPP)

In 2013, the EGAPP Working Group published the following recommendations for *PCA3* testing in prostate cancer, based on an AHRQ comparative effectiveness systematic review summarized above:[166]

- Evidence was insufficient to recommend *PCA3* testing to inform decisions for when to re-biopsy previously biopsy-negative patients for prostate cancer, or to inform decisions to conduct initial biopsies for prostate cancer in at-risk men (e.g., previous elevated PSA or suspicious digital rectal examination).
- Evidence was insufficient to recommend *PCA3* testing in men with cancer-positive biopsies to determine if the disease is indolent or aggressive in order to develop an optimal treatment plan.
- The overall certainty of clinical validity to predict the diagnosis of prostate cancer using *PCA3* is deemed “low.” Clinical use for diagnosis is discouraged unless further evidence supports improved clinical validity.
- The overall certainty of net health benefit is deemed “low.” Clinical use is discouraged unless further evidence supports improved clinical outcomes.

NATIONAL COMPREHENSIVE CANCER NETWORK

Prostate Cancer

The National Comprehensive Cancer Network (NCCN) guidelines for Prostate Cancer Early Detection (v.2.2024) suggest considering tests that may improve risk prediction.[167] *PCA3* is not recommended for use prior to biopsy. The guidelines note:

> “Biomarkers that improve the specificity of detection are not, as yet, mandated as first-line screening tests in conjuction with serum PSA. However, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to further define risk. Lower percent-free PSA and/or higher PSA density are associated with a greater risk of high-grade prostate cancer. The probability of high-grade cancer (Gleason score ≥ 3+4, Grade Group 2 or higher) may be further defined utilizing the Prostate Health Index (PHI), SelectMDx, 4Kscore, ExoDx Prostate Test, MyProstateScore (MPS), and IsoPSA. PCA3 score is potentially informative after a negative biopsy. Extent of validation of these tests across diverse populations is variable. It is not known how such tests could be applied in optimal combination with MRI.”

The NCCN guidelines for prostate cancer (v.4.2024) provide a table of tissue-based tests for prostate cancer prognosis.[168] The guidelines state that:

- Patients with NCCN low, favorable intermediate, unfavorable intermediate, or high-risk disease and life expectancy greater than or equal to 10 years may consider the use of Decipher, Oncotype DX Prostate, or Prolaris during initial risk stratification.
- Patients with unfavorable intermediate- and high-risk disease and life expectancy greater than or equal to 10 years may consider the use of Decipher or Prolaris. In addition, Decipher may be considered to inform adjuvant treatment if adverse features are found after radical prostatectomy and during workup for radical prostatectomy PSA persistence or recurrence (category 2B for the latter setting).
- The panel recommends the use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, PSADT, and 22-gene GC molecular assay to individualize treatment discussion. Patients with high 22-gene GC scores (GC >0.6) should be strongly considered for the addition of ADT to EBRT, particularly when the opportunity for early EBRT has been missed."

Bladder Cancer

The NCCN guidelines for bladder cancer (v.4.2024) recommend testing for *FGFR3* genetic alterations and immunohistochemistry testing for HER2 overexpression, but do not discuss the use of genomic subtyping classifiers.[169]

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

The U.S. Preventive Services Task Force published recommendations for Prostate Cancer Screening on May 2012. Genetic tests addressed in this policy, including *PCA3*, were not mentioned.

SUMMARY

There is not enough research to recommend using gene-based tests for prostate or bladder cancer screening, detection and management, as many important characteristics of these tests have not yet been determined. Some research shows that they might help predict the diagnosis or prognosis of prostate cancer, but it is not yet known how much information they add to currently available tests. More research is needed to demonstrate how these tests can improve outcomes for patients. Therefore, use of gene-based testing for screening, detection, and management of prostate or bladder cancer is considered investigational.

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CODES

Codes	Number	Description
CPT	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
	0016M	Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrinelike)
	0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
	0047U	Genomic Prostate Score® (GPS) Test, MDxHealth, Inc, MDxHealth, Inc
	0113U	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score
	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
	0343U	Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer
	0403U	Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch urine, algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer
	0424U	Oncology (prostate), exosome based analysis of 53 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RTqPCR), urine, reported as no molecular evidence, low-, moderate- or elevated-risk of prostate cancer
	0433U	Oncology (prostate), 5 DNA regulatory markers by quantitative PCR, whole blood, algorithm, including prostate-specific antigen, reported as likelihood of cancer
	0497U	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 6 genes (FOXM1, MCM3, MTUS1, TTC21B, ALAS1, and PPP2CA), utilizing formalinfixed paraffin-embedded (FFPE) tissue, algorithm reported as a risk score for prostate cancer
	0534U	Oncology (prostate), microRNA, single-nucleotide polymorphisms (SNPs) analysis by RT-PCR of 32 variants, using buccal swab, algorithm reported as a risk score
	0572U	Oncology (prostate), high-throughput telomere length quantification by FISH, whole blood, diagnostic algorithm reported as risk of prostate cancer
	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
	81541	Oncology (prostate), mrna gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score
	81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score

Codes	Number	Description
	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
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	

Date of Origin: *October 2012*