Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 3/1/25**
(See policy history boxes for previous effective dates)

Title: Gene Expression Profile Analysis for Risk Stratification for Prostate Cancer Management

Description/Background

Prostate Cancer

Prostate cancer is the second most common cancer diagnosed among men in the U.S. Autopsy studies in the pre-prostate-specific antigen (PSA) screening era have identified incidental cancerous foci in 30% of men 50 years of age, with incidence reaching 75% at age 80 years.[1]

Localized prostate cancers may appear very similar clinically at diagnosis.[2] However, they often exhibit diverse risk of progression that may not be captured by accepted clinical risk categories (e.g., D'Amico criteria) or prognostic tools that are based on clinical findings, including PSA titers, Gleason grade, or tumor stage.[3-7] In studies of conservative management, the risk of localized disease progression based on prostate cancer-specific survival rates at 10 years may range from 15%[8,9] to 20%[10] to perhaps 27% at 20-year follow-up.[11] Among elderly men (70 years or more) with this type of low-risk disease, comorbidities typically supervene as a cause of death; these men will die with prostate cancer present, rather than from the cancer. Other very similar-appearing low-risk tumors may progress unexpectedly rapidly, quickly disseminating and becoming incurable.

Risk Stratification in Newly Diagnosed Disease

In the United States, most prostate cancers are clinically localized at diagnosis due in part to the widespread use of PSA testing. Clinicopathologic characteristics are used to stratify patients by risk based on the extent of the primary tumor (T category), nearby lymph node involvement (N category), metastasis (M category), PSA level and Gleason score. The National Comprehensive Cancer Network and American Urological Association risk categories for clinically localized prostate cancer are similar, derived from the D'Amico criteria and broadly include low-, intermediate-, or high-risk as follows as well as subcategories within these groups:[12,13]

1. Low: T1-T2a and Gleason score ≤6 grade group 1 and PSA level ≤10 ng/mL;
2. Intermediate: T2b-T2c or Gleason score 3+4=7/Gleason grade group 2 or Gleason score 4+3=7/Gleason grade group 3 or PSA level 10-20 ng/mL;
3. High: T3a or Gleason score 8/Gleason grade group 4 or Gleason score 9-10/Gleason grade group 5 or PSA level >20 ng/mL.

Risk stratification is combined with patient age, life expectancy, and treatment preferences to make initial therapy decisions.

Monitoring After Prostatectomy
All normal prostate tissue and tumor tissue is theoretically removed during radical prostatectomy (RP), so the serum level of PSA should be undetectable following RP. Detectable PSA post-RP indicates residual prostate tissue and presumably persistent or recurrent disease. PSA is serially measured following RP to detect early disease recurrence. The National Comprehensive Cancer Network recommends monitoring serum PSA every 6 to 12 months for the first 5 years and annually thereafter.[12] Many recurrences following RP can be successfully treated. The American Urological Association has recommended a biochemical recurrence be defined as a serum PSA of 0.2 ng/mL or higher, which is confirmed by a second determination with a PSA level of 0.2 ng/mL or higher.[14]

Castration-Resistant Prostate Cancer
Androgen deprivation therapy (ADT) is generally the initial treatment for patients with advanced prostate cancer. ADT can produce tumor response and improve quality of life but most patients will eventually progress on ADT. Disease that progresses while the patient is on ADT is referred to as castration-resistant prostate cancer (CRPC). After progression, continued ADT is generally used in conjunction with other treatments. Androgen pathways are important in the progression of CRPC. Several drugs have been developed that either inhibit enzymes involved in androgen production or inhibit the androgen receptor, such as abiraterone and enzalutamide. Taxane chemotherapy with docetaxel or cabazitaxel may also be used after progression. Immunotherapy (sipuleucel-T) or radium 223 are options for select men.

Gene Expression Profile Analysis
Gene expression profiling is the measurement of the activity (i.e., expression) of thousands of genes at once, to create a global picture of cellular function. These profiles may distinguish between cells that are actively dividing, or show how the cells react to a particular treatment. Many experiments of this sort measure an entire genome simultaneously, that is, every gene present in a particular cell.

Several transcriptomics technologies can be used to generate the necessary data to analyze. DNA microarrays measure the relative activity of previously identified target genes. Sequence based techniques, like RNA-Seq, provide information on the sequences of genes in addition to their expression level.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Prolaris®, Oncotype Dx® Prostate, Oncotype DX

AR-V7 Nuclear Detect, Decipher® gene expression profiling, ConfirmMDx and the ProMark™ protein biomarker test 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 has chosen not to require any regulatory review of this test.

In November 2015, the FDA's Office of Public Health Strategy and Analysis published a document on public health evidence for FDA oversight of LDTs.[16] 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.

Medical Policy Statement

Gene expression analysis to guide management of prostate cancer has been established. It may be considered a useful option when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions for Decipher (for either of the following)**:**

- post-biopsy for NCCN very-low-, low-risk, favorable intermediate-, and unfavorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.
- post-radical prostatectomy:
    - for pT2 with positive margins;
    - any pT3 disease;
    - rising PSA (above nadir)

Inclusions for Oncotype DX Genomic Prostate Score, Prostate, Prolaris, ProMark:

- men with NCCN very-low-risk, low-risk, and favorable intermediate-risk prostate cancer who have a greater than 10 year life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.

Inclusions for AR-V7 testing:
Testing can be considered to help guide selection of therapy in the post abiraterone/enzalutamide metastatic castration-resistant prostate cancer (CRPC setting).

Proprietary Laboratory Analyses (PLA) Testing
A PLA test as an FDA-approved companion diagnostic to determine the appropriate therapeutic drug is considered **established** when the following criteria are met:

- Biomarker confirmation is required by an FDA-approved or -cleared test prior to initiating treatment (as described in the FDA prescribing label of the therapeutic in the section "Indications and Usage"), AND

- The test is an FDA-approved companion diagnostic

Information regarding FDA-approved companion diagnostic tests should be obtained from the FDA "List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)" website. www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

For accuracy, the reader is advised to access the information directly from the FDA site. (This website is updated frequently)

Exclusions:

- The use of more than one type of test to assess risk of prostate cancer progression (Oncotype DX **Genomic Prostate Score**, Decipher, Prolaris, or ProMark) is considered experimental/investigational.
- ConfirmMDx testing

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81479	81599	81541	81542	81551
0037U	0047U			

Other codes (investigational, not medically necessary, etc.):

0497U

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

INITIAL MANAGEMENT DECISION: ACTIVE SURVEILLANCE VS. THERAPEUTIC INTERVENTION

The divergent behavior of localized prostate cancers creates uncertainty whether to treat immediately or follow with active surveillance.[18,19] With active surveillance, the patient will forgo

immediate therapy and continue regular monitoring until signs or symptoms of disease progression are evident, at which point curative treatment is instituted.[20,21] A patient may alternatively choose potentially curative treatment upfront.[22] Surgery (i.e., radical prostatectomy [RP]) or external-beam radiotherapy (EBRT) is most commonly used to treat patients with localized prostate cancer. Complications most commonly reported with RP or EBRT and with the greatest variability are incontinence (0%-73%) and other genitourinary toxicities (irritative and obstructive symptoms); hematuria (typically ≤5%); gastrointestinal and bowel toxicity, including nausea and loose stools (25%-50%); proctopathy, including rectal pain and bleeding (10%-39%); and erectile dysfunction, including impotence (50%-90%).[13] A 2014 population-based retrospective cohort study using administrative hospital data, physician billing codes, and cancer registry data estimated the 5-year cumulative incidence of admission to hospital for a treatment-related complication following RP or EBRT to be 22% (95% confidence interval [CI], 21.7% to 22.7%).[23]

In the Prostate Testing for Cancer and Treatment (ProtecT) trial (2016), active surveillance, immediate RP, and immediate EBRT for the treatment of clinically localized prostate cancer were compared in 1643 men identified through prostate-specific antigen (PSA) testing.[24] About 90% of the participants had a PSA level less than 10 ng/mL; two-thirds were Gleason score 6 and 20% were Gleason score 7; all were clinical stage T1c or T2. The mean age was 62 years. At a median of 10-year follow-up, prostate cancer-specific survival was high and similar across the 3 treatment groups: 98.8% (95% CI, 97.4% to 99.5%) in active surveillance, 99.0% (95% CI, 97.2% to 99.6%) in the surgery group, and 99.6% (95% CI, 98.4% to 99.9%) in the radiotherapy (RT) group. Surgery and RT were associated with lower incidences of disease progression and metastases compared with active surveillance. Approximately 55% of men in the active surveillance group had received a radical treatment by the end of follow-up. Similarly, very high prostate cancer-specific survival and metastasis-free survival outcomes were reported by large, prospective cohorts of active surveillance patients in the U. S. and Canada.[25,26]

Prostate Cancer Intervention versus Observation Trial (PIVOT) randomized 731 men in the United States with localized prostate newly diagnosed cancer to RP or observation. The patients were 40% low-risk, 34% intermediate-risk and 21% high-risk. Results from PIVOT also concluded that RP did not prolong survival compared with observation through 12 years and 19.5 years of follow-up in the primary analyses including all risk groups.[27,28] However, among men with intermediate-risk tumors, surgery was associated with a 31% relative reduction in all-cause mortality compared with observation (hazard ratio [HR], 0.69; 95% CI, 0.49 to 0.98; absolute risk reduction, 12.6%).

An observational study by van den Bergh et al (2012) comparing sexual function of men with low-risk prostate cancer who chose active surveillance with men who received RT or RP found those who chose active surveillance were more often sexually active than similar men who received RP.[29] In a 2011 report of quality of life for men in the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), after a median follow-up of more than 12 years, distress caused by treatment-related side effects was reported significantly more often by men assigned to RP than by men assigned to watchful waiting.[30]

The American Urological Association (AUA), in joint guidelines (2017), have suggested that physicians recommend active surveillance for most men with low-risk localized prostate cancer but offer RP or RT to select low-risk, localized patients who have a high probability of

progression on active surveillance.[13] The guidelines also suggested that physicians should recommend RP or RT plus androgen deprivation therapy to patients with intermediate-risk prostate cancer and that RT alone or active surveillance may also be offered to select patients with favorable intermediate-risk localized cancer.

Clinical Context and Test Purpose
In men with newly diagnosed clinically localized prostate cancer, the purpose of gene expression profiling (GEP) and protein biomarker testing is to inform a decision whether to undergo immediate therapy or to forgo immediate therapy and begin active surveillance.

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest is individuals with newly diagnosed, localized prostate cancer, who have not undergone treatment for prostate cancer, and who are deciding between therapeutic intervention or active surveillance.

Intervention
Gene expression profiling refers to analysis of mRNA expression levels of many genes simultaneously in a tumor specimen, and protein biomarkers.[31-36] Two gene expression profiling tests and 1 protein biomarker test are intended to biologically stratify prostate cancers diagnosed on prostate needle biopsy: Prolaris (Myriad Genetics, Salt Lake City, UT) and Oncotype DX **Genomic Prostate Score** (Genomic Health, Redwood City, CA) are gene expression profiling tests that use archived tumor specimens as the mRNA source, reverse transcriptase polymerase chain reaction amplification, and the TaqMan low-density array platform (Applied Biosystems, Foster City, CA). A protein biomarker test, ProMark (Metamark Genetics, Cambridge, MA), is an automated quantitative imaging method to measure protein biomarkers by immunofluorescent staining in defined areas in intact formalin-fixed paraffin-embedded biopsy tissue, in order to provide independent prognostic information to aid in the stratification of patients with prostate cancer to active surveillance or therapy.

Comparators
Clinicopathologic risk stratification is currently being used to make decisions about prostate cancer management. Clinical characteristics (e.g., stage, biopsy Gleason grade, serum PSA) and demographic characteristics (e.g., as age, life expectancy) are combined to classify men according to risk. National Comprehensive Cancer Network (NCCN) and AUA provide treatment recommendations based on risk stratification.[12,37] The Kattan et al (2003) nomogram was developed to predict risk of indolent cancer in a low-risk population considering active surveillance.[38] The Cancer of the Prostate Risk Assessment (CAPRA) is a pretreatment nomogram that provides risk prediction of outcomes following RP developed from a cohort of RP patients.[39]

Outcomes
Beneficial outcomes resulting from a true test result are prolonged survival, improved quality of life, and reduction in unnecessary treatment-related adverse effects. Harmful outcomes resulting from a false test result are recurrence, metastases or death, and unnecessary

treatments. The outcomes of interest are listed in Table 1. The primary survival outcome of interest is disease-specific survival because overall survival is very high in this group.

Table 1. Outcomes of Interest for Individuals with Newly Diagnosed, Localized Prostate Cancer

Outcomes	Details
Overall survival	10-year survival
Disease-specific survival	10-year prostate cancer-free survival; 10-year prostate cancer death rate; 10-year recurrence rate
Quality of life	See Chen et al (2014)[40] for NCI-recommended health-related quality of life measures for localized prostate cancer
Treatment-related morbidity	Adverse effects of radiotherapy or radical prostatectomy

NCI: national cancer institute

Study Selection Criteria

For the evaluation of clinical validity of the Prolaris, Oncotype DX **Genomic Prostate Score**, ProMark protein biomarker, Decipher prostate cancer classifier, and Oncotype DX AR-V7 Nuclear Detect tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a validation cohort independent of the development cohort;
- Included a suitable reference standard (10-year prostate cancer−specific survival or death rate)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Prolaris®

Prolaris is used to quantify expression levels of 31 cell cycle progression (CCP) genes and 15 housekeeper genes to generate a CCP score. This section will review Prolaris for initial management decisions in newly diagnosed, localized cancer.

