APPLICATION STATEMENT

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

Clinical Coverage Guideline

Original Effective Date: 5/7/2015 - Revised: 7/9/2015
BACKGROUND

Prostate cancer is the most common cancer among American males.\(^1\) An estimated 233,000 new cases were diagnosed in 2014 and 29,480 deaths resulted from prostate cancer.\(^2\)

The survival rate at five years is 98.9% (all stages); this rate decreases to 28.0% once the cancer has distantly metastasized.\(^2\) There are an array of treatment options that are dependent on the aggressiveness of the cancer, the patient's age, etc. Options include, but are not limited to “watchful waiting”, surgery, radiotherapy, hormone therapy, chemotherapy, biologic therapy, bisphosphonate therapy, and targeted therapy.

Gene expression profiling (GEP) is laboratory testing that measures the activity (or expression) of multiple genes at once. As a result, a prognosis is given along with the ability to refine risk stratification and/or optimize treatment regimens primarily for cancer.\(^1\)

**Centers for Medicare and Medicaid Services**\(3,4\)

Noridian will provide limited coverage for the ConfirmMDx epigenetic assay for prostate cancer (MDxHealth, Irvine, CA) to reduce unnecessary repeat prostate biopsies. While prospective evidence is currently being generated, retrospective evidence of clinical utility supports the potential value of this diagnostic test and serves as adequate evidence of likely clinical utility to support limited coverage. Noridian is aware that MDxHealth has initiated the PASCUAL Clinical Trial to prospectively address outcomes to establish clinical utility. Although limited coverage of this assay does support data collection within the PASCUAL trial, participation in the PASCUAL trial is not a prerequisite to the limited coverage. Coverage is limited to providers enrolled in the ConfirmMDx Certification and Training Registry (CTR) program.

ConfirmMDx assesses the methylation status of 3 biomarkers (GSTP1, RASSF1, APC) associated with prostate cancer. ConfirmMDx is intended for use in patients with high-risk factors such as elevated/rising prostate-specific antigen (PSA) or abnormal digital rectal examination (DRE), with a negative or non-malignant abnormal histopathology finding (e.g., atypical cell or high grade prostate intraepithelial neoplasia (HGPIN)) in the previous biopsy, and is being considered for repeat biopsy. Several case/control studies in archived biopsy core tissue blocks demonstrated the sensitivity, specificity and high negative predictive value (NPV) of these biomarkers to predict cancer detection in a repeat biopsy procedure. Single biopsy cores, using as little as 20 microns from formalin-fixed, paraffin embedded (FFPE) tissue blocks or sections cut from blocks fixed on glass slides are used in this assay.

The performance of this assay in a large, blinded clinical validation study demonstrated a NPV of 90% which is considerably higher than that afforded by standard histopathology review. A mathematically-based budget impact model using the assay in urologic practices to decide upon the need for repeat biopsies reported significant cost and medical resource savings by avoiding unnecessary, invasive biopsies over current standard of care methods. Further logistic regression models using all pertinent risk factors for prostate cancer detection (patient age, serum PSA level, digital rectal exam, histopathological findings on the previous cancer-negative biopsy and the assay) from the clinical validation trial were analyzed to compare various metrics separately and in combination. Assay results and prior histopathology were the strongest predictors of missed cancers and these two measures combined had a higher performance than either alone.
The repeat biopsy rate for patients with an initial negative biopsy was reported to be approximately 40% in the Prostate, Lung, Ovarian and Lung (PLCO) screening trial suggesting that a majority of the patients undergoing repeat biopsies did not have cancer detected. A recently completed field observation study was conducted in 138 patients with negative biopsies and managed by the urologist receiving negative ConfirmMDx for Prostate Cancer assay findings from those patient's tissues. Only 6 of the 138 patients in that series had received a repeat biopsy yielding a 4.5% repeat biopsy rate.

POSITION STATEMENT

Applicable To:
☑ Medicaid – Hawaii
☑ Medicare – Hawaii

NOTE: For all other markets, please access the appropriate vendor for criteria and authorizations.

Oncotype Dx is considered medically necessary when ALL of the following are met:3,4

1. Males aged 40 to 85 years old that have undergone a previous cancer-negative prostate biopsy within 24 months and are being considered for a repeat biopsy due to persistent or elevated cancer-risk factors; AND
2. The previous negative prostate biopsy must have collected a minimum of 8 tissue cores (but not have received a saturation biopsy of > 24 tissue cores) and remaining FFPE tissue from all cores is available for testing; AND
3. Minimum tissue volume criteria of 20 microns of prostate biopsy core tissue is available (40 microns preferable); AND
4. Previous biopsy histology does not include a prior diagnosis of prostate cancer or cellular atypia suspicious for cancer (but may include the presence of high-grade prostatic intraepithelial neoplasia (HGPIN), proliferative inflammatory atrophy (PIA), or glandular inflammation); AND
5. Patient is not being managed by active surveillance for low stage prostate cancer, AND
6. Tissue was extracted using standard patterned biopsy core extraction (and not transurethral resection of the prostate (TURP)); AND
7. Patient has not been previously tested by ConfirmMDx from the same biopsy samples or similar molecular test; AND
8. Testing has been ordered by a physician who is certified in the MolDx approved ConfirmMDx Certification and Training Registry (CTR) program.

CODING

Covered CPT Codes
81479 Unlisted molecular pathology procedure

HCPCS Codes – No applicable codes.

Covered ICD-9-CM Diagnosis Codes
185 Malignant neoplasm of prostate
222.2 Benign neoplasm of prostate
233.4 Carcinoma in situ of prostate
236.5 Neoplasm of uncertain behavior of prostate
600.00 - 600.91 Hypertrophy of prostate
602.3 Dysplasia of prostate
790.93 Elevated prostate specific antigen (PSA)
796.4 Abnormal clinical findings (Abnormal DRE)
V10.46 Personal history of malignant neoplasm of prostate
ONCOTYPE DX FOR PROSTATE CANCER
HS-289

V16.42  Family history of malignant neoplasm of prostate
V76.44  Special screening for malignant neoplasm of prostate
V84.03  Genetic susceptibility to malignant neoplasm of prostate

Covered ICD-10-CM draft diagnosis codes:
C61    Malignant neoplasm of prostate
D29.1  Benign neoplasm of prostate
D07.5  Carcinoma in situ of prostate
D40.0  Neoplasm of uncertain behavior of prostate
N40.0  Enlarged prostate without lower urinary tract symptoms
N40.1  Enlarged prostate with lower urinary tract symptoms
N40.2  Nodular prostate without lower urinary tract symptoms
N40.3  Nodular prostate with lower urinary tract symptoms
N40.0  Enlarged prostate without lower urinary tract symptoms
N40.1  Enlarged prostate with lower urinary tract symptoms
N42.83 Cyst of prostate
N40.0  Enlarged prostate without lower urinary tract symptoms
N40.1  Enlarged prostate with lower urinary tract symptoms
N42.3  Dysplasia of prostate
R97.2  Elevated prostate specific antigen [PSA]
R68.89 Other general symptoms and signs
Z85.46 Personal history of malignant neoplasm of prostate
Z12.5  Special screening for malignant neoplasm of prostate
Z80.42 Family history of malignant neoplasm of prostate
Z15.03 Genetic susceptibility to malignant neoplasm of prostate


REFERENCES

MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>7/9/2015</td>
<td>Approved by MPC. Previously E/I; coverage now indicated. Updated applicable markets.</td>
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<tr>
<td>5/7/2015</td>
<td>Approved by MPC. New.</td>
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