

Medical Policy



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Title: Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

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Populations	Interventions	Comparators	Outcomes
Individuals: • With low- or intermediate-risk clinically localized untreated prostate cancer	Interventions of interest are: • Prolaris	Comparators of interest are: • Clinicopathologic risk stratification	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity
Individuals: • With low- or intermediate-risk clinically localized untreated prostate cancer	Interventions of interest are: • Oncotype DX Prostate	Comparators of interest are: • Clinicopathologic risk stratification	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With low- or intermediate-risk clinically localized untreated prostate cancer	Interventions of interest are: • ProMark protein biomarker test	Comparators of interest are: • Clinicopathologic risk stratification	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity
Individuals: • With localized prostate cancer treated with radical prostatectomy	Interventions of interest are: • Prolaris	Comparators of interest are: • Clinicopathologic risk stratification	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity
Individuals: • With localized prostate cancer treated with radical prostatectomy	Interventions of interest are: • Decipher prostate cancer classifier	Comparators of interest are: • Clinicopathologic risk stratification	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity
Individuals: • With metastatic castration-resistant prostate cancer	Interventions of interest are: • Oncotype DX AR-V7 Nuclear Detect	Comparators of interest are: • Standard clinical care	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity

DESCRIPTION

Gene expression profile analysis and protein biomarkers have been proposed as a means to risk-stratify patients with prostate cancer to guide treatment decisions. These tests are intended to be used either on prostate needle biopsy tissue to guide management decisions for active surveillance or therapeutic intervention, after radical prostatectomy (RP) to guide radiotherapy use, or to guide medication selection after progression in metastatic castration-resistant prostate cancer.

OBJECTIVE

The objective of this policy is to determine whether, compared with clinicopathologic risk stratification or when used with clinicopathologic risk stratification, tests of gene expression profiles and protein biomarkers improve outcomes in men with prostate cancer. The specific tests considered are the commercially available versions of Prolaris, Oncotype DX Prostate, ProMark, Decipher, and Oncotype DX AR-V7 Nuclear Detect.

BACKGROUND

Prostate Cancer

Prostate cancer is the second most common noncutaneous cancer diagnosed among men in the United States. Autopsy studies in the era before the availability of prostate-specific antigen (PSA) screening 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 clinical risk categories (eg, D'Amico criteria) or prognostic tools 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 older men (ages ≥ 70 years) with low-risk disease, comorbidities typically supervene as a cause of death; these men will die with prostate cancer present, rather than from cancer itself. 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}:

- Low: T1-T2a and Gleason score ≤ 6 /Gleason grade group 1 and PSA level ≤ 10 ng/mL;
- 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;
- 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 that biochemical recurrence be defined as a serum PSA of 0.2 ng/mL or higher, which is confirmed by the 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. After progression, continued ADT is generally used in conjunction with other treatments. Androgen pathways are important in the progression of castration-resistant prostate cancer. 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.

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 and Oncotype DX AR-V7 Nuclear Detect, Decipher® gene expression profiling test, 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 report suggesting FDA oversight of LDTs.¹⁵ 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 report asserted that patients are potentially receiving inappropriate prostate cancer care because there is no evidence that results from the test meaningfully improve clinical outcomes.

POLICY

- A. Multigene expression (Prolaris™; Oncotype DX) assay on prostate cancer tissue is considered **medically necessary** to determine prognosis when the following clinical conditions are met:
1. Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), **AND**
 2. FFPE prostate biopsy specimen with at least 0.5 mm of cancer length, **AND**
 3. Patient Stage as defined by the one of the following:
 - a. Low Risk Disease (T1-T2a AND Gleason Score \leq six AND PSA \leq 10 ng/mL), **OR**
 - b. Favorable Intermediate Risk (T2b-T2c OR Gleason score 3+4=7/grade group 2 OR PSA 10-20 ng/mL), **AND**
 4. Patient has an estimated life expectancy of greater than or equal to 10 years, **AND**
 5. Patient is a candidate for and is considering conservative therapy and would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), **AND**
 6. Result will be used to determine treatment between definitive therapy and conservative management, **AND**
 7. Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy.
- B. The use of gene expression analysis other than listed above, and protein biomarkers to guide management of prostate cancer, are considered **experimental / investigational** in all situations.

RATIONALE

The most recent MEDLINE database search was through September 4, 2018; publications were also submitted for consideration by test suppliers.

This review was informed by a TEC Assessment (2014) addressing disease detected on needle biopsy,¹⁶ and has been supplemented by a TEC Assessment (2015) addressing high-risk disease after prostatectomy.¹⁷

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 (ie, 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 $\leq 5\%$); 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 In a population-based retrospective cohort study using administrative hospital data, physician billing codes, and cancer registry data, Nam et al (2014) 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 United States and Canada.^{25,26}

The 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 that 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, 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), has 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 recommend RP or RT plus androgen deprivation therapy (ADT) 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 first question addressed in this evidence review is: Does GEP improve outcomes in newly diagnosed men with clinically localized prostate cancer, compared with clinicopathologic risk stratification or when used with clinicopathologic risk stratification? The specific questions differ by patient risk. For newly diagnosed patients at low risk, does GEP identify a group of patients who should receive immediate RP or RT instead of active surveillance? For newly diagnosed patients at intermediate risk, does GEP identify a group of patients who can safely forgo immediate RP or RT and be followed with active surveillance?

The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

GEP refers to the analysis of messenger RNA expression levels of many genes simultaneously in a tumor specimen and protein biomarkers.³¹⁻³⁶ Two GEP tests and 1 protein biomarker test are intended to stratify biologically prostate cancers diagnosed on prostate needle biopsy: Prolaris and Oncotype DX Prostate Cancer Assay are GEP tests that use archived tumor specimens as the messenger RNA source, reverse-transcriptase polymerase chain reaction amplification, and the TaqMan low-density array platform. A protein biomarker test, ProMark is an automated quantitative imaging method to measure protein biomarkers by immunofluorescent staining in defined areas in intact formalin-fixed paraffin-embedded (FFPE) biopsy tissue to provide independent prognostic information to aid in the stratification of patients with prostate cancer to active surveillance or therapy.

Comparators

Clinicopathologic risk stratification along with age/life expectancy and patient preference are currently being used to make decisions about prostate cancer management. Clinical characteristics (eg, stage, biopsy Gleason grade, serum PSA level) and demographic characteristics (eg, age, life expectancy) are combined to classify men according to risk. National Comprehensive Cancer Network (NCCN) and AUA have provided treatment recommendations based on risk stratification and life expectancy.^{12,37} The Kattan et al (2003) nomogram was developed to predict the 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 events. 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 events of radiotherapy or radical prostatectomy

NCI: National Cancer Institute.

Timing

Ten-year outcomes are of interest due to the prolonged natural history of localized prostate cancer.

Setting

Decisions about management of localized prostate cancer are typically made by patients and urologists and oncologists in the secondary or tertiary care setting.

Study Selection Criteria

For the evaluation of clinical validity of the Prolaris, Oncotype DX Prostate, 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.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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 reviews Prolaris for initial management decisions in newly diagnosed, localized cancer.

Clinically Valid

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

Three studies reporting clinical validity related to newly diagnosed men with clinically localized prostate cancer are summarized in Table 2.

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

Study	Design	Dates	Sites	N	Population
Cuzick et al (2012) ⁴¹	Retrospective cohort from prospective registry	1990-1996	6 U.K. registries; not screen-detected	349	Clinically localized; 66% Gleason score 6-7; 46% PSA level \leq 25 ng/mL
Cuzick et al (2015) ⁴²	Retrospective cohort from prospective registry	1990-2003	3 U.K. registries ^a ; not screen-detected	761	Clinically localized; 74% Gleason score \leq 7, mean PSA level 21 ng/mL
Lin et al (2018) ⁴³	<ul style="list-style-type: none"> Validation cohort: Subset of Cuzick et al (2015) Clinical testing cohort: Consecutive men with biopsies submitted for testing to manufacturer 	<ul style="list-style-type: none"> 1990-2003 2013-2016 	<ul style="list-style-type: none"> 3 U.K. registries^a; not screen-detected NA; manufacturer database 	<ul style="list-style-type: none"> 585 19,215 	<ul style="list-style-type: none"> See Cuzick et al (2015) Median PSA level, 5.6 ng/mL (IQR, 44-7.6 ng/mL) NCCN risk: <ul style="list-style-type: none"> Low, 57% Favorable intermediate, 20% Intermediate, 17% High, 7%

IQR: interquartile range; NA: not available; 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 Cell cycle expression data were read blind to all other data. Patients were identified from 6 cancer registries in Great Britain and were included if they had clinically localized prostate cancer diagnosed by needle biopsy between 1990 and 1996; were younger than 76 years at diagnosis; had a baseline PSA measurement; and were conservatively managed. Potentially eligible patients who underwent RP, died, showed evidence of metastatic disease within 6 months of diagnosis, or received hormone therapy before diagnostic biopsy were excluded. The original biopsy specimens were retrieved and centrally reviewed by a panel of expert urologic pathologists to confirm the diagnosis and, where necessary, to reassign Gleason scores.⁴⁴ Of 776 patients diagnosed by needle biopsy and for which a sample was available to review histology, needle biopsies were retrieved for 527 (68%), 442 (84%) of which had adequate material to assay. From the 442 samples, 349 (79%)

produced a CCP score and had complete baseline and follow-up information, representing 45% of 776 patients initially identified. The median follow-up time was 11.8 years. Ninety deaths from prostate cancer occurred within 2799 person-years.

