Prostate Cancer Gene Expression Testing Assays

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Link to Codes

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Clinical Indications

- Prostate cancer gene expression assay may be indicated when **ALL** of the following are present(1):
  - Decipher Prostate (ie, for biopsy or RP version for radical prostatectomy specimen) requested and **ALL** of the following(28)(29)(30)(31):N
    - Diagnosis of low-risk to high-risk prostate cancer[A]
    - Estimated life expectancy of 10 years or greater
    - No clinical or radiographic evidence of distant metastases
    - No therapy prior to tumor sampling (eg, androgen deprivation therapy, radiation therapy)
  - Outcome of testing will guide decision-making regarding definitive therapy (eg, radiation therapy, radical prostatectomy).

Alternatives

- Alternatives include management based on traditional clinicopathologic factors (eg, life expectancy, PSA level, Gleason score, Cancer of the Prostate Risk Assessment score).(1)

Evidence Summary

Background

Gene expression testing is used as a complement to conventional prognostic clinicopathologic factors, such as life expectancy, PSA level, and Gleason score, in an effort to help guide management of patients with prostate cancer. The utility of gene expression testing (ie, gene signatures) is determined by the test's ability to accurately reclassify patients into different risk strata after initial classification by conventional predictors.(2)(3)(4) **(EG 2)** Accurate risk stratification is important for patients with localized prostate cancer, as treatment options for this population can range from active surveillance to radiation therapy, radical surgery, and systemic therapy.(1)(5)(6) **(EG 2)**

In addition to the commercially available gene expression assays (Onco*type* DX, Decipher Prostate, Prolaris), several gene expression signatures have been developed and validated; however, the clinical utility and routine application of these molecular markers have yet to be established.(4)(7)(8) **(EG 2)**

Criteria

The evidence for the clinical indications found in this guideline includes 37 published peer reviewed articles and 2 specialty society or other evidence-based guidelines.

For Decipher Prostate (ie, for biopsy or RP version for radical prostatectomy specimen), evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** Decipher Prostate is a 22-gene panel that uses DNA microarray analysis to derive a genomic risk score from diagnostic prostate biopsies or prostatectomy specimens.(30)(31) **(EG 2)** The genomic risk score is further classified into 3 risk categories (low-risk, intermediate-risk, or high-risk) to estimate the potential for metastasis in patients after biopsy or radical prostatectomy, independent of features such as rising PSA level. Studies have since evaluated the classifier for use as a prognostic marker for several outcomes (eg, adverse pathology, risk of distant metastasis, prostate cancer-specific mortality).(32)(33)(34)(35) **(EG 2)** Not all studies evaluating Decipher Prostate derived the genomic risk score in the same way or used the same risk category cutoffs; several studies were further limited by the age of the banked tumor samples and availability of tissue from a subset of patients from the original study.(31)(32)(34)(36)(37)(38)(39)(40) **(EG 2)** A study of individual patient data from 5 retrospective cohorts of postprostatectomy patients who had negligible PSA level postoperatively and had previously undergone testing by the 22-gene genomic classifier (855 of 975 total study patients with data) reported that low-risk, intermediate-risk, and high-risk genomic categories were associated with 5-year risk of metastasis (2.4%, 5.8%, and 15.2%, respectively) and 10-year risk of metastasis (5.5%, 15.0%, and 26.7%, respectively). Patients in the genomic classifier high-risk category had the greatest metastasis risk, including independently of other clinicopathologic features (eg, preoperative PSA level, radical prostatectomy Gleason score, surgical margin status).(29) **(EG 1)** A prospective-retrospective study of Decipher Prostate in 265 patients with high-risk prostate cancer evaluated banked prostate biopsy specimens from 3 randomized trials with active control arms. The authors found, at a median follow-up of 11 years, that the genomic risk score was prognostic for distant metastases, prostate-specific cancer mortality, and overall survival.(30) **(EG 2)** Another prospective-retrospective study evaluated the genomic risk score in 226 archived radical prostatectomy specimens from the SAKK 09/10 (Swiss Group for Clinical Cancer Research) randomized trial, which compared dose escalation with conventional dosing of salvage radiation therapy to the prostate bed in patients who experienced biochemical recurrence after radical prostatectomy. Patients with tissue in the high-risk category by the 22-gene genomic classifier had lower 5-year freedom from biochemical progression compared with patients in the low-risk or intermediate-risk category by the genomic classifier (45% vs 71%, respectively).(31) **(EG 2)** Evidence supports the use of Decipher Prostate to assess prognosis in localized prostate cancer as a factor to consider during management decision-making. However, data validating its prediction of differential response to treatment by genomic risk score are considered insufficient; prospective trials are ongoing.(1)(35) **(EG 2)** Specialty society guidelines do not recommend routine use of Decipher Prostate in the evaluation of prostate cancer, citing the need for prospective randomized trials demonstrating clinical benefit.(5)(41)(42) **(EG 2)** An expert consensus guideline noted that use of Decipher Prostate may be considered in men post biopsy who have clinically localized disease (ie, low-risk,

