Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

Policy # 00403
Original Effective Date: 02/19/2014
Current Effective Date: 06/20/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer is addressed separately in medical policy 00272.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers gene expression analysis and protein biomarker to guide management of prostate cancer in all situations to be **investigational.***

Background/Overview

PROSTATE CANCER
Prostate cancer is the second most common noncutaneous cancer diagnosed among men in the United States. According to the National Cancer Institute, approximately 161,000 new cases are expected to be diagnosed in the United States in 2017 and more than 26,000 prostate cancer deaths will occur. 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.

Localized prostate cancers may appear very similar clinically at diagnosis. However, they often exhibit diverse risk of progression that may not be captured by clinical risk categories (e.g., D'Amico criteria) or prognostic tools based on clinical findings, including PSA titers, Gleason grade, or tumor stage. 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% to 20% to perhaps 27% at 20-year follow-up. 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 the 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 (NCCN) and American Urological Association (AUA) 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:

- Low: T1-T2a and Gleason score ≤6 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 NCCN recommends monitoring serum PSA every 6 to 12 months for the first 5 years and annually thereafter. Many recurrences following RP can be successfully treated. The AUA has recommended a biochemical recurrence (BCR) be defined as a serum PSA of 0.2 ng/mL or higher, which is confirmed by a second determination with a PSA level of 0.2 ng/mL or higher.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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 Amendments (CLIA). Prolaris®‡ (Myriad Genetics, Salt Lake City, UT), Oncotype DX®‡Prostate (Genomic Health, Redwood City, CA), and Decipher®‡ gene expression profiling (GEP) test (GenomeDx Biosciences, Vancouver, BC), and the ProMark™‡ protein biomarker test (Metamark Genetics, Cambridge, MA) 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. FDA has chosen not to require any regulatory review of this test.

In November 2015, the FDA's Office of Public Health Strategy and Analysis published a document on public health evidence for FDA oversight of LDTs. FDA argued that many tests need more FDA oversight than the regulatory requirements of CLIA. CLIA standards relate to laboratory operations, but do not address inaccuracies or unreliability of specific tests. Prolaris is among the 20 case studies in the document cited as needing FDA oversight. The document asserted that patients are potentially receiving inappropriate prostate cancer care because there is no evidence that results from the test meaningfully improve clinical outcomes.

Centers for Medicare and Medicaid Services (CMS)
Palmetto GBA, a local carrier, issued "limited coverage" determinations under the auspices of a Coverage with Data Development mechanism for the following tests (date effective): Prolaris (03/02/15), Decipher (03/02/15), Oncotype DX Prostate (10/05/15), and ProMark (10/10/2016).

Rationale/Source

Full-length publications were sought that describe the analytic validity (technical performance), clinical validity (prognostic accuracy), and clinical utility (accurately identifying men experiencing improved health outcomes by avoiding treatment or undergoing more appropriate therapies) of Prolaris, Oncotype DX Prostate, the ProMark protein biomarker test, and Decipher GEP.

LEVEL OF EVIDENCE

The level of evidence (LOE) will be evaluated using the Simon et al framework for study classification, and LOE for prognostic studies using archived specimens. Category A studies are prospective, randomized trials designed to evaluate prognostic markers; one such study would establish LOE 1. Category B studies are prospective trials designed for another purpose with retrospective analysis of archives sample that is prospectively described ("prospective–retrospective" studies); two or more such studies are required for LOE 1. Category C studies are prospective observational registry studies with treatment and follow-up not dictated. As noted by Simon et al, studies considered category C are LOE III but "may be validated to LOE II if two or more subsequent studies provide similar results. However, it is unlikely that category C studies would ever be sufficient to change practice, except under particularly compelling circumstances." Category D studies are retrospective in design and represent LOE IV and V.

INITIAL MANAGEMENT DECISION: ACTIVE SURVEILLANCE VS THERAPEUTIC INTERVENTION

Clinical Context and Test Purpose

In men newly diagnosed with clinically localized prostate cancer, the purpose of 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 divergent behavior of localized prostate cancers creates uncertainty whether to treat immediately or follow with active surveillance. 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. A patient may alternatively choose potentially curative treatment upfront. Surgery (i.e., RP) or external-beam radiotherapy (EBRT) is most commonly used to treat patients with localized prostate cancer. Complications most commonly reported with RP or EBRT and with the greatest variability are incontinence (0%-73%) and other genitourinary toxicities (irritative and obstructive symptoms); hematuria (typically ≤5%); gastrointestinal and bowel toxicity, including nausea and loose stools (25%-50%); proctopathy, including rectal pain and bleeding (10%-39%); and erectile dysfunction, including impotence (50%-90%). A 2014 population-based retrospective cohort study using administrative hospital data, physician billing codes, and cancer registry data estimated the 5-year cumulative incidence of admission to hospital for a treatment-related complication following RP or EBRT to be 22% (95% confidence interval [CI], 21.7% to 22.7%).

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 PSA testing. About 90% of the participants had 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.

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

The AUA, in joint guidelines (2017), have suggested that physicians recommend active surveillance for most men with low-risk localized prostate cancer but offer RP or RT to select low-risk, localized patients who have a high probability of progression on active surveillance. The guidelines also suggested that physicians should recommend RP or RT plus androgen deprivation therapy to patients with intermediate-risk prostate cancer and that RT alone or active surveillance may also be offered to select patients with favorable intermediate-risk localized cancer.

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 analysis of messenger ribonucleic acid (mRNA) expression levels of many genes simultaneously in a tumor specimen and protein biomarkers. 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 mRNA source, reverse-transcriptase polymerase chain reaction amplification, and the TaqMan low-density array platform (Applied Biosystems, Foster City, CA; acquired by Thermo Fisher Scientific, Waltham, MA). 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 (e.g., stage, biopsy Gleason grade, serum PSA level) and demographic characteristics (e.g., age, life expectancy) are combined to classify men according to risk. NCCN and AUA have provided treatment recommendations based on risk stratification and life expectancy. The Kattan et al (2003) nomogram was developed to predict the risk of indolent cancer in a low-risk population considering active surveillance. 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.

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) 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 in the secondary or tertiary care setting.

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

Analytic Validity
Although there is no reference standard for GEP tests, other measures of technical performance are relevant. They include reproducibility, tissue sample adequacy, potential batch effects, and test-set bias. Warf et al (2015) evaluated the precision of the CCP score using 6 FFPE biopsies (3 replicate scores) and 12 FFPE RP (4-6 replicate scores) specimens. Overall precision was estimated from replicate samples, intended to reflect combined variation from tissue dissection through gene expression. Across replicate samples, the standard deviation of the CCP score was 0.1 (95% CI, 0.08 to 0.13). After 8 weeks of sample storage, results were similar. In 2015, Myriad Genetics reported 95.3% of samples were adequate to produce a CCP score. Information is available on the performance of the TaqMan array platform used in Prolaris and Oncotype DX Prostate through the MicroArray Quality Control (MAQC) project. In the MAQC project, which was initiated and led by U.S. FDA scientists, expression data on 4 titration pools from 2 distinct reference RNA samples were generated at multiple test sites on 7 microarray-based and 3 alternative technology platforms, including TaqMan. According to investigators, the results offer a framework to assess the potential of array technologies as a tool to provide reliable gene expression data for clinical and regulatory purposes. The results showed very similar performance across platforms, with a median coefficient of variation ranging from 5% to 15% for the quantitative signal and concordance from 80% to 95% for the qualitative detection call between sample replicates.

Clinical Validity
Two studies reporting clinical validity related to newly diagnosed men with clinically localized prostate cancer were included as outlined in Table 2.

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

Study (Year)	Design	Dates	Sites	N	Population
Cuzick et al (2012)	Retrospective cohort from prospective registry (Simon category C)	1990-1996	6 UK registries; not screen-detected	349	Clinically localized; 66% Gleason score 6-7; 46% PSA level ≤25
Cuzick et al (2015)	Retrospective cohort from prospective registry (Simon category C)	1990-2003	3 UK registries[a]; not screen-detected	761	Clinically localized; 74% Gleason score ≤7, mean PSA level 21

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. 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 through 1996; were younger than 76 years at diagnosis; had a baseline PSA measurement; and were conservatively managed. Potentially eligible patients who underwent RP, died, showed evidence of metastatic disease within 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. 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; 95% CI, 1.62 to 2.53) 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 (95% CI, 1.31 to 2.09). 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 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 (e.g., 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. 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 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), 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.

