Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

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DESCRIPTION

Prostate cancer is the most diagnosed cancer and the second leading cause of cancer deaths in American individuals. In 2022, it is estimated that 268,490 individuals will be diagnosed with prostate cancer and an estimated number of deaths related to prostate cancer of 34,500.

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 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 individuals (ages > 70 years) with low-risk disease, comorbidities typically result in the cause of

death; these individuals will die with prostate cancer present, rather than from the cancer itself. Other very similar low risk tumors may progress unexpectedly rapidly, quickly disseminating and becoming incurable.

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, and broadly include very- low, low, intermediate (favorable intermediate and unfavorable intermediate), high or very high- risk as follows as well as subcategories within these groups:

<table>
<tr><th>Risk Group</th><th>Clinical/Pathologic Features</th></tr>
<tr><td>Very low</td><td>Has all of the following:
• cT1c
• Grade Group 1
• PSA <10 ng/mL
• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core
• PSA density <0.15 ng/mL/g</td></tr>
<tr><td>Low</td><td>Has all of the following but does not qualify for very low risk:
• cT1–cT2a
• Grade Group 1
• PSA <10 ng/mL</td></tr>
<tr><td>Intermediate</td><td>
<table>
<tr><td rowspan="2">Has all of the following:
• No high-risk group features
• No very-high-risk group features
• Has one or more intermediate risk factors (IRFs):
▸ cT2b–cT2c
▸ Grade Group 2 or 3
▸ PSA 10–20 ng/mL</td><td>Favorable intermediate</td><td>Has all of the following:
• 1 IRF
• Grade Group 1 or 2
• <50% biopsy cores positive (eg, <6 of 12 cores)[f]</td></tr>
<tr><td>Unfavorable intermediate</td><td>Has one or more of the following:
• 2 or 3 IRFs
• Grade Group 3
• ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[f]</td></tr>
</table>
</td></tr>
<tr><td>High</td><td>Has no very-high-risk features and has exactly one high-risk feature:
• cT3a OR
• Grade Group 4 or Grade Group 5 OR
• PSA >20 ng/mL</td></tr>
<tr><td>Very High</td><td>Has at least one of the following:
• cT3b–cT4
• Primary Gleason pattern 5
• 2 or 3 high-risk features
• >4 cores with Grade Group 4 or 5</td></tr>
</table>

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

Monitoring after radical prostatectomy (RP), all normal prostate tissue and tumor tissue is theoretically removed during RP and the serum level of PSA should be undetectable following RP. Detectable PSA post RP indicates residual prostate tissue and presumably persistent or recurrent disease. PSA is serially measured following RP to detect early disease recurrence. The National Comprehensive Cancer Network (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 American Urological Association (AUA) has recommended a biochemical recurrence be defined as a serum PSA of 0.2 ng/mL or higher, which is confirmed by a second determination with a PSA level of 0.2 ng/mL or higher.

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

Commercially Available Tests
The following are commercially available gene expression profiling (GEP) tests and protein biomarkers:

- **Decipher® Prostate Cancer Assay/ Decipher® Prostate Cancer Classifier** (GenomeDx Biosciences, Vancouver, BC) is a tissue- based tumor 22-biomarker gene expression profile test is intended to serve as a prognostic marker of cancer tumor aggressiveness in patients newly diagnosed with localized prostate cancer, and to calculate the probability of clinical metastasis within 5 years of radical prostatectomy (RP) surgery. The gene expression classifier is a continuous risk score between 0 and 1, and a categorization of that score into low, average, or high- risk at the time of biopsy to determine if a patient can be safely followed with active surveillance or should be considered for immediate treatment or following radical prostatectomy with associated probabilities of high-grade disease, 5- year metastatic risk, and 10- year prostate cancer specific mortality on final pathology.
- **OncotypeDx® Prostate Cancer Assay** (Genomic Health, Redwood City, CA) is a prostate biopsy- based gene expression profiling (GEP) test used to quantify expression levels of 12 cancer-related and 5 reference genes to generate a Genomic Prostate Score (GPS). In the final analysis, the cell cycle progression (CCP) score or GPS is combined in proprietary algorithms with clinical risk criteria (PSA, Gleason grade, tumor stage), that provides a biologic measure of cancer aggressiveness of individual lesions, and thus inform management decisions (decisions between active surveillance (AS) and immediate treatment).

- **Prolaris®** (Myriad Genetics, Salt Lake City, UT) is used to directly measure tumor cell growth characteristics for stratifying the risk of disease progression in prostate cancer patients. The 46 gene expression profiling test which includes 31 cell cycle progression (CCP) genes and 15 housekeeper genes to generate a CCP score. The testing combines traditional risk factors (Gleason score, PSA, clinical stage) with a molecular assessment and the Prolaris score which denotes the level of risk of progression. Patients who are identified has having a low or intermediate risk of disease progression may be candidates for surveillance. Patients who are identified as having a high-risk of progression may be candidates for active treatment. Therefore, this testing assists with individualized prostate cancer treatment/management decisions. Prolaris testing can be conducted on either biopsy samples collected for diagnosing prostate cancer or on postsurgical specimens obtained during radical prostatectomy. Adjuvant hormonal therapy and radiation treatment given before tissue sample collection to be tested using Prolaris interferes with the interpretation of tests results. Therefore, patients receiving these treatments before biopsy are not candidates for Prolaris testing.
- **ProMark™Protein Biomarker Test/ProMark™ Risk Score** (Metamark Genetics, Cambridge, MA) is a biopsy based prostate cancer prognostic test that utilizes an automated, quantitative protein based multiplex immunofluorescent in situ imaging platform to evaluate standard formalin-fixed, paraffin-embedded prostate tissue to differentiate indolent from aggressive prostate cancer. The assay measures 8 protein biomarkers (DERL1, PDSS2, pS6, YBX1, HSPA9, FUS, SMAD4, and CUL2) to generate an algorithmically derived risk score that indicates the aggressiveness of the prostate cancer. The ProMark Score is between 1 and 100, a low ProMark Score is indicative of less aggressive prostate cancer, and a high ProMark Score indicates the likelihood of a more aggressive prostate cancer.

Initial Management Decision: Active Surveillance and Therapeutic Intervention
In individuals newly diagnosed with clinically localized prostate cancer, the purpose of gene expression profiling (GEP) and protein biomarker testing is to inform a decision whether to undergo immediate therapy or to forgo immediate therapy and begin active surveillance (AS).

The divergent behavior of localized prostate cancers creates uncertainty whether to treat immediately or follow with active surveillance (AS). With active surveillance (AS) 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., radical prostatectomy [RP] or external beam radiotherapy [EBRT]) is most commonly used to treat patients with localized prostate cancer. Complications most commonly reported with RP or EBRT and with the greatest variability are incontinence (0%-73%) and other genitourinary toxicities (irritative and obstructive symptoms); hematuria (typically < 5%); gastrointestinal and bowel toxicity, including nausea and loose stools (25%-50%); proctopathy, including rectal pain and bleeding (10%-39%); and

erectile dysfunction, including impotence (50%-90%). A 2014 population based retrospective cohort study (Nam et.al.) 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 Hamdy et. al.), active surveillance, immediate radical prostatectomy (RP) and immediate external beam radiotherapy (EBRT) for the treatment of clinically localized prostate cancer were compared in 1643 men identified through prostate specific antigen (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 a lower incidence 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 Observational Trial (PIVOT) (Wilt et. al. 2012 and 2017) randomized 731 men in the United States with localized prostate newly diagnosed cancer to radical prostatectomy (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 ration [HR], 0.69; 95% CI, 0.49 to 0.98; absolute risk reduction 12.6%).

An observational study (2012 Van den Bergh et. al.) comparing sexual function of men with low- risk prostate cancer who chose active surveillance with men who received radiation therapy (RT) or radical prostatectomy (RP) found those who chose active surveillance were more often sexually active than similar men who received RP. In a 2011 report (Johanssen et. al.) 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 American Urological Association (AUA), in a joint guideline with ASTRO (American Society of Radiation Oncology) and SUO (Society of Urologic Oncology) (2017), have suggested that physicians recommend active surveillance for most men with low risk localized prostate cancer patients, and may offer definitive treatment (i.e. radical prostatectomy (RP) or radiotherapy (RT)) to select low- risk localized prostate cancer patients who may have a high probability of progression on active surveillance. The

guidelines also suggest that the physician should recommend radical prostatectomy (RP) or radiotherapy (RT) plus androgen deprivation therapy (ADT) as standard treatment options for patients with intermediate- risk localized prostate cancer.

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

Populations
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 (AS).

Interventions
Gene expression profiling (GEP) refers to analysis of messenger RNA (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 OncotypeDx 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. 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 score, serum PSA level) and demographic characteristics (e.g., age, life expectancy) are combined to classify individuals according to risk. National Comprehensive Cancer Network (NCCN) and American Urological Association (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) (Cooperberg et. al.) is a pretreatment nomogram that provides risk prediction of outcomes following radical prostatectomy (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 overall survival (OS) (10- year survival), disease specific survival (DSS) (10- year prostate cancer free survival; 10- year prostate cancer death rate; 10 -year recurrence rate), quality of life (QOL) and treatment related morbidity (adverse events of radiotherapy or radical prostatectomy).

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

Setting
To select a management strategy for localized prostate cancer clinicians should incorporate shared decision making with their patient by considering cancer severity (risk category), patient values and preferences, life expectancy, pre-treatment general functional and genitourinary symptoms, expected post treatment functional status, and potential for salvage treatment. Effective shared decision making in prostate cancer care requires clinicians to inform patients about immediate and long-term morbidity or side effects of proposed treatment of care options.

Prolaris
The Prolaris gene expression profile test combines the RNA expression levels of 31 genes involved in cell cycle progression (CCP) and 15 housekeeping genes to generate a Prolaris score (CCP score). This information in conjunction with conventional measures such a Gleason score and prostate specific antigen (PSA) levels, is intended to assist the clinician in predicting the aggressiveness of a patients' prostate cancer. Many prostate cancers are indolent, meaning they grow slowly and have a low risk of progression, but others are not. Accurately predicting the aggressiveness of prostate cancer and the risk of disease progression allows clinicians and patients to make more informed decisions about treatment options. This section will review Prolaris for initial management decisions in newly diagnosed, localized prostate cancer. Prolaris for the management after radical prostatectomy will be discussed in the following section.