intermediate-risk, or high-risk) and life expectancy of at least 10 years for additional risk stratification, and may be considered for radiation therapy decisions post prostatectomy, adjuvant therapy decisions in cases of adverse pathology, and for patients with PSA resistance/recurrence after radical prostatectomy. The guideline notes that the decision to use various risk stratification tools should consider the potential to impact management decisions rather than be performed reflexively.(1) **(EG 2)**

Inconclusive or Non-Supportive Evidence

For the Genomic Prostate Score (formerly known as the Onco*type* DX prostate cancer assay or the Onco*type* DX Genomic Prostate Score (GPS)), evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** The Genomic Prostate Score test involves a 17-gene (12 cancer-related genes and 5 reference genes) polymerase chain reaction assay that measures gene expression in diagnostic prostate needle biopsies, representing 4 biological pathways. The gene expression results are translated into a Genomic Prostate Score algorithm (a scale from 0 to 100) that reflects tumor biology and cancer aggressiveness such that a patient initially classified as low risk by conventional clinicopathologic criteria may be reclassified as either very low risk or intermediate risk.(9)(10)(11) **(EG 2)** A systematic review of prognostic markers for localized prostate cancer identified 3 studies of Onco*type* DX, including one analytical validity study and 2 clinical validity studies in patients at low to intermediate risk by clinicopathologic features (ie, Cancer of the Prostate Risk Assessment score or National Comprehensive Cancer Network (NCCN) risk criteria). The Onco*type* DX GPS provided additional limited information beyond the clinical risk criteria; the authors called for a higher level of evidence prior to incorporating the assay into routine practice.(12) **(EG 1)** An industry-sponsored retrospective study of Onco*type* DX testing of archived prostatectomy specimens in a single healthcare system (279 patients, including 64 prostate cancer-specific deaths and 79 metastatic events during a median follow-up of 9.8 years) reported a strong association of Onco*type* DX GPS with time to prostate-specific death, time to metastasis, and time to biochemical recurrence; these associations were again observed after multivariate adjustment for NCCN risk group, American Urological Association risk group, and Cancer of the Prostate Risk Assessment score.(13) **(EG 2)** A single-center cohort study, stratified to represent an original population of 2641 patients, prospectively evaluated the Onco*type* DX GPS by assaying archived radical prostatectomy specimens from 127 patients with clinical recurrence (local or distant metastatic by biopsy or imaging) and 374 patients without clinical recurrence and found that the Onco*type* DX GPS was independently associated with 20-year absolute risk of distant metastases and prostate cancer-specific mortality after statistical adjustment to offset use of the assay's development cohort. The Onco*type* DX GPS added incrementally to the assessment of risk obtained from clinical features. The authors noted the need for validation in prospective studies using cohorts not included in the assay development.(14) **(EG 2)** A retrospective study of Onco*type* DX GPS results from 201 Black men and 1144 White men with prostate cancer in 6 different cohorts found that the assay was similarly predictive in samples regardless of race.(15) **(EG 2)** Review articles note that the impact of Onco*type* DX testing on patient outcomes has not been studied in large prospective randomized clinical trials.(16)(17)(18)(19) **(EG 2)** A specialty society guideline does not recommend routine use of Onco*type* DX in the evaluation of prostate cancer, citing the need for prospective randomized trials demonstrating improvement of patient outcomes.(5) **(EG 2)** An expert consensus guideline notes that, for men with low-risk or favorable intermediate-risk localized prostate cancer who have a life expectancy of at least 10 years, the use of Onco*type* DX may be considered.(1) **(EG 2)**