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

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

Adapted from the Cuzick (2012) and Cuzick (2015) validation studies.
CCP: Cell Cycle Progression; CI: confidence interval; HR: hazard ratio.
[a] Adjusted for Gleason score and prostate-specific cancer level.
[b] Adjusted for Cancer of the Prostate Risk Assessment.
[c] For a 1-unit increase in CCP.

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

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

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

Table 5. Predicted Risk of Prostate Cancer Death at 10 Years by Clinical Cell Cycle Risk Score Groupings

		Cuzick et al (2015)
Clinical Cell Cycle Risk Score	N	10-Year Death Rate (95% Confidence Interval), %a
-1	Not reported	1.0 (0.2 to 1.8)
0		2.2 (0.7 to 3.4)
1		4.5 (2.3 to 7.0)
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)

Adapted from the Cuzick (2015) validation study.
[a] Estimated from digitizing a figure.

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 which would help in interpretation. However, given the data provided, several concerns arise. Even the lowest risk group shown in Cuzick (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 and half with PSA >25); however, a death rate of 20% is unlikely to be low enough to forgo immediate treatment.

Table 4 does not include the death rates by CCR score; however, the predicted 10-year prostate cancer death rates by CCR score were provided in a figure in Cuzick (2015). 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.

Systematic Reviews
In 2016, results of a systematic review and meta-analysis supported by Myriad Genetics were reported. 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 two "utility" studies are discussed in the following section. Two validity studies reported outcomes for disease-specific mortality but of the two only the Cuzick et al (2012) included newly diagnosed patients, so the pooled outcome is not relevant in this section.

Clinical Utility

Direct Evidence
We identified no studies that directly supported the clinical utility of Prolaris.

Indirect Evidence
Three decision-impact studies assessed the potential impact of Prolaris on physicians' treatment decisions in patients. The authors of each study (Crawford et al, 2014; Shore et al, 2014; Shore et al, 2016) 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 an indirect 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 the Cuzick (2015) authors, 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%. 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 (2012) or Cuzick (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 reported on a health technology assessment including a systematic review of the literature on the clinical utility of the Prolaris CCP. The literature search identified Crawford (2014) and Shore (2016). 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
The analytic validity of gene expression analysis for prostate cancer management using Prolaris was reported by Warf et al (2015) and supported by results from the MAQC project.

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. 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. Ten-year mortality rates based on CCP were inconsistent within Prolaris risk categories across Cuzick (2012) and Cuzick (2015). Numerical summaries of mortality rates for the CCR were provided in a figure in Cuzick (2015). The men included in the UK registries were not screen-selected, and a large proportion of the men in the validation studies were not low- or intermediate-risk. Validation studies were Simon category C.

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. Level 1 evidence as defined by Simon would be necessary.

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 GPS, which ranges from 0 to 100. Higher GPS scores indicate more risk.

Analytic Validity
Knezevic et al (2013) reported on the analytic validity of Oncotype DX Prostate. Estimates of analytic precision and reproducibility were derived from analysis of RNA prepared from 10 microdissected prostate tumor samples obtained by needle biopsy. Individual Gleason scores were assigned using the 2005 International Society of Urological Pathology consensus guidelines.

The results showed that the assay could accurately measure the expression of the 12 cancer-related and 5 reference genes over a range of absolute RNA inputs (0.005-320 ng); the limit of detection in a sample was 0.5 ng/µL. The analytic accuracy showed an average variation of less than 9.7% across all samples at RNA inputs typical of needle-biopsy specimens. The amplification efficiency for the 17 genes in the test ranged from 88% to 100%, with a median (SD) of 93% (6%) for all 17 genes in the assay. Analytic precision was assessed by examining variability between replicate results obtained using the same mRNA input. Reproducibility was measured by calculating both within- and between-mRNA input variation. A low input level of mRNA (5 ng) was used to reflect the lowest 2.5 percentile of a tumor sample of 0.023 cm^3. When converted to GPS units (unit measure for reporting test results), the standard deviation for analytic precision was 1.86 GPS units (95% CI, 1.60 to 2.20) on the 100-unit scale. The standard deviation for reproducibility was 2.11 GPS units (95% CI, 1.83 to 2.50) on the 100-point scale.

Clinical Validity

Three studies reporting clinical validity are included as outlined in Table 6. 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 independent clinical validation study cohort (N=395; University of California, San Francisco [UCSF] Database, 1998-2011). A second study, Cullen et al (2015), evaluated men with NCCN clinically very low to intermediate-risk undergoing prostatectomy. The third study, Whalen et al (2016), evaluated men in a clinical practice setting.

Table 6. Studies Reporting Clinical Validity of Oncotype DX Prostate

Study	Design	Dates	Sites	N	Population
Klein et al (2014)	Case-cohort from prospective registry (Simon category C)[a]	1998-2011	UCSF	395	Clinically localized; clinical stage T1/T2; PSA level ≤20, Gleason score ≤7; 3% African American
Cullen et al (2015)	Retrospective cohort from prospective longitudinal study (Simon category C)	1990-2011	U.S. military centers	382	Clinically localized; clinical stage T1/T2; PSA level ≤20, Gleason score ≤7; 20% African American
Whalen et al (2016)	Prospective observational cohort (Simon category C)	2013-2014	Mount Sinai Hospital	50	Clinically localized; clinical stage T1/T2; PSA level ≤20, Gleason score ≤7

PSA: prostate-specific antigen; UCSF: University of California, San Francisco.
[a] Only the validation sample cohort is listed.

Results from the Klein et al (2014) clinical validation study and prostatectomy study provided information on the potential clinical validity of this test. 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 6) was prospectively designed, used masked review of prostatectomy pathology results, and as such met the REMARK (Reporting Recommendations for Tumor Marker Prognostic Studies) guidelines for biomarker validation. The prostatectomy study used a case-cohort design to select a 1:3 ratio of recurrent to nonrecurrent patients. The prespecified primary end point of the validation study was the ability of the GPS to predict the likelihood of favorable pathology in the needle-biopsy specimen. Favorable pathology was defined as freedom from high-grade or non-organ-confined disease. In the prostatectomy study, the ability of the GPS to stratify patients further within AUA groupings was related to the clinical recurrence-free interval in regression-to-the-mean estimated survival curves. The Klein et al (2014) validation study results showed that the GPS could refine stratification of patients within specific NCCN criteria groupings, as summarized in Table 7. Proportions were estimated from a plot of GPS vs the percent likelihood of favorable pathology.

Table 7. 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 (2014) validation study.
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 suggest that the combination of GPS plus clinical criteria can reclassify patients on an individual basis within established clinical risk categories. However, whether these findings support a conclusion that the GPS could predict the disease-specific survival based solely on the level of pathology in a biopsy specimen is unclear. Moreover, extrapolation of this evidence to a true active surveillance population, for which the majority in the study would be otherwise eligible, is difficult because all patients had elective RP within 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 criteria 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 8. 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 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 8. 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 From the Klein (2014) prostatectomy study.
AUA: American Urological Association; GPS: Genomic Prostate Score.

A retrospective cohort study by Cullen et al (2015) included men with NCCN-defined very low through intermediate-risk prostate cancer undergoing RP within 6 months of diagnosis. 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 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 BCR occurred in 62 (15.4%). Estimates of 5-year BCR by GPS score are shown in Table 9. 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 10). 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 of GPS with final pathology at RP in a clinical practice setting. Eligible men were 50 years of age and older with more than 10 years of life expectancy, PSA levels of 20 ng/mL or less, stage cT1c-cT2c newly diagnosed, untreated prostate cancer, and who met NCCN classifications as very low risk, low-risk, or low-intermediate risk. Men were enrolled from May 2013 to August 2014 at an academic medical center. Genomic Health reclassified patients' cancers as "less favorable," "consistent with," or "more favorable" than what would have been predicted by their NCCN risk group. The primary outcome was adverse pathology at RP defined as any pT3 stage and primary Gleason grade of 4 or any pattern 5. Fifty patients had RP pathology, and the reclassification results for these participants are discussed here; 21 (42%) met the definition of adverse pathology. The NCCN risk classification categorized 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 11 as derived from data provided in the text. CIs were not provided.