The primary, unadjusted analysis found a 1-unit increase in CCP score associated with a 2-fold increase (HR=2.02) in the risk of dying from prostate cancer (see Table 3). In a multivariate model including CCP, Gleason score, and PSA level, the adjusted HR for a 1-unit increase in CCP score was 1.65. However, changes in HRs may not reflect meaningful changes in absolute risk. As is shown in Table 4, Kaplan-Meier analyses of 10-year risk of prostate cancer death are stratified by CCP score groupings. It appears that there might be a large change in risk for scores below 2 compared with above 2, but no CIs are reported so it is impossible to draw conclusions. Measures that would suggest improved discriminatory ability (eg, area under the curve [AUC] or reclassification) compared with an existing nomogram were not reported in Cuzick et al (2012). The authors did not provide evidence that the test could correctly reclassify men initially at high risk to lower risk to avoid overtreatment, or conversely, correctly reclassify those initially at low risk to high risk to avoid undertreatment.

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 The authors stated that the samples did not overlap with Cuzick et al (2012). Men were excluded if they had undergone RP or RT within 6 months of diagnosis. A combination of the CCP and CAPRA scores (called the combined clinical cell cycle risk [CCR] score) was used to predict prostate cancer death. There were 989 men who fit eligibility criteria; CCP scores were calculable for 761 (77%), and combined CCP and clinical variables were available for 585 (59%). Median age at diagnosis was 70.8 years, and median follow-up was 9.5 years. The prostate cancer mortality rate was 17% (n=100), with 29% (n=168) dying from competing causes. Higher CCP scores were associated with increased 10-year risk of prostate cancer mortality (see Table 5): 7% (CCP score <0), 15% (CCP score 0-1), 36% (CCP score 1-2), and 59% (CCP score >2). For the CCR score, the HR for 10-year prostate cancer mortality increased to 2.17 (95% CI, 1.83 to 2.57). The C statistic for the CAPRA score was 0.74; adding the CCP score increased the C statistic to 0.78 (no CIs for the C statistic were reported). Estimates with CIs for 10-year death rates for the CCR score are provided in a figure and given in Table 5 based on digitizing the figure. Note that the predictions appear to cross 100% for CCR of about 6. Treatment changes after 6 months were documented in only part of 1 of the 3 cohorts; at 24 months, 45% of the men in this cohort had undergone RT or prostatectomy.

Lin et al (2018)⁴³ validated a CCR cutoff of 0.8 using a subset of 585 conservatively managed men from the Cuzick (2015) cohort. Of the 585 men, 60 had CCR scores of 0.8 or less. Among the 284 men who were at low or intermediate risk by NCCN criteria, 59 had CCR scores of 0.8 or less. The text reports that the estimated 10-year prostate cancer mortality risk was 2.7% for men with CCR scores below the threshold and 3.3% (95% CI, 1.9% to 5.7%) at the threshold in the full cohort, and 2.3% below the threshold and 2.9% (95% CI, 1.3% to 6.7%) at the threshold in the cohort that excluded high-risk men. However, the Kaplan-Meier curves show an estimated prostate cancer mortality at 10 years of 0% for men with CCR of 0.8 or less in both cohorts. The Kaplan-Meier curve estimated prostate cancer mortality at 10 years for men with CCR greater than 0.8 was 20% in the full cohort and 9% in the cohort excluding high-risk men (see Table 5; precision estimates not provided).

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) ⁴¹	349	2.02 (1.62 to 2.53)	1.65 (1.31 to 2.09) ^a
Cuzick et al (2015) ⁴²	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) ⁴¹		Cuzick et al (2015) ⁴²	
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) ⁴²			Lin et al (2018) ⁴³ Using Data From Cuzick et al (2015) ⁴²		
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.

Lin et al (2018) also reported reclassification of men using the CCR score threshold (0.8) in a group of 19,215 consecutive patients whose biopsies were sent for ProLaris testing between 2013 and 2016 (see Table 6).⁴³ According to the table of clinicopathologic features of patients, 14685 of the 19215 men had low or favorable intermediate risk by NCCN risk classification. However, in the reclassification table and the text describing the table (see Table 6), the authors said that only 8177 of the 19,215 men met NCCN criteria for active surveillance based on low/favorable intermediate-risk clinicopathologic features. It is not clear why fewer men were categorized as meeting NCCN low/favorable intermediate criteria for the purposes of demonstrating reclassification and, therefore, it is not clear how many of the 14,685 men at low or intermediate risk by NCCN criteria would have been reclassified using the CCR threshold.

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.

The purpose of the gaps tables (see Tables 7 and 8) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 7. Relevance Gaps

Study	Population^a	Intervention^b	Comparator^c	Outcomes^d	Duration of Follow-Up^e
Cuzick et al (2012) ⁴¹	4. Not screen selected; higher risk than intended use	1. Thresholds not described		4. Reclassification not provided	
Cuzick et al (2015) ⁴²	4. Not screen selected; higher risk than intended use	1. Thresholds not described			
Lin et al (2018) ⁴³	Note. Validation cohort is from Cuzick (2015)				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 8. Study Design and Conduct Gaps

Study	Selection^a	Blinding^b	Delivery of Test^c	Selective Reporting^d	Data Completeness^e	Statistical^f
Cuzick et al (2012) ⁴¹	1. Unclear if all men meeting criteria were included				2,3. 349 of 776 had sufficient data for inclusion	1. CIs not reported for KM estimates at 10 y for CCP
Cuzick et al (2015) ⁴²	1. Unclear if all men meeting criteria were included				2,3. 585 of 989 had sufficient data for inclusion	1. CIs not reported for KM estimates

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Lin et al (2018) ⁴³	Note. Used data from Cuzick (2015) for validation cohort					at 10 y for CCP 1. CIs not reported for KM estimates at 10 y for CCR

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

CCP: Cell Cycle Progression; CCR: combined clinical cell cycle risk; CI: confidence interval; KM: Kaplan-Meier.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

In summary, Table 3 displays the association between CCP score adjusted for CAPRA; Table 4 shows the risk of death by groups of CCP score; and Table 5 shows predicted risk of death by CCR score, which is the combined CCP and CAPRA score. The CCR score is most relevant because it appears in the sample report provided by the manufacturer. Table 3 demonstrates an association between CCP and risk of death on the relative scale but does not necessarily indicate that there is a difference in absolute risk that would be meaningful for clinical decision making. Table 4 displays the estimated absolute risk of death for the CCP score but notably absent are CIs that would help in interpretation. However, given the data provided, several concerns arise. Even the lowest risk group shown in Cuzick et al (2012) has a 10-year death rate of 20%, which may be explained by the population characteristics (ie, not PSA screen-selected, a third with Gleason >7 score and half with PSA level >25 ng/mL); however, a death rate of 20% is unlikely to be low enough to forgo immediate treatment.⁴¹

Table 4 does not include the death rates by CCR score; however, the predicted 10-year prostate cancer death rates by CCR score were provided in a figure in Cuzick (2015). The predicted 10-year risk for CAPRA alone compared with CCR was provided in a dot plot in Cuzick (2015). The authors stated that CCR identified 11 men with a CAPRA score of 2 (indicating an estimated 10-year mortality rate of 4%) who "had a higher risk" based on CCR score. From the dot plot, it appears that for these 11 men, the 10-year mortality rate estimated by CCR score ranged from just greater than 4% to about 8%. The authors also indicated that for 31 men with CAPRA score of 3 (corresponding to a 10-year risk of death rate of 5.7%), the risk as estimated by CCR was less than 4.0% from the plot the CCR estimated risk appears to range from about 2.5% to 4% for those 31 men. It is not clear that either of these reclassifications would change estimated mortality enough to alter treatment decisions. Using data from Cuzick et al (2015) and a CCR cutoff of 0.8, Lin et al (2018) estimated that the 10-year death rate for men with low to favorable intermediate risk was 0% in men with CCR score of 0.8 or less and 9% for men with CCR score greater than 0.8, but precision estimates were not provided.

Systematic Reviews

The results of a systematic review and meta-analysis supported by Myriad Genetics were reported by Sommariva et al (2016).⁴⁵ Published and unpublished studies of prognostic validity or clinical utility of CCP testing were eligible for inclusion. Seven published studies were identified;

five were clinical validity studies. Two were reviewed in the previous paragraphs, and the remaining validity studies are reviewed below in the section on post-RP management. The other 2 “utility” studies are discussed in the following section. Two validity studies reported outcomes for disease-specific mortality^{41,46} but of the two only the Cuzick et al (2012) included newly diagnosed patients, so the pooled outcome is not relevant in this section.

Clinically Useful

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

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Three decision-impact studies have assessed the potential impact of Prolaris on physicians’ treatment decisions in patients.⁴⁷⁻⁴⁹ The authors of these studies—Crawford et al (2014),⁴⁷ Shore et al (2014),⁴⁸ and Shore et al (2016)⁴⁹—have suggested that their findings supported the “clinical utility” of the test, based on whether the results would lead to a change in treatment. Pathology results were not reported for these studies. Given the lack of established clinical validity and no reported outcomes, it is uncertain whether any treatment changes were clinically appropriate.

In trying to construct a chain of evidence from clinical validity to clinical utility, there are several obstacles to drawing conclusions. First, as noted in the clinical validity section, it is not clear if the test provides incremental value over the CAPRA score for decision making. In the example of reclassification given by Cuzick et al (2015), 11 men with a CAPRA estimated 10-year mortality risk rate of 4% were reclassified as having higher 10-year mortality estimated by CCR score with risk ranging from just greater than 4% to about 8%, and 31 men with CAPRA 10-year mortality risk rate of 5.7% were reclassified as having lower estimated risk by CCR of about 2.5% to 4%.⁴² It is not clear that these reclassifications would change treatment decisions.

