

Local Coverage Determination (LCD): MoIDX: ProMark Risk Score (L36704)

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Contractor Information

| CONTRACTOR NAME | CONTRACT TYPE | CONTRACT NUMBER | JURISDICTION | STATE(S) |
|------------------------------------|---------------|-----------------|--------------|---|
| Noridian Healthcare Solutions, LLC | A and B MAC | 01111 - MAC A | J - E | California - Entire State |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01112 - MAC B | J - E | California - Northern |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01182 - MAC B | J - E | California - Southern |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01211 - MAC A | J - E | American Samoa Guam Hawaii Northern Mariana Islands |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01212 - MAC B | J - E | American Samoa Guam Hawaii Northern Mariana Islands |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01311 - MAC A | J - E | Nevada |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01312 - MAC B | J - E | Nevada |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01911 - MAC A | J - E | American Samoa California - Entire State Guam Hawaii Nevada Northern Mariana Islands |

LCD Information

Document Information

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Proposed LCD in Comment Period

N/A

Revision Ending Date

N/A

Source Proposed LCD

DL36704

Retirement Date

N/A

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CMS National Coverage Policy

Title XVIII of the Social Security Act, §1862(a)(1)(A). Allows coverage and payment for only those services that are

considered to be reasonable and necessary.

Title XVIII of the Social Security Act, §1833(e). Prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

42 Code of Federal Regulations (CFR) 410.32(a). Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS On-Line Manual, Publication 100-02, *Medicare Benefit Policy Manual*, Chapter 15, §§80.0, 80.1.1, 80.2. Clinical Laboratory services.

CMS Internet-Only Manuals, Publication 100-04, Medicare Claims Processing Manual, Chapter 16, §50.5 Jurisdiction of Laboratory Claims, 60.12 Independent Laboratory Specimen Drawing, 60.2. Travel Allowance.

CMS Internet Online Manual Pub. 100-04 (Medicare Claims Processing Manual), Chapter 23 (Section 10) "Reporting ICD Diagnosis and Procedure Codes"

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This Contractor will provide limited coverage for the ProMark (Metamark Genetics) to help determine which patients with early stage, needle biopsy proven prostate cancer can be conservatively managed rather than treated with definitive surgery or radiation therapy.

Summary of Evidence

In 2014, nearly 233,000 men in the US will be diagnosed with prostate cancer, which accounts for 14% of all new cancer diagnosis. More than 29,000 men will die from this disease representing 5% of all cancer deaths. Gratefully 98.9% of men are surviving at 5 years (SEER).

Many individuals do not need treatment for their prostate cancer in as much as their prognosis is excellent even without treatment. However, physicians and patients struggle to know who can safely be observed versus the subgroup that needs more aggressive treatment to achieve cure, and recognize that definitive treatment for localized prostate cancer can have lifelong morbidities (Resnick 2013, Truong, 2013).

Traditionally, clinicopathologic characteristics are utilized to determine risk and subsequent treatment. Several nomograms have been introduced to try to determine who is at risk of developing metastatic disease and who, if treated early, could avoid this outcome. A representative nomogram taken from the NCCN (and AUA), divides early prostate cancer into several groups based initially on life expectancy, with a second stratification using clinical exam, reassessment of life expectancy, biopsy (Gleason score), PSA and imaging after 5 years.

These groups are detailed below:

Risk Category

Clinicopathologic Findings

| | Very Low | Low | Intermediate | High |
|----------------------------------|---|---|--|---|
| Treatment Options | <ul style="list-style-type: none"> T1c AND Gleason score ≤ 6 | <ul style="list-style-type: none"> T1-T2a AND Gleason score ≤ 6/Gleason grade group 1 AND PSA ≤ 10 ng/mL | <ul style="list-style-type: none"> T2b-T2c OR Gleason score 3+4=7/Gleason grade group 2 OR Gleason score 4+3=7/Gleason grade group 3 OR PSA 10-20 ng/mL | <ul style="list-style-type: none"> T3a OR Gleason score ≥ 8/Gleason grade group 4 OR Gleason score ≥ 10/Gleason grade group 5 OR PSA > 20 |
| ≥ 20 y life expectancy | <ul style="list-style-type: none"> Active Surveillance RT or Brachy RP (± LND) | <ul style="list-style-type: none"> Active Surveillance RT or Brachy RP (± LND) | <ul style="list-style-type: none"> RP (± LND) RT or Brachy ± Adj Horm | <ul style="list-style-type: none"> RT + Adj Horm RT + Brachy RP + LND |
| ≥ 10 y life expectancy | <ul style="list-style-type: none"> Active Surveillance | <ul style="list-style-type: none"> Active Surveillance RT or Brachy RP (± LND) | <ul style="list-style-type: none"> RP (± LND) RT or Brachy ± Adj Horm | <ul style="list-style-type: none"> RT + Adj Horm RT + Brachy RP + LND |
| < 10 y life expectancy | <ul style="list-style-type: none"> Observation | <ul style="list-style-type: none"> Observation | <ul style="list-style-type: none"> RT or Brachy ± Adj Horm Observation | <ul style="list-style-type: none"> N/A |