Table 9. Estimates of 5-Year Biochemical Recurrence With Oncotype DX Prostate

		Cullen et al (2015)
Genomic Prostate Score	**N**	**5-Year Biochemical Recurrence (95% Confidence Interval), %[a]**
10	Not reported	5.1 (2.7 to 9.1)
20		8.5 (5.8 to 13.4)
30		14.2 (10.2 to 19.0)
40		22.9 (18.0 to 28.8)
50		35.2 (27.1 to 45.4)
60		53.8 (38.6 to 65.6)
70		71.8 (50.6 to 89.3)
80		87.3 (64.2 to 98.0)

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

Table 10. Univariate and Multivariate Association Between GPS and Outcomes

Study (Year)	Outcome	N	Unadjusted	Multivariate
			Ratio (95% CI)	Ratio (95% CI)
Klein et al (2014) 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)	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)	Adverse pathology	50	NR	OR=1.4 (NR)[d]

Adapted from the Klein (2014) validation study, Cullen (2015), and Whalen (2016).
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, clinical Gleason score, and NCCN risk category.

Table 11. Risk of Adverse Pathology With Oncotype DX Prostate

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

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

Systematic Reviews

In 2016, Brand et al combined the Klein (2014) and Cullen (2015) studies using a patient-specific meta-analysis. The GPS was compared with the CAPRA score, NCCN risk group, and AUA risk group. The authors tested whether the GPS added predictive value for the likelihood of favorable pathology above the clinical risk assessment tools. The model including the GPS and CAPRA score provided the best risk discrimination; the AUC improved from 0.68 to 0.73 by adding the GPS to CAPRA score. The AUC improved from 0.64 to 0.70 by adding the GPS to the NCCN risk group. The improvements were reported to be significant but the CIs for AUC were not provided.

Clinical Utility

Direct Evidence

We identified no studies that directly supported the clinical utility of Oncotype DX Prostate.

Indirect Evidence

Decision-impact studies have assessed the potential impact of Oncotype DX Prostate on physicians' treatment decisions. 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.

Klein et al reported a decision-curve analysis that they proposed reflects the clinical utility of Oncotype DX Prostate. In this analysis, they compared the predictive impact of the GPS in combination with the CAPRA validated tool 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% (e.g., 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.

Finally, Badani et al (2015) prospectively evaluated the decision impact of obtaining a GPS in men with NCCN-defined very low- to intermediate-risk cancers. Following test results, recommendations for active surveillance increased from 41% to 51%. Actual treatments received and accuracy of predicted outcomes were not assessed, thereby limiting implications of the study. The study was supported by Genomic Health and all authors reported financial or other relationships with the funder.

Section Summary: Oncotype DX Prostate
The 2003 study by Knezevic et al has provided sufficient evidence to establish the analytic validity of Oncotype DX Prostate.

The evidence from 3 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. However, whether these findings support a conclusion that the GPS could predict disease-specific survival is unclear. 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. The publications also lack precision estimates for important variables such as risk estimates for recurrence or AUC estimates. All validation studies are Simon category C.

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 (i.e., active surveillance). This would reflect the clinical utility of the test. However, it is difficult to ascribe possible clinical utility of Oncotype DX 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. All validation studies were Simon category C.

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. Level 1 evidence as defined by Simon would be necessary.

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.

Analytic Validity
Shipitsin et al (2014) reported on the analytic validity of the automated quantitative multiplex immunofluorescence in situ imaging approach assessing: the ability of the test to quantitate markers in a defined region of interest (tumor vs surrounding benign), tissue quality control, assay staining format, and reproducibility. To evaluate tissue sample quality, they first assessed the staining intensities of several protein markers in benign tissue.Using these protein markers, they categorized prostate cancer tissue blocks into 4 quality groups, of which the best 2 groups were used to generate tumor microarray blocks; 508 prostatectomy specimens were used and, of these, 418 passed quality testing and were used for the tumor microarray blocks. For intraexperiment reproducibility, 2 consecutive sections from a prostate tumor test microarray block were stained in the same experiment and scatterplots compared the mean values of the staining intensities; signals from consecutive sections showed R^2 correlation values above 0.9 and differences in absolute values typically less than 10%.

Clinical Validity
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.

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; 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 12), also reported in Blume-Jensen (2015), to validate the assay's ability to distinguish "favorable" pathology (defined as Gleason score on prostatectomy ≤3+4 and organ-confined disease) from "nonfavorable" pathology (defined as Gleason score on prostatectomy ≥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 12. Clinical Validity of ProMark

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

Adapted from Blume-Jensen et al (2015).
RP: radical prostatectomy.
[a] Only the validation sample cohort N.

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

Section Summary: ProMark Protein Biomarker Test
Data are insufficient to establish the analytic and 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 biomarkers tests in patients who have prostate cancer and who have undergone RP is to inform management decisions.

For example, the optimal timing of RT after RP is debated. Adjuvant RT may maximize cancer control outcomes; however, early salvage RT (at first evidence of a rising serum PSA level) can minimize overtreatment and still lead to acceptable oncologic outcomes. Adjuvant RT in men with pT3 or margin-positive cancer has been compared with observation in RCTs; such comparisons have shown that adjuvant RT improves the biochemical and local control rates among patients with adverse pathology at RP. 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. RCTs comparing adjuvant with early salvage RT are underway. AUA has recommended that adjuvant RT should be offered to patients with adverse pathologic findings at RP, and salvage RT should be offered to patients with PSA or local recurrence after RP.

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 is individuals who have undergone RP for prostate cancer, and who are deciding on subsequent management such as adjuvant RT vs no adjuvant RT.

Interventions
Prolaris, 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.

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

Outcomes
Beneficial outcomes resulting from a true test result are prolonged survival, improved quality of life and reduction in unnecessary treatment-related adverse effects. Harmful outcomes resulting from a false test result are recurrence, metastases or death, and unnecessary treatments. The outcomes of interest are listed in Table 13.

Table 13. 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) for NCI-recommended health-related quality of life measures for localized prostate cancer
Treatment-related	Adverse events of radiotherapy or radical prostatectomy

morbidity

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 aretypically made by patients and urologists 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.

Analytic Validity

The analytic validity of Prolaris was described in the previous section.

Clinical Validity

Four studies reporting clinical validity in the post-RP management setting were included as outlined in Table 14. Three of these studies—Cuzick et al (2011), Cooperberg et al (2013), and Bishoff et al (2014)—reported on post-RP patients. Koch et al (2016) reported on post-RP patients with BCR. Freedland et al (2013) reported on post-RT patients but is included in this section for completeness.

Table 14. Studies Reporting Clinical Validity of Prolaris for Post-RP or Post-RT Management

Study	Design	Population	Dates	Sites	N
Postprostatectomy					
Cuzick et al (2011)	Retrospective cohort from prospective registry (Simon category C)	Clinical stage T1/T2; no neoadjuvant therapy; 71% PSA level ≤10, 96% Gleason score ≤7	1985-1995	Scott and White Clinic	366
Cooperberg et al (2013)	Retrospective cohort from prospective registry (Simon category C)	98% PSA level ≤20, 95% Gleason score ≤7; no neoadjuvant or adjuvant therapy	1994-2011	UCSF Registry	413
Bishoff et al (2014)	Retrospective cohort from medical records (Simon category D)	Clinical stage T1/T2; median PSA level 5.5-7.2; 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

Study	Design	Population	Dates	Sites	N
Koch et al (2016)	Retrospective cohort from medical records (Simon category D)	Median PSA level 6.5-11; 64% Gleason score ≤7; no adjuvant RT	1995-2010	Indiana University SOM	47
After external-beam radiotherapy					
Freedland et al (2013)	Retrospective cohort, source unclear (Simon category D)	97% clinical stage T1/T2; Median PSA level 8; 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. 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, Scott and White Clinic, in Texas). The primary end point was time to BCR, and the secondary end point was prostate cancer death. Myriad Genetics assessed CCP scores blindly. The median age of patients was 68 years (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, owing 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 we lack reclassification data and analysis of net benefit.