Given that the PIVOT trial supported RP for the intermediate-risk group, showing a 30% relative and 12% absolute benefit for overall survival, in order to be suitable for clinical decision making, the test would have to identify a lower risk group of intermediate-risk men with very high negative predictive value for survival with tight CIs. Because it is not clear how the Cuzick et al (2012) or Cuzick et al (2015) results would apply specifically to intermediate-risk men, it is not clear whether the test could be used to identify intermediate-risk men who can delay RP or RT.

Health Quality Ontario (2017) reported on a health technology assessment including a systematic review of the literature assessing the clinical utility of the Prolaris CCP.⁵⁰ The literature search identified Crawford et al (2014)⁴⁷ and Shore et al (2016).⁴⁹ Reviewers concluded that the GRADE

rating of the quality of evidence was very low and that there was no evidence on clinical outcomes of patients whose treatment was informed by CCP results.

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 level or Gleason score for tumor-specific mortality at 10-year follow-up based on HRs.⁴¹ Comparison with CAPRA score was not provided in Cuzick et al (2012). 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 Ten-year mortality rates based on CCP were inconsistent within Prolaris risk categories across Cuzick et al (2012) and Cuzick et al (2015). Numerical summaries of mortality rates for the CCR were provided in a figure in Cuzick (2015). The men included in the U.K. registries were not screen-selected, and a large proportion of the men in the validation studies were not low or intermediate risk.

No direct evidence is available to support the clinical utility of Prolaris for improving net outcomes of patients with localized prostate cancer. The chain of evidence is also incomplete. The ProtecT trial showed 99% ten-year disease-specific survival in all 3 treatment groups: active surveillance, RT, and RP including predominately low-risk but also some intermediate-risk men. AUA has recommended active surveillance in low-risk men. The low mortality rate estimated with tight precision makes it unlikely that a test intended to identify a subgroup of low-risk men with a net benefit from immediate treatment instead of active surveillance would find such a group.

The PIVOT trial preplanned subgroup analysis showed a reduction in mortality for RP compared with observation for men with intermediate risk; AUA has recommended RT or RP for such men. For intermediate-risk men, a test designed to identify men who can receive active surveillance instead of RP or RT would need to show very high negative predictive value for disease-specific mortality at 10 years and improvement in prediction compared with existing tools used to select such men. To forgo evidence-based beneficial treatment, there would have to be a very high standard of evidence for the clinical validity of the test.

Oncotype DX Prostate

The Oncotype DX Prostate 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 Genomic Prostate Score (GPS), which ranges from 0 to 100. Higher GPS scores indicate more risk.

Clinically Valid

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

Five studies reporting clinical validity are summarized in Table 9. One publication by Klein et al (2014) compiled results for 3 cohorts: two in test development including a contemporary (1997-2011) group of patients in a prostatectomy study (N=441; Cleveland Clinic database, 1987-2004) and a biopsy study (N=167; Cleveland Clinic database, 1998-2007); the third was an independent clinical validation study cohort (N=395; University of California, San Francisco [UCSF] Database, 1998-2011).⁵¹ A second study, Cullen et al (2015), evaluated men with NCCN clinically very low to intermediate risk undergoing prostatectomy.⁵² The third study, Whalen et al

(2016), evaluated men in a clinical practice setting.⁵³ The study by van Den Eeden et al (2018) included men from a cancer registry⁵⁴ and the study by Salmasi et al (2018) included men from an institutional database.⁵⁵

Table 9. Clinical Validity Studies Assessing Oncotype DX Prostate

Study	Design	Dates	Sites	N	Population
Klein et al (2014) ⁵¹	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) ⁵²	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
Whalen et al (2016) ⁵³	Prospective observational cohort (median follow-up, 5.2 y)	2013-2014	Mount Sinai Hospital	50	Clinically localized; clinical stage T1/T2; PSA level ≤20 ng/mL, Gleason score ≤7
Van Den Eeden et al (2018) ⁵⁴	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
Salmasi et al (2018) ⁵⁵	Retrospective cohort from institutional database	2010-2016	UCLA	134	NCCN very low, low- or intermediate-risk prostate cancer treated with RP; 11% African American

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.⁵⁶

Results from the clinical validation study and prostatectomy study by Klein et al (2014) provided information on the potential clinical validity of this test.⁵¹ The cohorts included men with a mix of low- to low-intermediate clinical risk characteristics using NCCN or AUA criteria. The Klein (2014) clinical validation study (see Table 9) was prospectively designed, used masked review of prostatectomy pathology results, and as such met the Reporting Recommendations for Tumor Marker Prognostic Studies guidelines for biomarker validation.⁵⁷ The prostatectomy study used a case-cohort design to select a 1:3 ratio of recurrent to nonrecurrent patients. Favorable pathology was defined as freedom from high-grade or non-organ-confined disease. In the prostatectomy study, the ability of the GPS to stratify patients further within AUA groupings was related to the clinical recurrence-free interval in regression-to-the-mean estimated survival curves. Results of the Klein et al (2014) validation study showed that the GPS could refine stratification of patients within specific NCCN criteria groupings, as summarized in Table 10. Proportions were estimated from a plot of GPS vs the percent likelihood of favorable pathology.⁵¹

Table 10. Reclassification of Prostate Cancer Risk Categories with Oncotype DX Prostate

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.⁵¹

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

The actual number of patients correctly or incorrectly reclassified across all 3 categories cannot be ascertained from the data provided. The results would suggest that the combination of GPS plus clinical criteria can reclassify patients on an individual basis within established clinical risk categories. Extrapolation of this evidence to a true active surveillance population, for which the

majority in the study would be otherwise eligible, is difficult because all patients had elective RP within 6 months of diagnostic biopsy.

The Klein et al (2014) prostatectomy study, although used to identify genes to include in the GPS, provided estimates of clinical recurrence rates stratified by AUA criteria⁵⁸ compared with rates after further stratification according to the GPS from the validation study. The survival curves for clinical recurrence reached nearly 18 years based on the dates individuals in the cohort were entered into the database (1987-2004). The reclassifications are summarized in Table 11. The GPS groups are grouped by tertiles defined in the overall study. Absolute rates and precision estimates of clinical recurrence by GPS low-, intermediate-, and high-risk groups were not reported. These data would suggest the GPS can reclassify patient risk of recurrence based on a specimen obtained at biopsy. However, the findings do not necessarily reflect a clinical scenario of predicting disease progression in untreated patients under active surveillance.

Table 11. Reclassification of Prostate Cancer 10-Year Clinical Recurrence Risk With Oncotype DX Prostate

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.⁵¹

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 prostate cancer undergoing RP within 6 months of diagnosis.⁵² The sample was obtained from men enrolled in the Center for Prostate Disease Research longitudinal study at 2 U.S. military medical centers. A Gleason score of 4 or 5 with the non-organ-confined disease was considered adverse pathology. Biopsies were available for 500 (57.9%) of 864 eligible patients; 382 (44.2% of eligible) with both adequate tissue for gene expression analysis and available RP pathology were included in the analysis. Selected patients were older (61.0 years vs 59.7 years, $p=0.013$) and had both higher Gleason scores ($p<0.001$) and NCCN risk classification (29.8% vs 32.9% intermediate, $p=0.035$). Median follow-up was 5.2 years and biochemical recurrence (BCR) occurred in 62 (15.4%). Estimates of 5-year BCR by GPS score are shown in Table 12. Adverse pathology was noted in 163 (34%) men. In an analysis adjusted for baseline characteristics, the GPS was associated with BCR-free survival and adverse pathology following RP (see Table 13). The GPS improved the C statistic for adverse pathology over NCCN risk alone from 0.63 to 0.72 (CIs not reported). Comparisons with other predictors such as CAPRA or Gleason score alone were not reported. Study implications were limited by the low proportion of eligible men in the analysis and differences between excluded and included men.

Whalen et al (2016) prospectively evaluated the correlation between GPS and final pathology at RP in a clinical practice setting.⁵³ Eligible men were 50 years of age and older with more than 10 years of life expectancy, PSA levels of 20 ng/mL or less, stage cT1c-cT2c newly diagnosed, untreated prostate cancer, and who met NCCN classifications as very low risk, low-risk, or low-intermediate risk. Men were enrolled from May 2013 to August 2014 at an academic medical center. Genomic Health reclassified patients' cancers as "less favorable," "consistent with," or "more favorable" than what would have been predicted by their NCCN risk group. Adverse

pathology at RP was defined as any pT3 stage and primary Gleason grade of 4 or any pattern 5. Fifty patients had RP pathology, and the reclassification results for these participants are discussed here; 21 (42%) met the definition of adverse pathology. The NCCN risk classification categorized 2 (4%) patients as very low risk, 34 (68%) as low risk, and 14 (28%) as low-intermediate risk. Twenty-three (46%) of patients were reclassified using GPS and the percentage with adverse pathology for the reclassification is shown in Table 14, as derived from data provided in the text. CIs were not provided.

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 a median follow-up of 9.8 years.⁵⁴ Characteristics are shown in Table 9. In an analysis adjusted for NCCN risk classifications, the GPS was associated with BCR-free survival, distant metastasis, and prostate cancer death following RP (see Table 13). Ten-year prostate cancer death by GPS score was displayed in a figure stratified by NCCN risk classification, which provides some information on potential reclassification. Ten-year prostate cancer death appears to be close to 0 for men who are NCCN low risk regardless of GPS score, indicating little useful reclassification of NCCN low-risk men based on GPS. For NCCN intermediate risk, the risk of prostate cancer death ranges from approximately zero for a GPS less than 40 to close to 40% for a GPS of 100. It is unclear how many men with GPS less than 40 were NCCN favorable intermediate risk.