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

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 through 1990 through 1996, were younger than 76 years at the time of diagnosis, had a baseline PSA measurement and were conservatively managed. Patients treated with radical prostatectomy or radiation therapy, within the first 6 -months after diagnosis or who died or showed evidence of metastatic disease within 6- months of diagnosis were exclude. Men who had hormone therapy before the diagnostic biopsy were also 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 (cell cycle progression) 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. A total of 90 deaths from prostate cancer occurred within the 2799 person-years of actual follow-up. In univariate analysis (n=349), the hazard ratio (HR) for death from prostate cancer was 2.02 (95% CI (1.62, 2.53), P<10-9) for a one unit increase in CCP score. The CCP score was only weakly correlated with standard prognostic factors and in a multivariate analysis. CCP score dominated (HR for one unit increase = 1.65, 95% CI (1.31, 2.09), P = 3 x 10-5), with Gleason score (P=5 x 10-4) and prostate specific antigen (PSA) (P=0.017) providing significant additional contributions. The authors concluded, based on exploratory analyses presented here there is evidence that the CCP score may have a non-linear impact on the predicted probability of prostate cancer death. This could either be due to a true non-linear relationship between the CCP score and risk of death from prostate cancer, or lack of proportional hazards in that the CCP is a better predictor of earlier deaths. Although the data set is not large enough to distinguish between these two possibilities, we think that the latter is likely to be at least a partial explanation. The most obvious clinical use of the CCP score is to help identify low- risk patients who can be safely managed by surveillance. In this series, we were unable to identify a clinically significant subgroup with a 10- year risk of dying from prostate cancer of less than 5%. However, the CCP score increased the ability to identify men with a less than 10% risk of dying from prostate cancer within 10 -years, from 7 to 14%. In addition, for patients with Gleason score of 6, where considerable uncertainty still exists as to appropriate treatment, the predicted 10 -year prostate cancer death rate with the addition of the CCP score ranged from 3.5 to 41.0% (compared with 5.1 to 20.9% using clinical parameters only). We believe this is relevant information when considering appropriate care. However, as deaths from prostate cancer are rare in this group, larger cohorts are needed to fully characterize the value of the CCP score in identifying very low- risk patients, and clearer relationship may emerge when more patients have been studied.

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 Great Britain 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 Cuziek et. al. (2012). Men were included in this study if they were aged < 76 years at diagnosis and had clinically localized prostate cancer diagnosed by needle biopsy. Patients treated by radical prostatectomy or radiation therapy within 6-months of

diagnosis were excluded. Additionally, those with objective evidence of metastatic disease (by bone scan, X-ray, radiograph, CT scan, MRI, bone biopsy, lymph node biopsy, pelvic lymph node dissection) or clinical indications of metastatic disease (including pathological fracture, soft tissue metastases, spinal compression, or bone pain), or a PSA measurement > 100 ng ml-1 at or within 6- months of diagnosis were also excluded. Men who had hormone therapy prior to the diagnostic biopsy were also excluded because of the influence of hormone treatment on interpreting Gleason score. Also, excluded were men who died within 6-months of diagnosis or had < 6 months of follow-up. Original histological specimens from the diagnostic procedure were requested and centrally reviewed by panel of urological pathologists to confirm diagnosis and reassign Gleason scores using a contemporary and consistent interpretation of the Gleason scoring system. The full cohort comprised of 989 men. A total of 145 (15%) samples had inadequate tumor and a further 83 (8%) failed CCP score quality assurance. For those with adequate amounts of tumor visible on the H&E (n=844), 90% produced a CCP score. One patient lacked information about extent of disease, two patients had missing baseline PSA information and a further 173 were missing clinical stage, leaving 585 with a CCP score and all clinical variables for analysis in the primary analysis cohort. In univariate analysis, the CCP score hazard ratio (HR) was 2.08 (95% CI (1.76, 2.46), P < 10-13) for one-unit change of the score. In multivariate analysis including CAPRA (Cancer of the Prostate Risk Assessment), the CCP score hazard ratio was 1.76 (95% CI (1.44, 2.14), P < 10-6). The predefined CCR (clinical cell cycle risk) score was highly predictive, hazard ratio 2.17 (95% CI (1.83, 2.57), $\chi 2$=89.0, P < 10-20) and captured virtually all available prognostic information. The authors concluded these results confirm our previous findings for the prognostic value of the CCP score measured in diagnostic needle biopsies. For conservatively managed patients, the CCP score was highly prognostic for death from prostate cancer and provided important independent information that could not be obtained from clinical data. In addition, this study provides a fully independent validation in a new data set of a predefined CCR score as a linear combination of the CCP score and clinical variables (combined in the CAPRA score), which almost completely accounted for all molecular and clinical prognostic information. Further work is needed to determine if DNA base or other markers can add useful information to our combined score.

In 2016, Sommariva et. al. performed a systematic review to assess the evidence on the value of the CCP (cell cycle progression) instrument in prostate cancer treatment by reviewing current publications and integrating the results via a 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.
The results show that use of the CCP score is better than existing assessments at elucidating the aggressive potential of prostate cancer in an individual. The pooled hazard ratio for biochemical recurrence (BCR) per 1-unit increase in the CCP score was 1.88 in a univariate model and 1.63 in a multivariate model. Four studies showed that CCP testing can impact the decisions of physicians regarding treatment, and potentially lead to a decrease in surgical interventions for low-risk patients. The authors concluded, this review offers a comprehensive review of existing evidence on CCP testing and provides

clinicians, patient's, and policy makers with a strong summary measure of its prognostic validity and clinical utility. It will be important to develop economic studies to measure the impact of such technology on health care systems.

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

Lin et. al. (2018) also reported reclassification of men using the clinical cell cycle risk (CCR) score threshold (0.8) in a group of 19,215 consecutive patients whose biopsies were sent for Prolaris testing between 2013 and 2016. According to the table of clinicopathologic features of patients, 14,685 of the 19,215 men had low or favorable intermediate- risk by NCCN risk classification. However, the authors said that only 8,177 of the 19,215 men met NCCN criteria for active surveillance based on low/favorable intermediate- risk clinicopathologic features. It is not clear why fewer men were categorized as meeting NCCN low/favorable intermediate criteria for the purposes of demonstrating reclassification and, therefore, it is not clear how many of the 14,685 men at low or intermediate risk by NCCN criteria would have been reclassified using the CCR threshold.

Clinically Useful

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

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

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

In 2014, Crawford et. al. completed a prospective study evaluating the impact of the cell cycle progression (CCP) test Prolaris on physician treatment recommendations for prostate cancer. Physicians ordering the CCP test in clinical practice completed surveys regarding treatment recommendations before and after they received and discussed the

test results with patients. Clinicians also rated the influence of the test result on treatment decisions. Treatment selections were confirmed via third-party audit of patient charts following final survey responses. Overall, 65% of cases showed a change between intended treatment pre -and post-CCP test reporting. Pre-CCP testing, 164 of 305 cases received a recommendation for interventional treatment. Post-CCP test, interventional therapy was recommended for 103 of these cases, a reduction of 37.2%. Conversely, 141 of 305 cases were recommended pre-CCP testing for non-interventional treatment; 108 of these remained with non-interventional treatment while 33 shifted to interventional options, a 23.4% increase. There was a 49.5% reduction in surgical interventions and a 29.6% reduction in radiation treatment. A third-party audit identified 80.2% concordance between the post-CCP testing treatment recommendation and actual treatment. Re-assignment to intervention or non-intervention generally correlated with the result of the CCP report. Study limitations included physician selection of patients for testing, no evaluation of patient input in therapeutic choice, and other potential treatment decision factors not queried by the survey. The authors concluded based on responses of ordering physicians, the CCP report adds meaningful new information to risk assessment for localized prostate cancer patients. Test results led to changes in treatment with reductions and increases in interventional treatment that were directionally aligned with prostate cancer risk specified by the test.

In 2016, Shore et. al. reported on the results from PROCEDE – 1000, a large, prospective registry designed to evaluate the impact of the cell cycle progression test on shared treatment decision making for patients with newly diagnosed with prostate cancer. Untreated patients with newly diagnosed prostate adenocarcinoma were enrolled in the study and the cell cycle progression test was performed on the initial prostate biopsy tissue. A set of 4 sequential surveys tracked changes relative to initial therapy recommendations (before cell cycle progression) based on clinicopathological parameters following physician review of the cell cycle progression test result, physician/patient review of the cell cycle progression test results and a minimum of 3 months of clinical follow-up (actual treatment). Of the 1,596 patients enrolled in this registry 1,206 were eligible for analysis. There was a significant reduction in the treatment burden recorded at each successive evaluation ($p < 0.0001$), with the mean number of treatments per patient decreasing from 1.72 before the cell cycle progression test to 1.16 in actual follow-up. The cell cycle progression test caused a change in actual treatment in 47.8% of patients. Of these changes 72.1% were reductions and 26.9% were increases in treatment. For each clinical risk category there was a significant change in treatment modality (intervention vs nonintervention) before versus after cell cycle progression testing ($p=0.0002$).

In 2017, Health Quality Ontario reported on a health technology assessment including a systematic review of the literature on the clinical utility, economic impact and patients' perceptions of the value of Prolaris CCP (cell cycle progression) test in low and intermediate- risk localized prostate cancer. The authors conducted a systematic review of the clinical and economic evidence of the CCP test in low and intermediate- risk, localized prostate cancer. Medical and health economic databases were searched from 2010 to June or July 2016. The critical appraisal of the clinical evidence included risk of

bias and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group criteria. We also analyzed the potential budget impact of adding the CCP test into current practice, from the perspective of the Ontario Ministry of Health and Long-Term Care. Qualitative interviews were conducted with men with prostate cancer, on the factors that influenced their treatment decision making. For the review of clinical effectiveness 3,021 citations were screened, and two before and after studies met inclusion criteria. In one study, the results of the CCP test appeared to change the treatment plan (from initial to final plan) in 64.9% of cases overall (GRADE rating of the quality of evidence: Very low). In the other study, the CCP test changed the treatment received in nearly half of cases overall, compared with the initial plan (GRADE: Very-low). No evidence was available on clinical outcomes of patients who treatment was informed by CCP results. For the review of cost effectiveness, 100 citations were identified and screened. No studies met the inclusion criteria. In the economic evaluation, it was estimated that publicly funding the CCP test would result in a total net budget impact of $41.3 million in the first 5 years, mostly due to the cost of the CCP test. In the model, the relatively cost savings ($7.3 million) due to treatment change (increased use of active surveillance and decreased use of interventional treatment) was not large enough to offset the high cost of the test. Patients viewed the test as potentially helpful but, due to the complexity of treatment decision making, the reviewers were unsure the test would ultimately change treatment choices. The authors concluded that they found no evidence to demonstrate the impact of the Prolaris CCP test on patient important clinical outcomes. The limited evidence available shows that the test appears to provide information that, when considered in addition to the clinical risk stratification, may change the treatment plan or actual treatment for some low and intermediate- risk prostate cancer patients. As a result, there is insufficient data to inform the cost-effectiveness of the CCP test.