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). A prognostic model was developed from the RP cohort described by Cuzick (2011). 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 15. The AUC for BCR with CAPRA-S alone ~~of~~ 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). The combined analysis included all 582 patients. Gleason scores were 7 or lower in 93% of men. In the combined cohorts, a unit increase in the CCP score increased the adjusted HR for BCR by 1.47 (95% CI, 1.23 to 1.76) (see Table 15). 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. 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 (OR) for metastatic disease or nonresponse was 3.72 (95% CI, 1.29 to 10.7) (see Table 15). Multivariate analysis was performed; however, due to the very small number of participants in the durable response group, CIs were very wide.

Table 15. 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)	BCR	9.4	366	HR=1.89 (1.54 to 2.31)	1.77 (1.40 to 2.22)[a]
	Prostate cancer death		337	HR=2.92 (2.38 to 3.57)	2.56 (1.85 to 3.53)[b]
Cooperberg et al (2013)	BCR	7	413	HR=2.1 (1.6 to 2.9)	1.7 (1.3 to 2.4)[c]
Bishoff et al (2014)	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)	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. 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 androgen deprivation therapy, 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. 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 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. 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.

Clinical Utility
Direct Evidence
We identified no studies to support directly the clinical utility of Prolaris.

Indirect Evidence: 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. 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% (i.e., 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
The analytic validity of gene expression analysis for prostate cancer management using Prolaris has been reported by Warf et al (2015) and supported by results from the MAQC project.

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. Cooperberg et al (2013) found the AUC for BCR improved from 0.73 (CAPRA-S alone) to 0.77 by adding CCP score. Bishoff et al (2014) and

Koch et al (2016) did not report any classification or discrimination measures. Koch was performed in patients who had a BCR following RP. All validation studies were Simon category C or D.

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. All validation studies were Simon category C or D. Simon category C studies are not sufficient to determine with confidence the prognosis of CCP score.

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

Analytic Validity
Published data on the analytic validity of the Decipher prostate cancer classifier consists of 1 study performed on surgical resection specimens from patients with prostate cancer identified in a postsurgery high-risk population. The Decipher test platform was performed in FFPE tissue to assess the differential expression in the discovery, validation, and clinical application. Matched FFPE and unfixed fresh-frozen specimens from paired tumor and normal samples from kidney, lung, and colon were compared, and the microarray signals derived from the degraded RNA extracted from FFPE specimens were found to be highly analogous to the signals from the RNA in the fresh-frozen specimens.

According to GenomeDx's website, additional analytic performance studies were conducted; the test was subjected to reagent and analytical verification studies in the laboratory according to the Clinical Laboratory Improvement Amendment guidelines; reproducibility was demonstrated by evaluation of day-to-day and operator-operator precision; and the assay showed concordant results between the clinical laboratory, research and development laboratories, and pathology.

Clinical Validity
The clinical validity of the Decipher test (genomic classifier [GC]) has been reported in 11 studies to predict metastasis, mortality, or BCR after RP in patients with postoperative high-risk features like pathologic stage T2 with positive margins, pathologic stage T3 disease, or a rising PSA level (see Tables 16 and 17).

Table 16. Studies Evaluating the Decipher Genomic Classifier

Study	Design	Outcome	Sites	Dates	N
Observation and RT samples					
Erho et al (2013) (training)	Nested case-control from registry	Metastases	Mayo Clinic	1987-2001	359

Study	Design	Outcome	Sites	Dates	N
	(Simon C)				
Erho et al (2013) (validate)					186
Karnes et al (2013)	Case-cohort from registry (Simon C)	Metastases (5 y)	Mayo Clinic	2000-2006	219
Ross et al (2014)[a] (BCR only)	Case-cohort from registry (Simon C)	Metastases (5 y)	Mayo Clinic	2000-2006	85
Cooperberg et al (2015)	Case-cohort from registry (Simon C)	PC mortality	CapSURE Registry	2000-2006	185
Karnes et al (2017)	Case-control and case-cohort from medical records (Simon D)	PC mortality (10 y)	Mayo Clinic, Johns Hopkins, Cleveland Clinic, Durham VA	1987-2010	561
Observation-only samples					
Klein et al (2015); Klein et al (2016)	Retrospective cohort from registry (Simon C)	Metastases (5 y, 10 y)	Cleveland Clinic	1993-2001	169
Ross et al (2016)	Case-cohort from registry (Simon C)	Metastases (10 y)	Johns Hopkins	1992-2010	260
Glass et al (2016)	Retrospective cohort from registry (Simon C)	Clinical recurrence (10 y)	Kaiser Permanente Northwest	1997-2009	224
RT-only samples					
Den et al (2014)	Retrospective cohort from registry (Simon C)	BCR	Thomas Jefferson	1999-2009	139
Den et al (2015)	Retrospective cohort from registry (Simon C)	Metastases	Thomas Jefferson, Mayo Clinic	1990-2009	188
Freedland et al (2016)	Retrospective cohort from registry (Simon C)	Metastases	Durham VA, Thomas Jefferson, Mayo Clinic	1991-2010	170

BCR: biochemical recurrence; CapSURE: Cancer of the Prostate Strategic Urologic Research Endeavor; PC: prostate cancer; RT: radiotherapy.
[a] Appears to be subgroup with BCR from Karnes et al (2013).

Table 17. Reported Prognostic Accuracies (Clinical Validity) of Decipher and Comparators

		AUC (95% CI)		
Study (Year)	**Outcome**	**GC**	**Comparator**	**GC + Comparator**
Observation and RT samples				
Erho (2013) (training)	Metastasis	0.90 (0.87 to 0.94)[e]	0.76 (0.67 to 0.83)[a,e]	0.91 (0.87 to 0.94)[a,e]

			AUC (95% CI)	
Erho (2013) (validate)		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)	Metastasis	0.79 (0.68 to 0.87)	0.64 (0.55 to 0.72)[d,f]	
Ross (2014)	Metastasis	0.82 (0.76 to 0.86)	0.70 (0.66 to 0.75)[a]	0.75 (0.69 to 0.80)
Cooperberg (2015)	PC mortality	0.78 (0.68 to 0.87)	0.75 (0.55 to 0.84)[b]	
Karnes (2017)	PC mortality	0.73 (0.67 to 0.78)	0.73 (0.68 to 0.78)	0.76 (0.71 to 0.82)
Observation-only samples				
Klein (2015); Klein (2016)	Metastasis	5 y: 0.77 (0.66 to 0.87) 10 y: 0.80 (0.58 to 0.95)	5 y: 0.75 (0.65 to 0.84)[c] 10 y: 0.75 (0.64 to 0.87)[h]	5 y: 0.79 (0.65 to 0.85) 10 y: 0.88 (0.76 to 0.96)
Ross (2016)	Metastasis	0.76 (0.65 to 0.84)	0.77 (0.69 to 0.85)[b]	0.87 (0.77 to 0.94)
Glass (2016)	Clinical recurrence	0.80 (NR)	0.73 (NR)[b]	0.84 (NR)
RT-only samples				
Den (2014)	BCR post-RT	0.75 (0.67 to 0.84)	0.70 (0.61 to 0.79)[c]	0.78 (0.69 to 0.86)
Den (2015)	Metastasis post-RT	0.83 (0.72 to 0.89)	0.66 (0.56 to 0.78)[b]	0.85 (0.79 to 0.93)
Freedland (2016)	Metastasis post-RT	0.85 (0.73 to 0.88)	0.65 (0.54 to 0.81)[g]	NR

AUC: area under the curve; BCR: biochemical recurrence; CI: confidence interval; GC: genomic classifier; NR: not reported; PC: 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.