Table 2. Clinical Validity Studies Assessing Prolaris for Informing Initial Management Decisions

Study (Year)	Design	Dates	Sites	N	Population
Cuzick et al (2012)[41]	Retrospective cohort from prospective registry	1990-1996	6 UK registries; not screen-detected	349	Clinically localized; 66% Gleason score 6-7; 46% PSA level ≤25ng/ml
Cuzick et al (2015)[42]	Retrospective cohort from prospective registry	1990-2003	3 UK registries[a]; not screen-detected	761	Clinically localized; 74% Gleason score ≤7; mean PSA level 21ng/ml
Lin et al (2018)[43]	• Validation cohort: Subset of Cuzick et al (2015) • Clinical testing cohort: Consecutive men with biopsies submitted for	1990-2003 2013-2016	• 3 U.K. registries[a]; not screen-detected • N/A;	585 19,215	• See Cuzick et al (2015) • Median PSA level, 5.6 ng/ml (IQR, 44-7.6

	testing to manufacturer		manufacturer database		ng/ml) NCCN risk: • Low, 57% • Favorable intermediate, 20% • Intermediate, 17% • High, 7%

IQR: interquartile range; NCCN: National Comprehensive Cancer Network; PSA: prostate-specific antigen
[a] No overlap in population with Cuzick et al (2012)

Cuzick et al (2012) examined the Prolaris® prognostic value for prostate cancer death in a conservatively managed needle biopsy cohort.[41] Total RNA was extracted from paraffin specimens. A CCP score was calculated from expression levels of 31 genes. Clinical variables consisted of centrally re-reviewed Gleason score, baseline prostate-specific antigen level, age, clinical stage, and extent of disease. The primary endpoint was death from prostate cancer. In univariate analysis (n=349), the hazard ratio (HR) for death from prostate cancer was 2.02 (95% CI (1.62, 2.53), P<10(-9)) for a one-unit increase in CCP score. The CCP score was only weakly correlated with standard prognostic factors and in a multivariate analysis, CCP score dominated (HR for one-unit increase=1.65, 95% CI (1.31, 2.09), P=3 × 10(-5)), with Gleason score (P=5 × 10(-4)) and prostate-specific antigen (PSA) (P=0.017) providing significant additional contributions. For conservatively managed patients, the CCP score is the strongest independent predictor of cancer death outcome yet described and may prove valuable in managing clinically localized prostate cancer.

Cuzick et al (2015) examined 3 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.[42] Paraffin sections from 761 men with clinically localized prostate cancer diagnosed by needle biopsy and managed conservatively in the United Kingdom, mostly between 2000 and 2003. The primary end point was prostate cancer death. Clinical variables consisted of centrally reviewed Gleason score, baseline PSA level, age, clinical stage, and extent of disease; these were combined into a single predefined risk assessment (CAPRA) score. Full data were available for 585 men who formed a fully independent validation cohort. In univariate analysis, the CCP score hazard ratio was 2.08 (95% CI (1.76, 2.46), P<10(-13)) for one unit change of the score. In multivariate analysis including CAPRA, the CCP score hazard ratio was 1.76 (95% CI (1.44, 2.14), P<10(-6)). The predefined CCR score was highly predictive, hazard ratio 2.17 (95% CI (1.83, 2.57), $\chi(2)=89.0$, P<10(-20)) and captured virtually all available prognostic information. The CCP score provides significant pretreatment prognostic information that cannot be provided by clinical variables and is useful for determining which patients can be safely managed conservatively, avoiding radical treatment.

Lin et al (2018) validated a CCR cutoff of 0.8 using a subset of 585 conservatively managed men from the Cuzick (2015) cohort.[43] The score threshold was selected based on the 90th percentile of CCR scores among men who might typically be considered for AS based on NCCN low/favorable intermediate risk criteria (CCR = 0.8). The threshold was validated using 10-year PCM in an unselected, conservatively managed cohort and in the subset of the same cohort after excluding men with high-risk features. The clinical effect was evaluated in a

contemporary clinical cohort. In the unselected validation cohort, men with CCR scores below the threshold had a predicted mean 10-year PCM of 2.7%, and the threshold significantly dichotomized low- and high-risk disease (P = 1.2 × 10). After excluding high-risk men from the validation cohort, men with CCR scores below the threshold had a predicted mean 10-year PCM of 2.3%, and the threshold significantly dichotomized low- and high-risk disease (P = 0.020). There were no prostate cancer-specific deaths in men with CCR scores below the threshold in either analysis. The proportion of men in the clinical testing cohort identified as candidates for AS was substantially higher using the threshold (68.8%) compared to clinicopathologic features alone (42.6%), while mean 10-year predicted PCM risks remained essentially identical (1.9% vs. 2.0%, respectively). The CCR score threshold appropriately dichotomized patients into low and high-risk groups for 10-year PCM, and may enable more appropriate selection of patients for AS.

Table 3. Univariate and Multivariate Associations Between CCP and Death From Prostate Cancer

Study	N	Unadjusted	Multivariate
		HR[c] (95% CI)	HR[c] (95% CI)
Cuzick et al (2012)	349	2.02 (1.62 to 2.53)	1.65 (1.31 to 2.09)[a]
Cuzick et al (2015)	585	2.08 (1.76 to 2.46)	1.76 (1.47 to 2.14)[b]

CCP: Cell Cycle Progression; CI: confidence interval; HR: hazard ratio.
[a] Adjusted for Gleason score and prostate-specific cancer level.
[b] Adjusted for Cancer of the Prostate Risk Assessment.
[c] For a 1-unit increase in CCP.

Table 4. Kaplan-Meier Estimates of Prostate Cancer Death at 10 Years by CCP Score Groupings in the Cuzick Validation Studies[c]

	Cuzick et al (2012)		Cuzick et al (2015)	
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 to ≤3	50	48.2	30[b]	59
>3	16	74.9		

CCP: Cell Cycle Progression.
[a] Confidence intervals were not reported.
[b] Grouped CCP score >2.
[c] No overlap in populations with Cuzick et al (2012) and Cuzick et al (2015).

Table 5. Predicted Risk of Prostate Cancer Death at 10 Years by CCR Score Groupings

Cuzick et al (2015)			Lin et al (2018) Using Data From Cuzick et al (2015)		
Clinical Cell Cycle Risk Score	***N***	***10-Year Death Rate (95% CI), %[a]***	***CCR Score***	***N***	***10-Year Death Rate (95% CI), %[d]***
-1	NR	1.0 (0.2 to 1.8)			
0		2.2 (0.7 to 3.4)	≤0.8	Full[b]: 60 Modified[c]: 59	Full: 0 (CI NR) Modified: 0 (CI NR)
1		4.5 (2.3 to 7.0)	>0.8	Full[b]: 525 Modified[c]: 225	Full: 19.9. (CI NR) Modified: 8.7 (CI NR)
2		9.9 (6.4 to 13.0)			

3		20.2 (16.2 to 24.1)			
4		43.1 (34.1 to 51.2)			
5		73.5 (59.4 to 92.8)			
6		109.7 (82.0 to 120.8)			

CCR: combined clinical cell cycle risk; CI: confidence interval; NR: not reported.
[a] Estimated from digitizing a figure.
[b] Including all men from the validation cohort (≈52% high risk).
[c] Excluding high-risk men in the validation cohort.
[d] Based on the Kaplan-Meier plots

Table 6. Reclassification of NCCN Risk Stratification Criteria for Active Surveillance With the CCR Score[a]

NCCN Risk Group	CCR Score ≤0.8	CCR Score >0.8	Total
Met NCCN criteria for active surveillance[b]	7463	714	8177[b]
Did not meet NCCN criteria for active surveillance[b]	5758	52809	11038[b]
Total	13221	5994	19215

CCR: combined clinical cell cycle risk; NCCN: National Comprehensive Cancer Network.
[a] Adapted from Lin et al (2018).[43]
[b] Sample sizes here do not match the number of men reported to be low and favorable intermediate vs intermediate and high risk.

Section Summary: Prolaris

In a cohort of men conservatively managed following needle biopsy, Cuzick et al (2012) suggested that the CCP score alone was more prognostic than either PSA or Gleason score for tumor-specific mortality at 10-year follow-up based on hazard ratios. Cuzick et al (2015) found that discrimination improved somewhat by adding the CCP score to the CAPRA score, as reflected in the C statistic.[42] For conservatively managed patients, the studies showed that the CCP score is the strongest independent predictor of cancer death outcome yet described and could prove valuable in managing clinically localized prostate cancer. The CCP score also provides significant pretreatment prognostic information that cannot be provided by clinical variables and is useful for determining which patients can be safely managed conservatively, avoiding radical treatment.

Oncotype Dx® Genomic Prostate Score

The Oncotype Dx **Genomic Prostate Score** assay includes 5 reference genes and 12 cancer genes that represent 4 molecular pathways of prostate cancer oncogenesis: androgen receptor, cellular organization, stromal response, and proliferation. The assay results are combined to produce a GPS, which ranges from 0 to 100. Higher GPS scores indicate more risk.

Table 7. Clinical Validity Studies Assessing Oncotype DX Genomic Prostate Score

Study	Design	Dates	Sites	N	Population
Klein et al (2014)[50]	Case-cohort from prospective registry[a]	1998-2011	UCSF	395	Clinically localized; clinical stage T1/T2; PSA level ≤20 ng/ml, Gleason score ≤7; 3% African American
Cullen et al (2015)[51]	Retrospective cohort from prospective longitudinal study	1990-2011	U.S. military centers	382	Clinically localized; clinical stage T1/T2; PSA level ≤20 ng/ml, Gleason score ≤7; 20% African American
Van Den Eeden et al (2018)[52]	Retrospective cohort from registry (median follow-up, 9.8 y)	1995-2010	Kaiser Permanente Northern California	259	Prostate cancer who underwent RP within 12 mo of diagnosis, NCCN risk: very low, 3%; low, 21%; intermediate, 67%; high, 9%; 11% African American
Eggener et	Prospective	2014-	Multi-center	489	Clinically localized; clinical stage

al (2019)[54]	observational cohort	2015			T1/T2; PSA level ≤20 ng/ml, Gleason score ≤6

NCCN: National Comprehensive Cancer Network; PSA: prostate-specific antigen; RP: radical prostatectomy; UCSF: University of California, San Francisco.
[a] Only the validation sample cohort is listed.[55]

Results from the Klein et al (2014) clinical validation study and prostatectomy study provided information on the potential clinical validity of this test.[50]

Gene expression was quantified by reverse transcription-polymerase chain reaction for three studies-a discovery prostatectomy study (n=441), a biopsy study (n=167), and a prospectively designed, independent clinical validation study (n=395)-testing retrospectively collected needle biopsies from contemporary (1997-2011) patients with low to intermediate clinical risk who were candidates for active surveillance (AS). The main outcome measures defining aggressive Pca were clinical recurrence, Pca death, and adverse pathology at prostatectomy. Cox proportional hazards regression models were used to evaluate the association between gene expression and time to event end points. Of the 732 candidate genes analyzed, 288 (39%) were found to predict clinical recurrence despite heterogeneity and multifocality, and 198 (27%) were predictive of aggressive disease after adjustment for prostate-specific antigen, Gleason score, and clinical stage. Further analysis identified 17 genes representing multiple biological pathways that were combined into the GPS algorithm. In the validation study, GPS predicted high-grade (odds ratio [OR] per 20 GPS units: 2.3; 95% confidence interval [CI], 1.5-3.7; p<0.001) and high-stage (OR per 20 GPS units: 1.9;95% CI, 1.3-3.0; p=0.003) at surgical pathology. GPS predicted high-grade and/or high-stage disease after controlling for established clinical factors (p<0.005) such as an OR of 2.1 (95% CI, 1.4-3.2) when adjusting for Cancer of the Prostate Risk Assessment score. A limitation of the validation study was the inclusion of men with low-volume intermediate-risk Pca (Gleason score 3+4), for whom some providers would not consider AS. Genes representing multiple biological pathways discriminate Pca aggressiveness in biopsy tissue despite tumor heterogeneity, multifocality, and limited sampling at time of biopsy. The biopsy-based 17-gene GPS improves prediction of the presence or absence of adverse pathology and may help men with Pca make more informed decisions between AS and immediate treatment.

Table 8. Reclassification of Prostate Cancer Risk Categories With Oncotype DX Genomic Prostate Score

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

Adapted from the Klein et al (2014) validation study. GPS: Genomic Prostate Score; NCCN: National Comprehensive Cancer Network.

Table 9. Reclassification of Prostate Cancer 10-Year Clinical Recurrence Risk With Oncotype DX Genomic Prostate Score

Overall 10-Year Risk (AUA Risk Level)	10-Year Risk (GPS Low-Risk Group), %	10-Year Risk (GPS Intermediate-Risk Group), %	10-Year Risk (GPS High-Risk 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

Adapted from the Klein et al (2014) prostatectomy study. AUA: American Urological Association; GPS: Genomic Prostate Score.

A retrospective cohort study by Cullen et al (2015) included men with NCCN-defined very low through intermediate risk PC undergoing RP within 6 months of diagnosis.[51] Biopsies from 431 men treated for National Comprehensive Cancer Network (NCCN) very low-, low-, or intermediate-risk Pca between 1990 and 2011 at two US military medical centers were tested to validate the association between GPS and biochemical recurrence (BCR) and to confirm the association with AP. Metastatic recurrence (MR) was also evaluated.