Table 1: NCCN 2017 V2 - Localized Prostate Cancer Risk Stratification and Treatment (PSA – Prostate Specific Antigen; RT – Radiation Therapy; RP – Radical Prostatectomy; LND – lymph node dissection; Adj Horm – Adjuvant Androgen Deprivation)

Use of these stratification and treatment approaches has led to high cure rates for early stage prostate cancer, yet it is widely accepted that many men are over-treated to achieve this cure rate. In the PIVOT trial (Wilt 2012) men with early prostate cancer, initially randomized to radical prostatectomy or observation, showed that over 12 years there was no difference in absolute mortality between the groups. However, this study was hampered by several factors including:

- Only 731 of 5023 eligible patients chose to participate in the study based on randomization criteria.
- In the group randomized to RP: only 85% of the men received definitive therapy (79% surgery; 6% other).
- In the observational group: 10% of the observation group received RP initially and additional 20% eventual received definitive treatment.
- Despite broad inclusion criteria, > 50% of patients had a PSA of <10 (median PSA of 7) and had biopsy proven T1c disease. Although there were a significant number of patients with Gleason score ≥7 (25%), 40% of men were classified initially as being low risk; and 30% were intermediate.

Although subgroups were small, it appears that high-risk groups (including those with PSA > 10) benefitted from RP. Furthermore, there was a trend for the intermediate risk patients to benefit from RP as well. The small number of patients willing to enter the study, and the high rate of crossover (both initially and subsequently) demonstrates the difficulty of doing observation trials in the United States.

Although there is early data that may suggest that some patients with intermediate risk prostate cancer could potentially be considered for active surveillance (AS) (Gleason Score 3+4 = 7, PSA < 10), the NCCN and other mainstream groups still do not recommend this approach, with the NCCN stating, "Active

surveillance of intermediate and high-risk clinically localized cancers is not recommended in patients with life expectancy ≥ 10 years as a category 1 recommendation. The shortcomings in the current system have driven the development of emerging biomarker-based tools for assessing risk.

ProMark Test

Test Description

ProMark 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 (Shipitsin 2014, Shipitsin 2014, Blume-Jensen 2015). The assay measures the signal intensity of 8 protein biomarkers (i.e., CUL2, DERL1, FUS, HSPA9, PDSS2, pS6, SMAD4 and YBX1) in tumor and benign prostate glands on FFPE biopsy tissue sections to generate an algorithmically derived risk score indicating the likelihood of having high-risk disease. Unlike DNA/RNA-based tests that require biopsy tissue to be homogenized prior to analysis, ProMark technology allows for analysis of proteins directly from the cancerous regions of interest. The test has shown the ability to predict prostate cancer aggressiveness regardless from which region the prostate biopsy was taken, a key feature and benefit given the considerable heterogeneity that exists in biopsied tissue (Shipitsin 2014).

Test Development and Performance

ProMark was validated through a series of studies from initial proof of concept to final marker lock-down and validation trials involving more than 1200 patients in a 3-phase program.

The assay development study was a non-interventional and retrospective study devised to define the best marker subset from those candidate proteins previously shown to correlate with both prostate pathology aggressiveness and lethal outcome. The study goal was to define a model able to distinguish between prostate pathology usually recommended for active surveillance ("GS 6"; surgical Gleason 3+3 and $\leq T3a$) versus those more likely to require prostatectomy ("non-GS 6"; surgical Gleason $\geq 3+4$ or non-localized $>T3a$ or N or M). This GS 6 versus non-GS 6 definition was based on studies showing that tumors with surgical Gleason 3+3 at prostatectomy do not metastasize. A logistic regression model was trained on the training set, and risk scores were obtained for samples in both the training and testing sets. The final marker coefficients were used in a logistic regression model for calculation of the risk score, a continuous scale from 0 to 1, which estimated the likelihood of "non-GS6" pathology.