All studies were conducted retrospectively from registry data or clinical records. The development study had a nested case-control design. The - and 10-year results of 1 study were published separately. Four were case-cohort studies, and 5 used retrospective cohorts. Because of the apparent overlap in samples, the number of unique patients in the studies is difficult to ascertain. Seven studies were supported by GenomeDx, which offers the Decipher test; all studies identified multiple authors as company employees. Studies were considered according to whether after RP men were observed or treated with RT (adjuvant or salvage), resulting in the following groupings: (1) observation or RT, (2) observation only, and (3) RT only.

Four studies, 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 for 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.

Validation Studies: Observation and RT Samples
Cooperberg et al (2015) evaluated the prognostic accuracy of the test for prostate cancer mortality; the others, for the development of metastasis (see Table 17). Karnes et al (2013) reported a 2.4% five-year cumulative incidence of metastasis in 338 men with GC scores of less than 0.4, but 22.5% in the 77 men with scores 0.6 or more. In men who had developed BCR, Ross et al (2014) found the GC score was associated with a 5-year cumulative incidence of metastases—10.0% in men with scores of 0.4 or lower vs 54.0% in those with higher scores. The GC AUCs for predicting metastases ranged from 0.75 to 0.82. The AUC for the comparators ranged from 0.64 to 0.76. 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).

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 1 was incorrectly reclassified with a CAPRA-S score greater than 6 to low risk; all men had CAPRA-S scores of 3 or more.[79] Similarly, Karnes et al (2017) found that adding the GC to CAPRA improved the AUC from 0.73 to 0.76 with highly overlapping CIs.

Validation Studies: Observation-Only Samples
Three validation studies reported in 4 publications—Klein et al (2015), Klein et al (2016), Ross et al (2016), and Glass et al (2016) —excluded men receiving any adjuvant therapy following RP over median follow-up periods ranging from 7.8 to 9 years. The Klein and the Ross studies assessed the prognostic accuracy for metastasis through 5 years or 10 years. Glass assessed the prognostic accuracy for clinical recurrence, defined as local, regional, or distant recurrence or metastasis confirmed by clinical or radiologic evidence. Ross reported a 6.5% 5-year cumulative incidence of metastases in men with GC scores of 0.45 or lower, compared with 30.3% in those with scores higher than 0.60. The AUCs are shown in Table 17. Glass reported a 2.6% clinical recurrence rate by 10 years for patients with GC scores less than 0.45 and a 13.5% recurrence rate for those with score 0.45 or greater. Ross et al reported 10-year cumulative incidence of metastases stratified by GC and CAPRA-S. The GC appeared to discriminate within intermediate CAPRA-S categories. Of note, the reclassification employed a different lower cutoff score (0.45 instead of 0.40), "…based on a recently refined optimization algorithm."

Validation Studies: RT-Only Samples
Three analyses of overlapping retrospectively assembled cohorts of men undergoing either adjuvant or salvage RT. One study examined the prognostic ability of the GC for BCR, while the others examined its prognostic ability for metastases. Median follow-up in Den et al (2014) and Den et al (2015) exceeded 10 years; the median follow-up in Freedland et al (2016) was 7.4 years. Just over three-quarters of the men in the studies had positive surgical margins or a larger proportion than in the other validation studies. Den et al (2014) found that the GC's AUC for BCR was 0.75 compared with 0.70 for the Stephenson nomogram. The

AUCs for the clinical outcomes are shown in Table 17. In Den (2015), 7 (21.2%) of men with high GC scores (>0.6) developed metastases compared with 12 (15.2%) men with CAPRA-S scores exceeding 5. However, overall only 19 (10.1%) men had developed metastases. Among the 160 men who did not, the GC reclassified 27 of 67 men with high CAPRA-S scores into a low-risk group, but, given the small number of men developing metastases, the reclassifications were somewhat uncertain. The authors also explored whether the classifier might identify men likely to benefit from adjuvant RT over salvage therapy, suggesting that adjuvant therapy might be preferred in men with a GC score greater than 0.4. However, that result was based on only 14 men with GC scores of 0.4 and 3 men with lower values. In Freedland, 20 men developed metastases. In a reclassification analysis, 31 (39%) patients in the upper 2 tertiles of risk by Briganti were classified as low risk by the GC, and one of them developed metastases during follow-up. Seventy-three (49%) patients who were categorized as intermediate or high risk using CAPRA-S were classified as GC low risk; three developed metastases during follow-up.

Systematic Reviews
Spratt et al (2017) reported an individual patient-level data meta-analysis of five of the studies described in the previous section. Data from patients randomly selected from the case-cohort studies (total N=855 patients) were included. The pooled 10-year metastases incidence was 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).

Clinical Utility
Direct Evidence
No studies reporting direct evidence were identified.

Indirect Evidence: Decision Curves
Eight studies have included decision curves comparing the net benefit of different strategies using metastases or survival as the outcome (see Table 18). In observational and RT samples from Karnes et al (2013) and Ross et al (2014), over a 15% to 25% range of thresholds for decision making (i.e., suspected probability of developing metastases) would be expected to identify correctly as few as no men or as many as 4 per 100 likely to experience metastases. This range of thresholds makes several assumptions: 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 (e.g., about 1 additional patient would be likely to experience metastases without an increase in false positives). In Ross, 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. 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) 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 18. Reported Net Benefit of the Decipher Classifier vs Comparators

Study	Outcome	Range of Net Benefit vs	
		Treat None	Best Comparator
Observation and RT samples			
Karnes et al (2013)	Metastasis	0.009 to 0.020	-0.004 to 0.003
Ross et al (2014)	Metastasis	0.09 to 0.13	0.036 to 0.040
Cooperberg et al (2015)	PC mortality	0.003[a]	0.003[a]
Lobo et al (2015) with Karnes et al (2013) cohort	Metastasis or death	NR	0.017
Karnes et al (2017)	PC mortality	-0.01 to 0.015	-0.01 to 0.01
Observation-only samples			
Klein et al (2015)	Metastasis	0.008 to 0.025	0.000 to 0.012
Ross et al (2016)	Metastasis	0.09 to 0.12	0.003 to 0.004
RT-only samples			
Den et al (2015)	Metastasis post-RT	0.09 to 0.11	0.03 to 0.04
Lobo et al (2015) with Den et al (2014) cohort	Metastasis or death	NR	0.015

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

Indirect Evidence: Changes in Management
Several studies have compared physician's treatment recommendations before and after receiving GC results. 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.

Indirect Evidence: Analysis of 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. The men were from 4 cohorts previously described (Karnes et al, 2013; Den et al, 2014; Ross et al, 2016; Freedland et al, 2016). 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 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
The analytic validity of the Decipher test has been reported in a published study. Clinical validity has been evaluated in overlapping validation samples (including the development test set). The validation studies consisted of observational data obtained from registries with archived samples. All validation studies are Simon category C or D. Simon category C studies are insufficient to determine with confidence the prognosis of high-risk individuals. Ten-year disease-specific survival outcomes from a Simon category A or multiple, independent Simon category B studies are needed. Although each study evaluated different outcomes (i.e., metastasis, prostate cancer–specific mortality, BCR) in samples with different populations, all studies reported some incremental improvement in discrimination. CIs of AUC frequently overlapped between Decipher and comparators. Results did not consistently demonstrate meaningful improvement in reclassification—possibly most importantly to higher risk categories. The performance over clinicopathologic predictors did not appear consistently and meaningfully improved. It is not clear whether the group of patients identified as high risk would have a net benefit from adjuvant instead of early salvage RT.