Salmasi et al (2018) reported on a retrospective cohort from a UCLA institutional database of men with NCCN very low, low-, or intermediate-risk prostate cancer treated with RP between 2010 and 2016 who had undergone simultaneous 3 tesla multiparametric magnetic resonance imaging fusion targeted and systematic biopsies within the 6-month period prior to RP (see Table 9). The association between GPS and adverse pathology is shown in Table 13. The authors also reported an AUC for a model including Gleason score, GPS, and highest Prostate Imaging Reporting and Data System score determined by magnetic resonance imaging was 0.79 (95% CI, 0.71 to 0.87). The AUC of other models had overlapping CIs; the AUC of a model with Gleason score and highest Prostate Imaging Reporting and Data System score was 0.69 (95% CI, 0.59 to 0.78); and another model including Gleason score and PSA level was 0.68 (95% CI, 0.58 to 0.78).

Table 12. Estimates of 5-Year Biochemical Recurrence with Oncotype DX Prostate

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).⁵²

^a Estimated from digitizing a figure.

Table 13. Univariate and Multivariate Association Between GPS and Outcomes

Study	Outcome	N	Unadjusted	Multivariate
			Ratio (95% CI)	Ratio (95% CI)
Klein et al (2014) ⁵¹ validation study	Adverse pathology	395	OR=2.1 (1.4 to 3.2)	1.9 (1.3 to 2.8) ^a
Cullen et al (2015) ⁵²	BCR	392	HR=2.9 (2.0 to 4.2)	2.7 (1.8 to 3.8) ^b
	Adverse pathology	392	HR=3.2 (2.1 to 5.0)	HR=2.7 (1.8 to 4.4) ^c
Whalen et al (2016) ⁵³	Adverse pathology	50	NR	OR=1.4 (NR) ^d
Van Den Eeden et al (2018) ⁵⁴	Distant metastasis	259	HR=2.8 (1.6 to 4.6)	HR= 2.3 (1.4 to 3.9) ^a
	Prostate-cancer death	259	HR=3.2 (1.8 to 5.7)	HR=2.7 (1.5 to 4.8) ^a
	BCR	259	HR=2.5 (1.6 to 3.9)	HR=2.1 (1.4 to 3.1) ^a
Salmasi et al (2018) ⁵⁵	Adverse pathology	134	OR=3.8 (2.1 to 7.4)	OR=2.9 (1.5 to 5.9) ^e

BCR: biochemical recurrence; CI: confidence interval; GPS: Genomic Prostate Score; HR: hazard ratio; NCCN: National Comprehensive Cancer Network; NR: not reported; OR: odds ratio.

^a Per 20-point increase in GPS; adjusted for NCCN risk group.

^b Per 20-point increase in GPS; adjusted for NCCN risk group and medical center.

^c Per 20-point increase in GPS; adjusted for NCCN risk group and age.

^d As a continuous variable, adjusted for age, prostate-specific antigen level, clinical Gleason score, and NCCN risk category.

^e Per 20-point increase in GPS; adjusted for Gleason score, magnetic resonance imaging score, and prostate-specific antigen level.

Table 14. Risk of Adverse Pathology with Oncotype DX Prostate

Overall AP Risk, % (NCCN Risk Level)	n	AP Risk, n (%)	AP Risk, n (%)	AP Risk, n (%)
		(GPS Less Favorable Group; n=5)	(GPS Consistent With Group; n=29)	(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).⁵³

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

Systematic Reviews

Brand et al (2016) combined the Klein et al (2014) and Cullen et al (2015) studies using a patient-specific meta-analysis.⁵⁹ The GPS was compared with the CAPRA score, NCCN risk group, and AUA risk group. Reviewers 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 the CAPRA score. The AUC improved from 0.64 to 0.70 by adding the GPS to the NCCN risk group. The improvements were reported to be significant but the CIs for AUC were not provided.

Tables 15 and 16 display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 15. Relevance Gaps

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Klein et al (2014) ⁵¹ validation study	4. All patients had RP			1. Survival outcomes not included	
Cullen et al (2015) ⁵²	4. All patients had RP		3. No comparison to other risk predictors	1. Survival outcomes not included	1. 10-y outcomes not provided
Whalen et al (2016) ⁵³	4. All patients had RP			1. Survival outcomes not included	1. 10-y outcomes not provided
Van Den Eeden et al (2018) ⁵⁴	4. All patients had RP				
Salmasi et al (2018) ⁵⁵	4. All patients had RP			1. Survival outcomes not included	1. Follow-up duration unclear

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

RP: radical prostatectomy.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 16. Study Design and Conduct Gaps

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Klein et al (2014) ⁵¹ validation study						1. CIs for reclassification not provided
Cullen et al (2015) ⁵²						1. CIs for AUC and reclassification not provided
Whalen et al (2016) ⁵³						1. CIs for reclassification not provided
Van Den Eeden et al (2018) ⁵⁴						
Salmasi et al (2018) ⁵⁵						

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

AUC: area under the curve; CI: confidence interval.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

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

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Decision-impact studies have assessed the potential impact of Oncotype DX Prostate on physicians' and patients' treatment decisions.⁶⁰⁻⁶² As with the previously evaluated test, given the lack of established clinical validity and no reported outcomes, it is uncertain whether any treatment changes were clinically appropriate. Decision-impact studies have also indicated that men classified as low risk by guidelines criteria, and thus meeting guidelines criteria for active surveillance, are more likely to receive active surveillance if they are *tested* with the Oncotype DX Prostate test.^{61,63,64} These arguments would suggest that the test may be a useful behavioral modifier. However, comparison with educational or quality improvement initiatives designed to improve the uptake of active surveillance in low-risk men has not been provided.

Klein et al (2014)⁵¹ reported a decision-curve analysis⁶⁵ that they proposed reflects the clinical utility of Oncotype DX Prostate. In this analysis, they compared the predictive impact of the GPS plus the CAPRA validated tool⁶⁶ with the CAPRA score alone on the net benefit for the outcomes of patients with high-grade disease (Gleason score >4+3), high-stage disease, and combined high-grade and high-stage disease. They reported that, over a range of threshold probabilities for implementing treatment, "...incorporation of the GPS would be expected to lead to fewer treatments of patients who have favorable pathology at prostatectomy without increasing the number of patients with adverse pathology left untreated." For example, at a threshold risk of 40% (eg, a man weighing the harms of prostatectomy vs the benefit of active surveillance at 4:6), the test could identify 2 per 100 men with high-grade or high-stage disease at a fixed false-positive rate, compared with using the CAPRA score alone. Thus, an individual patient could use the findings to assess his balance of benefits and harms (net benefit) when weighing the choice to proceed immediately to curative RP with its attendant adverse sequelae, or deciding to enter an active surveillance program. The latter would have an immediate benefit realized by forgoing RP, but might be associated with greater downstream risks of disease progression and subsequent therapies. However, no CIs were presented for the decision-curve analysis.

Section Summary: Oncotype DX Prostate

The evidence from 5 studies on clinical validity for Oncotype DX Prostate has suggested the GPS can reclassify a patient's risk of recurrence or risk of adverse pathology at RP based on a biopsy specimen.⁵¹⁻⁵³ One study provided a figure with data on the reclassification of disease-specific survival using NCCN and GPS.⁵⁴ Ten-year prostate cancer death appears to be close to 0 for men who are NCCN low risk regardless of GPS score, indicating little useful reclassification of NCCN low-risk men based on GPS. For NCCN intermediate risk, the risk of prostate cancer death ranges

from approximately zero for a GPS less than 40 to close to 40% for a GPS of 100. It is unclear how many of the men with a GPS less than 40 were NCCN favorable intermediate risk. Moreover, generalizing this evidence to a true active surveillance population, for which most in the study would be otherwise eligible, is difficult because all patients had elective RP. Thus, the findings do not reflect a clinical scenario of predicting the risk of 10-year disease-specific survival in untreated patients under active surveillance. Some publications also lacked precision estimates for important variables such as risk estimates for recurrence or AUC estimates.

No direct evidence of clinical utility was found. The chain of evidence is also incomplete. Klein's decision-curve analyses have suggested the potential for the combined GPS and CAPRA score data to help patients make decisions based on relative risks associated with immediate treatment or deferred treatment (ie, active surveillance). This would reflect the clinical utility of the test. However, it is difficult to ascribe possible clinical utility of Oncotype DX Prostate in active surveillance because all patients regardless of clinical criteria elected RP within 6 months of diagnostic biopsy. Moreover, the validity of using tumor pathology as a surrogate for cancer-specific death is unclear. Reports from validation studies lack precision estimates for important variables such as risk estimates for recurrence.

The ProtecT trial showed 99% ten-year disease-specific survival in all 3 treatment groups: active surveillance, RT, and RP, including predominately low-risk but also some intermediate-risk men. AUA has recommended active surveillance in low-risk men. The low mortality rate estimated with tight precision makes it unlikely that a test intended to identify a subgroup of low-risk men with a net benefit from treatment instead of active surveillance would find such a group.

The PIVOT trial preplanned subgroup analysis showed a reduction in mortality for RP compared with observation for men at intermediate risk; AUA has recommended RT or RP for such men. For intermediate-risk men, a test designed to identify men who can receive active surveillance instead of RP or RT would need to show very high negative predictive value for disease-specific mortality at 10 years and improvement in prediction compared with existing tools used to select such men. For these men to forgo evidence-based beneficial treatment, there would have to be a very high standard of evidence for the clinical validity of the test.