Section Summary
Based on review of the peer reviewed medical literature the available evidence shows that the test appears to provide information that when considered in addition to the clinical risk stratification allows physicians to determine which patients with early prostate cancer are candidates for active surveillance or observation and are more likely to have a good outcome without needing to receive definitive treatment.

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

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

Klein et. al. (2014) reported on a clinical validation study to identify and validate a biopsy- based gene expression signature that predicts clinical recurrence, prostate cancer (PCa) death and adverse pathology. Gene expression was quantified by reverse transcription-polymerase chain reaction for three studies-a discovery prostatectomy study (n=441), a biopsy study (n=167), and a prospectively designed, independent clinical validation study (n=395)-testing retrospectively collected needle biopsies from contemporary (1997-2011) patients with low to intermediate clinical risk who were candidates for active surveillance (AS). The main outcome measures defining aggressive PCa were clinical recurrence, PCa death, and adverse pathology at prostatectomy. Cox proportional hazards regression models were used to evaluate the association between gene expression and time to event end points. Results from the prostatectomy and biopsy studies were used to develop and lock a multigene-expression-based signature, called the Genomic Prostate Score (GPS); in the validation study, logistic regression was used to test the association between the GPS and pathologic stage and grade at prostatectomy. Decision-curve analysis and risk profiles were used together with clinical and pathologic characteristics to evaluate clinical utility. Of the 732 candidate genes analyzed, 288 (39%) were found to predict clinical recurrence despite heterogeneity and multi-focality, and 198 (27%) were predictive of aggressive disease after adjustment for prostate-specific antigen, Gleason score, and clinical stage. Further analysis identified 17 genes representing multiple biological pathways that were combined into the GPS algorithm. In the validation study, GPS predicted high-grade (odds ratio [OR] per 20 GPS units: 2.3; 95% confidence interval [CI], 1.5-3.7; $p<0.001$), and high stage (OR per 20 GPS units: 1.9; 95% CI, 1.3-3.0; $p=0.003$) at surgical pathology. GPS predicted high-grade and/or high-stage disease after controlling for established clinical factors ($p<0.005$) such as an OR of 2.1 (95% CI, 1.4-3.2) when adjusting for Cancer of the Prostate Risk Assessment (CAPRA) score. A limitation of the validation study was the inclusion of men with low-volume intermediate-risk PCa (Gleason score 3+4), for whom some providers would not consider AS. 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. Also, the data suggests 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.

A retrospective cohort study by Cullen et.al. (2015) included biopsies from 431 men treated for National Comprehensive Cancer Network (NCCN) very- low, low, or intermediate- risk prostate cancer (PCa) between 1990 and 2011 at two U.S. military medical centers and were tested to validate the association between GPS (Genomic Prostate Score) and biochemical recurrence (BCR) and to confirm the association with

AP (adverse pathology). Metastatic recurrence (MR) was also evaluated. Cox proportional hazards models were used for BCR and MR, and logistic regression was used for AP. Central pathology review was performed by one uropatholgist. AP was defined as primary Gleason pattern 4 or any pattern 5 and/or pT3 disease. Selected patients were older (61.0- years vs 59.7- years, p=0.013) and had both higher Gleason scores (p<0.001) and NCCN risk classification (29.8% vs 32.9% intermediate, p=0.035). Median follow-up was 5.2 -years and biochemical recurrence (BCR) occurred in 62 (15.4%). GPS results (scale: 0-100) were obtained in 402 cases (93%); 62 men (15%) experienced BCR, 5 developed metastases, and 163 had AP.

Estimates of 5 -Year Biochemical Recurrence with OncotypeDx Prostate

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

Adverse pathology was noted in 163 (34% of men). In an analysis adjusted for baseline characteristics, the GPS was associated with BCR-free survival and adverse pathology following radical prostatectomy (RP), see the below table:

Univariate and Multivariate Association Between GPS and Outcomes

Outcome	N	Univariate Ratio (95% CI)	Multivariate Ratio (95% CI)
Biochemical Recurrence (BCR)	392	HR = 2.9 (2.0 to 4.2)	2.7 (1.8 to 3.8)
Adverse Pathology (AP)	392	HR = 3.2 (2.1 to 5.0)	HR = 2.7 (1.8 to 4.4)

CI= confidence interval; HR= hazard ratio

The Genomic Prostate Score (GPS) improved the C statistic (concordance statistic) for adverse pathology over NCCN risk alone from 0.63 to 0.72. 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 difference between excluded and included men.

Whalen et. al. (2016) prospectively evaluated the correlation of Genomic Prostate Score (GPS) with final pathology at radical prostatectomy (RP) in a clinical practice setting. Eligible men were 50 years of age and older with more than 10- years 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 radical prostatectomy (RP) defined as any pT3 stage and primary Gleason grade 4 or any pattern 5. ROC (receiver operating characteristics) analyses was used to determine the optimal cutoff point of likelihood of favorable pathology for each NCCN risk group. A total of 95 patients were enrolled and 50 patients (53%) underwent radical prostatectomy. Adverse pathology was found in 21 patients (42%), grouped as very low risk 0%, low risk 32.4% and low volume intermediate risk 71.4%. Among those with low- risk disease, ROC analysis determined that a likelihood of favorable pathology cutoff of 76% or greater performed the best, correctly classifying 91.2% of patients with a sensitivity of 95.7% and specificity of 81.8% and AUC (area under the curve) 0.95. For intermediate risk patients the optimal likelihood of favorable pathology cutoff was 68% or greater, with 92.3% correct, sensitivity 75%, specificity 100% and AUC 0.95.

In 2018, Van Den Eeden et. al. completed a retrospective study using a stratified cohort sampling design performed in a cohort of men with localized prostate cancer treated with radical prostatectomy (RP). RNA from archival diagnostic biopsies was assayed to generate GPS (Genomic Prostate Score) results. They assessed the association between GPS and time to metastasis and PCD in prespecified uni- and- multivariable statistical analyses, based on Cox proportional hazard models accounting for sampling weights. The final study population consisted of 279 men with low, intermediate, and high-risk prostate cancer (PCa) between 1995 and 2010 (median follow-up 9.8- years), and included 64 PCD (prostate cancer death) and 79 metastases. Valid GPS results were obtained for 259 (93%). In univariable analysis, GPS was strongly associated with time to PCD, hazard ratio (HR)/20 GPS units=3.23 (95% confidence interval [CI] 1.84-5.65; $p<0.001$), and time to metastasis, HR/20 units=2.75 (95% CI 1.63-4.63; $p<0.001$). The association between GPS and both end points remained significant after adjusting for National Comprehensive Cancer Network, American Urological Association, and Cancer of the Prostate Risk Assessment (CAPRA) risks ($p<0.001$). No patient with low- or intermediate-risk disease and a GPS of<20 developed metastases or PCD (n=31). In receiver operating characteristic analysis of PCD at 10- years, GPS improved the c-statistic from 0.78 (CAPRA alone) to 0.84 (GPS+CAPRA; $p<0.001$). A limitation of the study was that patients were treated during an era when definitive treatment was standard of care with little adoption of active surveillance. The author's concluded GPS is a strong independent predictor of long-term outcomes in clinically localized PCa in men treated with RP and may improve risk stratification for men with newly diagnosed disease.

Salmasi et.al., (2018), investigated the ability of the prostate score assay to predict adverse pathology findings in the setting of magnetic resonance imaging guided prostate biopsy. They identified men diagnosed with NCCN (National Comprehensive Cancer Network) very- low, low or intermediate- risk prostate cancer who underwent simultaneous multiparametric magnetic resonance imaging fusion targeted and systematic

prostate biopsy with subsequent radical prostatectomy within 6- months. Prostate score assay testing was performed on biopsy tissue with the highest Gleason score. The primary outcome of the study was adverse pathology findings, defined as Gleason score 4 + 3 or greater disease and/or pT3+ at radical prostatectomy. Independent predictors of adverse pathology findings were determined in a multivariable model to adjust for clinical parameters. A total of 134 men were eligible for primary analysis. On univariable analysis the UCLA score, magnetic resonance imaging, prostate score assay results and biopsy Gleason score were significant predictors of adverse pathology findings. After multivariable adjustment prostate score assay values remained a significant predictor of adverse pathology results (prostate score assay per 20 U OR 3.28, 95% CI 1.74-6.62, p <0.001). A wide and overlapping distribution of prostate score assay results was seen across PI-RADS® (Prostate Imaging Reporting and Data System) version 2 scores. The authors concluded, the prostate score assay result is an independent predictor of adverse pathology findings in patients who were diagnosed with very- low, low, or intermediate -risk prostate cancer in the setting of multiparametric magnetic resonance imaging fusion prostate biopsy. This assay can be useful as an independent technology or an adjunct technology to multiparametric magnetic resonance imaging to individualize risk stratification of low and intermediate -risk prostate cancer.

Systematic Reviews
In 2016, Brand et. al. combined the Klein (2014) and Cullen (2015) studies using a patient specific meta-analysis (MA). The patient specific meta-analysis (MA) was performed on data from these 2 studies (732 patients) using the Genomic Prostate Score (GPS; scale 0 to 100) together with the Cancer of the Prostate Risk Assessment (CAPRA) score or National Comprehensive Cancer Network (NCCN) risk groups as predictors of the likelihood of favorable pathology (LFP). Risk profile curves associating GPS with LFP by CAPRA score and NCCN risk group were generated. Decision curves and receiver operating characteristics (ROC) curves were calculated using patient specific MA risk estimates. A model utilizing GPS and CAPRA provided the most risk discrimination. The area under the receiver operating characteristic curve (AUC) improved from 0.68 to 0.73 by adding the GPS to CAPRA score. The AUC improved from 0.64 to 0.70 by adding the GPS to the NCCN risk group. The improvements were reported to be significant, but the confidence intervals (CIs) were not provided.

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

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

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

Decision impact studies have assessed the potential impact of OncotypeDx Prostate on physicians' treatment decisions. Decision-impact studies have also indicated that men classified as low -risk by guidelines criteria, and thus meeting guidelines criteria for active surveillance, are more likely to receive active surveillance if they are tested with the Oncotype DX Prostate test. These arguments would suggest that the test may be a useful behavioral modifier.