SUMMARY OF EVIDENCE
Initial Management Decision: Active Surveillance vs Therapeutic Intervention
For individuals who have low-risk clinically localized untreated prostate cancer who receive Prolaris, Oncotype DX Prostate, or ProMark protein biomarker test, the evidence includes studies of analytic validity and studies of clinical validity using archived samples from patients in mixed risk categories. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. 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 individuals who have intermediate-risk clinically localized untreated prostate cancer who receive Prolaris, the evidence includes a study of analytic validity and retrospective cohort studies of clinical validity using archived samples in patients of mixed risk categories and a decision-curve analysis providing indirect evidence of clinical utility. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. Evidence of improved clinical validity or prognostic accuracy for prostate cancer death using Prolaris CCP 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. All validation studies are Simon category C. 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 2 studies of analytic validity, 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, test accuracy and validity, 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. All validation studies are Simon category C or D. 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 study of analytic validity, a retrospective cohort study of clinical validity using archived samples, and no studies of clinical utility. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. Current evidence does not support improved outcomes with ProMark given that only a single clinical validity study was 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 who are treated with RP who receive Prolaris, the evidence includes a study of analytic validity and retrospective cohort studies of clinical validity using archived samples. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. Evidence of improved clinical validity or prognostic accuracy for prostate cancer death using the Prolaris CCP score in patients after prostatectomy has shown some improvement in areas under the receiver operating characteristic curve over clinicopathologic risk stratification tools. All validation studies are Simon category C or D. 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, test accuracy and validity, quality of life, and treatment-related morbidity. The clinical validity of the Decipher GC 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 consistent improved reclassification—particularly to higher risk categories—or whether the test could be used to predict which men will benefit from RT. All validation studies are Simon category C or D. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management", 2.04.111, 11:2017.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin.* Jan 2017;67(1):7-30. PMID 28055103
3. Dall'Era MA, Cooperberg MR, Chan JM, et al. Active surveillance for early-stage prostate cancer: review of the current literature. *Cancer.* Apr 15 2008;112(8):1650-1659. PMID 18306379
4. Bangma CH, Roemeling S, Schroder FH. Overdiagnosis and overtreatment of early detected prostate cancer. *World J Urol.* Mar 2007;25(1):3-9. PMID 17364211
5. Johansson JE, Andren O, Andersson SO, et al. Natural history of early, localized prostate cancer. *JAMA.* Jun 9 2004;291(22):2713-2719. PMID 15187052
6. Ploussard G, Epstein JI, Montironi R, et al. The contemporary concept of significant versus insignificant prostate cancer. *Eur Urol.* Aug 2011;60(2):291-303. PMID 21601982
7. Harnden P, Naylor B, Shelley MD, et al. The clinical management of patients with a small volume of prostatic cancer on biopsy: what are the risks of progression? A systematic review and meta-analysis. *Cancer.* Mar 1 2008;112(5):971-981. PMID 18186496
8. Brimo F, Montironi R, Egevad L, et al. Contemporary grading for prostate cancer: implications for patient care. *Eur Urol.* May 2013;63(5):892-901. PMID 23092544
9. Eylert MF, Persad R. Management of prostate cancer. *Br J Hosp Med (Lond).* Feb 2012;73(2):95-99. PMID 22504752
10. Eastham JA, Kattan MW, Fearn P, et al. Local progression among men with conservatively treated localized prostate cancer: results from the Transatlantic Prostate Group. *Eur Urol.* Feb 2008;53(2):347-354. PMID 17544572
11. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med.* May 12 2005;352(19):1977-1984. PMID 15888698
12. Thompson IM, Jr., Goodman PJ, Tangen CM, et al. Long-term survival of participants in the prostate cancer prevention trial. *N Engl J Med.* Aug 15 2013;369(7):603-610. PMID 23944298
13. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA.* May 4 2005;293(17):2095-2101. PMID 15870412
14. National Comprehensive Cancer Network (NCCN). NCCN Clincal Practice Guidelines in Oncology: Prostate Cancer. Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed July 17, 2017.
15. American Urological Association (AUA). Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. 2017; http://www.auanet.org/guidelines/clinically-localized-prostate-cancer-new-(aua/astro/suo-guideline-2017). Accessed July 17, 2017.
16. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. *J Urol.* Aug 2013;190(2):441-449. PMID 23707439
17. Food and Drug Administration (FDA). The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies. 2015; http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf. Accessed November 8, 2017.
18. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Gene Expression Analysis for Prostate Cancer Management. *TEC Assessments.* 2014;Volume 28:Tab 11.
19. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Gene Expression Profiling for Prostate Cancer Management. *TEC Assessments.* 2015;Volume 29:Tab 9.
20. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst.* Nov 4 2009;101(21):1446-1452. PMID 19815849
21. Borley N, Feneley MR. Prostate cancer: diagnosis and staging. *Asian J Androl.* Jan 2009;11(1):74-80. PMID 19050692
22. Freedland SJ. Screening, risk assessment, and the approach to therapy in patients with prostate cancer. *Cancer.* Mar 15 2011;117(6):1123-1135. PMID 20960523
23. Whitson JM, Carroll PR. Active surveillance for early-stage prostate cancer: defining the triggers for intervention. *J Clin Oncol.* Jun 10 2010;28(17):2807-2809. PMID 20439633
24. Albertsen PC. Treatment of localized prostate cancer: when is active surveillance appropriate? *Nat Rev Clin Oncol.* Jul 2010;7(7):394-400. PMID 20440282
25. Ip S, Dahabreh IJ, Chung M, et al. An evidence review of active surveillance in men with localized prostate cancer. *Evid Rep Technol Assess (Full Rep).* Dec 2011(204):1-341. PMID 23126653

26. Nam RK, Cheung P, Herschorn S, et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. *Lancet Oncol.* Feb 2014;15(2):223-231. PMID 24440474
27. Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med.* Oct 13 2016;375(15):1415-1424. PMID 27626136
28. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med.* Jul 19 2012;367(3):203-213. PMID 22808955
29. Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of prostatectomy versus observation for early prostate cancer. *N Engl J Med.* Jul 13 2017;377(2):132-142. PMID 28700844
30. van den Bergh RC, Korfage IJ, Roobol MJ, et al. Sexual function with localized prostate cancer: active surveillance vs radical therapy. *BJU Int.* Oct 2012;110(7):1032-1039. PMID 22260273
31. Johansson E, Steineck G, Holmberg L, et al. Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian Prostate Cancer Group-4 randomised trial. *Lancet Oncol.* Sep 2011;12(9):891-899. PMID 21821474
32. Wu CL, Schroeder BE, Ma XJ, et al. Development and validation of a 32-gene prognostic index for prostate cancer progression. *Proc Natl Acad Sci U S A.* Apr 9 2013;110(15):6121-6126. PMID 23533275
33. Spans L, Clinckemalie L, Helsen C, et al. The genomic landscape of prostate cancer. *Int J Mol Sci.* May 24 2013;14(6):10822-10851. PMID 23708091
34. Schoenborn JR, Nelson P, Fang M. Genomic profiling defines subtypes of prostate cancer with the potential for therapeutic stratification. *Clin Cancer Res.* Aug 1 2013;19(15):4058-4066. PMID 23704282
35. Huang J, Wang JK, Sun Y. Molecular pathology of prostate cancer revealed by next-generation sequencing: opportunities for genome-based personalized therapy. *Curr Opin Urol.* May 2013;23(3):189-193. PMID 23385974
36. Yu YP, Song C, Tseng G, et al. Genome abnormalities precede prostate cancer and predict clinical relapse. *Am J Pathol.* Jun 2012;180(6):2240-2248. PMID 22569189
37. Agell L, Hernandez S, Nonell L, et al. A 12-gene expression signature is associated with aggressive histological in prostate cancer: SEC14L1 and TCEB1 genes are potential markers of progression. *Am J Pathol.* Nov 2012;181(5):1585-1594. PMID 23083832
38. Thompson I, Thrasher JB, Aus G, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol.* Jun 2007;177(6):2106-2131. PMID 17509297
39. Kattan MW, Eastham JA, Wheeler TM, et al. Counseling men with prostate cancer: a nomogram for predicting the presence of small, moderately differentiated, confined tumors. *J Urol.* Nov 2003;170(5):1792-1797. PMID 14532778
40. Cooperberg MR, Freedland SJ, Pasta DJ, et al. Multiinstitutional validation of the UCSF cancer of the prostate risk assessment for prediction of recurrence after radical prostatectomy. *Cancer.* Nov 15 2006;107(10):2384-2391. PMID 17039503
41. Chen RC, Chang P, Vetter RJ, et al. Recommended patient-reported core set of symptoms to measure in prostate cancer treatment trials. *J Natl Cancer Inst.* Jul 2014;106(7). PMID 25006192
42. Warf MB, Fosso PG, Hughes E, et al. Analytical validation of a proliferation-based molecular signature used as a prognostic marker in early stage lung adenocarcinoma. *Biomark Med.* Jul 2015;9(9):901-910. PMID 26158298
43. Cuzick J, Stone S, Fisher G, et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. *Br J Cancer.* Jul 28 2015;113(3):382-389. PMID 26103570
44. MAQC Consortium. The MicroArray Quality Control (MAQC) project shows inter- and intraplatform reproducibility of gene expression measurements. *Nat Biotechnol.* Sep 2006;24(9):1151-1161. PMID 16964229
45. Cuzick J, Berney DM, Fisher G, et al. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. *Br J Cancer.* Mar 13 2012;106(6):1095-1099. PMID 22361632
46. Montironi R, Mazzucchelli R, Scarpelli M, et al. Gleason grading of prostate cancer in needle biopsies or radical prostatectomy specimens: contemporary approach, current clinical significance and sources of pathology discrepancies. *BJU Int.* Jun 2005;95(8):1146-1152. PMID 15877724
47. Sommariva S, Tarricone R, Lazzeri M, et al. Prognostic value of the Cell Cycle Progression Score in patients with prostate cancer: a systematic review and meta-analysis. *Eur Urol.* Jan 2016;69(1):107-115. PMID 25481455
48. Cuzick J, Swanson GP, Fisher G, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. *Lancet Oncol.* Mar 2011;12(3):245-255. PMID 21310658
49. Crawford ED, Scholz MC, Kar AJ, et al. Cell cycle progression score and treatment decisions in prostate cancer: results from an ongoing registry. *Curr Med Res Opin.* Jun 2014;30(6):1025-1031. PMID 24576172