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 a continuous number between 0 and 1, which estimates the probability of "non-GS 6" pathology.

Clinically Valid

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

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.⁶⁷

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 values 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 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% of 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 in a second blinded validation study of 276 cases (see Table 17), also reported in Blume-Jensen (2015), to validate the assay’s ability to distinguish “favorable” pathology (defined as Gleason score on prostatectomy $\leq 3+4$ and organ-confined disease) from “nonfavorable” pathology (defined as Gleason score on prostatectomy $\geq 4+3$ 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 17. Clinical Validity of ProMark

Study	Design ^a	Outcome	Site	N
Blume-Jensen et al (2015) ⁶⁷	Retrospective cohort ^a	Favorable pathology at RP	Montreal, QC	276 ^a

RP: radical prostatectomy.

^aOnly the validation sample cohort N.

Clinically Useful

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

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No published studies on the clinical utility of the ProMark test were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical utility of the ProMark test has not been established, a chain of evidence supporting the test’s clinical utility cannot be constructed.

Section Summary: ProMark Protein Biomarker Test

Data are insufficient to establish the clinical validity or the clinical utility of the ProMark test.

Management Decision After RP

Clinical Context and Test Purpose

The purpose of GEP and protein biomarker testing 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 debated. Adjuvant RT may maximize cancer control outcomes; early salvage RT (at first evidence of a rising serum PSA level) 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 randomized controlled trials (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.

Several observational analyses have shown conflicting conclusions whether adjuvant RT is favored over early salvage RT.⁷²⁻⁷⁴ RCTs comparing adjuvant with early salvage RT are underway.

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.^{14,75} 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 GEP or protein biomarker testing, compared with clinicopathologic risk stratification or when used with clinicopathologic risk stratification, improve outcomes in men following RP?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals who have undergone RP for prostate cancer, and who are deciding on subsequent management such as adjuvant RT or 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

The test being considered is Prolaris, which, described in the previous section, is also intended to classify individuals who have undergone RP.

Decipher is a tissue-based tumor 22-biomarker GEP test intended to classify high-risk individuals who have undergone RP. The cutpoints 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 (eg, stage, biopsy Gleason grade, serum PSA level, surgical margin, disease involvement) and demographic characteristics (eg, 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^{76,77} and Cancer of the Prostate Risk Assessment–Surgical (CAPRA-S) nomogram⁷⁸ 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 events. Harmful outcomes resulting from a false test result are recurrence, metastases or death, and unnecessary treatments. The outcomes of interest are listed in Table 18.

Table 18. 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.

Timing

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

Setting

Decisions about management of prostate cancer following RP are typically made by patients and urologists and oncologists in the secondary or tertiary care setting.

Prolaris

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

Clinically Valid

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

Four studies reporting clinical validity in the post-RP management setting are summarized in Table 19. Three of these studies—Cuzick et al (2011),⁴⁶ Cooperberg et al (2013),⁵⁶ and Bishoff et al (2014)⁷⁹—reported on post-RP patients. Koch et al (2016)⁸⁰ reported on post-RP patients with

BCR. Freedland et al (2013)⁸¹ reported on post-RT patients but is included in this section for completeness.

Table 19. Clinical Validity Studies Assessing Prolaris for Post-RP or Post-RT Management

Study	Design	Population	Dates	Sites	N
After prostatectomy					
Cuzick et al (2011) ⁴⁶	Retrospective cohort from prospective registry	Clinical stage T1/T2; no neoadjuvant therapy; 71% PSA level ≤10 ng/mL, 96% Gleason score ≤7	1985-1995	Scott and White Clinic	366
Cooperberg et al (2013) ⁵⁶	Retrospective cohort from prospective registry	98% PSA level ≤20 ng/mL, 95% Gleason score ≤7; no neoadjuvant or adjuvant therapy	1994-2011	UCSF Registry	413
Bishoff et al (2014) ⁷⁹	Retrospective cohort from medical records	Clinical stage T1/T2; median PSA level 5.5-7.2 ng/mL; between 91% and 94% Gleason score ≤7; between 3% and 19% with adjuvant therapy	2005-2006	Martini Clinic	283
			1994-2005	Durham VAMC	176
			1997-2004	Intermountain Healthcare	123
Koch et al (2016) ⁸⁰	Retrospective cohort from medical records	Median PSA level 6.5-11 ng/mL; 64% Gleason score ≤7; no adjuvant RT	1995-2010	Indiana University SOM	47
After external-beam radiotherapy					
Freedland et al (2013) ⁸¹	Retrospective cohort, source unclear	97% clinical stage T1/T2; Median PSA level 8 ng/mL; 88% Gleason score ≤7; 53% no concurrent hormone use; 57% African American	1991-2006	Durham VAMC	141

PSA: prostate-specific antigen; RP: radical prostatectomy; RT: radiotherapy; 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.⁴⁶ 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 is not described. Men conservatively managed after RP between 1985 and 1995 were identified from a tumor registry (n=366 with CCP scores). 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 (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 (see Table 15). Analyses of prostate cancer deaths in the RP cohort were problematic, due to only 12 (3%) deaths. The clinical score included PSA level, stage, positive surgical margins, and Gleason score. The AUC for BCR within 5 years in the RP cohort was 0.825 for the clinical score and 0.842 for the CCR score. Although the CCP increased the AUC by 2%, whether that improvement is clinically useful is unclear because reclassification data and analysis of net benefit are lacking.

Cooperberg et al (2013) evaluated the CCP score in an 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).⁵⁶ A prognostic model was developed from the RP cohort described by Cuzick et al (2011).⁴⁶ The validation cohort was obtained from patients identified from the 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 association with BCR is shown in Table 20. The AUC for BCR with CAPRA-S alone was 0.73, increasing to 0.77 for the combined CCR 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).⁷⁹ The combined analysis included all 582 patients. Gleason scores were 7 or lower in 93% of men. In the combined cohorts, a unit increase in the CCP score increased the adjusted HR for BCR by 1.47 (see Table 20). Metastatic events (n=12) were too few to draw conclusions.

Koch et al (2016) evaluated whether the CCP score could discriminate between systemic disease and local recurrence in patients with BCR after RP.⁸⁰ All 60 patients given 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. Data from 5 patients were excluded for failing to meet 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 the analysis. Outcomes were 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 for metastatic disease or nonresponse was 3.72 (see Table 20). Multivariate analysis was performed; however, due to the very small number of participants in the durable response group, CIs were very wide.

Table 20. Univariate and Multivariate Associations Between Prolaris CCP and Outcomes in Post-RP Clinical Validation Studies

Study	Outcomes	Median FU, y	N	Unadjusted	Multivariate
				Ratio (95% CI)	Ratio (95% CI)
Cuzick et al (2011) ⁴⁶	BCR	9.4	366	HR=1.89 (1.54 to 2.31)	1.77 (1.40 to 2.22) ^a
	Prostate cancer death			HR=2.92 (2.38 to 3.57)	
Cooperberg et al (2013) ⁵⁶	BCR	7	413	HR=2.1 (1.6 to 2.9)	1.7 (1.3 to 2.4) ^c
Bishoff et al (2014) ⁷⁹	BCR	5/7 ^f	582	HR=1.60 (1.35 to 1.90)	1.47 (1.23 to 1.76) ^d
Koch et al (2016) ⁸⁰	Metastatic disease or nonresponse	9.4	47	OR=3.72 (1.29 to 10.7)	10.4 (2.05 to 90.1) ^e

BCR: biochemical recurrence; CCP: Cell Cycle Progression; CI: confidence interval; FU: follow-up; HR: hazard ratio; OR: odds ratio; PSA: prostate-specific antigen; RP: radical prostatectomy.

^a Per 1-unit increase in CCP. Adjusted for PSA level, Gleason score, pathologic 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 level, 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 level, Gleason score, and adjuvant treatment.

^e Per 1-unit increase in CCP. Adjusted for Gleason score, time from surgery to BCR, and PSA level.

^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 were treated with EBRT from 1991 to 2006, with biopsy samples and follow-up of at least 3 years. Nineteen (13%) of men experienced BCR by 5 years. The univariate HR for BCR for each 1-unit increase in CCP was 2.55 (95% CI, 1.43 to 4.55). The multivariable HR for BCR associated with a 1-unit increase in CCP, including adjustment for pretreatment PSA level, Gleason, percent positive cores, and concurrent ADT, was 2.11 (95% CI, 1.05 to 4.25).

Systematic Reviews

As described in the previous Prolaris section, results of an industry-sponsored systematic review and meta-analysis were reported.⁴⁵ Seven published studies were identified; all have been reviewed in the previous paragraphs (needle biopsy conservative management cohorts, postprostatectomy cohorts, and EBRT cohort). Including 4 validity studies^{46,56,79,81} that reported outcomes of BCR in post-RP cohorts, the pooled estimate of the HR, calculated with random-effects meta-analytic methods, for BCR for a 1-unit increase in CCP score was 1.9 (95% CI, 1.6 to 2.3). Two studies reported outcomes for disease-specific mortality.^{41,46} Since only one of those was a post-RP study, the pooled HRs are not relevant here. There was evidence of heterogeneity in both models; reviewers did not report any variables associated with heterogeneity.