In 2014, Klein et. al. identified and validated a biopsy-based gene expression signature that predicts clinical recurrence, prostate cancer (PCa) death, and adverse pathology. Gene expression was quantified by reverse transcription-polymerase chain reaction for three studies-a discovery prostatectomy study (n=441), a biopsy study (n=167), and a prospectively designed, independent clinical validation study (n=395) testing retrospectively collected needle biopsies from contemporary (1997-2011) patients with low to intermediate clinical risk who were candidates for active surveillance (AS). The main outcome measures defining aggressive PCa were clinical recurrence, PCa death, and adverse pathology at prostatectomy. Cox proportional hazards regression models were used to evaluate the association between gene expression and time to event end points. Results from the prostatectomy and biopsy studies were used to develop and lock a multigene-expression-based signature, called the Genomic Prostate Score (GPS); in the validation study, logistic regression was used to test the association between the GPS and pathologic stage and grade at prostatectomy. Decision-curve analysis and risk profiles were used together with clinical and pathologic characteristics to evaluate clinical utility. Of the 732 candidate genes analyzed, 288 (39%) were found to predict clinical recurrence despite heterogeneity and multifocality, and 198 (27%) were predictive of aggressive disease after adjustment for prostate-specific antigen, Gleason score, and clinical stage. Further analysis identified 17 genes representing multiple biological pathways that were combined into the GPS algorithm. In the validation study, GPS predicted high-grade (odds ratio [OR] per 20 GPS units: 2.3; 95% confidence interval [CI], 1.5-3.7; $p<0.001$) and high stage, (OR per 20 GPS units: 1.9; 95% CI, 1.3-3.0; $p=0.003$) at surgical pathology. GPS predicted high-grade and/or high-stage disease after controlling for established clinical factors ($p<0.005$) such as an OR of 2.1 (95% CI, 1.4-3.2) when adjusting for Cancer of the Prostate Risk Assessment score. A limitation of the validation study was the inclusion of men with low-volume intermediate-risk PCa (Gleason score 3+4), for whom some providers would not consider AS. The authors concluded, Genes representing multiple biological pathways discriminate PCa aggressiveness in biopsy tissue despite tumor heterogeneity, multifocality, and limited sampling at time of biopsy. The biopsy-based 17-gene GPS improves prediction of the presence or absence of adverse pathology and may help men with PCa make more informed decisions between AS and immediate treatment.

Prostate cancer (PCa) is often present in multiple locations within the prostate and has variable characteristics. We identified genes with expression associated with aggressive

PCa to develop a biopsy-based, multigene signature, the Genomic Prostate Score (GPS). GPS was validated for its ability to predict men who have high-grade or high-stage PCa at diagnosis and may help men diagnosed with PCa decide between active surveillance and immediate definitive treatment.

Badani et. al. (2015) prospectively evaluated the decision impact of obtaining a Genomic Prostate Score (GPS) in men with National Comprehensive Cancer Network (NCCN) defined very- low, low, and low – intermediate risk prostate cancer. 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
The evidence from 3 studies on clinical validity (Klein et. al. 2014; Cullen et. al. 2015; Whalen et. al. 2016) for OncotypeDx Prostate has suggested the Genomic Prostate Score (GPS) can reclassify a patient's risk of recurrence or risk of adverse pathology at radical prostatectomy (RP) based on a biopsy specimen. Also, a decision curve analysis suggested the potential for the combined Genomic Prostate Score (GPS) and CAPRA (Cancer of the Prostate Risk Assessment) 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 clinical utility of the test.

ProMark Protein Biomarker Test
The ProMark Protein Biomarker test includes 8 protein biomarkers (DERL1, PDSS2, pS6, YBX1, HSPA9, FUS, SMAD4, and CUL2) that predict prostate pathology aggressiveness. The ProMark Score is between 1 and 100, a low ProMark Score is indicative of less aggressive prostate cancer, and a high ProMark Score indicates the likelihood of a more aggressive prostate cancer.

In 2015, Roth et. al. conducted a study to evaluate the cost effectiveness of using the 8-protein prostate cancer prognostic assay to inform treatment decisions compared with usual care. They developed a simulation model to estimate quality adjusted life year (QALY) and cost outcomes for the 8-protein assay and usual care strategies. Risk classification outcomes, treatment distributions, costs, health state utilities, and mortality rates were derived from the assay's validation study and the peer reviewed literature. Outcomes included incremental QALYs, costs, and cost effectiveness ratios. They conducted one-way and probabilistic sensitivity analyses to evaluate the most influential inputs and to explore joint uncertainty in outcomes, respectively. The 8-protein assay strategy resulted in 0.04 more QALY and $700 less in costs compared with usual care (and thus was "dominant"). The cost effectiveness of the assay strategy was most sensitive to the assay cost, the active surveillance health state utility, and the proportion of low- risk patients receiving active surveillance versus treatment in usual care. In the probabilistic sensitivity analyses, the assays strategy decreased cost and increased QALYs in 86.9% and 58.3% of simulations, respectively. The authors concluded,

assuming that ongoing prospective studies support the results of retrospective validation studies, the 8-protein prognostic assay strategy for prostate cancer is likely to be cost effective alternative to usual guideline- based care in biopsy Gleason 3+3 and 3+4 early-stage prostate cancer.

Implications for practice: Prostate cancer prognostic assays such as the 8-protein assay can provided information about disease aggressiveness that may improve decisions about use of active surveillance versus invasive treatment in Gleason 3 + 3 and 3 + 4 disease. This study, the first cost-effectiveness evaluation of this type of assay reported in the peer-reviewed literature, found that the assay strategy is expected to result in increased quality-adjusted survival and decreased cost compared with usual care. The findings demonstrate the potential for prognostic assays to be dominant strategies in this clinical setting, in which many patients currently receive invasive treatment but derive limited clinical benefit.

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

In 2014, Shipitsin et. al. developed a performance-based strategy to identify protein biomarkers predictive of prostate cancer aggressiveness and lethality regardless of biopsy sampling variation. Prostatectomy samples from a large patient cohort with long follow-up were blindly assessed by expert pathologists who identified the tissue regions with the highest and lowest Gleason grade from each patient. To simulate biopsy sampling error, a core from a high and low Gleason area from each patient sample was used to generate a high or low tumor microarray retrospectively. Using a quantitative proteomics approach, they identified from 160 candidates 12 biomarkers that predicted prostate cancer aggressiveness (surgical Gleason and TNM stage) and lethal outcome robustly in both high and low Gleason areas. Conversely, a previously reported lethal outcome predictive marker signature for prostatectomy tissue was unable to perform under circumstances of maximal sample error. The authors concluded, our results have important implications for cancer biomarker discovery in general and development of a sampling error-resistant clinical biopsy test for prediction of prostate cancer aggressiveness.

Blume-Jensen et. al. (2015) reported on a study of 381 biopsies matched to prostatectomy used to develop an 8-biomarker proteomic assay to predict prostate final pathology on prostatectomy specimen using risk scores. A second blinded study of 276 cases validated this assay's ability to distinguish "favorable" versus "non-favorable" pathology independently and relative to current risk classification systems National Comprehensive Cancer Network (NCCN and D'Amico). A favorable biomarker risk score of ≤0.33, and a non-favorable risk score of >0.80 (possible range between 0 and 1) were defined on "false-negative" and "false-positive" rates of 10% and 5%, respectively. Results from the study showed that, at a risk score of less than or equal to 0.33, predictive values for favorable pathology in very low-risk and low-risk NCCN and low-risk D'Amico groups were 95%, 81.5%, and 87.2%, respectively, higher than for these current risk

classification groups themselves (80.3%, 63.8%, and 70.6%, respectively). The predictive value for non-favorable pathology was 76.9% at biomarker risk scores >0.8 across all risk groups. Increased biomarker risk scores correlated with decreased frequency of favorable cases across all risk groups. The validation study met its two co-primary endpoints, separating favorable from non-favorable pathology (AUC, 0.68; $P < 0.0001$; OR, 20.9) and GS-6 versus non-GS-6 pathology (AUC, 0.65; $P < 0.0001$; OR, 12.95). The authors concluded this study supports further evaluation of this biopsy based prognostic biomarkers assay for personalized prognostication of prostate cancer and its impact on therapeutic choice. The ability to provide differential information for the individual patient relative to current risk stratification systems, in which prognostic values are more limited, makes it a potentially useful addition in practice to improve accuracy of clinical decision.

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

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

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

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

Section Summary
Based on the review of the peer reviewed medical literature one clinical validity study suggests that ProMark Protein Biomarker test offers additional prognostic information for patients compared with NCCN risk categories alone.

Decipher Prostate Cancer Test/Decipher Prostate Cancer Classifier
Decipher® Prostate Cancer Assay/ Decipher® Prostate Cancer Classifier is a tissue-based tumor 22-biomarker gene expression profile test is intended to serve as a prognostic marker of cancer tumor aggressiveness in patients newly diagnosed with localized prostate cancer. The gene expression classifier is a continuous risk score between 0 and 1, and a categorization of that score into low, average, or high risk at the time of biopsy to determine if a patient can be safely followed with active surveillance or should be considered for immediate treatment.

Clinically Valid

In 2015, Tomlins et. al. conducted a retrospective study to determine if prostate cancer molecular subtyping could be performed from the "extra" data generated by a clinically available prognostic assay (Decipher), which genome-wide microarray expression profiling from formalin fixed paraffin embedded (FFPE) tissue to determine a prognostic score using the expression of 22 genes. Clinical assessment may aid in disease stratification, complementing available prognostic tests. They analyzed Affymetrix Gene Chip expression profiles for 1577 patients from eight radical prostatectomy cohorts, including 1351 cases assessed using the Decipher prognostic assay (GenomeDx Biosciences, San Diego, CA, USA) performed in a laboratory with Clinical Laboratory Improvements Amendment certification. A microarray-based (m-) random forest ERG classification model was trained and validated. Outlier expression analysis was used to predict other mutually exclusive non-ERG ETS gene rearrangements (ETS(+)) or SPINK1 overexpression (SPINK1(+)). Outcome measurements were associations with clinical features and outcomes by multivariate logistic regression analysis and receiver operating curves. The m-ERG classifier showed 95% accuracy in an independent validation subset (155 samples). Across cohorts, 45% of prostate cancers were classified as m-ERG(+), 9% as m-ETS(+), 8% as m-SPINK1(+), and 38% as triple negative (m-ERG(-)/m-ETS(-)/m-SPINK1(-)). Gene expression profiling supports three underlying molecularly defined groups: m-ERG(+), m-ETS(+), and m-SPINK1(+)/triple negative. On multivariate analysis, m-ERG(+) tumors were associated with lower preoperative serum prostate-specific antigen and Gleason scores, but greater extraprostatic extension ($p<0.001$). m-ETS(+) tumors were associated with seminal vesicle invasion ($p=0.01$), while m-SPINK1(+)/triple negative tumors had higher Gleason scores and were more frequent in Black/African American patients ($p<0.001$). Clinical outcomes were not significantly different among subtypes. The authors concluded, although we demonstrate that molecular subtypes are not prognostic in the post-prostatectomy setting (nor impact the performance of currently available prognostic signatures), we anticipate that molecular subtyping will complement prognostic- based tests in several areas of prostate cancer management including non-radical prostatectomy patients.