50. Shore N, Concepcion R, Saltzstein D, et al. Clinical utility of a biopsy-based cell cycle gene expression assay in localized prostate cancer. *Curr Med Res Opin.* Apr 2014;30(4):547-553. PMID 24320750
51. Shore ND, Kella N, Moran B, et al. Impact of the cell cycle progression test on physician and patient treatment selection for localized prostate cancer. *J Urol.* Mar 2016;195(3):612-618. PMID 26403586
52. Health Quality O. Prolaris Cell Cycle Progression test for localized prostate cancer: a health technology assessment. *Ont Health Technol Assess Ser.* Jun 2017;17(6):1-75. PMID 28572867
53. Knezevic D, Goddard AD, Natraj N, et al. Analytical validation of the Oncotype DX prostate cancer assay - a clinical RT-PCR assay optimized for prostate needle biopsies. *BMC Genomics.* Oct 08 2013;14:690. PMID 24103217
54. Epstein JI, Allsbrook WC, Jr., Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol.* Sep 2005;29(9):1228-1242. PMID 16096414
55. Klein EA, Cooperberg MR, Magi-Galluzzi C, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur Urol.* Sep 2014;66(3):550-560. PMID 24836057
56. Cullen J, Rosner IL, Brand TC, et al. A biopsy-based 17-gene Genomic Prostate Score predicts recurrence after radical prostatectomy and adverse surgical pathology in a racially diverse population of men with clinically low- and intermediate-risk prostate cancer. *Eur Urol.* Jul 2015;68(1):123-131. PMID 25465337
57. Whalen MJ, Hackert V, Rothberg MB, et al. Prospective correlation between likelihood of favorable pathology on the 17-Gene Genomic Prostate Score and actual pathological outcomes at radical prostatectomy. *Urol Pract.* Sep 2016;3(5):379-386. PMID
58. Cooperberg MR, Simko JP, Cowan JE, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. *J Clin Oncol.* Apr 10 2013;31(11):1428-1434. PMID 23460710
59. McShane LM, Altman DG, Sauerbrei W, et al. Reporting recommendations for tumor marker prognostic studies. *J Clin Oncol.* Dec 20 2005;23(36):9067-9072. PMID 16172462
60. Brand TC, Zhang N, Crager MR, et al. Patient-specific meta-analysis of 2 clinical validation studies to predict pathologic outcomes in prostate cancer using the 17-Gene Genomic Prostate Score. *Urology.* Mar 2016;89:69-75. PMID 26723180
61. Albala D, Kemeter MJ, Febbo PG, et al. Health Economic Impact and Prospective Clinical Utility of Oncotype DX(R) Genomic Prostate Score. *Rev Urol.* Nov 2016;18(3):123-132. PMID 27833462
62. Eure G, Germany R, Given R, et al. Use of a 17-Gene Prognostic Assay in Contemporary Urologic Practice: Results of an Interim Analysis in an Observational Cohort. *Urology.* Sep 2017;107:67-75. PMID 28454985
63. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making.* Nov-Dec 2006;26(6):565-574. PMID 17099194
64. Cooperberg MR, Broering JM, Carroll PR. Risk assessment for prostate cancer metastasis and mortality at the time of diagnosis. *J Natl Cancer Inst.* Jun 16 2009;101(12):878-887. PMID 19509351
65. Badani KK, Kemeter MJ, Febbo PG, et al. The impact of a biopsy based 17-Gene Genomic Prostate Score on treatment recommendations in men with newly diagnosed clinically prostate cancer who are candidates for active surveillance. *Urol Pract.* 2015;2(4):181-189. PMID not Indexed in Pubmed
66. Shipitsin M, Small C, Giladi E, et al. Automated quantitative multiplex immunofluorescence in situ imaging identifies phospho-S6 and phospho-PRAS40 as predictive protein biomarkers for prostate cancer lethality. *Proteome Sci.* Jul 2014;12:40. PMID 25075204
67. Blume-Jensen P, Berman DM, Rimm DL, et al. Development and clinical validation of an in situ biopsy-based multimarker assay for risk stratification in prostate cancer. *Clin Cancer Res.* Jun 1 2015;21(11):2591-2600. PMID 25733599
68. Den RB, Yousefi K, Trabulsi EJ, et al. Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. *J Clin Oncol.* Mar 10 2015;33(8):944-951. PMID 25667284
69. Thompson IM, Jr., Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *Jama.* Nov 15 2006;296(19):2329-2335. PMID 17105795
70. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet.* Dec 08 2012;380(9858):2018-2027. PMID 23084481
71. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol.* Jun 20 2009;27(18):2924-2930. PMID 19433689
72. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol.* May 20 2007;25(15):2035-2041. PMID 17513807
73. Cooperberg MR, Hilton JF, Carroll PR. The CAPRA-S score: A straightforward tool for improved prediction of outcomes after radical prostatectomy. *Cancer.* Nov 15 2011;117(22):5039-5046. PMID 21647869