GPS results (scale: 0-100) were obtained in 402 cases (93%); 62 men (15%) experienced BCR, 5 developed metastases, and 163 had AP. Median follow-up was 5.2 yr. GPS predicted time to BCR in univariable analysis (hazard ratio per 20 GPS units [HR/20 units]: 2.9; p<0.001) and after adjusting for NCCN risk group (HR/20 units: 2.7; p<0.001). GPS also predicted time to metastases (HR/20 units: 3.8; p=0.032), although the event rate was low (n=5). GPS was strongly associated with AP (odds ratio per 20 GPS units: 3.3; p<0.001), adjusted for NCCN risk group. In AA and Caucasian men, the median GPS was 30.3 for both, the distributions of GPS results were similar, and GPS was similarly predictive of outcome. The association of GPS with near- and long-term clinical end points establishes the assay as a strong independent measure of Pca aggressiveness. Tumor aggressiveness, as measured by GPS, and outcomes were similar in AA and Caucasian men in this equal-access health care system.

Van Den Eeden et al (2018) reported on a retrospective study using a stratified cohort sampling design including 279 of 6184 men who were diagnosed with prostate cancer within a registry between 1995 and 2010 and underwent RP within 12 months of diagnosis, with median follow-up of 9.8 years.[53] An assessment of the association between GPS and time to metastasis and Pca-specific death (PCD) in prespecified uni- and multivariable statistical analyses, based on Cox proportional hazard models accounting for sampling weights.[52] Valid GPS results were obtained for 259 (93%). In univariable analysis, GPS was strongly associated with time to PCD, hazard ratio (HR)/20 GPS units=3.23 (95% confidence interval [CI] 1.84-5.65; p<0.001), and time to metastasis, HR/20 units=2.75 (95% CI 1.63-4.63; p<0.001). The association between GPS and both end points remained significant after adjusting for National Comprehensive Cancer Network, American Urological Association, and Cancer of the Prostate Risk Assessment (CAPRA) risks (p<0.001). No patient with low- or intermediate-risk disease and a GPS of<20 developed metastases or PCD (n=31). In receiver operating characteristic analysis of PCD at 10 yr, GPS improved the c-statistic from 0.78 (CAPRA alone) to 0.84 (GPS+CAPRA; p<0.001). A limitation of the study was that patients were treated during an era when definitive treatment was standard of care with little adoption of active surveillance. The authors concluded that GPS is a strong independent predictor of long-term outcomes in clinically localized Pca in men treated with RP and may improve risk stratification for men with newly diagnosed disease.

Eggener et al (2019) reported on the validation of the 17-gene Oncotype DX GPS biopsy-based gene expression assay as a predictor of adverse pathology.[54] One hundred fourteen patients (treated by 59 physicians from 19 sites) elected RP and 40 (35%) had AP. GPS result was a significant predictor of AP (odds ratio per 20 GPS units [OR/20 units]: 2.2; 95% CI 1.2-4.1; P = .008) in univariable analysis and remained significant after adjustment for biopsy Gleason score, clinical T-stage, and log PSA (OR/20 units: 1.9; 95% CI 1.0-3.8; P = .04), or NCCN risk group (OR/20 units: 2.0; 95% CI 1.1-3.7; P = .02). Mean pre-GPS Decisional Conflict Scale score was 27 (95% CI 24-31), which improved significantly after GPS testing to 14 (95% CI 11-17) (P < .001). In this multi-institutional study, the GPS assay was

prospectively confirmed as an independent predictor of AP at surgery. GPS testing was associated with reduced patient decisional conflict.

Table 10. Estimates of 5-Year Biochemical Recurrence With Oncotype DX Genomic Prostate Score

Genomic Prostate Score	N	5-Year Biochemical Recurrence (95% Confidence Interval), %[a]
10	Not reported	5.1 (2.7 to 9.1)
20		8.5 (5.8 to 13.4)
30		14.2 (10.2 to 19.0)
40		22.9 (18.0 to 28.8)
50		35.2 (27.1 to 45.4)
60		53.8 (38.6 to 65.6)
70		71.8 (50.6 to 89.3)
80		87.3 (64.2 to 98.0)

Adapted from Cullen et al (2015).
[a] Estimated from digitizing a figure.

Table 11. Risk of Adverse Pathology With Oncotype DX Genomic Prostate Score

Overall AP Risk, % (NCCN Risk Level)	N	AP Risk, n (%) (GPS Less Favorable Group; n=5)	AP Risk, n (%) (GPS Consistent With Group; n=29)	AP Risk, n (%) (GPS More Favorable Group; n=18)
0% (very low)	2	-	0	-
32% (low)	34	5 (100)	6 (21)	0
71% (low-intermediate)	14	-	10 (34)	0

Adapted from Whalen et al (2016).[52] AP: adverse pathology; GPS: Genomic Prostate Score; NCCN: National Comprehensive Cancer Network.

Systematic Reviews

In 2016, Brand et al combined the Klein et al (2014) and Cullen et al (2015) studies using a patient-specific meta-analysis.[55] 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. GPS adds predictive value to 3 widely used clinical classifiers, and identifies a larger proportion of low-risk patients than identified by clinical risk group alone.

Section Summary: Oncotype Dx® Genomic Prostate Score

The evidence from 4 studies on clinical validity for Oncotype Dx **Genomic Prostate Score** suggests the GPS can reclassify a patient's risk of recurrence based on a specimen obtained at biopsy. One study provided a figure with data on reclassification of disease-specific survival using NCCN and GPS. Genes representing multiple biological pathways discriminate Pca aggressiveness in biopsy tissue despite tumor heterogeneity, multifocality, and limited sampling at time of biopsy. The biopsy-based 17-gene GPS appears to improve prediction of the presence or absence of adverse pathology and may help men with Pca make more informed decisions between AS and immediate treatment. The association of GPS with near- and long-term clinical end points establishes the assay as a strong independent measure of Pca aggressiveness.

Decipher® Biopsy

This section reviews Decipher for initial management decisions in men with newly diagnosed, localized prostate cancer.

Four retrospective cohort studies reporting the clinical validity of Decipher Biopsy in men with newly diagnosed, localized prostate cancer are summarized in Tables 17 and 18.

Table 12. Characteristics of Clinical Validity Studies Assessing the Decipher for Initial Management

Study	Study Population	Design	Comparator	Outcome	Sites	Dates
Berlin et al (2018)[66]	Intermediate-risk Pca treated with curative-intent dose-escalated image-guided RT without neoadjuvant, concomitant or adjuvant ADT	Retrospective cohort from registry	NCCN risk groups	BCR, Metastasis	Tertiary care center, probably in Ontario	2005-2011
Nguyen et al (2017)[67]	Treated with first-line RP or first-line RT plus ADT, had adverse pathology at surgery (defined as either preoperative PSA >20 ng/ml, step pT3 or margin-positive, or RP grade group ≥4), the vast majority of whom had presented with intermediate- or high-risk Pca	Retrospective cohort from manufacturer database	NCCN risk groups; clinical nomogram (CAPRA)	Metastases; Pca mortality (5 y)	7 tertiary referral clinics including Cleveland Clinic, Johns Hopkins	1987-2014
Ross et al (2014)[84]	Treated with first line RP	Retrospective cohort	NCCN risk groups	Metastases; mortality	Mayo clinic	2000-2006
Ross et al (2016)[87]	Treated with first line RP	Retrospective cohort	NCCN risk groups	Metastases; mortality	Mayo clinic	1992-2010

ADT: Androgen deprivation therapy; BCR: biochemical recurrence; CAPRA-S: Cancer of the Prostate Risk Assessment Postsurgical; NCCN: National Comprehensive Cancer Network; Pca: prostate cancer; RP: radical prostatectomy; RT: radiotherapy.

Berlin et al (2018) reported on the utility of the genomic classifier (GC) to better identify patients with intermediate-risk prostate cancer (IR-Pca) who are sufficiently treated by RT alone.[66] By NCCN subclassification, 33 (27.3%) and 87 (71.9%) of men were classified as having favorable and unfavorable IR-Pca, respectively (1 case unclassifiable). GC scores were high in 3 favorable IR-Pca and low in 60 unfavorable IR-Pca. Higher GC scores, but not NCCN risk subgroups, were associated with biochemical relapse (hazard ratio, 1.36; 95% confidence interval [CI], 1.09-1.71] per 10% increase; P = .007) and metastasis (hazard ratio, 2.05; 95% CI, 1.24-4.24; P = .004). GC predicted biochemical failure at 5 years (area under the curve, 0.78; 95% CI, 0.59-0.91), and the combinatorial NCCN + GC model significantly outperformed the NCCN alone model for predicting early-onset metastasis (area under the curve for 5-year metastasis of 0.89 vs. 0.86 [GC alone] vs. 0.54 [NCCN alone]). The accuracy of the GC for predicting disease recurrence in IR-Pca patients treated with dose-escalated RT alone was demonstrated. The findings highlight the need to evaluate this GC in a prospective clinical trial investigating the role of androgen deprivation therapy-RT in genomic-defined IR-Pca subgroups.

Nguyen et al (2017) evaluated how a GC that predicts the risk of metastasis after prostatectomy would impact adjuvant treatment recommendations made by radiation oncologists and urologists.[67] Twenty-six radiation oncologists and 20 urologists with genitourinary oncology expertise reviewed de-identified clinical results from 11 patients after radical prostatectomy and made adjuvant treatment recommendations. The same cases were later randomized and reassigned, and treatment recommendations were made using the clinical information and GC test results together. Using clinical information alone, observation was recommended in 42% of decisions made by urologists vs 23% by radiation oncologists (P < .0001). The GC test results altered 35% and 45% of treatment recommendations made by radiation oncologists and urologists, respectively. Multivariate analysis showed GC risk was the strongest factor influencing treatment recommendations by both specialties, with an adjusted odds ratio of 4.17 (95% confidence interval [CI], 2.26-7.70) and 6.51 (95% CI, 4.29-9.88) for radiation oncologists and urologists, respectively. GC results indicating high metastatic risk resulted in intensification of treatment, whereas low metastatic risk resulted in less aggressive recommendations. The GC results increased interdisciplinary agreement in treatment recommendations, as the odds of a recommendation for adjuvant treatment by urologists vs radiation oncologists increased from 0.27 (95% CI, 0.17-0.44) to 0.46 (95% CI, 0.29-0.75) after results of the GC test were available. The GC test significantly influenced adjuvant postprostatectomy treatment recommendations, reduced disagreement between radiation oncologists and urologists and has the potential to enhance personalization of postprostatectomy care.

Ross et al (2014) evaluated Decipher GC for its ability to predict metastasis following biochemical recurrence (BCR).[84] The study population included 85 clinically high-risk patients who developed BCR after RP. GC scores stratified men with BCR into those who would or would not develop metastasis (8% of patients with low versus 40% with high scores developed metastasis, P<0.001). The area under the curve for predicting metastasis after BCR was 0.82 (95% CI, 0.76-0.86) for GC, compared to GS 0.64 (0.58-0.70), PSAdT 0.69 (0.61-0.77) and ttBCR 0.52 (0.46-0.59). Decision curve analysis showed that GC scores had a higher overall net benefit compared to models based solely on clinicopathologic features. In multivariable modeling with clinicopathologic variables, GC score was the only significant predictor of metastasis (P=0.003). When compared to clinicopathologic variables, GC better predicted metastatic progression among this cohort of men with BCR following RP. While confirmatory studies are needed, these results suggest that use of GC may allow for better selection of men requiring earlier initiation of treatment at the time of BCR.

In 2016, Ross et al evaluated the Decipher GC in a natural history cohort of men at risk who received no additional treatment until the time of metastatic progression.[87] This retrospective case-cohort design included 356 men who underwent RP between 1992 and 2010 at intermediate or high risk and received no additional treatment until the time of metastasis.

Ninety six patients had unavailable tumor blocks or failed microarray quality control. Decipher scores were then obtained for 260 patients, of whom 99 experienced metastasis. Decipher correlated with increased cumulative incidence of biochemical recurrence, metastasis, and prostate cancer-specific mortality (p<0.01). The cumulative incidence of metastasis was 12% and 47%for patients with low and high Decipher scores, respectively, at 10 yr after RP. Decipher was independently prognostic of metastasis in multivariable analysis (hazard ratio 1.26 per 10% increase; p<0.01). Decipher had a c-index of 0.76 and increased the c-index of Eggener and CAPRA-S risk models from 0.76 and 0.77 to 0.86 and 0.87, respectively, at 10 yr

after RP. In a patient population that received no adjuvant or salvage therapy after prostatectomy until metastatic progression, higher Decipher scores correlated with clinical events, and inclusion of Decipher scores improved the prognostic performance of validated clinicopathologic risk models. These results confirm the utility already reported for Decipher.

Section Summary: Decipher® Biopsy
For individuals who have low- or intermediate-risk clinically localized untreated prostate cancer who receive Decipher Biopsy, the evidence includes retrospective cohort studies of clinical validity using archived samples in intermediate-risk patients and no studies of clinical utility. The relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. For intermediate-risk men, the accuracy of the GC for predicting disease recurrence in IR-Pca patients treated with dose-escalated RT alone was demonstrated in Berlin et al. Nguyen et al demonstrated that the GC test significantly influenced adjuvant postprostatectomy treatment recommendations, reduced disagreement between radiation oncologists and urologists and has the potential to enhance personalization of postprostatectomy care while the results of Ross et al confirm the utility already reported for Decipher in men postpostatetcomy.

