Local Coverage Determination (LCD): MolDX: Prolaris™ Prostate Cancer Genomic Assay for Men with Favorable Intermediate Risk Disease (L37082)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Noridian Healthcare Solutions, LLC	A and B MAC	02101 - MAC A	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02102 - MAC B	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02201 - MAC A	J - F	Idaho
Noridian Healthcare Solutions, LLC	A and B MAC	02202 - MAC B	J - F	Idaho
Noridian Healthcare Solutions, LLC	A and B MAC	02301 - MAC A	J - F	Oregon
Noridian Healthcare Solutions, LLC	A and B MAC	02302 - MAC B	J - F	Oregon
Noridian Healthcare Solutions, LLC	A and B MAC	02401 - MAC A	J - F	Washington
Noridian Healthcare Solutions, LLC	A and B MAC	02402 - MAC B	J - F	Washington
Noridian Healthcare Solutions, LLC	A and B MAC	03101 - MAC A	J - F	Arizona
Noridian Healthcare Solutions, LLC	A and B MAC	03102 - MAC B	J - F	Arizona
Noridian Healthcare Solutions, LLC	A and B MAC	03201 - MAC A	J - F	Montana
Noridian Healthcare Solutions, LLC	A and B MAC	03202 - MAC B	J - F	Montana
Noridian Healthcare Solutions, LLC	A and B MAC	03301 - MAC A	J - F	North Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03302 - MAC B	J - F	North Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03401 - MAC A	J - F	South Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03402 - MAC B	J - F	South Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03501 - MAC A	J - F	Utah
Noridian Healthcare Solutions, LLC	A and B MAC	03502 - MAC B	J - F	Utah
Noridian Healthcare Solutions, LLC	A and B MAC	03601 - MAC A	J - F	Wyoming
Noridian Healthcare Solutions, LLC	A and B MAC	03602 - MAC B	J - F	Wyoming

LCD Information

Document Information

LCD ID
L37082

Original Effective Date
For services performed on or after 09/25/2017

LCD Title
MolDX: Prolaris™ Prostate Cancer Genomic Assay for Men with Favorable Intermediate Risk Disease

Proposed LCD in Comment Period
N/A

Source Proposed LCD
DL37082

AMA CPT / ADA CDT / AHA NUBC Copyright Statement

Revision Effective Date
For services performed on or after 12/01/2019

Revision Ending Date
N/A

Retirement Date
N/A

Notice Period Start Date
08/10/2017

Notice Period End Date
09/24/2017

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 Prolaris™ prostate cancer assay (Myriad, Salt Lake City, UT) to help determine which patients with favorable intermediate risk, needle biopsy proven prostate cancer (as defined below), can be conservatively managed rather than treated with definitive surgery or radiation therapy.

Summary of Evidence

In 2016, nearly 180,890 men in the US will be diagnosed with prostate cancer, which accounts for 10.7% of all new cancer diagnosis. More than 26,120 men will die from this disease representing 4.4% of all cancer deaths. Gratefully, 98.9% of men are surviving at 5 years.

Many men 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 monitored versus the subgroup that needs more aggressive treatment to achieve cure, recognizing that definitive treatment for localized prostate cancer can have lifelong morbidities.

Traditionally, clinicopathologic characteristics are utilized to determine risk and subsequent treatment. Risk categories for clinically localized prostate cancer include low-, intermediate-, or high-risk. The majority of men diagnosed with prostate cancer are categorized as low- or intermediate- risk. Within the intermediate-risk group, more recent recognition of clinical heterogeneity and variability in prognoses has led to a further subdivision into favorable (defined below as per NCCN 2017) and unfavorable intermediate-risk.

Several risk stratification approaches, including those from the NCCN and AUA, 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 one taken from the NCCN, 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.