Clinically Useful

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

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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.⁵⁶ A combined CCR predictor appeared only slightly better than CAPRA-S alone for thresholds of approximately 30% or more. For example, at a threshold of 30% (ie, meaning a man would value the harm-to-benefit of treatment such as RT as 3:7), the CCR score would detect about 2 more men per 100 likely to experience BCR if the false-positive rate was fixed. However, the lack of CIs for the decision-curve analysis, together with the small difference, is consistent with an uncertain net benefit obtained by adding CCP to the CAPRA-S score. Also, it is not clear whether the group of patients identified as high risk of experiencing BCR would have a net benefit from adjuvant instead of early salvage RT.

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 that the CCP score offered little improvement in the AUC (2%) over clinicopathologic predictors and did not examine reclassification.⁴⁶ Cooperberg et al (2013) found the AUC for BCR improved from 0.73 (CAPRA-S

alone) to 0.77 by adding CCP score.⁵⁶ Bishoff et al (2014)⁷⁹ and Koch et al (2016)⁸⁰ did not report any classification or discrimination measures. Koch et al (2016) was performed in patients who had a BCR following RP.

No direct evidence is available to support the clinical utility of Prolaris for improving net outcomes of patients with localized prostate cancer following RP. The chain of evidence is also incomplete. Decision-curve analysis did not provide convincing evidence of meaningful improvement in net benefit by incorporating the CCP score. Prolaris CCP score may have an association with BCR, but disease-specific survival outcomes were not reported. A larger number of disease-specific survival events and precision estimates for discrimination measures are needed.

Decipher Prostate Cancer Classifier

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.

Clinically Valid

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

The clinical validity of the Decipher test (GC) has been reported in 11 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 (see Tables 21 and 22).^{68,82-92}

Table 21. Characteristics of Clinical Validity Studies Assessing the Decipher Genomic Classifier

Study	Study Population	Design	Comparator	Outcome	Sites	Dates
Berlin et al (2018) ⁹³	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
Spratt et al (2018) ⁹⁴	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	Clinicopathologic I risk factors (eg, 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 (eg, preop PSA, EPE, GS); clinical nomogram (CAPRA-S)	PCa mortality (10 y)	Mayo Clinic, Johns Hopkins, Cleveland Clinic, Durham VA	1987-2010

Study	Study Population	Design	Comparator	Outcome	Sites	Dates
Nguyen et al (2017) ⁹⁵	Treated with first-line RP or first-line RT plus ADT, had adverse pathology at surgery (defined as either preoperative PSA >20 ng/mL, stage 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
Freedland et al (2016) ⁸⁹	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 (eg, preop PSA, EPE, GS); Clinical nomogram (Briganti, CAPRA-S)	Metastases	Durham VA, Thomas Jefferson, Mayo Clinic	1991-2010
Glass et al (2016) ⁹⁰	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	Clinical risk factors (age at diagnosis); Clinical nomogram (CAPRA-S)	Clinical recurrence (10 y)	Kaiser Permanente Northwest	1997-2009
Ross et al (2016) ⁹⁶	Clinically localized PCa after RP; CAPRA-S score ≥3, pathologic GS ≥7, post-RP PSA nadir <0.2 ng/mL, and sufficient tissue and clinical data; no nodal disease prior to surgery; no treatment before metastasis; 8% African American	Case cohort from registry	Clinicopathologic risk factors (eg, preop PSA, EPE, GS); clinical nomogram (CAPRA-S, Eggener)	Metastases (10 y)	Johns Hopkins	1992-2010
Ross (2016) ⁹⁶	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 (eg, 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) ⁸⁴	Clinically localized PCa after RP; preop PSA >20 ng/mL, stage pT3b, or pathologic GS ≥8; no neoadjuvant	Case cohort from registry	Clinicopathologic risk factors (eg, preop PSA, EPE, GS); clinical	PCa mortality	CapSURE Registry	2000-2006

Study	Study Population	Design	Comparator	Outcome	Sites	Dates
Den et al (2015) ⁶⁸	treatment; achieve PSA nadir after surgery 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	nomogram (CAPRA-S) Clinicopathologic risk factors (eg, preop PSA, EPE, GS); clinical nomogram (CAPRA-S)	Metastases	Thomas Jefferson, Mayo Clinic	1990-2009
Klein et al (2015) ⁸² ; Klein et al (2016) ⁹¹	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 (eg, pre-op PSA, EPE, GS); clinical nomogram (Stephenson, CAPRA-S)	Metastases (5 y, 10 y)	Cleveland Clinic	1993-2001
Den et al (2014) ⁸³	Clinically localized PCa after RP; pT3 or margin-positive disease; received post-RP RT; no neoadjuvant treatment; 39% BCR; 13% African American	Retrospective cohort from registry	Clinicopathologic risk factors (eg, preop PSA, EPE, GS); clinical nomogram (Stephenson, CAPRA-S)	BCR	Thomas Jefferson	1999-2009
Ross et al (2014) ^{85,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 (eg, preop PSA, EPE, GS); clinical nomogram (Stephenson, CAPRA-S)	Metastases (5 y)	Mayo Clinic	2000-2006
Erho et al (2013) ⁸⁷ (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 (eg, preop PSA, EPE, GS)	Metastases	Mayo Clinic	1987-2001
Karnes et al (2013) ⁸⁶	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 (eg, preop PSA, EPE, GS); clinical nomogram (Stephenson)	Metastases (5 y)	Mayo Clinic	2000-2006

ART: adjuvant radiotherapy; CAPRA-S: Cancer of the Prostate Risk Assessment Postsurgical; BCR: biochemical recurrence; EPE: extraprostatic extension; GS: Gleason Score; MRD: minimal disease residual; NCCN: National Comprehensive Cancer Network; PCa: prostate cancer; preop: preoperative; RP: radical prostatectomy; RT: radiotherapy; SM: surgical margins; SRT: salvage radiotherapy; SVI: seminal vesicle invasion; ADT: androgen deprivation therapy.

^a Appears to be subgroup with BCR from Karnes et al (2013).

Table 22. 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) ⁹⁴ ; 95% received RT	Metastasis	5.6 (2.0 to 19.4)	0.86 (0.80 to 0.94)	0.69 (0.41 to 0.89) ^b	0.83 (0.70 to 1)
Berlin (2018) ⁹³	Metastasis (5 y)	2.1 (1.2 to 4.2)	0.86 (NR)	0.54 (NR) ^h	0.89 (NR)
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)
Nguyen (2017) ⁹⁵	Metastasis (5 y)	1.4 (1.1 to 1.8)	0.74 (0.63 to 0.83)	0.66 (0.53 to 0.77) ^h	0.74 (0.66 to 0.82) ^h
Freedland (2016) ⁸⁹	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) ⁹⁶	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) ⁹⁰	Metastasis	1.5 (p=0.011)	0.73 (0.49 to 0.95) ^c	0.80 (0.64 to 0.92)	0.84 (0.70 to 0.96)
Cooperberg (2015) ⁸⁴	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) ⁸² ; Klein (2016) ⁹¹	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) ⁶⁸	Metastasis post-RT	1.9 (p<0.001)	0.83 (0.72 to 0.89)	0.66 (0.56 to 0.78) ^b	0.85 (0.79 to 0.93)
Ross (2014) ⁸⁵	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) ⁸³	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) ⁸⁷	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) ⁸⁶	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.

¹ 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.⁸⁷ The 5- and 10-year results of 1 study were published separately.^{82,91} Four were case-cohort studies, and 8 used retrospective cohorts. Nine studies were supported by GenomeDx, which offers the Decipher test; all studies identified multiple authors as company employees. 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,^{84-87,93,94} 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 23. The GC AUCs for predicting metastases are shown in Table 22. 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).⁸⁶

The cumulative incidence of metastases by risk group is shown in Table 24. Three studies reported prostate cancer–specific mortality; only one of which included 10-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 23. Metastasis by GC Risk Group

Study	FU Time, y	N	Patients in Risk Group, %			Metastasis Rate, %		
			Low	Int	High	Low	Int	High
Spratt et al (2018) ⁹⁴	10	561	46	28	26	0	3	23
Berlin et al (2018) ⁹³	4	121	73	15	12	0	12	7
Ross et al (2016) ⁹⁶	5	422	57	27	16	7	10	22
Freedland et al (2016) ⁸⁹	10	170	51	31	18	3	8	33
Glass et al (2016) ⁹⁰	10	224	NR	NR	NR	0	3	
Ross et al (2016) ⁸⁸	10	260	73	17	10	8	20	32
Klein et al (2015) ⁸²	5	169	NR	NR	NR	5	NR	18
Den et al (2015) ⁶⁸	5	188	41	39	20	0	9	29
Den et al (2014) ⁸³	5	139	21	38	41	0	5	17
Ross et al (2014) ⁸⁵	5	85	NR	NR	NR	9	54	
Karnes et al (2013) ⁸⁶	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 somewhat—of the 19 men with CAPRA-S scores of 5 or lower, 12 were correctly reclassified to the highest GC risk, and one was incorrectly reclassified with a CAPRA-S score greater than 6 to low risk; all men had CAPRA-S scores of 3 or more.⁸⁴

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 25. Samples sizes and precision estimates for the cross-tabulations were not provided.

Table 24. 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
Nguyen et al (2017) ⁹⁵	5	235	60	18	23	4	7	23
Cooperberg et al (2015) ⁸⁴	5	185	54	22	24	6	3	30

FU: follow-up; Int: intermediate.

Table 25. Cross-Tabulation of 10-Year Cumulative Incidence of Prostate Cancer–Specific Mortality by GC and CAPRA

CAPRA-S Risk 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.

Tables 26 and 27 display notable gaps identified in each study. The gaps analysis focus on 10-year prostate cancer–specific mortality outcomes (ie, Karnes et al [2018]⁹²).