In 2018, Kim et. al. conducted a study validating the Decipher test for predicting adverse pathology in candidates for prostate cancer active surveillance. Many men diagnosed with prostate cancer are active surveillance (AS) candidates. However, AS may be associated with increased risk of disease progression and metastasis due to delayed therapy. Genomic classifiers, e.g., Decipher may allow better risk stratification in newly diagnosed prostate cancers for AS. Decipher was initially assessed in a prospective cohort of prostatectomies to explore the correlation with clinically meaningful biologic characteristics and then assessed in diagnostic biopsies from a retrospective multicenter cohort of 266 men with National Comprehensive Cancer Network (NCCN) very low/low and favorable-intermediate risk prostate cancer. Decipher and Cancer of the Prostate Risk Assessment (CAPRA) were compared as predictors of adverse pathology (AP) for which there is universal agreement that patients with long life-expectancy are not suitable candidates for AS (primary pattern 4 or 5, advanced local stage [pT3b or greater] or lymph node involvement). Decipher from prostatectomies was significantly associated

with adverse pathologic features (p-values < 0.001). Decipher from the 266 diagnostic biopsies (64.7% NCCN-very-low/low and 35.3% favorable-intermediate) was an independent predictor of AP (odds ratio 1.29 per 10% increase, 95% confidence interval [CI] 1.03-1.61, p-value 0.025) when adjusting for CAPRA. CAPRA area under curve (AUC) was 0.57, (95% CI 0.47-0.68). Adding Decipher to CAPRA increased the AUC to 0.65 (95% CI 0.58-0.70). NPV, which determines the degree of confidence in the absence of AP for patients, was 91% (95% CI 87-94%) and 96% (95% CI 90-99%) for Decipher thresholds of 0.45 and 0.2, respectively. Using a threshold of 0.2, Decipher was a significant predictor of AP when adjusting for CAPRA (p-value 0.016). The authors concluded Decipher can be applied to prostate biopsies from NCCN-very-low/low and favorable-intermediate risk patients to predict absence of adverse pathologic features. These patients are predicted to be good candidates for active surveillance.

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

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

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

In 2018, Spratt et. al. aimed to develop a novel clinical-genomic risk grouping system that can readily be incorporated into treatment guidelines for localized prostate cancer. Two multicenter retrospective cohorts (n=991) were used for training and validation of the clinical genomic risk groups (radical prostatectomy [RP] samples), and two additional cohorts (n= 5,937) were used for reclassification analysis (prospective cohort I, 4,960 RP samples) and (prospective cohort II, 977 pretreatment biopsy samples) that included demographic and baseline clinical and pathologic information. These patients were deidentified and aggregated from routine clinical use of the Decipher prostate cancer classifier test. Competing risks analysis was used to estimate the risk of distant metastasis. Time-dependent c-indices were constructed to compare clinicopathologic risk models with the clinical-genomic risk groups. Results With a median follow-up of 8 years for patients in the training cohort, 10-year distant metastasis rates for National Comprehensive Cancer Network (NCCN) low, favorable-intermediate, unfavorable-intermediate, and high-risk were 7.3%, 9.2%, 38.0%, and 39.5%, respectively. In contrast, the three-tier clinical-genomic risk groups had 10-year distant metastasis rates of 3.5%, 29.4%, and 54.6%, for low-, intermediate-, and high-risk, respectively, which were consistent in the validation cohort (0%, 25.9%, and 55.2%, respectively). C-indices for the clinical-genomic risk grouping system (0.84; 95% CI, 0.61 to 0.93) were improved over NCCN (0.73; 95% CI, 0.60 to 0.86) and Cancer of the Prostate Risk Assessment

(0.74; 95% CI, 0.65 to 0.84), and 30% of patients using NCCN low/intermediate/high would be reclassified by the new three-tier system and 67% of patients would be reclassified from NCCN six-tier (very-low- to very-high-risk) by the new six-tier system. The authors concluded, a commercially available genomic classifier in combination with standard clinicopathologic variables can generate a simple-to-use clinical genomic risk grouping that more accurately identifies patients at low, intermediate, and high-risk for metastasis and can be easily incorporated into current guidelines to better risk-stratify patients.

Section Summary
Based on review of the peer reviewed medical literature the potential usefulness of this test is that it allows physicians to determine which patients with early prostate cancer are candidates for active surveillance (AS) and are more likely to have a good outcome without needing to receive definitive treatment.

Management Decision After Radical Prostatectomy (RP)

Clinical Context and Test Purpose
The purpose of gene expression profiling and protein biomarkers tests in individuals who have prostate cancer and who have undergone radical prostatectomy is to inform management decisions.

For example, the optimal timing of radiation therapy (RT) after radical prostatectomy (RP) is debated. Adjuvant radiation therapy (RT) may maximize cancer control outcomes; however, early salvage radiation therapy (RT) (at first evidence of rising serum PSA level) can minimize overtreatment and still lead to acceptable oncologic outcomes. Adjuvant RT in individuals with pT3 or margin positive cancer has been compared with observation in randomized controlled trials (RCTs); such comparisons have shown that adjuvant RT improves the biochemical and local control rates among patients with adverse pathology at RP. 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 salvage RT. RCTs comparing adjuvant with early- stage RT are underway. American Urological Association (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.

Populations
The relevant population of interest is individuals who have undergone radical prostatectomy (RP) for prostate cancer, and who are deciding on subsequent management such as adjuvant radiation therapy (RT) versus no adjuvant RT.

Interventions
Prolaris is also intended to classify individuals who have undergone radical prostatectomy (RP).

Decipher is a tissue- based tumor 22-biomarker gene expression profiling (GEP) test intended to classify high risk individuals who have undergone RP. The gene expression classifier is a continuous risk score between 0 and 1, and a categorization of that score following radical prostatectomy shows the associated probabilities of high-grade disease, 5- year metastatic risk, and 10 -year prostate cancer specific mortality on final pathology.

Comparators
Clinicopathologic risk stratification is currently being used to make decisions about prostate cancer management following radical prostatectomy (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. The National Comprehensive Cancer Network (NCCN) and the American Urological Association (AUA) provide risk stratification guidelines. The Stephenson nomogram and the 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 are prolonged survival, improved quality of life and reduction in unnecessary treatment related adverse effects. Harmful outcomes resulting from false test result are recurrence, metastases or death, and unnecessary treatments. Outcomes of interest are 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 and treatment related morbidity (adverse events of radiotherapy or radical prostatectomy).

Timing
Ten- year outcomes are of interest due to the prolonged nature of prostate cancer.

Setting
Decisions about management of prostate cancer following radical prostatectomy (RP) are typically 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 radical prostatectomy (RP).

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

Cuzick et. al. (2011) examined the potential use of the Prolaris CCP (cell cycle progression) test combined with a clinical score following radical prostatectomy (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 (TURP), which is not a population of interest here, and so it 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 (biochemical recurrence), and the secondary end point was prostate cancer death. Myriad Genetics assessed CCP scores blindly. The median age of patients was 68 years and median follow-up 9.4 years. Cancers were clinically staged as T3 in 34%; following RP, 64 was judged pathologic stage T3. After prostatectomy, the CCP score was useful for predicting biochemical recurrence in the univariate analysis (hazard ratio for a 1-unit change [doubling] in CCP 1·89; 95% CI 1·54-2·31; p=5·6×10-9)) and the best multivariate analysis (1·77, 1·40-2·22; p=4·3×10-6). In the best predictive model (final multivariate analysis), the CCP score, and prostate-specific antigen (PSA) concentration were the most important variables and were more significant than any other clinical variable. Analyses of prostate cancer deaths in the RP cohort was problematic, owing to only 12 (3%) deaths. The AUC (area under the curve) for BCR within 5 years of the RP cohort as 0.825 for the clinical score and 0.842 for the combined score including the CCP score. Although the CCP score increased the AUC by 2%, whether that improvement is clinically useful is unclear because of the lack of reclassification data and analysis of net benefit.

Cooperberg et. al. (2013) evaluated the cell cycle progression (CCP) score, in predicting radical prostatectomy (RP) outcomes. RNA was quantified from paraffin embedded RP specimens. The CCP score was calculated as average expression of 31 CCP genes, normalized to 15 housekeeper genes. Recurrence was defined as two prostate specific antigen (PSA) levels ≥ 0.2 ng/mL or any salvage treatment. Associations between CCP score and recurrence were examined, with adjustment for clinical and pathologic variables using Cox proportional hazards regression and partial likelihood ratio tests. The CCP score was assessed for independent prognostic utility beyond a standard postoperative risk assessment, Cancer of the Prostate Risk Assessment post-surgical (CAPRA-S) score, and a score combining CAPRA-S and CCP was validated. 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. Eighty-two (19.9%) of 413 men experienced recurrence. The hazard ratio (HR) for each unit increase in CCP score (range, -1.62 to 2.16) was 2.1 (95% CI, 1.6 to 2.9); with adjustment for CAPRA-S, the HR was 1.7 (95% CI, 1.3 to 2.4). The score was able to sub-stratify patients with low clinical risk as defined by CAPRA-S ≤ 2 (HR, 2.3; 95% CI, 1.4 to 3.7). Combining the CCP and CAPRA-S improved the concordance index for both the overall cohort and low-risk subset; the combined CAPRA-S + CCP score

consistently predicted outcomes across the range of clinical risk. This combined score outperformed both individual scores on decision curve analysis. The authors concluded the CCP score was validated to have significant prognostic accuracy after controlling for all available clinical and pathologic data. The score may improve accuracy of risk stratification for men with clinically localized prostate cancer, including those with low-risk disease. Future studies will include explicit heterogeneity studies to compare CCP score findings between biopsy and prostatectomy tissues and from different samples taken from the same tumor. Although heterogeneity may have been a potential source of misclassification in our study, it would tend, if anything to bias the results toward null. The real- world effectiveness of this assay depends on its applicability in the community setting. Also, postoperative risk prediction models may perform differently in academic and community- based settings, so future validation in nonacademic cohorts will also be important.