These groups are detailed below:

	Risk Category			
	Very Low	**Low**	**Intermediate**	**High**
Clinicopathologic Findings	• T1c **AND** • Gleason score ≤ 6/Gleason grade group 1 **AND** • PSA ≤ 10 ng/mL **AND** • < 3 prostate cores with tumor **AND** • ≤ 50% tumor in any core **AND** • PSA density of < 0.15 ng/mL/g	• T1-T2a **AND** • Gleason score ≤ 6/Gleason grade group 1 **AND** • PSA ≤ 10 ng/mL	• 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	• T3a **OR** • Gleason Score 8/Gleason grade group 4 **OR** • Gleason score 9 - 10/Gleason grade group 5 **OR** • PSA > 20 ng/mL
Treatment Options				
≥ 20 y life expectancy	• Active Surveillance • RT or Brachy • RP (± LND)			
≥ 10 y life expectancy	• Active Surveillance	• Active Surveillance • RT or Brachy • RP (± LND)	• RP (± LND) • RT ± Adj Horm Brachy • Brachy	• RT + Adj Horm • RT + Brachy ± Adj

				• Horm • RP + LND
< 10 y life expectancy	• Observation	• Observation	• RT ± Adj Horm Brachy • Brachy • Observation	• 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)

The treatment algorithm for intermediate risk patients found in the 2017 NCCN guidelines for Prostate Cancer includes footnote "o" on page PROS-4 stating that men with "favorable intermediate-risk prostate cancer (predominant Gleason grade 3 [i.e., Gleason score 3+4=7/Gleason grade group 2], and percentage of positive biopsy cores <50 percent, and no more than one NCCN intermediate risk factor) can be considered for active surveillance". The NCCN also acknowledges that such a choice "should be approached with caution, include informed decision-making, and use close monitoring for progression".

Use of clinical/pathologic 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 the cure rate. In the PIVOT trial 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 problems 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 definitively 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.

Recent reports on prostate cancer diagnosis and management in the United States evaluated data from the US National Cancer Data Base and the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) to summarize the use of various treatments, including changes over time. Although the use of active surveillance for men with low-risk prostate cancer increased over time, it was utilized in only 18.4 - 40% of patients despite societal guidelines supporting its use in this population. In the intermediate-risk group, active surveillance was pursued in only 4-8% of patients. The availability of molecular diagnostic tests that provide a more accurate prediction of oncologic endpoints like 10-year disease specific mortality, compared to standard clinical and pathologic features, provides an opportunity to identify men who may safely pursue active surveillance and increase physician/patient

confidence in that choice. The benefits associated with active surveillance and foregoing immediate intervention for appropriate men include a reduction in treatment related complications and avoidance of adverse events like erectile dysfunction, urinary incontinence, bowel dysfunction, and depression.

Prolaris™ Prostate Cancer

Assay Test Description

Prolaris™ is an RNA based assay measuring the expression of 31 cell cycle progression (CCP) genes and 15 "housekeeping" genes that act as internal controls and normalization standards in each patient sample. The assay is performed on formalin fixed paraffin-embedded (FFPE) prostate cancer blocks. The assay results are reported as a numerical score along with accompanying interpretive information.

The Prolaris test report that is delivered to the ordering physician includes:

- The patient's Prolaris Score (i.e. cell cycle progression score or "CCP");
- The patient's estimated 10-year prostate cancer mortality risk based on his Prolaris Score in combination with his CAPRA score (the combined clinical-cell-cycle risk score, or "CCR");
- A depiction of a threshold for prostate cancer mortality risk below which active surveillance may be safely considered.

The active surveillance threshold was developed based on the CCR score distribution in a training cohort of commercially tested men who might typically be considered for active surveillance according to the NCCN*, based on their clinical characteristics alone (n = 505). The training cohort included men meeting the following criteria: Gleason score ≤ 3+4; PSA < 10 ng/ml; <25% positive cores; and T-stage ≤ T2a (N=505). A threshold for the CCR score of 0.8 was conservatively selected such that 90% of the men in the training cohort had scores below the threshold.