The validation study cohort (N=276) was separate and independent from the assay development cohort, and comprised biopsy samples with matched prostatectomy specimens. It was a non-interventional, blinded, prospectively designed, retrospectively collected clinical study to predict prostate pathology on its own and relative to current systems for patient risk categorization. A risk score was generated for each sample. Inclusion criteria were biopsies with a centralized Gleason score 3+3 or 3+4 (biopsies with discordant grading by two expert pathologists of 3+4 and 4+3 were included as well), and matched prostatectomy with pathologic TNM staging, PSA level, and resulting surgical Gleason score. Central review was performed on biopsies, whereas for prostatectomies the investigators relied on the original pathology annotation, due to practical challenges in accessing all the different locations where these had been conducted; however, all prostatectomy pathology annotation was done according to new ISUP (the International Society of Urological Pathology) classification. Matched prostatectomy samples with annotated surgical Gleason scores ultimately classified the tumor as "favorable" or "non-favorable" for the purposes of evaluating assay results. Sample sizes were statistically designed, with power greater than 95% for both cohorts. ROCs and corresponding AUCs determined for the 8-biomarker risk score quantitatively evaluated performance of the assay.

Favorable (Gleason $\leq 3+4$ and organ-confined disease ($\leq T2$)) versus non-favorable (Gleason $\geq 4+3$ or non-

organ-confined disease (T3a, T3b, N, or M)) pathology were co-primary endpoints in the validation study. The other co-primary endpoints were "GS6" pathology (Gleason 3+3 and localized disease (\leq T3a)) versus "non-GS 6" pathology (Gleason \geq 3+4 or non-localized disease (T3b, N, or M)). The analysis for "favorable" pathology yielded an AUC of 0.68 with 95% CI, 0.61-0.74. The associated P value was <0.0001 , with an OR for risk score of 20.9 per unit change. "GS 6" pathology yielded an AUC of 0.65 with 95% CI, 0.58-0.72. The associated P value was <0.0001 , with an OR for risk score of 12.6 per unit change.

The intended use of ProMark is to categorize a patient to favorable versus non-favorable disease pathology based on his risk score on the specificity curve (not provided). The PPV for favorable pathology, at a risk score of ≤ 0.33 , was 83.6% (specificity, 90%). Conversely, at a risk score of >0.80 , 76.9% had non-favorable disease (i.e., only 23.1% of patients in the high-risk score category had favorable disease). This translates to 39% of patients in this study population having risk scores ≤ 0.33 or >0.8 , of which 81% were correctly identified by ProMark. Of patients with intermediate risk scores ($0.33 < \text{risk score} \leq 0.8$), 58.3% had favorable disease. The PPV of ProMark was also compared with those of the NCCN and D'Amico risk categories. The PPV for favorable pathology, at a risk score of ≤ 0.33 , was 75% for patients in the NCCN intermediate-risk category; 81.5% for NCCN low-risk patients, and 95% for NCCN very low-risk, with an overall PPV for favorable pathology of 85%. This contrasts favorably with the PPVs obtained for the NCCN risk categories alone, which were 40.9% for intermediate risk, 63.8% for low-risk, and 80.3% for very low-risk.

These findings suggest that the ProMark risk score provides additional confidence that a patient categorized to the NCCN very low-risk group indeed has a favorable pathology based on his biopsy from 80.3% to 95%. Conversely, the predictive value for non-favorable pathology was 76.9% at a risk score >0.8 , but reached 100% at a risk score cutoff point of >0.9 . For all NCCN and D'Amico risk categories, a higher ProMark risk score correlated with decreased frequency of favorable cases.

Analysis of Evidence (Rationale for Determination)

Level of Evidence

Quality - Limited to Moderate

Strength - Limited to Moderate

Weight - Limited

Criteria for Coverage

The ProMark assay is covered only when the following clinical conditions are met:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), **and**
- Patient Stage as defined by the one of the following:
 - Very Low Risk Disease (T1c **AND** Gleason Score ≤ 6 **AND** PSA ≤ 10 ng/mL **AND** $\leq 50\%$ cancer in any core **AND** PSA density of < 0.15 ng/mL/g) **OR**
 - Low Risk Disease (T1-T2a **AND** Gleason Score ≤ 6 **AND** PSA ≤ 10 ng/mL), **and**
- Patient has an estimated life expectancy of greater than or equal to 10 years, **and**
- Patient is a candidate for and is considering conservative therapy and yet and would be eligible for definitive

- therapy (radical prostatectomy, radiation therapy or brachytherapy), **and**
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, **and**
- Test is ordered by a physician certified in the Metamark Genetics Certification and Training Registry (CTR), **and**
- Patient is monitored for disease progression according to active surveillance guidelines as recorded in NCCN guidelines, **and**
- Physician must report the development of metastasis or prostate cancer deaths in patients not treated definitively who were deemed low risk by the assay.