Bisoff et. al. (2014) evaluated the prognostic usefulness of the cell cycle progression (CCP) score derived from biopsy specimens in men treated with radical prostatectomy (RP). The study included 3 cohorts: The Martini Clinic (283), Durham Veterans Affairs Medical Center (176) and Intermountain Healthcare (123). The score was derived from simulated biopsy (Martini Clinic) or diagnostic biopsy (Durham Veterans Affairs Medical Center and Intermountain Healthcare) and evaluated for an association with biochemical recurrence and metastatic disease. The combined analysis included 582 patients. Univariate analysis (HR per score unit 1.60, 95% CI 1.35-1.90, p=2.4×10-7) and multivariate analysis (HR per score unit 1.47, 95% CI 1.23-1.76, p=4.7×10-5). Metastatic events (n=12) were too few to draw conclusions.

Koch et. al. (2016) evaluated whether the CCP (cell cycle progression) score could discriminate between systemic disease and local recurrence in patients with biochemical recurrence (BCR) after radical prostatectomy (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 score. 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). Multivariate analysis was performed; however, due to the very small number of participants in the durable response group, CIs (confidence intervals) were very wide. The authors concluded this study is limited by its retrospective nature and small patient cohort size. Nonetheless, this is the largest population of prostate cancer patients with metastatic disease evaluated for the role of CCP score thus far in this

setting. Larger studies are necessary to validate these results and prove that the score adds prognostic information after adjusting for clinical variables.

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

No studies were identified that directly supported the clinical utility of Prolaris for management after radical prostatectomy (RP).

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

Section Summary
Four identified studies examined the clinical validity of Prolaris in men after radical prostatectomy (RP) using a biochemical recurrence (BCR) or systemic disease end point. Cuzieck et. al. (2011) found that the CCP (cell cycle progression) score offered little improvement in the AUC (area under the curve) (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 et. al. study was performed in patients who had a BCR following RP.

No direct evidence is available to support the clinical utility of Prolaris for improving net health outcomes of patients with localized prostate cancer following radical prostatectomy (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 (cell cycle progression) score. Polaris CCP score may have an association with biochemical recurrence (BCR), but disease-specific survival outcomes were not reported. A larger number of disease-specific survival events and precision estimates for discrimination measures are needed.

Decipher Prostate Cancer Test/Decipher Prostate Cancer Classifier
The Decipher Prostate Cancer Test/Decipher Prostate Cancer Classifier uses the expression of the biomarkers (22 RNA biomarkers) associated with the aggressive prostate cancer and calculates the probability of clinical metastasis within 5 years of radical prostatectomy (RP) surgery. This gene expression profiling (GEP) test is a continuous risk score between 0 and 1, with higher risk scores indicating a greater probability of developing metastasis.

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

The clinical validity of the Decipher Prostate Cancer Test/Decipher Prostate Cancer Classifier has been reported in studies to predict metastasis, mortality, or biochemical recurrence (BCR) after radical prostatectomy (RP) in patients with postoperative high-risk features like pathologic state T2 with positive margins, pathologic stage T3 disease, or rising PSA level.

Validation Studies: Observation and RT Samples
Cooperberg et. al. (2015) and Karnes et. al. (2017) evaluated the prognostic accuracy of the test for prostate cancer mortality, the others, for the development of metastasis. Karnes et. al. (2013) reported a 2.4% five- year cumulative incidence of metastasis in 338 men with genomic classifier (GC) scores of less than 0.4, but 22.5% in the 77 men with scores 0.6 or more. In men wo had developed biochemical recurrence (BCR), Ross et. al. (2014) found the GC score was associated with a 5- year cumulative incidence of metastasis in 10% of men with scores of 0.4 or lower versus 54.0% in those with higher scores. The GC and AUCs (area under the curve) for predicting metastasis ranged from 0.75 to 0.82. The AUC for the comparators ranged from 0.66 to 0.75. Among the 69 men developing metastasis in Karnes et. al. (2013), of the 29 Gleason scores of 7 or lower, 10 were correctly reclassified to the highs 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 (Cancer of the Prostate Risk Assessment-Surgical score), 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. Similarly, Karnes et. al. (2017) found that adding the GC to CAPRA-S improved the AUC from 0.73 to 0.77 with highly overlapping CIs (confidence intervals).

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 radical prostatectomy (RP) over median follow-up periods ranging from 7.8 to 9 years. The Klein and Ross studies assessed the prognostic accuracy for metastasis through 5 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, on the basis of previously defined CAPRA-S (Cancer of the Prostate Risk Assessment-Surgical score) risk categories, 6, 58 and 36% of men were classified as low (0–2), intermediate (3–5) and high risk (6-12), respectively and the cumulative incidence of metastasis at 10 years post RP was 11.3, 3.3 and 21.4%, respectively. In contrast, the Decipher score classified 57, 27 and 16% as low (< 0.45), intermediate (0.45–0.60) and high risk (> 0.60), respectively. Cumulative incidence of metastasis at 10 years post RP was 6.8, 10.3 and 21.9% for these risk groups. The AUCs (area under the curve) are shown in the above table. Glass reported a 2.6% clinical recurrence rate by 10 years among patients with low Decipher scores but

13.6% among those with high Decipher scores (p=0.02). Ross et. al reported 10- year cumulative incidence of metastasis stratified by GC (genomic classifier) and CAPRA-S. The GC appeared to discriminate within intermediate CAPRA-S categories.

Validation Studies: RT Only samples
Three analyses of overlapping retrospectively assembled cohorts of men undergoing either adjuvant or salvage RT (radiation therapy). One study examined the prognostic ability of the genomic classifier (GC) for BCR (biochemical recurrence), while the others examined its prognostic ability for metastasis. Median follow-up in Den et. al. (2014) and Den et. al (2015) exceeded 10 years; the medial 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. Den et. al. (2014) found that the GCs AUC (area under the curve) for BCR was 0.75 compared with 0.70 for the Stephenson nomogram. The AUCs for the clinical outcomes are in the above table. In Den (2015), 7 (21.2%) of men with high GC scores (> 0.6) developed metastasis compared with 12 (15.2%) men with CAPRA-S (Cancer of the Prostate Risk Assessment-Surgical) scores exceeding 5. However, over all 19 (10.1%) men had developed metastasis. 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 metastasis 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 (2016), 20 men developed metastasis. In reclassification analysis, 31 (39%) of patients in the upper 2 levels of risk by Briganti were classified as low-risk by the GC, and one of them developed metastases during follow-up. Seventy-three (49%) of patients who were categorized as intermediate or high -risk using CAPRA-S were classified as GC low- risk; three developed metastases during follow-up.

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

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

No studies reporting direct evidence of clinical utility were identified.

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

Decision Curves

Studies have included decision curves comparing the net benefit of different strategies using metastases or survival as the outcome. 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 genomic classifier (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 (confidence intervals) 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 (Cancer of the Prostate Risk Assessment-Surgical) 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.

Spratt et. al. (2018), evaluated if a 22-gene genomic classifier can independently predict development of metastasis in men with PSA persistence postoperatively. A multi-institutional study of 477 men who underwent radical prostatectomy (RP) between 1990 and 2015 from three academic centers. Patients were categorized as detectable PSA (n=150) or undetectable (n=327) based on post-RP PSA nadir ≥0.1 ng/ml. Cumulative incidence curves for metastasis were constructed using Fine-Gray competing risks analysis. Penalized Cox univariable and multivariable (MVA) proportional hazards models were performed to evaluate the association of the genomic classifier with metastasis. The median follow-up for censored patients was 57 mo. The median time from RP to first postoperative PSA was 1.4 mo. Detectable PSA patients were more likely to have higher adverse pathologic features compared with undetectable PSA patients. On MVA, only genomic high-risk (hazard ratio [HR]: 5.95, 95% confidence interval [CI]: 2.02-19.41, p=0.001), detectable PSA (HR: 4.26, 95% CI: 1.16-21.8, p=0.03), and lymph node invasion (HR: 12.2, 95% CI: 2.46-70.7, p=0.003) remained prognostic factors for metastasis. Among detectable PSA patients, the 5-yr metastasis rate was 0.90% for genomic low/intermediate and 18% for genomic high risk (p<0.001).

Genomic high risk remained independently prognostic on MVA (HR: 5.61, 95% CI: 1.48-22.7, p=0.01) among detectable PSA patients. C-index for Cancer of the Prostate Risk Assessment Postsurgical score, Gandaglia nomogram, and the genomic classifier plus either Cancer of the Prostate Risk Assessment Postsurgical score or Gandaglia were 0.69, 0.68, and 0.82 or 0.81, respectively. Sample size was a limitation. The authors concluded, despite patients with a detectable PSA harboring significantly higher rates of aggressive clinicopathologic features, Decipher independently predicts for metastasis. Prospective validation of these findings is warranted and will be collected as part of the ongoing randomized trial NRG GU-002.

In 2018, Karnes et. al. validated the 22 gene Decipher genomic classifier (GC) to predict prostate cancer-specific mortality (PCSM) in men with adverse pathologic features after radical prostatectomy (RP). Men with adverse pathologic features: pT3, pN1, positive margins, or Gleason score >7 who underwent RP in 1987-2010 at Johns Hopkins, Cleveland Clinic, Mayo Clinic, and Durham Veteran's Affairs Hospital. We also analyzed subgroups at high risk (prostate-specific antigen >20 ng/ml, RP Gleason score 8-10, or stage >pT3b), or very high risk of PCSM (biochemical recurrence in <2- years [BCR2], or men who developed metastasis after RP [MET]). Logistic regression evaluated the association of GC with PCSM within 10- years of RP (PCSM10), adjusted for the Cancer of the Prostate Risk Assessment Postsurgical Score (CAPRA-S). GC performance was evaluated with area under the receiver operating characteristic curve (AUC) and decision curves. Five hundred and sixty-one men (112 with PCSM10), median follow-up 13.0 -years (patients without PCSM10). For high GC score (> 0.6) versus low-intermediate (≤ 0.6), the odds ratio for PCSM10 adjusted for CAPRA-S was 3.91 (95% confidence interval: 2.43-6.29), with AUC=0.77, an increase of 0.04 compared with CAPRA-S. Subgroup odds ratios were 3.96, 3.06, and 1.95 for high risk, BCR2, or MET, respectively (all p<0.05), with AUCs 0.64-0.72. GC stratified cumulative PCSM10 incidence from 2.8% to 30%. Combined use of case-control and cohort data is a potential limitation. In a large cohort with the longest follow-up to date, Decipher GC demonstrated clinically important prediction of PCSM at 10 year, independent of CAPRA-S, in men with adverse pathologic features, BCR2, or MET after RP.