The threshold of 0.8 was then validated in two independent cohorts (combined n=765) of conservatively managed men with known outcomes for prostate cancer specific mortality (PCM). The Prolaris Score was a strong prognostic indicator in both validation cohorts, based on previous publications (See references 2 & 3). The threshold was able to dichotomize men into significantly different risk groups. There were no prostate cancer deaths in the group of men with CCR scores below the threshold of 0.8. The CCR score of 0.8 corresponded to a 10-year predicted risk of PCM of about 3%. In summary, the threshold for the CCR score of 0.8 distinguishes men with prostate cancer who may safely pursue active surveillance from those who may not be good candidates.

**NCCN Guidelines state that men with favorable intermediate-risk prostate cancer may be considered for active surveillance. Our training cohort included a conservative version of favorable intermediate including ≤ 3+4 with all other low-risk factors.*

Test Performance

The clinical performance of this assay was assessed in several retrospective validation studies. These include two British cohorts of men diagnosed with prostate cancer on biopsy and then treated conservatively; and an additional cohort of men diagnosed by TURP and conservatively managed. Further validation was performed in various other

cohorts including men who underwent radical prostatectomy, and men treated with definitive radiotherapy. The Prolaris™ cell cycle progression score (CCP) was found to be an independent and more robust prognostic factor for disease related death than traditional clinicopathologic factors although disease stage and Gleason score consistently portended a more negative prognostic picture.

Criteria for Coverage

The Prolaris™ assay is covered for men with favorable intermediate risk prostate cancer 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
- FFPE prostate biopsy specimen with at least 0.5 mm of cancer length, and
- Patients with favorable intermediate-risk disease, defined by the NCCN as follows:
    - Predominant Gleason grade 3 (i.e. Gleason score 3+4=7), percentage of positive cores <50%, and no more than 1 NCCN intermediate-risk factor)
      NCCN intermediate risk factors include T2b-T2c, Gleason score 7, and PSA 10-20 ng/mL
- 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
- Result will be used to determine treatment between definitive therapy and conservative management, and
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, and
- Patient is monitored for disease progression according to established standard of care.

Analysis of Evidence
(Rationale for Determination)

Level of Evidence

Quality – Moderate

Strength – Moderate

Weight –Moderate

This contractor recognizes that the evidence of clinical utility for the use of Prolaris for patients with favorable intermediate risk, needle biopsy proven prostate cancer that can be conservatively managed rather than treated with

definitive surgery or radiation therapy is promising at the current time. However, this contractor believes that the endpoints (see below) in the clinical registry currently in progress will generate sufficient data to demonstrate the utility of this test. Continued coverage for Prolaris testing for favorable intermediate risk patients is dependent on annual review of prospectively derived scientific data and peer-reviewed publications that demonstrate enhanced clinical utility for Prolaris testing. In this subgroup of patients.

Studies that demonstrate the following are currently underway by Myriad by demonstrating:

1. Favorable intermediate risk patients with low Prolaris scores who choose AS are not at high risk of definitive treatment during monitoring for disease progression.
    - Within this group of patients, the rate of definitive treatment intervention is expected to be <20%.
    - In the absence of a universally accepted timeframe for repeat biopsies within existing AS recommendations, men should be monitored for disease progression per NCCN guidelines v3.2016 "Principles of Active Surveillance", with the expectation of a repeat biopsy within 18 months of enrollment.
    - For each patient who pursues definitive treatment (after initially pursuing AS), the time on active surveillance and the reason for intervention will be collected, including:
        - Increase in tumor volume or Gleason score on subsequent biopsy
        - For patients who choose radical prostatectomy, the pathology report from the surgical specimen will be recorded
        - Imaging suggestive of disease progression (Response Evaluation Criteria in Solid Tumors; RECIST)
        - Patient choice in absence of the above

2. Among the group of patients described in 1) above, those who proceed to definitive treatment will not be at a >20% risk of disease progression, as defined by biochemical recurrence, metastases, or DSM.