ProMark™ Protein Biomarker Test
The ProMark assay includes 8 biomarkers that predict prostate pathology aggressiveness and lethal outcomes: *DERL1*, *PDSS2*, *pS6*, *YBX1*, *HSPA9*, *FUS*, *SMAD4*, and *CUL2*. The assay results are combined using predefined coefficients for each marker from a logistic regression model to calculate a risk score. The risk score is continuous number between 0 and 1, which estimates the probability of “non–GS 6” pathology.

Blume-Jensen et al (2015) reported on a study of 381 biopsies matched to prostatectomy specimens used to develop an 8-biomarker proteomic assay to predict prostate final pathology on prostatectomy specimen using risk scores.[68]

Biomarker risk scores were defined as favorable if less than or equal to 0.33 and nonfavorable if greater than 0.80 with a possible range between 0 and 1 based on false-negative and false-positive rates of 10% and 5%, respectively. The risk score generated for each patient was compared with 2 current risk stratification systems, NCCN guideline categories and the D’Amico system. Results from the study showed that, at a risk score of less than or equal to 0.33, the predictive value of the assay for favorable pathology in very low- and low-risk NCCN and low-risk D’Amico groups were 95%, 81.5%, and 87.2%, respectively, while the NCCN and D’Amico risk classification groups alone had predictive values of 80.3%, 63.8%, and 70.6%, respectively. The positive predictive value for identifying favorable disease with a risk score of less than or equal to 0.33 was 83.6% (specificity, 90%). At a risk score of greater than 0.80, 77% had nonfavorable disease. Overall, 39% of the patients in the study had risk scores less than or equal to 0.33 or greater than 0.8, 81% or which were correctly identified with the 8-biomarker assay. Of the patients with intermediate risk scores (>0.33 to ≤0.8), 58.3% had favorable disease.

The performance of the assay was evaluated on a second blinded study of 276 cases to validate the assay’s ability to distinguish “favorable” pathology (defined as Gleason score on prostatectomy less than or equal to 3+4 and organ-confined disease) versus “nonfavorable” pathology (defined as Gleason score on prostatectomy greater than or equal to 4+3 or non-

organ-defined disease). The second validation study separated favorable from nonfavorable pathology (AUC=0.68; 95% CI, 0.61 to 0.74).

Table 13. Clinical Validity of ProMark

Study	Design[a]	Outcome	Site	N
Blume-Jensen et al (2015)[68]	Retrospective cohort[a]	Favorable pathology at RP	Montreal, QC	276[a]

RP: radical prostatectomy.
[a] Only the validation sample cohort N.

Section Summary: ProMark™ Protein Biomarker Test

The Blume-Jensen study showed the 8-biomarker assay provided individualized, independent prognostic information relative to current risk stratification systems, and may improve the precision of clinical decision making following prostate biopsy. .

MANAGEMENT DECISION AFTER RP

Clinical Context and Test Purpose

The purpose of gene expression profiling (GEP) and protein biomarkers tests in patients who have prostate cancer and who have undergone RP is to inform management decisions.

For example, the optimal timing of RT after RP is a debate. Adjuvant RT may maximize cancer control outcomes; salvage RT can minimize overtreatment and still lead to acceptable oncologic outcomes.[68] Adjuvant RT in men with pT3 or margin-positive cancer has been compared with observation in RCTs; such comparisons have shown that adjuvant RT improves the biochemical and local control rates among patients with adverse pathology at RP.[69-71] Although the observation arms in these trials included men who received adjuvant therapy, the trials did not directly compare early salvage RT with immediate adjuvant RT because they included varying or unspecified thresholds for the initiation of salvage therapy RT.

Guidelines have recommended that adjuvant RT be offered to patients with adverse pathologic findings at RP, and salvage RT be offered to patients with PSA or local recurrence after RP.[14,72] However, many men treated with RT will never experience recurrence after surgery and therefore receive no benefit while experiencing harm from RT. Therefore, a test that could be used to identify men who meet criteria for adjuvant or early salvage RT but can safely receive observation instead would be useful.

Other post-RP clinical questions for which GEP or protein biomarker testing might be useful is in guiding systemic treatment (ADT and/or chemotherapy) in men receiving RT.

The second question addressed in this evidence review is: Does gene expression profiling or tests of protein biomarkers, compared with clinicopathologic risk stratification or when used with clinicopathologic risk stratification, improve outcomes in men following RP?

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is individuals who have undergone RP treatment for prostate cancer, and who are deciding on subsequent management such as adjuvant RT versus no adjuvant RT. The Decipher results report says that "Decipher is intended for use in those patients who present with specific risk factors for the recurrence of prostate cancer after radical prostatectomy: (1) stage T2 disease with positive surgical margins, or (2) stage T3 disease, or (3) rising prostate-specific antigen (PSA) levels after initial PSA nadir."

Interventions

Prolaris, described in the previous section, is also intended to classify low-to-intermediate risk individuals who have undergone RP.

Decipher is a tissue-based tumor 22-biomarker gene expression profiling test intended to classify high- risk individuals who have undergone RP. The cut-points 0.45 and 0.60 are used to categorize men using a low-, intermediate- , and high-risk genomic classifier (GC) on the Decipher test results report.

Comparators

Clinicopathologic risk stratification is currently being used to make decisions about prostate cancer management following RP. Clinical characteristics (e.g., stage, biopsy Gleason grade, serum PSA, surgical margin, disease involvement) and demographic characteristics (e.g., age, life expectancy) are combined to classify men according to risk. As described previously, NCCN and AUA provide risk-stratification guidelines.[12,14] The Stephenson nomogram[73,74] and Cancer of the Prostate Risk Assessment–Surgical (CAPRA-S) nomogram[75] can be used to predict outcomes after RP.

Outcomes

Beneficial outcomes resulting from a true test result are prolonged survival, improved quality of life and reduction in unnecessary treatment-related adverse effects. Harmful outcomes resulting from a false test result are recurrence, metastases or death, and unnecessary treatments. The outcomes of interest are listed in Table 14.

Table 14. Outcomes of Interest for Individuals After Radical Prostatectomy

Outcome	Details
Overall survival	10-year survival
Disease-specific survival	10-year prostate cancer-free survival; 10-year prostate cancer death rate; 10-year recurrence rate
Quality of life	See Chen et al (2014)[40] for NCI-recommended health-related quality of life measures for localized prostate cancer
Treatment-related morbidity	Adverse events of radiotherapy or radical prostatectomy

NCI: National Cancer Institute.

Ten-year outcomes are of interest due to the prolonged natural history of prostate cancer and low number of events observed.

Prolaris

Prolaris used for initial management decisions was described in the previous section. This section will review Prolaris for management after RP.

Four studies reporting clinical validity in the post-RP management setting were included as outlined in Table 15. Three of these studies-Cuzick et al (2011),[76] Cooperberg et al (2013)[55] and Bishoff et al (2014)[77] -reported on post-RP patients. Koch et al (2016)[78] reported on post-RP patients with BCR. Freedland et al (2013)[79] reported on post-RT patients but is included in this section for completeness.

Table 15. Studies Reporting Clinical Validity of Prolaris for post-RP or post-RT management

Study	Design[a]	Outcome	Dates	Sites	N
Postprostatectomy					
Cuzick et al (2011)[76]	Retrospective cohort from prospective registry	BCR (median follow-up, 9.4 y)	1985-1995	Scott and White Clinic	366
Cooperberg et al (2013)[55]	Retrospective cohort from prospective registry	BCR (median follow-up, 7 y)	1994-2011	UCSF Registry	413
Bishoff et al (2014)[77]	Retrospective cohort from medical records	BCR (median follow-up, 5 y, 7 y, NR for 3 cohorts)	2005-2006 1994-2005 1997-2004	Martini Clinic Durham VAMC Intermountain Healthcare	283 176 123
Koch et al (2016)[78]	Retrospective cohort from medical records	Systemic disease (median follow-up, 9.4 y)	1995-2010	Indiana University SOM	47
After external-beam radiotherapy					
Freedland et al (2013)[79]	Retrospective cohort, source unclear	BCR	1991-2006	Durham VAMC	141

BCR: biochemical recurrence; NR: not reported; PC: prostate cancer; SOM: school of medicine; UCSF: University of California, San Francisco; VAMC: veterans affairs medical center

Cuzick et al (2011) examined the potential use of the Prolaris CCP test combined with a clinical score following RP, using a retrospective cohort of archived samples from a tumor registry.[76] 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 after RP between 1985 and 1995 were identified from a tumor registry (n=366 with CCP scores, Scott and White Clinic, in Texas). The primary end point was time to 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) (see Table 13). 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 5 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 noteworthy. For conservatively managed patients, the CCP score is the strongest independent predictor of cancer death outcome yet described and may prove valuable in managing clinically prostate cancer patients.

Cooperberg et al (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 using a prospective-retrospective design (conforming to a ProBE study design).[55] A prognostic model was developed from the RP cohort described by Cuzick et al (2011).[76] 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 (19.9%) men. The unadjusted hazard ratio for BCR increased by 2.1 (95% CI, 1.6 to 2.9) per unit increase in CCP score (see Table 22). A predictive model for the combined CCP/CAPRA-S score developed in the Cuzick et al (2011)[76] 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 score.

Bishoff et al (2014) examined the prognostic ability of the CCP score in 3 cohorts: the 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).[77] 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 hazard ratio for BCR by 1.47 (95% CI, 1.23 to 1.76) . The cell cycle progression score derived from a biopsy sample was associated with adverse outcomes after surgery. These results indicate that the score can be used at disease diagnosis to better define patient prognosis and enable more appropriate clinical care.

Koch et al (2016) evaluated whether the CCP score could discriminate between systemic disease and local recurrence in patients with BCR after RP.[78] All 60 patients treated with RP as primary therapy at an academic medical center between 1995 and 2010 for whom samples were available and who had a BCR and either developed metastatic disease or received salvage EBRT with at least 2 years of follow-up were eligible for retrospective analysis (N=60). Data from 5 patients were excluded for failing to meeting clinical eligibility requirements (no clarification provided) or because data were incomplete; sample blocks from 3 patients contained insufficient tumor for assay and data from 6 patients were excluded due to lack of "passing" CCP scores. Forty-seven patients were included in analysis. The outcome was classified into 3 categories: (1) metastatic disease (n=22), (2) nonresponse to salvage EBRT (n=14), and (3) durable response to salvage EBRT (n=11). Analyses were performed with a binary outcome (categories 1 and 2 combined). For each 1-unit change in the CCP score, the univariate odds ratio (OR) for metastatic disease or nonresponse was 3.72 (95% CI, 1.29 to 10.7) . Elevated CCP score was associated with increased risk of systemic disease, indicating that CCP score may be useful in identifying patients with BCR who are most likely to benefit from salvage radiation therapy.

Table 16. Univariate and Multivariate Association Between Prolaris CCP and Outcomes in Post-RP Clinical Validation Studies

Study	Outcome	N	Median FU, y	Unadjusted	Multivariate
				Ratio (95% CI)	Ratio (95% CI)
Cuzick et al (2011)	BCR	366	9.4	HR=1.89 (1.54-2.31)	1.77 (1.40-2.22)[a]
	Prostate cancer death	337		HR=2.92 (2.38-3.57)	2.56 (1.85-3.53)[b]
Cooperberg et al (2013)	BCR	413	7	HR=2.1 (1.6-2.9)	1.7 (1.3-2.4)[c]
Bishoff et al (2014)	BCR	582	5/7[f]	HR=1.60 (1.35-	1.47 (1.23-1.76)[d]

				1.90)	
Koch et al (2016)	Metastatic disease or nonresponse	47	9.4	OR=3.72 (1.29-10.7)	10.4 (2.05-90.1)[e]

BCR: biochemical recurrence; CCP: cell cycle progression; CI: confidence interval; HR: hazard ratio; OR: odd ration; PSA: prostate-specific antigen; RP: radical prostatectomy

[a] Per 1 unit increase in CCP. Adjusted for PSA, gleason score, pathological T stage and grade, positive surgical margins, extracapsular extension, bladder involvement, seminal vesicle involvement, positive lymph node, and age

[b] Per 1 unit increase in CCP. Adjusted for gleason score, PSA, Ki67, and cancer extent

[c] Per 1 unit increase in CCP. Adjusted for cancer of the prostate risk assessment—surgical

[d] Per 1 unit increase in CCP. Adjusted for PSA, gleason score, and adjuvant treatment

[e] Per 1 unit increase in CCP. Adjusted for gleason score, time from surgery to BCR, and PSA

[f] Not reported for 3 cohorts

Although not a study of management, post-RP, Freedland et al (2013) described the prognostic ability of the CCP score for predicting BCR in men who received primary EBRT.[81] The retrospective data included 141 men diagnosed with prostate cancer who had biopsy samples and follow-up of at least 3 years who were treated with EBRT from 1991 to 2006. Nineteen (13%) of men experienced BCR by 5 years. The univariate hazard ratio for BCR for each 1-unit increase in CCP was 2.55 (95% CI, 1.43 to 4.55). The multivariable hazard ratio for BCR associated with 1-unit increase in CCP, including adjustment for pretreatment PSA, Gleason, percent positive cores, and concurrent androgen deprivation therapy, was 2.11 (95% CI, 1.05 to 4.25).