Table 26. Relevance Gaps

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Karnes et al (2018) ⁹²					

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 27. Study Design and Conduct Gaps

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Karnes et al (2018) ⁹²	2. Unclear if included men were consecutive or random samples of those meeting eligibility criteria					1. CIs for prostate cancer–specific mortality by GC low/high risk and reclassification not provided

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

CI: confidence interval.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Systematic Reviews

Spratt et al (2017)⁹⁷ reported an individual patient-level data meta-analysis of 5 studies described in the previous section.^{83,86,88-90} 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 (CIs not reported).

Clinically Useful

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

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No studies reporting direct evidence were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Decision Curves: Studies have included decision curves comparing the net benefit of different strategies using metastases or survival as the outcome (see Table 28).^{68,82,84-86,88,92,98} In observational and RT samples from Karnes et al (2013)⁸⁶ and Ross et al (2014),⁸⁵ using a 15% to 25% range of thresholds for decision making (ie, 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. No CIs were provided for the net benefit estimates and uncertainty cannot be evaluated. In the 2 observation-only samples, although 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 (eg, about 1 additional patient would be likely to experience metastases without an increase in false positives).^{82,88} In Ross (2014), the net benefit for CAPRA-S score exceeded that of the GC, with the net benefit of the GC plus CAPRA-S score being slightly better than the CAPRA-S score alone.⁸⁸ Finally, among men undergoing RT, decision curves suggested that the test would identify 3 or 4 men developing metastases per 100 tested at a fixed false-positive rate. Lobo et al (2015)⁹⁸ 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 (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 (2014), the estimated 10-year probability of metastasis or death was 0.28 (95% CI, 0.27 to 0.29) for usual care compared with 0.26 (95% CI, 0.25 to 0.27) for GC-based treatment.

Table 28. Reported Net Benefit of the Decipher Classifier vs Comparators

Study	Outcome	Range of Net Benefit vs	
		Treat None	Best Comparator
Spratt et al (2018) ⁹⁴	Metastasis	-0.003 to 0.015	NR
Karnes et al (2018) ⁹²	PC mortality	0.01 to 0.015	NR
Ross et al (2016) ⁹⁶	Metastasis	0.05 to 0.17	NR
Freedland (2016) ⁸⁹	Metastasis	0.01 to 0.043	0 to 0.02
Lobo et al (2015) ⁹⁸ with Karnes et al (2013) ⁸⁶ cohort	Metastasis or death	NR	0.017
Cooperberg et al (2015) ⁸⁴	PCa mortality	0.003 ^a	0.003 ^a
Klein et al (2015) ⁸²	Metastasis	0.008 to 0.025	0.000 to 0.012
Den et al (2015) ⁶⁸	Metastasis post-RT	0.09 to 0.11	0.03 to 0.04
Lobo et al (2015) ⁹⁸ with Den et al (2014) ⁸³ cohort	Metastasis or death	NR	0.015
Ross et al (2014) ⁸⁵	Metastasis	0.09 to 0.13	0.036 to 0.040
Karnes et al (2013) ⁸⁶	Metastasis	0.009 to 0.020	-0.004 to 0.003

NR: not reported; PCa: prostate cancer; RT: radiotherapy.

^aFor 25% threshold.

Changes in Management: Several studies have compared physician's treatment recommendations before and after receiving GC results.^{62,99-103} Because the studies did not include information on outcomes and clinical validity has not been established, it is not known whether these treatment decisions represent a clinical improvement in management.

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.⁹⁶ The men were from 4 cohorts previously described (Karnes et al [2013]⁸⁶; Den et al [2014]⁸³; Ross et al [2016]⁹⁶; Freedland et al [2016]⁸⁹). 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 end point was metastasis. Thirty-seven men developed metastasis, and the median follow-up was 8 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). Men with low CAPRA-S or low Decipher scores had a low risk of metastatic events regardless of treatment selection, and men with high CAPRA-S or Decipher scores benefitted from adjuvant RT compared with the other treatments.

Section Summary: Decipher 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 (ie, 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 10 years, by GC low, intermediate, and high risk are needed as well as reclassification analyses of prostate cancer-specific survival compared with comparators. Results

did not consistently demonstrate meaningful improvement in reclassification—possibly most importantly to lower risk categories. It is not clear whether the group of patients identified low risk using Decipher could be managed with observation instead of adjuvant or early salvage RT.

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 (eg, abiraterone, enzalutamide), or a taxane (eg, docetaxel).

Multiple approved therapeutic options exist for the treatment of men with mCRPC, which are given in conjunction with continued 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 PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is men with mCRPC who have progressed on an ARS inhibitor (eg, enzalutamide, abiraterone), have a good performance status (ie, 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.¹⁰⁴ 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 (HR=0.24; 95% CI, 0.10 to 0.57).¹⁰⁵ 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.¹⁰⁶

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.

Timing

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.¹⁰⁷ Outcomes with at least 1 year of follow-up of those surviving would be preferred.

Setting

Decisions about management of localized prostate cancer are typically made by patients, urologists, and oncologists in the secondary or tertiary care setting.

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.

Clinically Valid

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

Two studies were not included in this assessment of clinical validity because they reported results in the developmental cohort.^{105,106} One published clinical validity study was identified meeting selection criteria.¹⁰⁸ Characteristics of the study are provided in Table 29. 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 29. Characteristics of Clinical Validity Studies Assessing Oncotype DX AR-V7

Study	Study Population	Design	Outcome Measure	Threshold for Positive Index Test	Blinding of Assessors	Comment
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	

CTC: circulating tumor cell; OS: overall survival.

Results of the validation study are shown in Table 30. Median follow-up time in surviving men was not provided. Sixty-eight men were still in the risk set at 12 months. Numerically, men treated with ARS inhibitors had the longest overall survival if they were AR-V7–negative and had the shortest overall survival if they were AR-V7–positive. The unadjusted HR for overall survival for ARS inhibitors vs taxanes was statistically significantly greater than 1 (favoring ARS inhibitors) in the AR-V7–negative men, while there was no statistically significant difference in overall survival (but with an unadjusted HR favoring taxanes) in AR-V7–positive men. A test of interaction for AR-V7 status by treatment was not provided. The analysis was further stratified by a binary prognostic risk score (high vs low) developed from the training cohort and including clinical biomarkers (see Table 31). However, the additional stratification resulted in the group that was AR-V7–positive and receiving ARS inhibitors including fewer than ten men for both high- and low-risk.

Table 30. 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 tx)	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					AR-V7+ 0.6 (0.3 to 1.4); 0.25		AR-V7– 1.7 (1.0 to 2.8); 0.05	
Interaction p					Not reported			

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

Table 31. Cross-Tabulation of AR-V7 Status and Clinical Risk Score

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

Adapted from Scher et al (2018).¹⁰⁸

Tables 32 and 33 display notable gaps identified in each study.

Table 32. Relevance Gaps of Clinical Validity Studies Assessing Oncotype DX AR-V7

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Scher et al (2018) ¹⁰⁸					1. Median follow-up in surviving men not clear but overall <50% of men had 12-mo follow-up

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 33. Study Design and Conduct Gaps of Clinical Validity Studies Assessing Oncotype DX AR-V7

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Scher et al (2018) ¹⁰⁸	2. Unclear if original 248 samples included were consecutive or randomly chosen from eligible					1. Interaction p value not provided

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

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

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No studies reporting direct evidence were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical utility of the Oncotype DX AR-V7 test has not been established, a chain of evidence supporting the test's clinical utility cannot be constructed.

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 the United Kingdom including men with progressing mCRPC undergoing a 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 AR-V7–positive men (0.6; 95% CI, 0.3 to 1.4). However, a test of interaction for AR-V7 status by treatment was not provided.

SUMMARY OF EVIDENCE

Initial Management Decision: Active Surveillance vs Therapeutic Intervention

For individuals who have low- or intermediate-risk clinically localized untreated prostate cancer who receive Prolaris, the evidence includes retrospective cohort studies of clinical validity using archived samples in patients of mixed risk categories. Relevant outcomes include overall survival, disease-specific survival, quality of life, and treatment-related morbidity. For the low-risk group, the ProtecT trial showed 99% ten-year disease-specific survival in mostly low-risk patients receiving active surveillance. The low mortality rate estimated with tight precision makes it unlikely that a test intended to identify a subgroup of low-risk men with a net benefit from immediate treatment instead of active surveillance would find such a group. For the intermediate-risk group, the evidence of improved clinical validity or prognostic accuracy for prostate cancer death using Prolaris Cell Cycle Progression score in patients managed conservatively after needle biopsy has shown some improvement in areas under the receiver operating characteristic curve over clinicopathologic risk stratification tools. There is limited indirect evidence for potential clinical utility. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have low- or intermediate-risk clinically localized untreated prostate cancer who receive Oncotype DX Prostate, the evidence includes case-cohort and retrospective cohort studies of clinical validity using archived samples in patients of mixed risk categories, and a decision-curve analysis examining indirect evidence of clinical utility. Relevant outcomes include overall survival, disease-specific survival, quality of life, and treatment-related morbidity. Evidence for clinical validity and potential clinical utility of Oncotype DX Prostate in patients with

clinically localized prostate cancer derives from a study predicting adverse pathology after RP. The validity of using tumor pathology as a surrogate for risk of progression and cancer-specific death is unclear. It is also unclear whether results from an RP population can be generalized to an active surveillance population. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have low- or intermediate-risk clinically localized untreated prostate cancer who receive the ProMark protein biomarker test, the evidence includes a retrospective cohort study of clinical validity using archived samples and no studies of clinical utility. Relevant outcomes include overall survival, disease-specific survival, quality of life, and treatment-related morbidity. Current evidence does not support improved outcomes with ProMark given that only a single clinical validity study is available. The evidence is insufficient to determine the effects of the technology on health outcomes.