74. Bishoff JT, Freedland SJ, Gerber L, et al. Prognostic utility of the cell cycle progression score generated from biopsy in men treated with prostatectomy. *J Urol.* Aug 2014;192(2):409-414. PMID 24508632
75. Koch MO, Cho JS, Kaimakliotis HZ, et al. Use of the cell cycle progression (CCP) score for predicting systemic disease and response to radiation of biochemical recurrence. *Cancer Biomark.* Jun 7 2016;17(1):83-88. PMID 27314296
76. Freedland SJ, Gerber L, Reid J, et al. Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. *Int J Radiat Oncol Biol Phys.* Aug 1 2013;86(5):848-853. PMID 23755923
77. Abdueva D, Wing M, Schaub B, et al. Quantitative expression profiling in formalin-fixed paraffin-embedded samples by affymetrix microarrays. *J Mol Diagn.* Jul 2010;12(4):409-417. PMID 20522636
78. Klein EA, Yousefi K, Haddad Z, et al. A genomic classifier improves prediction of metastatic disease within 5 years after surgery in node-negative high-risk prostate cancer patients managed by radical prostatectomy without adjuvant therapy. *Eur Urol.* Apr 2015;67(4):778-786. PMID 25466945
79. Den RB, Feng FY, Showalter TN, et al. Genomic prostate cancer classifier predicts biochemical failure and metastases in patients after postoperative radiation therapy. *Int J Radiat Oncol Biol Phys.* Aug 1 2014;89(5):1038-1046. PMID 25035207
80. Cooperberg MR, Davicioni E, Crisan A, et al. Combined value of validated clinical and genomic risk stratification tools for predicting prostate cancer mortality in a high-risk prostatectomy cohort. *Eur Urol.* Feb 2015;67(2):326-333. PMID 24998118
81. Ross AE, Feng FY, Ghadessi M, et al. A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy. *Prostate Cancer Prostatic Dis.* Mar 2014;17(1):64-69. PMID 24145624
82. Karnes RJ, Bergstralh EJ, Davicioni E, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. *J Urol.* Dec 2013;190(6):2047-2053. PMID 23770138
83. Erho N, Crisan A, Vergara IA, et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. *PLoS One.* Jul 2013;8(6):e66855. PMID 23826159
84. Ross AE, Johnson MH, Yousefi K, et al. Tissue-based genomics augments post-prostatectomy risk stratification in a natural history cohort of intermediate- and high-risk men. *Eur Urol.* Jan 2016;69(1):9. PMID 26058959
85. Freedland SJ, Choeurng V, Howard L, et al. Utilization of a genomic classifier for prediction of metastasis following salvage radiation therapy after radical prostatectomy. *Eur Urol.* Oct 2016;70(4):588-596. PMID 26806658
86. Glass AG, Leo MC, Haddad Z, et al. Validation of a genomic classifier for predicting post-prostatectomy recurrence in a community based health care setting. *J Urol.* Jun 2016;195(6):1748-1753. PMID 26626216
87. Klein EA, Haddad Z, Yousefi K, et al. Decipher genomic classifier measured on prostate biopsy predicts metastasis risk. *Urology.* Apr 2016;90:148-152. PMID 26809071
88. Karnes RJ, Choeurng V, Ross AE, et al. Validation of a Genomic Risk Classifier to Predict Prostate Cancer-specific Mortality in Men with Adverse Pathologic Features. *Eur Urol.* Apr 08 2017. PMID 28400167
89. Ross AE, Den RB, Yousefi K, et al. Efficacy of post-operative radiation in a prostatectomy cohort adjusted for clinical and genomic risk. *Prostate Cancer Prostatic Dis.* Sep 2016;19(3):277-282. PMID 27136742
90. Spratt DE, Yousefi K, Deheshi S, et al. Individual patient-level meta-analysis of the performance of the decipher genomic classifier in high-risk men after prostatectomy to predict development of metastatic disease. *J Clin Oncol.* Jun 20 2017;35(18):1991-1998. PMID 28358655
91. Lobo JM, Dicker AP, Buerki C, et al. Evaluating the clinical impact of a genomic classifier in prostate cancer using individualized decision analysis. *PLoS One.* Apr 2015;10(3):e0116866. PMID 25837660
92. Badani K, Thompson DJ, Buerki C, et al. Impact of a genomic classifier of metastatic risk on postoperative treatment recommendations for prostate cancer patients: a report from the DECIDE study group. *Oncotarget.* Apr 2013;4(4):600-609. PMID 23592338
93. Michalopoulos SN, Kella N, Payne R, et al. Influence of a genomic classifier on post-operative treatment decisions in high-risk prostate cancer patients: results from the PRO-ACT study. *Curr Med Res Opin.* Aug 2014;30(8):1547-1556. PMID 24803160
94. Nguyen PL, Shin H, Yousefi K, et al. Impact of a genomic classifier of metastatic risk on postprostatectomy treatment recommendations by radiation oncologists and urologists. *Urology.* Jul 2015;86(1):35-40. PMID 26142578
95. Badani KK, Thompson DJ, Brown G, et al. Effect of a genomic classifier test on clinical practice decisions for patients with high-risk prostate cancer after surgery. *BJU Int.* Mar 2015;115(3):419-429. PMID 24784420
96. Gore JL, du Plessis M, Santiago-Jimenez M, et al. Decipher test impacts decision making among patients considering adjuvant and salvage treatment after radical prostatectomy: Interim results from the Multicenter Prospective PRO-IMPACT study. *Cancer.* Aug 01 2017;123(15):2850-2859. PMID 28422278
97. Prensner JR, Zhao S, Erho N, et al. RNA biomarkers associated with metastatic progression in prostate cancer: a multi-institutional high-throughput analysis of SChLAP1. *Lancet Oncol.* Dec 2014;15(13):1469-1480. PMID 25456366

98. Tomlins SA, Alshalalfa M, Davicioni E, et al. Characterization of 1577 primary prostate cancers reveals novel biological and clinicopathologic insights into molecular subtypes. *Eur Urol.* Oct 2015;68(4):555-567. PMID 25964175
99. Yamoah K, Johnson MH, Choeurng V, et al. Novel biomarker signature that may predict aggressive disease in african american men with prostate cancer. *J Clin Oncol.* Sep 1 2015;33(25):2789-2796. PMID 26195723
100. Fisher G, Yang ZH, Kudahetti S, et al. Prognostic value of Ki-67 for prostate cancer death in a conservatively managed cohort. *Br J Cancer.* Feb 5 2013;108(2):271-277. PMID 23329234
101. Khor LY, Bae K, Paulus R, et al. MDM2 and Ki-67 predict for distant metastasis and mortality in men treated with radiotherapy and androgen deprivation for prostate cancer: RTOG 92-02. *J Clin Oncol.* Jul 1 2009;27(19):3177-3184. PMID 19470936
102. Li R, Heydon K, Hammond ME, et al. Ki-67 staining index predicts distant metastasis and survival in locally advanced prostate cancer treated with radiotherapy: an analysis of patients in radiation therapy oncology group protocol 86-10. *Clin Cancer Res.* Jun 15 2004;10(12 Pt 1):4118-4124. PMID 15217948
103. Verhoven B, Yan Y, Ritter M, et al. Ki-67 is an independent predictor of metastasis and cause-specific mortality for prostate cancer patients treated on Radiation Therapy Oncology Group (RTOG) 94-08. *Int J Radiat Oncol Biol Phys.* Jun 1 2013;86(2):317-323. PMID 23474109
104. Cuzick J, Yang ZH, Fisher G, et al. Prognostic value of PTEN loss in men with conservatively managed localised prostate cancer. *Br J Cancer.* Jun 25 2013;108(12):2582-2589. PMID 23695019
105. Lotan TL, Gurel B, Sutcliffe S, et al. PTEN protein loss by immunostaining: analytic validation and prognostic indicator for a high risk surgical cohort of prostate cancer patients. *Clin Cancer Res.* Oct 15 2011;17(20):6563-6573. PMID 21878536
106. Lotan TL, Carvalho FL, Peskoe SB, et al. PTEN loss is associated with upgrading of prostate cancer from biopsy to radical prostatectomy. *Mod Pathol.* Jan 2015;28(1):128-137. PMID 24993522
107. National Institute for Health and Care Excellence (NICE). Prostate cancer: diagnosis and management [CG175]. 2014; https://www.nice.org.uk/guidance/cg175/chapter/1-recommendations. Accessed August 24, 2017.
108. Palmetto GBA. MolDX LCDs. https://www.palmettogba.com/moldx Accessed Aug 29, 2017.
109. Jeter EK. Payer Coverage of Molecular Diagnostics [PowerPoint slides]. 2015 Oct; http://www.anco-online.org/MolDxJeter.pdf. Accessed August 24, 2017.

Policy History

Original Effective Date: 02/19/2014
Current Effective Date: 06/20/2018

02/06/2014	Medical Policy Committee review
02/19/2014	Medical Policy Implementation Committee approval. New policy.
06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Implementation Committee approval. Policy statement unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Promark and Decipher tests added to the policy. Policy statement updated by adding “protein biomarkers”. Title change.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Extensive updates to rationale and references.
08/01/2017	Coding update
06/07/2018	Medical Policy Committee review
06/20/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/01/2018	Coding update
08/07/2018	Coding update

Next Scheduled Review Date: 06/2019

Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

Policy # 00403
Original Effective Date: 02/19/2014
Current Effective Date: 06/20/2018

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0005U, 81479, 81539, 81541, 81599, 84999 Code added eff date 7/1/18: 0047U
HCPCS	No codes
ICD-10 Diagnosis	C61

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.