Decision Curves

In a decision-curve analysis, Cooperberg et al (2013) found the CAPRA-S score superior to CCP alone (as well as treat-none or treat-all strategies) in men after prostatectomy.[55] 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 RT as 3:7), the combined CCP/CAPRA-S score would detect about 2 more men per 100 likely to experience BCR if the false-positive rate was fixed. The CCP score was validated to have significant prognostic accuracy after controlling for all available clinical and pathologic data. The score may improve accuracy of risk stratification for men with clinically localized prostate cancer, including those with low-risk disease.

Section Summary: Prolaris

Four identified studies examined the clinical validity of Prolaris in men after RP using a BCR or systemic disease end point. Cuzick et al (2011) found the CCP score is the strongest independent predictor of cancer death outcome yet described and may prove valuable in managing clinically localized prostate cancer.

Cooperberg et al (2013) found the AUC for BCR improved from 0.73 (CAPRA-S alone) to 0.77 by adding CCP score.[55] Bishoff et al (2014)[77] and Koch et al (2016)[78] Found elevated CCP score was associated with increased risk of systemic disease, indicating that CCP score may be useful in identifying patients with BCR who are most likely to benefit from salvage radiation therapy**.**

Decipher Prostate RP

Decipher used for initial management decisions was described in the previous section. This section reviews Decipher for management after RP.

The Decipher 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.

The clinical validity of the Decipher test (GC) has been reported in multiple studies to predict metastasis, mortality, or BCR after RP in men with postoperative high-risk features like pathologic stage T2 with positive margins, pathologic stage T3 disease, or a rising PSA level .[80,81,82,83,84,85,86,87,88,89,90]

Table 17. Characteristics of Clinical Validity Studies Assessing the Decipher Genomic Classifier

Study	Study Population	Design	Comparator	Outcome	Sites	Dates
Spratt et al (2018)[91]	Clinically localized Pca after RP; serious PSA levels post-RP documented; no neoadjuvant ADT; 31% with detectable PSA 8 wk post-RP	Retrospective cohort from registry	Clinicopathological risk factors (e.g., preop PSA, SM, RP grade group)	Metastases (5 y)	MD Anderson, Durham VA, Thomas Jefferson	1990-2015
Karnes et al (2018)[92]	Clinically localized Pca after RP; pathologic GS ≥7, pT3, pN1, or margin- positive; no neoadjuvant treatment; ≥10 y follow-up for patient alive	Retrospective cohort from registry	Clinicopathologic risk factors (e.g., preop PSA, EPE, GS); clinical nomogram (CAPRA-S)	Pca mortality (10 y)	Mayo Clinic, Johns Hopkins, Cleveland Clinic, Durham VA	1987-2010
Freedland et al (2016)[88]	Clinically localized Pca after RP; received postoperative SRT; pathologic node-negative disease; undetectable post-RP PSA; no neoadjuvant or adjuvant treatment; 32% African American	Retrospective cohort from registry	Clinicopathologic risk factors (e.g., preop PSA, EPE, GS); clinical nomogram (Briganti, CAPRA-S)	Metastases	Durham VA, Thomas Jeff erson, Mayo Clinic	1991-2010
Glass et al (2016)[89]	Clinically localized Pca after RP; preop PSA >20 ng/mL, stage pT3, margin-positive, or pathologic GS ≥8; no neoadjuvant or adjuvant treatment; 2% African American	Retrospective cohort from registry	Clinicopathologic risk factors (e.g., preop PSA, EPE, GS); clinical nomogram (CAPRA-S)	Clinical recurrence (10 y)	Kaiser Permanente Northwest	1997-2009
Ross et al (2016)[93]	Clinically localized Pca after RP; CAPRA-S score ≥3, pathologic GS ≥7, post-RP PSA nadir <0.2 ng/mL, and sufficient tissue	Case cohort from registry	Clinicopathologic risk factors (e.g., preop PSA, EPE, GS); clinical nomogram (CAPRA-S, Eggener)	Metastases (10 y)	Johns Hopkins	1992-2010

	and clinical data; no nodal disease prior to surgery; no treatment before metastasis; 8% African American					
Ross (2016)[93]	Clinically localized Pca after RP; stage pT3 or margin-positive; achieve PSA nadir after surgery; no node-positive; no neoadjuvant treatment; no hormone-only treatment prior to metastasis; no SRT for PSA >10 ng/mL	Retrospective cohort from registry	Clinical variables (e.g., ART, MRD-SRT, SRT, no-RT); clinical nomogram (CAPRA-S)	Metastasis (10-y)	Mayo Clinic, Johns Hopkins, Durham VA, Thomas Jefferson	1990-2010
Cooperberg et al (2015)[83]	Clinically localized Pca after RP; preop PSA >20 ng/mL, stage pT3b, or pathologic GS ≥8; no neoadjuvant treatment; achieve PSA nadir after surgery	Case cohort from registry	Clinicopathologic risk factors (e.g., preop PSA, EPE, GS); clinical nomogram (CAPRA-S)	Pca mortality	CapSURE Registry	2000-2006
Den et al (2015)[80]	Clinically localized Pca after RP; pT3 or margin-positive disease; received post-RP RT; no neoadjuvant treatment; no lymph node invasion	Retrospective cohort from registry	Clinicopathologic risk factors (e.g., preop PSA, EPE, GS); clinical nomogram (CAPRA-S)	Metastases	Thomas Jefferson, Mayo Clinic	1990-2009
Klein et al (2015)[81,]; Klein et al (2016)[90]	Clinically localized Pca after RP; preop PSA >20 ng/mL, stage pT3, margin-positive or pathologic GS ≥8; pathologic node-negative disease; undetectable post-RP PSA; no neoadjuvant or adjuvant treatment; ≥5 y follow-up for censored patients; 8% African American	Retrospective cohort from registry	Clinicopathologic risk factors (e.g., pre-op PSA, EPE, GS); clinical nomogram (Stephenson, CAPRA-S)	Metastases (5 y, 10 y)	Cleveland Clinic	1993-2001
Den et al (2014)[82]	Clinically localized Pca after RP; pT3 or margin-positive disease; received post-RP RT; no neoadjuvant	Retrospective cohort from registry	Clinicopathologic risk factors (e.g., preop PSA, EPE, GS); clinical nomogram (Stephenson, CAPRA-S)	BCR	Thomas Jefferson	1999-2009

	treatment; 39% BCR; 13% African American					
Ross et al (2014)[84.a] (BCR only)	Clinically localized Pca with BCR after RP; preop PSA >20 ng/mL, pathologic GS ≥8, SVI or Mayo Clinic nomogram score ≥10; no neoadjuvant treatment	Case cohort from registry	Clinicopathologic risk factors (e.g., preop PSA, EPE, GS); clinical nomogram (Stephenson, CAPRA-S)	Metastases (5 y)	Mayo Clinic	2000-2006
Erho et al (2013)[86.] (validation)	Clinically localized Pca after RP; 32% no evidence of disease post-RP within 7 y of follow-up; 34% BCR post-RP with no clinical metastasis within 5 y of BCR; 34% clinical metastasis within 5 y of BCR	Nested case-control from registry	Clinicopathologic risk factors (e.g., preop PSA, EPE, GS)	Metastases	Mayo Clinic	1987-2001
Karnes et al (2013)[85]	Clinically localized Pca after RP; preop PSA >20 ng/mL, pathologic GS ≥8, SVI or Mayo Clinic nomogram score ≥10; no neoadjuvant treatment	Case cohort from registry	Clinicopathologic risk factors (e.g., preop PSA, EPE, GS); clinical nomogram (Stephenson)	Metastases (5 y)	Mayo Clinic	2000-2006

ART: adjuvant radiotherapy; CARPA-S: Cancer of the Prostate Risk Assessment Postsurgical; BCR: biochemical recurrence; EPE: extraprostatic extension; GS: Gleason Score; MRD: minimal disease residual; Pca: prostate cancer; preop: preoperative; RP: radical prostatectomy; RT: radiotherapy; SM: surgical margins; SRT: salvage radiotherapy; SVI: seminal vesicle invasion.
[a] Appears to be subgroup with BCR from Karnes et al (2013).

Table 18. Reported Prognostic Accuracies for Metastasis or PC Mortality of Decipher as a Continuous Score and Comparators

Study	Outcome	AHR/AOR (95% CI) for Association Between GC and Outcome	AUC (95% CI)		
			GC	Comparator	GC + Comparator
Spratt (2018)[91]; 95% received RT	Metastasis	NR	0.86 (0.80 to 0.94)	0.69 (0.41 to 0.89)[b]	0.83 (0.70 to 1)
Karnes (2018)[92]	Pca mortality	1.3 (1.2 to 1.5)	0.73 (0.67 to 0.78)	0.73 (0.68 to 0.78)	0.76 (0.71 to 0.82)
Freedland (2016)[88]	Metastasis post-RT	1.6 (1.1 to 2.1)	0.85 (0.73 to 0.88)	0.65 (0.54 to 0.81)[g]	NR
Ross (2016)[93]	Metastasis	1.3 (1.1 to 1.5)	0.76 (0.65 to 0.84)	0.77 (0.69 to 0.85)[b]	0.87 (0.77 to 0.94)
Glass (2016)[89]	Metastasis	1.5 (p=0.011)	0.80 (0.64 to 0.92)	0.73 (0.49 to 0.95)[c]	0.84 (0.70 to 0.96)
Cooperberg (2015)[83]	Pca mortality	1.8 (1.5 to 2.3)	0.78 (0.68 to 0.87)	0.75 (0.55 to 0.84)[b]	
Klein (2015)[81]; Klein (2016)90	Metastasis 5 y Metastasis 10 y	1.5 (1.1 to 2.1) 1.7 (1.1 to 2.8)	0.77 (0.66 to 0.87) 0.80 (0.58 to 0.95)	0.75 (0.65 to 0.84)[c] 0.75 (0.64 to 0.87)[h]	0.79 (0.65 to 0.85) 0.88 (0.76 to 0.96)
Den (2015)[80]	Metastasis post-RT	1.9 (p<0.001)	0.78 (0.64 to 0.91)	0.70 (0.49 to 0.90)[b]	0.85 (0.79 to 0.93)
Ross (2014)[84]	Metastasis	1.4 (p=0.003)	0.82 (0.76 to 0.86)	0.70 (0.66 to 0.75)[a]	0.75 (0.69 to 0.80)
Den (2014)[82]	Metastasis	NR	0.70 (0.49 to 0.90)[d]	0.78 (0.64 to 0.91)	0.80 (0.68 to 0.93)
Erho (2013)[86]	Metastasis	1.4 (p<0.001)	0.75 (0.70 to 0.81)[e]	0.69 (0.60 to 0.77)[a,e]	0.74 (0.65 to 0.82)[a,e]
Karnes (2013)[85]	Metastasis	1.5 (p<0.001)	0.79 (0.68 to 0.87)	0.64 (0.55 to 0.72)[d,f]	

AHR: adjusted hazard ratio; AOR: adjusted odds ratio; AUC: area under the curve; CI: confidence interval; GC: genomic classifier; NR: not reported; Pca: prostate cancer; RT: radiotherapy.
[a] Clinical classifier includes Gleason score, extracapsular extension, positive surgical margins, seminal vesicle invasion, or lymph node involvement.
[b] Cancer of the Prostate Risk Assessment-Surgical.
[c] Stephenson nomogram.
[d] Only reported vs single clinical predictors.
[e] AUC CI obtained by digitizing figure.
[f] Gleason score.
[g] Briganti score.
[h] National Comprehensive Cancer Network risk categories.
[i] With detectable PSA post-RP.

All studies were conducted retrospectively from registry data or clinical records. The development study had a nested case-control design.[86] The 5- and 10-year results of one study were published separately.[81,90] Four were case-cohort studies and eight used retrospective cohorts. Nine studies were supported by GenomeDx (now Decipher Corp), which offers the Decipher test. The cutpoints used to classify men into low-, intermediate- and high-risk by GC score were updated in 2016. Only 1 study (Karnes et al [2018][92]) has reported 10-year prostate cancer-specific survival after the update in the cutpoints.

Several studies,[83,84,85,86,93,91,93] including the test (validation) sample from the development study, examined men observed following RP and undergoing adjuvant or salvage RT. Median follow-up periods ranged from 6.4 to 16.9 years. The distributions of Gleason scores in the studies varied from 17.8% to 49.3% for those with Gleason scores of 8 or higher and from 0.4% to 15.1% for those with scores of 6 or lower. Extracapsular extension of the tumor ranged from 42.7% and 72.3% of men across studies.

Association between GC continuous score and metastasis or prostate cancer-specific mortality is shown in Table 25. The GC AUCs for predicting metastases are shown in Table 24. Among the 69 men developing metastases in Karnes et al (2013), of the 29 with Gleason scores of 7

or lower, 10 were correctly reclassified to the highest GC risk (score >0.6), but of the 40 men with Gleason scores of 8 or higher, 10 were incorrectly reclassified to the lowest GC risk group (score <0.4).85

The cumulative incidence of metastases by risk group is shown in Table 26. Two studies reported prostate cancer-specific mortality; only one of which included ten-year outcomes. Precision estimates were not provided. Values in the tables below may be estimated from figures when exact values were not provided in article text or tables.