For Prolaris, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** The Prolaris genomic test involves a 46-gene (31 cell cycle progression genes and 15 housekeeper genes) polymerase chain reaction assay that measures gene expression in diagnostic prostate needle biopsies or postprostatectomy pathology samples to derive a cell cycle progression score predictive of prostate cancer aggressiveness (eg, biochemical recurrence, death from prostate cancer).(20)(21)(22) **(EG 2)** The Prolaris cell cycle progression score may predict the 10-year risk of prostate cancer death when measured in biopsy specimens and the risk of subsequent disease progression when measured in radical prostatectomy specimens.(11) **(EG 2)** A systematic review of prognostic markers for localized prostate cancer identified 7 studies evaluating Prolaris. The authors noted that the number of cell cycle progression genes that were analyzed varied as a function of the quality of a given specimen (ie, from 21 to 31 genes); 85% to 90% of samples were successfully evaluated in the studies reviewed. Older samples had a lower proportion of valid tests as compared with freshly fixed samples. Prolaris has been reported to add information for patients who are classified as low risk or intermediate risk by the Cancer of the Prostate Risk Assessment score; however, the authors noted that methodological limitations (eg, short follow-up, lack of details regarding conservative therapy used in various trials, simulation of some biopsy results, low number of events) hindered conclusions about the assay and called for higher levels of evidence to be gathered before the assay is used in routine clinical practice.(12) **(EG 1)** Another systematic review was unable to identify studies that evaluated the impact of Prolaris on patient outcomes.(23) **(EG 1)** An industry-sponsored study determined a clinical cell cycle risk score threshold to aid in decisions about patients' suitability for active surveillance based on training and validation cohorts. The threshold was then confirmed using a cohort of consecutive unselected men with prostate cancer who underwent Prolaris testing and

met clinicopathologic criteria for active surveillance. More men were identified to be active surveillance candidates by Prolaris testing than by clinicopathologic criteria (69% vs 43%, respectively); however, no outcomes data were available for confirmation of the value of this cutoff.(24) **(EG 2)** Tumor heterogeneity and sampling error may impact the performance of Prolaris,(25) which was developed using core samples obtained from prostatectomy tissue.(25)(26) **(EG 2)** Review articles note that the impact of Prolaris testing on patient outcomes has not been studied.(17)(18)(19)(27) **(EG 2)** A specialty society guideline does not recommend routine use of Prolaris in the evaluation of prostate cancer, citing the need for prospective randomized trials demonstrating clinical benefit.(5) **(EG 2)** An expert consensus guideline notes that the clinical utility of Prolaris has not been demonstrated in randomized clinical trials assessing long-term outcomes. It also notes that, for men with low-risk, intermediate-risk (ie, favorable or unfavorable intermediate-risk), or high-risk localized prostate cancer who have a life expectancy of at least 10 years, use of Prolaris may be considered.(1) **(EG 2)**

Rationale

Use of this MCG care guideline helps the clinician determine if a particular treatment, medication, or service might be appropriate for a specific patient, taking into account their unique health complexities.

Use of these evidence-based clinical criteria to support decision making benefits the patient by identifying patient-specific complex clinical factors and conditions, promoting personalized treatment. Utilizing evidence-based clinical criteria promotes patient safety by helping ensure that potential patient benefits outweigh the risks. In addition, the use of evidence-based guidelines can increase consistency in treatment thresholds, leading to less variation in care and promoting equitable treatment among patients.

Related CMS Coverage Guidance

This guideline supplements but does not replace, modify, or supersede existing Medicare regulations or applicable National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs).

Code of Federal Regulations (CFR): 42 CFR 419.22(43); 42 CFR 422.101(44)

Internet-Only Manual (IOM) Citations: CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 14 - Medical Devices(45); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 15 - Covered Medical and Other Health Services(46); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 16 - General Exclusions from Coverage(47)

Medicare Coverage Determinations: Medicare Coverage Database(48)

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Footnotes

[A] An expert consensus guideline defines low-risk prostate cancer as having clinical stage T1 to T2a, Grade Group 1, and PSA level less than 10 ng/mL (mcg/L) but not meeting the criteria for very low-risk prostate cancer, which must have all of the following features: clinical stage T1c; Grade Group 1; PSA level of less than 10 ng/mL (mcg/L); fewer than 3 prostate biopsy cores positive, with each core having 50% or less cancer in that core; and PSA density of less than 0.15 ng/mL/g (mcg/L/g). Intermediate-risk prostate cancer has one or more intermediate-risk factors, which include clinical stage T2b to T2c, Grade Group 2 or 3, and PSA level ranging from 10 to 20 ng/mL (mcg/L), yet does not have high-risk features or very high-risk features. High-risk prostate cancer is defined as having one or more high-risk features, which include clinical stage T3 to T4, Grade Group 4 or 5, and PSA level greater than 20 ng/mL (mcg/L); however, high-risk prostate cancer does not meet criteria for very high-risk prostate cancer. Very-high risk prostate cancer is defined as having 2 or more of the following features: clinical stage T3 to T4, Grade Group 4 or 5, and PSA level greater than 40 ng/mL (mcg/L).(1) [A in Context Link 1]

Codes

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