Certification and Training Registry (CTR) Program

Because of the complicated nature of management decisions utilizing the ProMark assay and the potential for adverse harm to patients if the test is not used appropriately, testing must be furnished only by physicians who are enrolled in a MoDx approved ProMark CTR program. This serves to assure the appropriate selection of patients, compliance with management decisions and stringent follow up to ensure the benefits of the test outweigh its risks. As part of this requirement Metamark will provide to the Contractor reports every 6 months in a mutually agreed upon format.

The goals of the Metamark Genetics ProMark CTR program are as follows:

- To ensure that physicians understand the limitations of the test based on its validation, **and**
- To inform prescribers and patients on the safe-use conditions for ProMark assay, **and**
- To make a good faith effort to identify any safety concerns from the use of the test, **and**
- To facilitate understanding of the incremental clinical utility of the test versus adherence to current NCCN guidelines

This Contractor expects Metamark Genetics to:

- Establish and maintain the ProMark Certification and Training Registry (CTR);
- Ensure that healthcare providers who order the ProMark assay are registered and certified in the ProMark CTR program and that the ProMark assay is available only through these providers;
- Maintain a secure registry database of Metamark's ProMark CTR providers and obtain from referring physicians;
 - NCCN risk group and treatment recommendation based on current NCCN guidelines prior to receipt of test result;
 - Test result (i.e., ProMark Risk Score), and
 - Treatment recommendation based on test results, and
 - Final physician-patient treatment decision, and
 - Report utilization data by clinic-pathologic staging;
 - Any subsequent change in patient treatment decision, even if the patient has not progressed, and
 - Immediately report (for patients not treated definitively who were deemed very low or low risk by the assay)
 - Progression as defined by current NCCN guidelines for patients on AS, or
 - Development of metastases, or
 - Prostate cancer deaths.
- Share all required data and reports in a HIPAA compliant fashion.

Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all

Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

N/A

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the policy, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

N/A

CPT/HCPCS Codes

Group 1 Paragraph:

N/A

Group 1 Codes:

| CODE | DESCRIPTION |
|-------|--|
| 81479 | UNLISTED MOLECULAR PATHOLOGY PROCEDURE |

ICD-10 Codes that Support Medical Necessity

Group 1 Paragraph:

N/A

Group 1 Codes:

| ICD-10 CODE | DESCRIPTION |
|-------------|--------------------------------|
| C61 | Malignant neoplasm of prostate |

ICD-10 Codes that DO NOT Support Medical Necessity

N/A

Additional ICD-10 Information

N/A

General Information

Associated Information

N/A

Sources of Information

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9. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367:203-13

Revision History Information

| REVISION HISTORY DATE | REVISION HISTORY NUMBER | REVISION HISTORY EXPLANATION | REASON(S) FOR CHANGE |
|-----------------------|-------------------------|---|--|
| 01/01/2018 | R2 | Removed CDD from title and added 21st Century Cures Act fields. | <ul style="list-style-type: none">• Creation of Uniform LCDs With Other MAC Jurisdiction |
| 01/01/2018 | R1 | <p>Added additional information to Low, Intermediate, and High categories in Clinocopathologic Findings. Updated the NCCN Prostate Cancer Guidelines to 2017, V2.</p> <p>12/11/2017: At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.</p> | <ul style="list-style-type: none">• Creation of Uniform LCDs With Other MAC Jurisdiction |

Associated Documents

Attachments

N/A

Related Local Coverage Documents

LCD(s)

DL36704

- (MCD Archive Site)

Related National Coverage Documents

N/A

Public Version(s)

Updated on 04/03/2018 with effective dates 01/01/2018 - N/A

Updated on 12/14/2017 with effective dates 01/01/2018 - N/A

Updated on 03/21/2017 with effective dates 06/01/2017 - N/A

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- biomarker
- prostate
- MoIDX