Table 19. Metastasis by GC Risk Group

Study	FU Time, y	N	Patients in Risk Group, %	Metastasis Rate, %				
					High	Low	Int	High
Spratt et al (2018)[91]	10	561	46	28	26	0	3	23
Ross et al (2016)[93]	5	422	57	27	16	7	10	22
Freedland et al (2016)[88]	10	170	51	31	18	3	8	33
Glass et al (2016)[89]	10	224	NR	NR	NR	0	3	
Ross et al (2016)[87]	10	260	73	17	10	8	20	32
Klein et al (2015)[81]								
Den et al (2015)[80]	5	188	41	39	20	0	9	29
Den et al (2014)[82]	5	139	21	38	41	0	5	17
Ross et al (2014)[84]	5	85	NR	NR	NR	9	54	
Karnes et al (2013)[85]	5	219	51	22	27	2	6	22

FU: follow-up; GC: genomic classifier; Int: intermediate; NR: not reported.

For prostate cancer mortality, compared with CAPRA-S, Cooperberg et al (2015) found that the GC improved reclassification of the 19 men with CAPRA-S scores of 5 or lower, 12 were correctly reclassified to the highest GC risk, and 1 was incorrectly reclassified with a CAPRA-S score greater than 6 to low-risk; all men had CAPRA-S scores of 3 or more.[83]

Of note, Karnes et al (2018) reported the preferred outcome for this review (10-year prostate cancer-specific survival).[92] The authors found that adding the GC to CAPRA improved the AUC from 0.73 to 0.76 with highly overlapping CIs. The 10-year cumulative incidence of prostate cancer-specific mortality by CAPRA and GC risk categories are shown in Table 21. Samples sizes and precision estimates for the cross-tabulations were not provided.

Table 20. Prostate-Cancer-Specific Mortality by Genomic Classifier Risk Group

Study	FU, y	N	Patients in Risk Group, %	5-Year Metastasis Rate, %				
			Low	Int	High	Low	Int	High
Karnes et al (2018)[92]	10	561	58	17	25	12	13	45
Cooperberg et al (2015)[83]	5	185	54	22	24	6	3	30

FU: follow-up; Int: intermediate

Table 21. Cross-Tabulation of Ten-Year Cumulative Incidence of Prostate Cancer-Specific Mortality by GC and CAPRA

CAPRA-S Rish Category	Decipher GC Risk Category, %	
	Low/Intermediate (≤0.6)	High (>0.6)
Low-risk (<6)	2.8 (CI NR)	18 (CI NR)
High-risk (≥6)	5.5 (CI NR)	30 (CI NR)

Adapted from Karnes et al (2018).[92.]
CAPRA: Cancer of the Prostate Risk Assessment; CI: confidence interval; GC: genomic classifier; NR: not reported.

Systematic Reviews

Spratt et al (2017)[94] reported an individual patient-level data meta-analysis of 5 studies described in the previous section.[82,85,87,88,89] Data from patients randomly selected from the case-cohort studies (total n=855 patients) were included. The pooled 10-year metastases incidence rates were 5.5%, 15.0%, and 26.7% for GC low-, intermediate-, and high-risk, respectively (p<0.001, CIs not reported). The AUC for 10-year distant metastasis of the clinical model alone was 0.76, which increased to 0.81 with the inclusion of GC.

Decision Curves

Studies have included decision curves comparing the net benefit of different strategies using metastases or survival as the outcome.[80,81,83,84,85,87,92,95,92] In observational and RT samples from Karnes et al (2013)[85] and Ross et al (2014),[84] using a 15% to 25% range of thresholds for decision making (i.e., suspected probability of developing metastases) would be expected to identify correctly as few as no men or as many as 4 per 100 likely to experience metastases. This range of thresholds assumes several things: it assumes those making the decisions are relying on the GC result for adjuvant RT decisions, compared with treating based on the best comparator test, and it assumes no increase in false-positives. In the two observation-only samples, the GC improved the net benefit over a "treat none" strategy over 15% to 25% thresholds, it appeared to offer little over the comparator test (e.g., about one additional patient would be likely to experience metastases without an increase in false-positives).[81,87] In Ross et al (2014), when compared to clinicopathologic variables, GC better predicted metastatic progression among this cohort of men with BCR following RP. While confirmatory studies are needed, these results suggest that use of GC may allow for better selection of men requiring earlier initiation of treatment at the time of BCR.[87] Lobo et al (2015)[95] reported an individualized decision analysis comparing the GC with "usual care" using data from the cohorts in Karnes et al (2013) and Den et al (2014). The usual care probabilities of receiving each treatment were derived from the published literature. A 6% threshold for the GC score was used for GC-based treatment. Using the cohort from Karnes et al (2013), the estimated 10-year probability of metastasis or death was 0.32 (95% CI, 0.32 to 0.33) for usual care compared with 0.31 (95% CI, 0.30 to 0.32) for GC-based treatment. In the cohort from Den et al (2014), patients treated with post-RP RT, GC is prognostic for the development of clinical metastasis beyond routine clinical and pathologic features. Although preliminary, patients with low GC scores are best treated with salvage RT, whereas those with high GC scores benefit from adjuvant therapy. These findings provide the first rational selection of timing for post-RP RT .

Table 22. Reported Net Benefit of the Decipher Classifier vs. Comparators

Study	Outcome	Range of Net Benefit vs.	
		Treat None	Best Comparator
Spratt et al (2018)[91]	Metastasis	-0.003 to 0.002	NR
Karnes et al (2018)[92]	PC mortality	0.06 to 0.09	0.045 to 0.095
Ross et al (2016)[93]	Metastasis	0.045 to 0.075	0.09 to 0.12
Freedland (2016)[88]	Metastasis	0.01 to 0.045	0 to 0.02
Lobo et al (2015)[95,] with Karnes et al (2013)[85,] cohort	Metastasis or death	NR	0.017
Cooperberg et al (2015)[83]	Pca mortality	0.003[a]	NR
Klein et al (2015)[81]	Metastasis	0.008 to 0.025	0.000 to 0.012
Den et al (2015)[80]	Metastasis post-RT	0.02 to 0.03	-0.01 to 0.001

Lobo et al (2015)[95] with Den et al (2014)[82] cohort	Metastasis or death	NR	0.015
Ross et al (2014)[84]	Metastasis	0.09 to 0.13	0.036 to 0.040
Karnes et al (2013)[85]	Metastasis	0.009 to 0.020	-0.004 to 0.003

NR: not reported; Pca: prostate cancer; RT: radiotherapy.
[a] For 25% threshold.

The Association Between the GC and Treatment Effects

Ross et al (2016) reported on results of a retrospective, comparative study of RT after RP for 422 men with pT3 disease or positive margins.[93] The men were from 4 cohorts previously described (Karnes et al [2013][85]; Den et al [2014][82]; Ross et al [2016][93]; Freedland et al [2016][88]). The 4 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 a 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 the treatment effect was dependent on genomic risk (interaction p=0.16 for CAPRA-S, p=0.39 for Decipher). In a patient population that received no adjuvant or salvage therapy after prostatectomy until metastatic progression, higher Decipher scores correlated with clinical events, and inclusion of Decipher scores improved the prognostic performance of validated clinicopathologic risk models. These results confirm the utility already reported for Decipher..

Section Summary: Decipher RP Prostate Cancer Classifier

Clinical validity has been evaluated in overlapping validation samples (including the development test set). The validation studies consisted of observational data obtained from registries or medical records with archived samples. Although each study evaluated different outcomes (i.e., metastasis, prostate cancer-specific mortality, BCR) in samples with different populations, all studies reported some incremental improvement in discrimination. CIs of AUC frequently overlapped between Decipher and comparators. Only 1 study (Karnes et al [2018][92]) reported 10-year disease-specific survival. Estimates with CIs of outcomes, particularly disease-specific mortality at ten years, by GC low-, intermediate-, and high-risk are needed as well as reclassification analyses of prostate cancer-specific survival compared with comparators. Results demonstrate meaningful improvement in reclassification-possibly most importantly to lower risk categories. Decipher improved identification of patients most at risk of metastatic progression and death after radical prostatectomy.

MANAGEMENT DECISION IN CASTRATION-RESISTANT PROSTATE CANCER

Clinical Context and Test Purpose

In men with metastatic castration-resistant prostate cancer (mCRPC), the purpose of protein biomarker assessment of circulating tumor cells (CTCs) is to inform a decision whether to administer androgen receptor signaling (ARS) inhibitors (e.g., abiraterone, enzalutamide), or a taxane (e.g., docetaxel).

Multiple approved therapeutic options exist for treatment of men with mCRPC, which are given in conjunction with continued androgen deprivation therapy (ADT). In particular, ARS inhibitors and taxane based chemotherapy have both demonstrated effectiveness in prolonging survival but head-to-head comparisons of ARS inhibitors and taxanes in RCTs are lacking. Optimal sequencing of available treatments has also not been established. Guidelines have suggested that both ARS inhibitors and chemotherapy are appropriate for men with mCRPC who have

sufficiently good performance status to tolerate chemotherapy as first-line treatment of mCRPC. In practice, sequencing depends on several factors such as sites and extent of disease, rates of progression, ease and convenience of administration, side effects, comorbidities, and patient preferences. However, unless a man has rapidly progressive, symptomatic disease, ARS inhibitors are generally used as first-line treatment of mCRPC because they are orally administered and have lower toxicity. After disease progression on first-line ARS inhibitor, men could then receive another ARS inhibitor or another systemic therapy, usually a taxane.

A test that could inform the choice of second-line therapy would fill an unmet management need. The androgen-receptor isoform encoded by splice variant 7 lacks the ligand-binding domain that is the target of the ARS inhibitors enzalutamide and abiraterone. Therefore detection of androgen-receptor splice variant 7 messenger RNA (AR-V7) in CTCs from men with mCRPC might be associated with lack of response to enzalutamide and abiraterone but not with lack of response to taxanes.

The question addressed in this section of the evidence review is: Does GEP testing improve the net health outcome in men with mCRPC compared with standard clinical care without AR-V7 testing?

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest is men with mCRPC who have progressed on an ARS inhibitor (e.g., enzalutamide, abiraterone), have good performance status (i.e., are able to tolerate chemotherapy), and who are deciding between a second ARS inhibitor or a taxane.

Interventions
The test being considered is the Oncotype DX AR-V7 Nuclear Detect. Detection of AR-V7 in men with progressive mCRPC is associated with resistance to the ARS inhibitors abiraterone and enzalutamide.[96] The Oncotype DX AR-V7 Nuclear Detect test is a liquid biopsy test that detects CTCs with nuclear expression of the AR-V7 truncated protein. The test reports a score of AR-V7−positive or −negative. Scher et al (2016) described the development of the test and results in the development cohort in which they observed longer overall survival for men taking taxanes compared with ARS inhibitors when AR-V7– positive CTCs were detected before therapy (hazard ratio, 0.24; 95% CI, 0.10 to 0.57).[97] Scher et al (2017) explored whether expanding the AR-V7 scoring criteria to include both nuclear and cytoplasmic AR-V7 localization improved prediction in the same development cohort and concluded that the expanded “nuclear-agnostic” AR-V7 scoring criterion was less prognostic for men on ARS inhibitor therapy.[98]

Comparators
Since there are no head-to-head comparisons of ARS inhibitors and taxanes in RCTs to determine optimal second- and subsequent-line therapies, in standard clinical care, physicians and men with mCRPC are making treatment decisions based on patient preference, disease characteristics, and comorbidities.

Outcomes

Beneficial outcomes resulting from a true test result are prolonged survival, improved quality of life, and reduction in unnecessary treatment-related adverse events. Harmful outcomes resulting from a false test result are unnecessary treatments and shortened survival. The primary survival outcome of interest is overall survival.

In a systematic review of randomized phase 3 trials of systemic therapies for CRPC, which included 23 trials (total N=13,909 men), the median overall survival was 19 months.[99] Outcomes with at least 1 year of follow-up of those surviving would be preferred.

Oncotype DX AR-V7 Nuclear Detect

Oncotype DX AR-V7 Nuclear Detect is used to detect nuclear-localized AR-V7 protein in CTCs of men with mCRPC who have failed first-line therapy and are considering additional ARS inhibitor therapy.

Two studies were not included in this assessment of clinical validity because they reported results in the developmental cohort.[97,100] One published clinical validity study was identified meeting selection criteria.[98] Characteristics of the study are provided in Table 18. Briefly, Scher et al (2018) reported results of a blinded validation study including 142 samples from patients with histologically confirmed, progressing mCRPC from 3 centers in the United States and the United Kingdom from 2012 to 2016. The samples were collected prior to administration of second-line or greater ARS inhibitors or taxanes.