Changes in Management
Several studies have compared physician's treatment recommendations before and after receiving genomic classifier (GC) results.

Ross et al (2016) reported on results of a retrospective, comparative study of radiation therapy (RT) after radical prostatectomy (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 (Cancer of the Prostate Risk Assessment-Surgical score) (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
Clinical validity has been evaluated in overlapping validation samples (including the development test set). The validation studies consisted of observational data obtained from registries or medical records with archived samples. Although each study evaluated different outcomes (i.e., metastasis, prostate cancer–specific mortality [PCSM], biochemical recurrence [BCR]) in samples with different populations all studies reported some incremental improvement in discrimination and determining subsequent management such as adjuvant radiation therapy (RT) versus no adjuvant RT following radical prostatectomy.

Summary of Evidence
Treatment paradigms for men with prostate cancer have been developed, and they are based on assessing the risk of a patient having an unfavorable outcome due to prostate cancer within the patient's expected lifetime. Patients at higher risk are recommended to have a greater intensity of treatment. Within the favorable intermediate risk stratum, active surveillance is a recommended treatment approach, though it likely remains underutilized, and selecting patients who are likely to have poor prostate cancer related mortality in the absence of higher intensity treatment is imprecise based on clinical and pathological risk classification. While there are no randomized controlled trials, numerous retrospective and prospective clinical validity studies have all had similar and consistent findings, providing evidence that these tests can accurately risk stratify patients based on genetic information. While research has not definitively shown that such risk stratification improves outcomes in terms of either better prostate cancer outcomes or overall reductions in treatment related adverse events, there is sufficient evidence these tests are able to better inform patient and clinician decisions that must presently be made in a state of significant uncertainty. As such, these tests provide clinically actionable incremental information that fits into existing evidence based or consensus recommended prostate cancer treatment paradigms. The National Comprehensive Cancer Network (NCCN) guideline for prostate cancer version 2.2021 states the following regarding tumor multigene molecular testing: Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that men with low or favorable intermediate disease may consider the use of Decipher, Oncotype DX Prostate, Prolaris or ProMark during initial risk stratification. Indirect evidence of clinical utility rests on clinical validity, therefore, based on review of the peer reviewed medical literature, the evidence is sufficient to determine that the technology results in meaningful improvement in net health outcomes for Decipher, Oncotype DX Prostate, Prolaris or ProMark on biopsy specimens for prostate cancer risk stratification/prognosis to inform initial management decisions, either active surveillance or immediate therapy in men newly diagnosed with clinically localized untreated prostate

cancer who have an estimated life expectancy of $\geq$ 10 -years and meet the medical necessity criteria outlined below in the Policy section of this medical policy.

For individuals who have localized prostate cancer who are treated with radical prostatectomy (RP) and who receive the Decipher prostate cancer classifier, the evidence includes 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. The clinical validity of the Decipher genomic classifier (GC) has been evaluated in samples of patients with high-risk prostate cancer undergoing different interventions following RP. Studies reported incremental improvement in discrimination and determining subsequent management such as adjuvant radiation therapy (RT) versus no adjuvant RT following radical prostatectomy. Indirect evidence of clinical utility rests on clinical validity. The National Comprehensive Cancer Network (NCCN) guideline for prostate cancer version 2.2021 states the following: Decipher may be considered post radical prostatectomy for pT2 with positive margins; any pT3 disease; rising PSA (above nadir) (category 2B). Based on review of the peer reviewed medical literature the evidence is sufficient to determine that the technology results in meaningful improvement in net health outcomes for individuals that meet the medical necessity criteria outlined below in the Policy section of this medical policy.

For individuals who have localized prostate cancer who are treated with radical prostatectomy (RP) who receive Prolaris the evidence includes retrospective cohort studies of clinical validity using archived samples. Evidence of improved clinical validity or prognostic accuracy for prostate cancer death using the Prolaris Cell Cycle Progression score in patients after prostatectomy has shown some improvement. However, no direct evidence is available to support the clinical utility of Prolaris for improving net health outcomes of patients with localized prostate cancer following radical prostatectomy (RP). The decision curve analysis did not provide convincing evidence of meaningful improvement in net benefit by incorporating the CCP (cell cycle progression) score. Prolaris CCP score may have an association with biochemical recurrence (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. The National Comprehensive Cancer Network (NCCN) guideline for prostate cancer version 2.2021 does not recommend the use of Prolaris tissue- based testing post radical prostatectomy (RP) to inform management decisions. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)
Prostate Cancer Version 3.2022

Table 1 below provides on overview of each test, and populations where each test independently predicts outcome. These molecular biomarker tests have been developed

with extensive industry support, guidance, and involvement and have been marketed under the less rigorous FDA regulatory pathway for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that patients with low or favorable intermediate disease and life expectancy greater than or equal to 10 years may consider the use of Decipher, Oncotype DX Prostate or Prolaris during initial risk stratification. Patients with unfavorable intermediate and high- risk disease and life expectancy greater than or equal to 10- years may consider the use of Decipher or Prolaris. In addition, Decipher may be considered to inform adjuvant treatment if adverse features are found after radical prostatectomy and during workup for radical prostatectomy PSA persistence or recurrence (category 2B for the latter setting). Future comparative effectiveness research may allow these tests and others like them to gain additional evidence regarding their utility for better risk stratification of men with prostate cancer.

Table 1 Available Tissue Based Tests for Prostate Cancer Prognosis

Test	Platform	Populations Studied	Outcome(s) Reported (Test Independently Predicts)	Molecular Diagnostic Services Program (MolDX) Recommendations
Decipher	Whole transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	Post radical prostatectomy (RP), adverse pathology high risk features	• Metastasis • Prostate cancer specific mortality • Postoperative radiation sensitivity (PORTOS)	Cover post-biopsy for NCCN very low and low risk, favorable intermediate and unfavorable intermediate risk prostate cancer in patients with at least 10 -years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy Cover post RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
Decipher	Whole transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide	Post RP, biochemical recurrence/PSA persistence	• Metastasis • Prostate cancer specific mortality • Postoperative radiation	Cover post-biopsy for NCCN very low and low risk, favorable intermediate and unfavorable

Test	Platform	Populations Studied	Outcome(s) Reported (Test Independently Predicts)	Molecular Diagnostic Services Program (MolDX) Recommendations
	microarray optimized for FFPE tissue		sensitivity (PORTOS)	intermediate risk prostate cancer in patients with at least 10 -years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy Cover post RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
Decipher	Whole transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	Post RP, adjuvant,or post-recurrence radiation	• Metastasis • Prostate cancer specific mortality • Postoperative radiation sensitivity (PORTOS)	Cover post-biopsy for NCCN very low and low risk, favorable intermediate and unfavorable intermediate risk prostate cancer in patients with at least 10 -years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy Cover post RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
Decipher	Whole transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray	Biopsy, localized prostate cancer post RP or EBRT	• Non-organ confined (pT3) or grade group 3 disease at RP • Lymph node metastasis • Biochemical failure/recurrence	Cover post-biopsy for NCCN very low and low risk, favorable intermediate and unfavorable intermediate risk prostate cancer in

Test	Platform	Populations Studied	Outcome(s) Reported (Test Independently Predicts)	Molecular Diagnostic Services Program (MolDX) Recommendations
	optimized for FFPE tissue		• Metastasis • Prostate cancer specific mortality • Grade Group ≥ disease at RP	patients with at least 10- years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy Cover post RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
Decipher	Whole transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	M0 CRPC	• Metastasis – free survival	Cover post-biopsy for NCCN very low and low risk, favorable intermediate and unfavorable intermediate risk prostate cancer in patients with at least 10 -years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy Cover post RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
Ki-67	IHC	Biopsy, low – to - intermediate risk treated RP	• Non-organ confined pT3 or Group Grade ≥ 4 disease on RP	Not recommended
Ki-67	IHC	Biopsy, conservatively managed (active surveillance)	• Prostate cancer specific mortality	Not recommended

Test	Platform	Populations Studied	Outcome(s) Reported (Test Independently Predicts)	Molecular Diagnostic Services Program (MolDX) Recommendations
OncotypeDx Prostate	Quantitative RT-PCR for 12 prostate cancer related genes and 5 housekeeping controls	Biopsy, very low- to-high risk treated with RP	• Metastases • Prostate cancer specific mortality • Grade Group ≥3 and/or pT3+ disease at RP • Biochemical recurrence	Cover post-biopsy for NCCN very low, low risk and favorable intermediate risk prostate cancer in patients with at least 10- years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
Prolaris	Quantitative RT-PCR for 31 cell cycle related genes and 15 housekeeping controls	Biopsy Gleans Grade 3+3 or 3+4	• Non-organ confined pT3 or Grade Group ≥3 on RP	Cover post biopsy for NCCN very low, low- risk and favorable intermediate risk prostate cancer in patients with at least 10 -years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
Prolaris	Quantitative RT-PCR for 31 cell cycle related genes and 15 housekeeping controls	Biopsy, conservatively managed (active surveillance)	• Prostate cancer specific mortality	Cover post biopsy for NCCN very- low, low risk and favorable intermediate- risk prostate cancer in patients with at

Test	Platform	Populations Studied	Outcome(s) Reported (Test Independently Predicts)	Molecular Diagnostic Services Program (MolDX) Recommendations
				least 10- years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
Prolaris	Quantitative RT-PCR for 31 cell cycle related genes and 15 housekeeping controls	Biopsy, localized prostate cancer	• Biochemical recurrence • Metastasis	Cover post biopsy for NCCN very- low, low- risk and favorable intermediate risk prostate cancer in patients with at least 10- years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
Prolaris	Quantitative RT-PCR for 31 cell cycle related genes and 15 housekeeping controls	Biopsy, intermediate risk treated with EBRT	• Biochemical recurrence	Cover post biopsy for NCCN very- low, low- risk and favorable intermediate risk prostate cancer in patients with at least 10 -years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy

Test	Platform	Populations Studied	Outcome(s) Reported (Test Independently Predicts)	Molecular Diagnostic Services Program (MolDX) Recommendations
Prolaris	Quantitative RT-PCR for 31 cell cycle related genes and 15 housekeeping controls	RP, node negative localized prostate cancer	• Biochemical recurrence	Cover post biopsy for NCCN very- low, low- risk and favorable intermediate risk prostate cancer in patients with at least 10- years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
PTEN	Fluorescent in situ hybridization or IHC	Biopsy Grade Group 1	• Upgrading to Grade Group ≥3on RP	Not recommended
PTEN	Fluorescent in situ hybridization or IHC	RP, high risk localized disease	• Biochemical recurrence	Not recommended

Principles of Risk Stratification

Table 1. Initial Risk Stratification for Clinically Localized Disease				
Category	**Tool**	**Predictive**	**Prognostic**	**Endpoint Trained For**
Clinical	NCCN	No	Yes	BCR*
	STAR-CAP[1]	No	Yes	PCSM
	CAPRA[3]	No	Yes	BCR
	MSKCC[4]	No	Yes	BCR and PCSM
Imaging	MRI	No	Yes	-
	PET	No	Yes	-
Gene Expression Testing	Decipher	No	Yes	Metastasis
	Prolaris	No	Yes	Time to BCR and time to death from prostate cancer
	Oncotype DX Prostate	No	Yes	Adverse pathology
Germline Testing	BRCA2	No	Yes	-
*Very-low, low, favorable-intermediate, unfavorable-intermediate, high, very-high, and regional prostate cancer.				