Management Decision After Radical Prostatectomy

For individuals who have localized prostate cancer treated with RP who receive Prolaris, the evidence includes retrospective cohort studies of clinical validity using archived samples. Relevant outcomes include overall survival, disease-specific survival, quality of life, and treatment-related morbidity. Evidence of improved clinical validity or prognostic accuracy for prostate cancer death using the Prolaris Cell Cycle Progression score in patients after prostatectomy has shown some improvement in areas under the receiver operating characteristic curve over clinicopathologic risk stratification tools. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have localized prostate cancer who are treated with RP and who receive the Decipher prostate cancer classifier, the evidence includes a study of analytic validity, prospective and retrospective studies of clinical validity using overlapping archived samples, decision-curve analyses examining indirect evidence of clinical utility, and prospective decision-impact studies without pathology or clinical outcomes. Relevant outcomes include overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The clinical validity of the Decipher genomic classifier has been evaluated in samples of patients with high-risk prostate cancer undergoing different interventions following RP. Studies reported some incremental improvement in discrimination. However, it is unclear whether there is consistently improved reclassification—particularly to higher risk categories—or whether the test could be used to predict which men will benefit from radiotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Management Decision in Castration-Resistant Prostate Cancer

For individuals who have metastatic castration-resistant prostate cancer who receive the Oncotype DX AR-V7 Nuclear Detect, the evidence includes a retrospective cohort study of clinical validity using archived samples, and no studies of clinical utility. Relevant outcomes include overall survival, disease-specific survival, quality of life, and treatment-related morbidity. Current evidence does not support improved outcomes with Oncotype DX AR-V7 Nuclear Detect, given that only a single clinical validity study, meeting inclusion criteria was available. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRACTICE GUIDELINES AND POSITION STATEMENTS

The National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines for prostate cancer (v.4.2018) provide a table of tissue-based tests for prostate cancer prognosis (see Table 34).¹² The Network panel suggested that men with low or favorable intermediate clinically localized disease may consider Decipher, Oncotype DX Prostate, Prolaris, or ProMark during initial risk stratification and Decipher may be considered during workup for radical prostatectomy, although the panel warned that the utility of these assays has not been fully assessed in randomized controlled trials. The guidelines also state that “AR-V7 assays are promising predictors of abiraterone and enzalutamide resistance, but they have not yet been validated prospectively and externally.”

Table 34. Available Tissue-Based Tests for Prostate Cancer Prognosis¹²

Test	Platform	Population	Outcomes
Decipher	Whole transcriptome 1.4 RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	Post RP, adverse pathology/high-risk features	Metastasis; prostate cancer-specific mortality
		Post RP, biochemical recurrence	Metastasis; biochemical failure
		Post RP, adjuvant or salvage radiotherapy	Metastasis
Ki-67	IHC	Biopsy, intermediate- to high-risk treated with EBRT	Metastasis
		Biopsy, active surveillance	Prostate cancer-specific mortality
Oncotype DX	Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls	Biopsy, low- to intermediate-risk treated with RP	Non-organ-confined pT3 or Gleason grade 4 disease on RP
Prolaris	Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls	TURP, active surveillance	Prostate cancer-specific mortality
		Biopsy, active surveillance	Prostate cancer-specific mortality
		Biopsy, localized prostate cancer	Biochemical recurrence; metastasis
		Biopsy, intermediate-risk, treated with EBRT	Biochemical failure
		RP, node-negative localized prostate cancer	Biochemical recurrence
ProMark	Multiplex immunofluorescent staining of 8 proteins	Biopsy, Gleason grade 3+3 or 3+4	Non-organ-confined pT3 or Gleason 4 disease on RP
PTEN	Fluorescent in situ hybridization or IHC	TURP, active surveillance	Prostate cancer-specific mortality
		Biopsy, Gleason grade 3+3 RP, high-risk localized disease	Upgrading to Gleason 4 on RP Biochemical recurrence

EBRT: external-beam radiotherapy; FFPE: formalin-fixed, paraffin-embedded; IHC: immunohistochemical; NCCN: National Comprehensive Cancer Network; PSA: prostate-specific antigen; PTEN: phosphatase and tensin homolog; RNA: ribonucleic acid; RP: radical prostatectomy; RT-PCR: reverse-transcriptase polymerase chain reaction; TURP: transurethral resection of the prostate.

American Urological Association et al

The American Urological Association, American Society for Radiation Oncology, and the Society of Urologic Oncology (2017, 2018) published joint guidelines on the management of clinically localized prostate cancer.^{13,109,110} The guidelines stated that among most low-risk localized prostate cancer patients, genomic biomarkers have not demonstrated a clear role in the selection of active surveillance or in the follow-up of patients on active surveillance.

The American Urological Association (2018) published guidelines for castration-resistant prostate cancer.¹¹¹ The guidelines do not mention AR-V7 assays.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2014) updated its guidance on the diagnosis and management of prostate cancer.¹¹² The guidance did not address gene expression profile testing.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 35.

Table 35. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
<i>Prolaris</i>			
NCT03152448 ^a	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	1500	Jan 2024
NCT03290508 ^a	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
<i>Oncotype DX</i>			
NCT02668276 ^a	The Impact of a Gene Expression Profile on Treatment Choice and Outcome Among Minority Men Newly Diagnosed With Prostate Cancer: A Randomized Trial	300	Aug 2022
<i>Decipher</i>			
NCT02609269	Decipher Genomics Resource Information Database (GIRD)	10,000	Dec 2020
NCT02723734	Validation Study on the Impact of Decipher Testing – VANDAAM Study	240	May 2021
<i>PTEN</i>			
NCT01350180 ^a	Assessing DNA Changes in High Risk Prostate Cancer to Determine Prognosis	132	Dec 2017 (ongoing)
<i>AR-V7</i>			
NCT02269982	Development of Circulating Molecular Predictors of Chemotherapy and Novel Hormonal Therapy Benefit in Men With Metastatic Castration Resistant Prostate Cancer (mCRPC)	120	Nov 2018
Unpublished			
<i>Prolaris</i>			
NCT03511235 ^a	Clinical Outcomes in Men With Prostate Cancer Who Selected Active Surveillance Using Prolaris® Testing	850	Aug 2018 (completed)
NCT02454595 ^a	Registry to Measure the Impact of Adding Genomic Testing	116	Jul 2017 (terminated)
NCT02209584 ^a	An Open Registry to Measure the Impact of Adding Genomic Testing (Prolaris®) on the Treatment Decision Following Biopsy in Newly Diagnosed Prostate Cancer Patients by Specialists	274	Dec 2015 (completed)
NCT01954004 ^a	An Open Registry to Measure the Impact of Adding Genomic Testing (Prolaris®) on the Treatment Decision Following Biopsy in Newly Diagnosed Prostate Cancer Patients	1270	Sep 2014 (completed)
<i>Decipher</i>			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02080689 ^a	Prospective Clinical Utility Study to Assess the Impact of Decipher on Treatment Decisions after Surgery (PRO-IMPACT)	286	Feb 2017 (completed)

NCT: national clinical trial; PTEN: phosphatase and tensin homolog.

CODING

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

CPT/HCPCS

81479	Unlisted molecular pathology procedure
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score
81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (<i>GSTP1</i> , <i>APC</i> , <i>RASSF1</i>), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy
81599	Unlisted multianalyte assay with algorithmic analysis
0011M	Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and/or urine, algorithms to predict high-grade prostate cancer risk
0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score

ICD-10 Diagnoses

C61	Malignant neoplasm of prostate
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REVISIONS

02-19-2016	Policy added to the bcbsks.com web site on 01-20-2016; effective 30 days after publication.
01-04-2017	Updated Description section.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> ▪ Removed CPT code: 84999.
	Updated References section.
	Added Appendix section.
01-01-2018	Updated Description section.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> ▪ Added CPT codes: 81541, 81551.
	Updated References section.
03-28-2018	In Coding section:

	<ul style="list-style-type: none"> ▪ Added CPT code: 0011M.
07-01-2018	In Coding section: <ul style="list-style-type: none"> ▪ Added CPT code: 0047U.
04-15-2019	Updated Description section. In Policy section: <ul style="list-style-type: none"> ▪ Removed previous policy language, "Use of gene expression analysis and protein biomarkers to guide management of prostate cancer is considered experimental / investigational in all situations." ▪ Added new policy language, "A. Multigene expression (Prolaris™; Oncotype DX) assay on prostate cancer tissue is considered medically necessary to determine prognosis when the following clinical conditions are met: 1. Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), AND 2. FFPE prostate biopsy specimen with at least 0.5 mm of cancer length, AND 3. Patient Stage as defined by the one of the following: a) Low Risk Disease (T1-T2a AND Gleason Score ≤ six AND PSA ≤10 ng/mL), OR b) Favorable Intermediate Risk (T2b-T2c OR Gleason score 3+4=7/grade group 2 OR PSA 10-20 ng/mL), AND 4. Patient has an estimated life expectancy of greater than or equal to 10 years, AND 5. Patient is a candidate for and is considering conservative therapy and would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), AND 6. Result will be used to determine treatment between definitive therapy and conservative management, AND 7. Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy. B. The use of gene expression analysis other than listed above, and protein biomarkers to guide management of prostate cancer, are considered experimental / investigational in all situations.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> ▪ Added ICD-10 code: C61.
	Updated References section.
	Removed Appendix section.

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