Table 23. Characteristics of Clinical Validity Studies Assessing Oncotype DX AR-V7

Study	Study Population	Design	Outcome Measure	Threshold for Positive Index Test	Blinding of Assessors
Scher et al (2018)[108]	Men with progressing mCRPC undergoing change in therapy	Retrospective; unclear whether samples were consecutive or randomly chosen from eligible	OS (68 men with 12-mo follow-up, 15 men with 24-mo follow-up, 6 men with 36-mo (follow-up)	At least 1 CTC with an intact nucleus and nuclear-localized AR-V7 signal-to-noise ratio above a prespecified background intensity	Yes
Armstrong et al (2019)[101]	Men with progressive, high-risk mCRPC initiating standard-of-care treatment with enzalutamide or abiraterone. Prior exposure to enzalutamide or abiraterone was permitted for men who were planning to receive the alternative agent	Prospective, consecutive	PFS (primary) Response rates (PSA and radiographic) OS (secondary)	Johns Hopkins and Epic AR-V7 assays; results for both assays reported	Yes

CTC: circulating tumor cell; OS: overall survival

Results of the validation study are shown in Table 32. Scher et al (2018) Evaluated if expanding the positivity criteria to include both nuclear and cytoplasmic AR-V7 localization would identify more patients who would benefit from a taxane over an ARSI. A total of 34

(18%) samples were AR-V7-positive using nuclear-specific criteria, and 56 (29%) were AR-V7-positive using nuclear-agnostic criteria. Following ARSi treatment, none of the 16 nuclear-specific AR-V7-positive samples and six of the 32 (19%) nuclear-agnostic AR-V7-positive samples had ≥50% PTPC at 12 weeks. The strongest baseline factor influencing OS was the interaction between the presence of nuclear-specific AR-V7-positive CTCs and treatment with a taxane (hazard ratio 0.24, 95% confidence interval 0.078-0.79; p=0.019). This interaction was not significant when nuclear-agnostic criteria were used.

Table 24. Results of Clinical Validity Studies Assessing Oncotype DX AR-V7

Study	Initial N	Final N	Excluded Samples	AR-V7+, %	Median OS (mo) by AR-V7 and Next-Line Therapy			
					AR-V7+ ARS Inhibitor	AR-V7+ Taxane	AR-V7- ARS Inhibitor	AR-V7- Taxane
Scher et al (2018)[108]	248	142 (70 before ARS inhibitor tx, 72 before taxane)	144 (93 obtained before first-line tx, 24 duplicates, 23 second-line tx other than ARS inhibitor or taxane, 2 insufficient material, 2 missing clinical data)	24	7.3	14.3	19.8	12.8
HR (95% CI); p ARS vs.taxane interation					0.6 (0.3 to 1.4);0.25		1.7 (1.0 to 2.8);0.05	
p					Not reported			
Armstrong et al (2019)[101]	118	107	2 unevaluable (1%)	10	ARS inhibitor: 8.4 Taxane: NR	ARS Inhibitor: 25.5 Taxane: NR		
HR (95% CI);p ARS vs. taxane					Not reported			
p					Not reported			

ARS: androgen receptor signaling; CI: confidence interval; HR: hazard ratio; OS: overall survival; tx: treatment.

Table 25. Cross-Tabulation of AR-V7 Status and Clinical Risk Score

		Risk Score		
		High	Low	Total
AR-V7	Positive	24	10	34
	Negative	46	62	108
	Total	70	72	142

Adapted from Scher et al (2018)[98]

Section Summary: Oncotype DX AR-V7 Nuclear Detect

Multiple, high-quality studies of the marketed version of the test (including current algorithms and cutoffs), in populations independent of the developmental cohort, that include the intended-use population and have consistent and precise results are needed to characterize the performance characteristics. One retrospective analysis of 142 men from the United States and United Kingdom including men with progressing mCRPC undergoing change in therapy is available. The median follow-up in surviving men is unclear, but, overall, 68 men had 12 months of follow-up, 15 men had 24 months of follow-up, and 6 men had 36 months of follow-up. Men treated with ARS inhibitors had the longest overall survival if they were AR-V7−negative (median, 19.8 months) and had shortest overall survival if they were AR-V7−positive (median, 7.3 months). The unadjusted HR for overall survival was statistically significantly longer for ARS inhibitors compared with taxanes in the AR-V7−negative men (HR=1.7; 95% CI, 1.0 to 2.8) but not in ARV7−positive men (0.6; 95% CI, 0.3 to 1.4).

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 26.

Table 26. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Prolaris			
NCT04404894[a]	Long-Term Prospective Registry to Evaluate Treatment Decisions and Clinical Outcomes in Prostate Cancer Patients From Diverse Urology Practice Settings Following Prolaris® Testing		Nov 2031
Decipher			
NCT05050084[a]	Parallel Phase III Randomized Trials of Genomic-Risk Stratified Unfavorable Intermediate Risk Prostate Cancer: De-Intensification and Intensification Clinical Trial Evaluation (GUIDANCE)	2050	Apr 2037
NCT04484818	A Phase III Double Blinded Study of Early Intervention After RADICAl ProstaTEctomy With Androgen Deprivation Therapy With or Without Darolutamide vs. Placebo in Men at Highest Risk of Prostate Cancer Metastasis by Genomic Stratification (ERADICATE)	810	May 2028
NCT04513717	Parallel Phase III Randomized Trials for High Risk Prostate Cancer Evaluating De-Intensification for Lower Genomic Risk and Intensification of Concurrent Therapy for Higher Genomic Risk With Radiation (PREDICT-RT*)	2478	Dec 2038
Unpublished			
NCT03152448a	Two-part prospective study to measure impact of Prolaris® testing added to treatment decision following biopsy in newly diagnosed prostate cancer patients to measure prediction of progression/recurrence in men treated at VAMC	1509	Jan 2024
NCT03290508a	Long-term prospective registry to evaluate treatment decisions and clinical outcomes in patients with favorable intermediate-risk localized prostate cancer following cell cycle progression (CCP) testing (Prolaris® test)	6000	Sep 2027
NCT04396808	Genomics in Michigan to AdJust Outcomes in Prostate canceR (G-MAJOR): A Randomized Multi-center Study for Men With Newly Diagnosed Favorable Risk Prostate Cancer	900	Nov 2023
NCT04396808	Genomics in Michigan to AdJust Outcomes in Prostate Random (G-MAJOR): A Randomized Multicenter Study for Men With Newly Diagnosed Favorable Risk Prostate Cancer	900	Sep 2023

NCT02723734	Validation Study on the Impact of Decipher Testing - VANDAAM Study	250	May 2023

NCT: national clinical trial; PTEN: phosphatase and tensin homolog.
[a] Denotes industry-sponsored or cosponsored trial.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Society of Clinical Oncology

In 2020, the American Society of Clinical Onclology (ASCO) published a guideline on molecular biomarkers in localized prostate cancer.[104] The guidelines state, "Currently, there are no strong data or expert guidelines to support active surveillance in otherwise healthy men with Grade Group 3 or higher cancer; therefore, we would consider the use of genomic biomarkers only in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect a physician's recommendation or a patient's choice for surveillance versus treatment, but they should not be used routinely."

Specific recommendations included the following:
Molecular biomarkers to identify patients with prostate cancer who are most likely to benefit from active surveillance:

- Recommendation 1.1. Commercially available molecular biomarkers (i.e. Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
- Recommendation 1.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Molecular biomarkers to diagnose clinically significant prostate cancer:

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

Molecular biomarkers to guide the decision of post prostatectomy adjuvant versus salvage radiation:

- Recommendation 3.1. The Expert Panel recommends consideration of a commercially available molecular biomarker (e.g., Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of

genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
- Recommendation 3.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

National Comprehensive Cancer Network (NCCN)
The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (v.4.2024)[12] provide a table of tissue-based tests for prostate cancer prognosis. The guidelines include the following statements related to risk stratification:
The guidelines include the following statements related to risk stratification:
- Patients with NCCN low, favorable intermediate, unfavorable intermediate, or high-risk disease and life expectancy ≥10 y may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, and Prolaris.
- 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 also recommended that "the use of AR-V7 tests in circulating tumor cells can be considered to help guide selection of therapy in the post-abiraterone/enzalutamide metastatic castration-resistant prostate cancer setting."

American Urological Association et al
In 2017 and 2018, the American Urological Association, American Society for Radiation Oncology, and the Society of Urologic Oncology published joint guidelines on the management of clinically localized prostate cancer.[13,99,100] 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)"

In 2018, the American Urological Association published guidelines for castration-resistant prostate cancer.[105] The guidelines do not mention AR-V7 assays.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence updated its guidance on the diagnosis and management of prostate cancer in 2019 (updated 2021).[106] The guidance did not address gene expression profile analysis.

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for Prolaris® or Oncotype Dx® **Genomic Prostate Score** have been identified.

Government Regulations
National/Local:

Local Coverage Determination (L38433). MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease. Effective for services on or after 02/01/2024.

This is a limited coverage policy for the **DECIPHER**® Biopsy Prostate Cancer Classifier Assay. The test is considered reasonable and necessary to help identify men with localized Favorable Intermediate Risk Disease Prostate Cancer and a life expectancy of at least 10 years who are good candidates for active surveillance.

DECIPHER is covered for men with prostate cancer for the following indication:
A man with localized or biochemically recurrent adenocarcinoma of the prostate (i.e. no clinical evidence of metastasis) who have a life expectancy of greater than or equal to 10 years if he is a candidate for and is considering (or being considered for) at least one of the following:

- Conservative management and yet would be eligible for definitive therapy (radical prostatectomy, radiation or brachytherapy), or
- Radiation therapy and yet would be eligible for the addition of a brachytherapy boost, or
- Radiation therapy and yet would be eligible for the addition of short-term androgen deprivation therapy, or
- Radiation therapy with short-term androgen deprivation therapy yet would be eligible for the use of long term androgen deprivation therapy, or
- Radiation with standard androgen deprivation therapy yet would be eligible for systemic therapy intensification using next generation androgen signaling inhibitors or chemotherapy, or
- Observation post-prostatectomy yet would be eligible for the addition of post-operative adjuvant radiotherapy, or
- Salvage radiotherapy post-prostatectomy yet would be eligible for the addition of androgen deprivation therapy, or

The following criteria must also be met for coverage:

- The assay is performed on FFPE prostate biopsy or radical prostatectomy specimen, and
- Result will be used to determine treatment according to established practice guidelines, and
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy or radical prostatectomy, and
- Patient is monitored for disease progression according to established standard of care

Additionally, a similar transcriptome-based test with analytical and clinical validity at least as good as **DECIPHER** will be considered reasonable and necessary for the same indications. Analytical and clinical validity will be assessed through the technical assessment process.

L37911, effective on or after 11/01/19. MolDX: Decipher® Biopsy Prostate Cancer Classifier Assay for Men with Very Low and Low Risk Disease. Retired.
This Medicare contractor will provide limited coverage for the Decipher® Biopsy Prostate Cancer Classifier Assay (Decipher Biosciences) for men with NCCN low risk and very low risk prostate cancer only when the following clinical conditions are met:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), and
- FFPE prostate biopsy specimen with at least 0.5 mm of cancer length, and
- Patients with low risk or very low risk as defined by the NCCN as follows:
    - Low Risk:
        - Stage T1 or T2a
        - PSA less than 10 ng/mL
        - Gleason score 6 or less (Grade Group 1) OR
    - Very Low Risk: Stage T1c
        - PSA less than 10 ng/mL
        - Gleason score 6 or less (grade group 1)
        - Not more than two cores with cancer
        - Less than or equal to 50 percent of core involved with cancer
        - PSA density less than 0.15
- Patient has an estimated life expectancy of greater than or equal to 10 years, and
- Patient is a candidate for and is considering conservative therapy and yet would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), and
- Result will be used to determine treatment between definitive therapy and conservative management by active surveillance (AS) and
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, and
- Patient is monitored for disease progression based on the established standard of care, including at least a repeat biopsy at 1 year.

L36787 effective on or after 11/01/19. MolDX: Prolaris™ Prostate Cancer Genomic Assay. Retired 10/27/2022. WPS GHA will provide limited coverage for the Prolaris™ prostate cancer assay (Myriad, Salt Lake City, UT) to help determine which patients with early stage, needle biopsy proven prostate cancer, can be conservatively managed rather than treated with definitive surgery or radiation therapy.
The Prolaris™ assay will be covered only when the following clinical conditions are met:

- A needle biopsy has confirmed localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), **AND**
- The FFPE prostate biopsy specimen is at least 0.5 mm of cancer length, **AND**
- The patient Stage as defined by the *one* of the following:
    - *Very Low Risk Disease* (T1c **AND** Gleason Score ≤ 6 **AND** PSA ≤ 10 ng/mL **AND** <3 prostate cores with tumor **AND** ≤ 50% cancer in any core **AND** PSA density of < 0.15 ng/mL/g) **OR**
    - *Low Risk Disease* (T1-T2a **AND** Gleason Score ≤ 6 **AND** PSA ≤ 10 ng/mL), **AND**
- Patient has an estimated life expectancy of greater than or equal to 10 years, **AND**
- Patient is a candidate for and is considering conservative therapy and yet and would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), **AND**
- Result will be used to determine treatment between definitive therapy and conservative management, **AND**
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, **AND**
- Test is ordered by a physician certified in the Myriad Prolaris™ Certification and Training Registry (CTR), **AND**

- Patient is monitored for disease progression according to established standard of care, **AND**
- Physician must report the development of metastasis or prostate cancer deaths in patients not treated definitively who were deemed low risk by the assay.

L37226, effective on or after 11/01/19. MolDX: Prolaris™ Prostate Cancer Genomic Assay for Men with Favorable Intermediate Risk Disease. Retired 10/28/2021.

This contractor will provide limited coverage for the Prolaris ™ prostate cancer assay (Myriad, Salt Lake City, UT) to help determine which patients with favorable intermediate risk, needle biopsy proven prostate cancer (as defined below), can be conservatively managed rather than treated with definitive surgery or radiation therapy.