Table 2. Tumor-Based Molecular Assays Can be Considered in Patients with Life Expectancy ≥10y as follows:						
	Very low risk	Low risk	Favorable intermediate risk	Unfavorable intermediate risk	High risk	Very high risk
Decipher	No	Yes	Yes	Yes	Yes	No
Prolaris	No	Yes	Yes	Yes	Yes	No
Oncotype DX Prostate	No	Yes	Yes	No	No	No

American Society of Clinical Oncology (ASCO)

In 2020, the American Society of Clinical Oncology (ASCO) issued a guideline on molecular biomarkers in localized prostate cancer which included the following recommendations:

Specific recommendations included the following:

Molecular biomarkers to identify patients with prostate cancer who are most likely to benefit from active surveillance:

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

Molecular biomarkers to diagnose clinically significant prostate cancer:

- Recommendation 2.1. Commercially available molecular biomarkers (i.e. Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine

clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate).

- Recommendation 2.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

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

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

Recommendation 3.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

American Urological Association (AUA)

In 2017, American Urological Association (AUA)/American Society of Radiation Oncology (ASTRO) and Society Urologic Oncology (SUO) issued a guideline for clinically localized prostate cancer, which includes the following recommendations:

- **Very Low/Low Risk Disease**
    - Clinicians should recommend active surveillance as the best available care option for very- low-risk localized prostate cancer patients (Strong Recommendation; Evidence Level: Grade A)
    - Clinicians should recommend active surveillance as the preferable care option for most low-risk localized prostate cancer patients (Moderate Recommendation; Evidence Level: Grade B)
    - Clinicians may offer definitive treatment (i.e. radical prostatectomy or radiotherapy) to select low-risk localized prostate cancer patients who may have a high probability of progression on active surveillance (Conditional Recommendation; Evidence Level: Grade B)
    - Among most low risk localized prostate cancer patients, tissue based genomic biomarkers have not shown a clear role in the selection of candidates for active surveillance (Expert Opinion)
- **Intermediate Risk Disease**
    - Clinicians should recommend radical prostatectomy or radiotherapy plus androgen deprivation therapy (ADT) as standard treatment options for

patients with intermediate risk localized prostate cancer (Strong Recommendation; Evidence Level: Grade A)
    - Active surveillance may be offered to select patients with favorable intermediate risk localized prostate cancer; however, patients should be informed that this comes with a higher risk of developing metastases compared to definitive treatment (Conditional Recommendation; Evidence Level: Grade C)
- **Active Surveillance**
    - Localized prostate cancer patients who elect active surveillance should have accurate disease staging including systemic biopsy with ultrasound or MRI guided imaging (Clinical Principle)
    - Localized prostate cancer patients undergoing active surveillance should have routine surveillance PSA testing and digital rectal exams (Strong Recommendation; Evidence Level: Grade B)
    - Localized prostate cancer patients undergoing surveillance should be encouraged to have a confirmatory biopsy within the initial two years and surveillance biopsies thereafter (Clinical Principle)
    - Clinicians may consider multiparametric prostate MRI as a component of active surveillance for localized prostate cancer patients (Expert Opinion)
    - Tissue based genomic biomarkers have not shown a clear role in active surveillance for localized prostate cancer and are not necessary for following up. (Expert Opinion)
    - Clinicians should offer definitive treatment to localized prostate cancer patients undergoing active surveillance who develop adverse reclassification (Moderate Recommendation; Evidence Level: Grade B)
- **Post-Treatment Follow-Up**
    - Clinicians should monitor localized prostate cancer patients post therapy with PSA, even though not all PSA recurrences are associated with metastatic disease and prostate cancer specific death. (Clinical Principle)

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Prolaris®, Oncotype DX® Prostate Cancer Assay and Decipher® gene expression profiling, and the Promark™ protein biomarker test is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

In November 2015, the FDA's Office of Public Health Strategy and Analysis published a document on public health evidence for FDA oversight of LDTs. FDA argued that many tests need more FDA oversight that 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.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policies

- 02.04.56 Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
- 02.04.25 Prostate Specific Antigen Screening for Prostate Cancer

Use of gene expression profiling (GEP) analysis Oncotype DX Prostate, Prolaris, Decipher or use of protein biomarker ProMark performed on prostate biopsy specimen to guide management of prostate cancer may be considered **medically necessary** if **ALL** of the follow criteria are met:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement); **and**
- The individual has not received pelvic radiation or androgen deprivation therapy (ADT) prior to the biopsy; **and**
- The individual's stage and risk stratification are defined as the following:
    - Low- risk disease defined by NCCN (National Comprehensive Cancer Network):
        - cT1-cT2a; **and**
        - Grade Group 1/Gleason Score 6 or less; **and**
        - PSA < 10 ng/mL; **OR**
    - Favorable intermediate risk defined by NCCN (National Comprehensive Cancer Network):
        - cT2b-cT2c; **and**
        - PSA 10-20 ng/mL; **and**
        - Grade Group 1 (Gleason Score 6 or less) or Grade Group 2 (Gleason Score 3+4=7); **and**
        - < 50% biopsy cores positive; **and**
    - The individual has an estimated life expectancy of ≥ 10 -years; **and**
    - The individual is a candidate for and is considering conservative therapy (active surveillance) and yet would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy).

Use of gene expression profiling (GEP) analysis or use of protein biomarker testing performed on prostate biopsy specimen is considered **investigational** when the above criteria are not met due to the lack of evidence demonstrating an impact on improved net health outcomes.

Use of gene expression profiling (GEP) analysis Decipher after radical prostatectomy (RP) using the individual's radical prostatectomy (RP) specimen to guide subsequent management of prostate cancer may be considered **medically necessary** if **ALL** of the following criteria are met:

- Individual with localized prostate cancer who has undergone a radical prostatectomy (RP) within the previous 60- months; **and**
- Individual is being considered for postoperative secondary therapy (i.e. radiation therapy) due to one or more cancer-recurrence risk factors (pre-PSA serum levels [4 or greater] and Gleason score [7 or greater]/Grade Group [2 or greater]; **and**
- Individual must have achieved initial PSA nadir (defined as PSA at or below 0.2 ng/ml) within 120 days of radical prostatectomy (RP) surgery; **and**
- Individual does not have any evidence of distant metastasis; **and**
- Individual has not received any neo-adjuvant treatment prior to radical prostatectomy (RP); **and**
- Individual's surgical pathology report or medical records must have documented presence of adverse pathology for one of the following:
    - Pathological stage pT2 disease with a positive surgical margin; **or**
    - Pathological state pT3 disease (e.g. extraprostatic extension, seminal vesicle invasion, bladder neck invasion); **or**
    - Rising PSA after initial PSA nadir; **and**
- The individual has an estimated life expectancy of ≥ 10- years.

Use of gene expression profiling (GEP) analysis or use of protein biomarker testing after radical prostatectomy (RP) is considered **investigational** when the above criteria are not met due to the lack of evidence demonstrating an impact on improved net health outcomes.

Policy Guidelines
International Society of Urological Pathologists

Risk Group	ISUP Grade Group	Gleason Score
Low	Grade Group 1	Gleason Score ≤ 6
Intermediate Favorable	Grade Group 2	Gleason Score 7 (3+4)
Intermediate Unfavorable	Grade Group 3	Gleason Score 7 (4+3)
High	Grade Group 4	Gleason Score 8
Very High	Grade Group 5	Gleason Score 9-10

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81541 Oncology (prostate), mRNA gene expression profiling by real-time PT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as disease-specific mortality risk (Prolaris®)
- 81542 Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score (Decipher®, Decipher® Prostate Cancer Assay or Decipher® Prostate Cancer Classifier)
- 81479 Unlisted molecular pathology procedures (when specified as Promark™/Promark™ Protein Biomarker Test/Promark™ Risk Score)
- 81599 Unlisted multianalyte assay with algorithmic analysis (when specified as Promark™/ Promark™ Protein Biomarker Test/Promark™ Risk Score)
- 84999 Unlisted chemistry procedure (when specified as Promark™/ Promark™ Protein Biomarker Test/Promark™ Risk Score)
- 0047U Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score (Oncotype DX Prostate or Oncotype DX Prostate Cancer Assay)

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- MoIDX: ProMark Risk Score. Local Coverage Determination (L36665)
- MoIDX: Decipher Prostate Cancer Classifier Assay. Local Coverage Determination (L35868)
- MoIDX Decipher Biopsy Prostate Cancer Classifier Assay for Men with Very Low and Low Risk Disease (L37785)
- MoIDX Decipher Biopsy Prostate Cancer Classifier Assay for Men with Favorable Intermediate Risk Disease: Proposed LCD (DL38035)
- MoIDX: Prolaris Prostate Cancer Genomic Assay. Local Coverage Determination (L35869)
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POLICY HISTORY

Date	Reason	Action
May 2022	Annual Review	Policy Renewed
May 2021	Annual Review	Policy Renewed
May 2020	Annual Review	Policy Renewed
December 2019	Interim Review	Policy Revised
May 2019	Annual Review	Policy Revised
May 2018	Annual Review	Policy Revised
May 2017	Annual Review	Policy Revised
June 2016		New Medical Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
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