3. Toward further demonstration of clinical utility, additional data collected will include
    - The rate of AS, and
    - Subsequent definitive treatment intervention, and
    - Disease progression among men with favorable intermediate risk prostate cancer who do NOT receive a Prolaris test.

This additional data is expected to firmly establish clinical utility by identifying men with intermediate risk prostate cancer with a low Prolaris score who can be comfortable with AS and avoid unnecessary procedures and/or interventions.

General Information

Associated Information

Note also active LCD L36350 MolDX-CDD: Prolaris™ Prostate Cancer Genomic Assay.

Sources of Information

N/A

Bibliography

1. Bishoff JT, Freedland SJ, Gerber L, et al. Prognostic utility of the CCP score generated from biopsy in men treated with prostatectomy. J Urol. 2014 Aug;192(2):409-14.

2. Cuzick J, Berney DM, Fisher G, et al. Transatlantic Prostate Group. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. Br J Cancer. 2012 Mar 13;106(6):1095-9.

3. Cuzick J, Stone S, Fisher G, et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. Br J Cancer. 2015 Jul;113(3):382-9.

4. Cuzick J, Swanson GP, Fisher G, et al. Transatlantic Prostate Group. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. Lancet Oncol. 2011 Mar;12(3):245-55.

5. Freedland SJ, Gerber L, Reid J, et al. Prognostic Utility of Cell Cycle Progression Score in Men With Prostate Cancer After Primary External Beam Radiation Therapy. Int J Radiat Oncol Biol Phys. 2013 Aug 1;86(5):848-53.

6. National Cancer Institute (U.S.), Surveillance and Epidemiology End Results (SEER), update Sept 12, 2016. https://seer.cancer.gov/statfacts/html/prost.html

7. NCCN Prostate Cancer Guideline Version 2.2017.

8. Resnick MJ et al. Long-Term Functional Outcomes after Treatment for Localized Prostate Cancer. N Engl J Med 2013;368:436-45.

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

10. Cooperberg MR, Carroll PR. Trends in Management for Patients With Localized Prostate Cancer, 1990-2013. JAMA. 2015 Jul 7;314(1):80-2. doi:10.1001/jama.2015.6036. PubMed PMID: 26151271.

11. Maurice MJ, Kim SP, Abouassaly R. Current Status of Prostate Cancer Diagnosis and Management in the United States. JAMA Oncol. 2016 Nov 1;2(11):1505-7. doi:10.1001/jamaoncol.2016.1785. PubMed PMID: 27356204.

12. Cuzick J, Stone S, Fisher G et al. Validation of an Active Surveillance Threshold for the CCP Score in Conservatively Managed Men with Localized Prostate Cancer. Presented at American Urological Association Annual Meeting, May 2015.

Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
12/01/2019	R3	The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.	• Other (The LCD is revised to remove CPT/HCPCS codes in

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		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.	the Keyword Section of the LCD.)
12/01/2019	R2	As required by CR 10901, all billing and coding information has been moved to the companion article, this article is linked to the LCD. 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	• Revisions Due To Code Removal
01/01/2018	R1	LCD is revised to replace 81479 with 81541 effective 1/1/2018.	• Creation of Uniform LCDs With Other MAC Jurisdiction

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)
A57691 - Billing and Coding: MolDX: Prolaris™ Prostate Cancer Genomic Assay for Men with Favorable Intermediate Risk Disease
A55669 - Response to Comments: MolDX: Prolaris™ Prostate Cancer Genomic Assay for Men with Favorable Intermediate Risk Disease
LCD(s)
DL37082
- (MCD Archive Site)

Related National Coverage Documents

N/A

Public Version(s)

Updated on 01/29/2020 with effective dates 12/01/2019 - N/A
Updated on 11/12/2019 with effective dates 12/01/2019 - N/A

Updated on 08/16/2018 with effective dates 01/01/2018 - 11/30/2019
Updated on 07/27/2017 with effective dates 09/25/2017 - N/A

Keywords

N/A