The Prolaris ™ assay is covered for men with favorable intermediate risk prostate cancer only when the following clinical conditions are met:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), and
- FFPE prostate biopsy specimen with at least 0.5 mm of cancer length, and
- Patients with favorable intermediate-risk disease, defined by the NCCN as follows:
    - Predominant Gleason grade 3 (i.e. Gleason score 3+4=7), percentage of positive cores <50%, and no more than 1 NCCN intermediate-risk factor)
      NCCN intermediate risk factors include T2b-T2c, Gleason score 7, and PSA10-20 ng/mL
- Patient has an estimated life expectancy of greater than or equal to 10 years, and
- Patient is a candidate for and is considering conservative therapy and yet and would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), and
- Result will be used to determine treatment between definitive therapy and conservative management, and
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, and
- Patient is monitored for disease progression according to established standard of care.

L36789, effective on or after 08/27/2020. MolDX: Genomic Health™ Oncotype DX® Prostate Cancer Assay. Retired 10/27/2022.

WPS GHA will provide limited coverage for the Oncotype DX® Prostate Cancer Assay (Genomic Health™) to help determine which patients with early stage, needle biopsy proven prostate cancer, can be conservatively managed rather than treated with definitive surgery or radiation therapy.

The Oncotype DX® Prostate Cancer Assay is covered only when the following clinical conditions are met:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), **and**
- Patient stage as defined by the one of the following:
    - Very Low Risk Disease (T1c AND Gleason Score = 6 AND PSA = 10 ng/mL AND <3 prostate cores with tumor AND = 50% cancer in any core AND PSA density of < 0.15 ng/mL/g) OR
    - Low Risk Disease (T1-T2a AND Gleason Score = 6 AND PSA = 10 ng/mL), Patient has an estimated life expectancy of ≥ 10 years, and
- Patient has a life expectancy of 10-20 years,

- Patient is a candidate for and is considering conservative therapy and yet and would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), and
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, and
- Test is ordered by a physician certified in the Genomic Health™ Oncotype DX® Prostate Cancer Assay Certification and Training Registry (CTR), and
- Patient is monitored for disease progression according to active surveillance guidelines as recorded in NNCN guidelines, and
- Physician must report the development of metastasis or prostate cancer deaths in patients not treated definitively who were deemed low risk by the assay.

L37915, effective on or after 11/01/2020. MolDX: Oncotype DX AR-V7 Nucleus Detect for Men with Metastatic Castrate Resistant Prostate Cancer (MCRPC). Retired 7/24/2021.
This contractor will provide limited coverage for the Oncotype DX AR-V7 Nucleus Detect to help determine which patients with metastatic castrate resistant prostate cancer may benefit from androgen receptor signaling inhibitor therapy and which may benefit from chemotherapy.
Oncotype DX AR-V7 Nuclear Detect assay is covered as follows:

1. Patients will have progressive mCRPC as defined by the Prostate Cancer Working Group 2 guidelines (a minimum of 2 rising prostate-specific antigen (PSA) levels 1 or more weeks apart, new lesions by bone scintigraphy, and/or new or enlarging soft tissue lesions by computed tomography (CT) or magnetic resonance imaging (MRI)).
2. Patients will have failed one ARSi, specifically Enzalutamide (Xtandi), Apalutamide (Erleada), or Abiraterone (Zytiga).
3. Patients will be considered appropriate for treatment by their treating physician for the alternative ARSi as a single agent.
4. Circulating tumor cells (CTC) with nuclear expression of AR-V7 protein will be assessed prior to initiation of therapy.
5. Decision impact analysis: We expect that < 15% of nuclear AR-V7-positive patients will receive an ARSi.
6. Efficacy analysis: Nuclear AR-V7-negative patients who receive an ARSi will have similar or better time on therapy than untested mCRPC patients (meeting above criteria) receiving ARSi.

L37667, effective on or after 06/25/2020. MolDX: Oncotype DX® Genomic Prostate Score for Men with Favorable Intermediate Risk Prostate Cancer. Retired 11/07/2020.
This contractor will provide limited coverage for the Oncotype DX® Genomic Prostate Score (Genomic Health®) (hereafter GPS) to help determine which patients with favorable intermediate-risk, needle biopsy proven prostate cancer, can be conservatively managed rather than treated with definitive surgery or radiation therapy.
Oncotype DX Genomic Prostate Score test is covered for men with favorable intermediate risk prostate cancer only when the following clinical conditions are met:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), and
- FFPE prostate biopsy specimen with at least 0.5 mm of cancer length, and NCCN Favorable Intermediate-risk disease defined as:
    - Gleason Grade Group 2 (Gleason Sum 3+4=7), and
- Patient has an estimated life expectancy of greater than or equal to 10 years, and

- Patient is a candidate for and is considering conservative therapy and yet would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), and
- Result will be used to determine treatment between definitive therapy and conservative management, and
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, and Patient is monitored for disease progression according to established standard of care.

L37011, effective on or after 12/28/2023. MolDX: ProMark Risk Score.
This Contractor will provide limited coverage for the ProMark (Metamark Genetics) to help determine which patients with early stage, needle biopsy proven prostate cancer can be conservatively managed rather than treated with definitive surgery or radiation therapy.
The ProMark assay is covered only when the following clinical conditions are met:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), **and**
- Patient Stage as defined by one of the following:
    - Very Low Risk Disease (T1c **AND** Gleason Score ≤ 6 **AND** PSA ≤ 10 ng/mL **AND** <3 prostate cores with tumor **AND** ≤ 50% cancer in any core **AND** PSA density of < 0.15 ng/mL/g) **OR**
    - Low Risk Disease (T1-T2a **AND** Gleason Score ≤ 6 **AND** PSA ≤ 10 ng/mL), **and**
- Patient has an estimated life expectancy of greater than or equal to 10 years, **and**
- Patient is a candidate for and is considering conservative therapy and yet and would be eligible for definitive therapy (radical prostectomy, radiation therapy or brachytherapy), **and**
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, **and**
- Test is ordered by a physician certified in the Metamark Genetics Certification and Training Registry (CTR), **and**
- Patient is monitored for disease progression according to active surveillance guidelines as recorded in NCCN guidelines, **and**
- Physician must report the development of metastasis or prostate cancer deaths in patients not treated definitively who were deemed low risk by the assay.

L37005 effective on or after 11/26/2020. MolDX: ConfirmMDX Epigenetic Molecular Assay. Retired 08/20/2022.
Coverage conditions:

1. Males aged 40 to 85 years old that have undergone a previous cancer-negative prostate biopsy within 24 months and are being considered for a repeat biopsy due to persistent or elevated cancer-risk factors, **and**
2. The previous negative prostate biopsy must have collected a minimum of 8 tissue cores (but not have received a saturation biopsy of > 24 tissue cores) and remaining FFPE tissue from all cores is available for testing, **and**
3. Minimum tissue volume criteria of 20 microns of prostate biopsy core tissue is available (40 microns preferable), **and**
4. Previous biopsy histology does not include a prior diagnosis of prostate cancer or cellular atypia suspicious for cancer (but may include the presence of high-grade prostatic intraepithelial neoplasia (HGPIN), proliferative inflammatory atrophy (PIA), or glandular inflammation), **and**

5. Patient is not being managed by active surveillance for low stage prostate cancer, **and**
6. Tissue was extracted using standard patterned biopsy core extraction (and not transurethral resection of the prostate (TURP), **and**
7. Patient has not been previously tested by ConfirmMDx from the same biopsy samples or similar molecular test.

L39042. MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer. Effective on or after 07/27/2023.

Coverage Indications, Limitations, and/or Medical Necessity

There are two applications of molecular biomarkers to risk-stratify patients at increased risk for prostate cancer:

A non-invasive or minimally invasive test, the results of which are obtained to inform the decision to perform an initial biopsy (pre-biopsy).

A test performed to further refine risk when a biopsy has been performed but does not clearly indicate malignancy on histopathologic examination (post-biopsy). Such a test can potentially obviate the need for a repeat biopsy.

This contractor provides limited coverage for molecular Deoxyribonucleic acid/ribonucleic acid (DNA/RNA) biomarker tests for the diagnosis of prostate cancer that help differentiate men who may or may not benefit from a prostate biopsy when ALL of the following conditions are met:

The patient must not have an established diagnosis of prostate cancer.

The beneficiary is a candidate for prostate biopsy or repeat prostate biopsy, according to a consensus guideline [(i.e., National Comprehensive Cancer Network® (NCCN), American Society of Clinical Oncology®(ASCO), American Urological Association (AUA)].

a) For men ≤ 75 years of age - Prostate Specific Antigen (PSA) (or adjusted PSA in special populations, i.e., patients taking 5alpha-reductase inhibitors) OR repeat PSA are >3 and <10ng/mL AND/OR Digital Rectal Exam (DRE) findings are very suspicious for cancer.
b) For men > 75 years of age - PSA (or adjusted PSA in special populations, i.e., patients taking 5-alpha-reductase inhibitors) OR repeat PSA are ≥4 and <10ng/mL AND/OR DRE findings are very suspicious for cancer.

EXCEPTION: a molecular biomarker test may be performed in men with PSA levels >10 ng/mL who are being considered for repeat biopsy IF appropriate according to consensus guidelines AND according to the following: the specific biomarker test has been validated in men with PSA levels>10 ng/mL AND a Multiparametric MRI (mpMRI) is negative, if performed.

The beneficiary has not had a prostate biopsy OR has had a previous negative or non-malignant but abnormal histopathology finding (i.e., atypical small acinar proliferation (ASAP) or high-grade prostatic intraepithelial neoplasia (HGPIN) on prostate biopsy).

Patients under consideration for a repeat biopsy have first undergone repeat PSA and/or DRE testing as recommended by consensus guidelines

The beneficiary would benefit from treatment of prostate cancer and patient management will be impacted by use of a biomarker in a manner already demonstrated in the peer-reviewed published literature to improve patient outcomes.

The medical record supports the medical necessity for the biomarker test.

Testing is performed according to the intended use of the test in the intended patient population for which the test was developed and validated.

Testing must be performed according to Clinical Laboratory Improvement Amendments (CLIA) and/or Food and Drug Administration (FDA) regulations in an accredited laboratory.

For a given clinical indication (pre-OR post-biopsy), only one molecular biomarker may be performed UNLESS a second test, meeting all the criteria established herein, is reasonable and necessary as an adjunct to the first test, according to criteria established in this policy.

If the test relies on an algorithm which may range in complexity from a threshold determination of a single numeric value to a complex mathematical or computational function, the algorithm must be validated in a cohort that is not a development cohort for the algorithm.

The analytes measured have demonstrated clinical validity and clinical utility (i.e., improved detection or discrimination of cancer or high-grade cancer or reduction in the need for biopsy) in the peer-reviewed published literature, establishing a clear and significant biological/molecular basis for stratifying patients and subsequently selecting (either positively or negatively) their clinical management decision within a clearly defined population.

The test is ordered by a physician specialist in the management of prostate cancer, such as a urologist or oncologist. An exception may be made in geographic locations where the specialist(s) cannot be reasonably reached by the beneficiary and the ordering provider is located closer to the beneficiary's place of residence than the nearest specialist. We would generally expect that beneficiaries for whom the test is ordered under this exception to be living in rural locations, islands, or some other location where access to care is limited.

NOTE: If the patient is considered higher risk (due to relevant family or personal cancer history, relevant high-risk genetic mutations, African ancestry, or other clinical parameters highly suspicious for cancer including a persistent and significant increase in PSA), a biopsy may still be warranted. These relative indications for biopsy should be taken into consideration as part of a shared decision-making process regarding whether to proceed with a biopsy.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

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

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/14	2/18/14	2/28/14	Joint policy established
7/1/15	4/21/15	5/8/15	Routine maintenance. Updated rationale and references.
7/1/16	4/19/16	4/19/16	Routine policy maintenance. Updated references and rationale.
1/1/17	10/11/16	10/11/16	Added coverage guidelines for Oncotype Dx for Medicare under government section. Removed blue cross complete section.
1/1/18	10/19/17	10/19/17	Added code 0005U as Noncovered. Routine policy maintenance. Reorganization of rationale section.
5/1/18	2/20/18	2/20/18	Code update, added codes 81541 and 81551 as E/I. Updated background and rationale section, added references 14, 50, 60-61, 87 and 89. No change in policy status.
7/1/19	4/16/19		Added ConfirmMDx testing to body of policy as E/I. New E/I indication added for assays, AR-V7), updated rationale, references 43, 54-55, 92-94, 104-108. Removed code 0005U from policy and added to Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer policy.
7/1/20	4/14/20		Added code 81542 effective 1/1/20 as E/I. Also added 81479. Reviewed NCCN guidelines. Reorganized evidence review to distinguish Decipher biopsy and Decipher RP test. Added reference #101. No change in policy status.
7/1/21	4/20/21		Updated CMS section, routine policy maintenance, no change in policy status.
9/1/21	6/15/21		Policy status changed to established with criteria per NCCN guidelines for testing. Policy rewritten for established status, two references added.

3/1/22	12/14/21		Added code 0047U as established representing Oncotype Dx.
3/1/23	12/20/22		Routine policy maintenance, added language for PLA testing. No change in policy status.
3/1/24	12/19/23		Updated inclusion/exclusion sections per NCCN guidelines. Added code 0037U as established. Vendor managed: N/A (ds)
3/1/25	12/17/24		Routine policy maintenance, added “genomic prostate score” to Oncotype Dx testing, Code 0497U added as E/I. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENE EXPRESSION PROFILE ANALYSIS FOR RISK STRATIFICATION FOR PROSTATE CANCER MANAGEMENT

Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered per policy indications.
BCNA (Medicare Advantage)	See Government Regulations section of policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

- **Administrative Guidelines:**

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.