# Local Coverage Determination (LCD): MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease (L38292)

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# Contractor Information

| CONTRACTOR NAME | CONTRACT TYPE | CONTRACT NUMBER | JURISDICTION | STATE(S) |
|---|---|---|---|---|
| Palmetto GBA | A and B MAC | 10111 - MAC A | J - J | Alabama |
| Palmetto GBA | A and B MAC | 10112 - MAC B | J - J | Alabama |
| Palmetto GBA | A and B MAC | 10211 - MAC A | J - J | Georgia |
| Palmetto GBA | A and B MAC | 10212 - MAC B | J - J | Georgia |
| Palmetto GBA | A and B MAC | 10311 - MAC A | J - J | Tennessee |
| Palmetto GBA | A and B MAC | 10312 - MAC B | J - J | Tennessee |
| Palmetto GBA | A and B and HHH MAC | 11201 - MAC A | J - M | South Carolina |
| Palmetto GBA | A and B and HHH MAC | 11202 - MAC B | J - M | South Carolina |
| Palmetto GBA | A and B and HHH MAC | 11301 - MAC A | J - M | Virginia |
| Palmetto GBA | A and B and HHH MAC | 11302 - MAC B | J - M | Virginia |
| Palmetto GBA | A and B and HHH MAC | 11401 - MAC A | J - M | West Virginia |
| Palmetto GBA | A and B and HHH MAC | 11402 - MAC B | J - M | West Virginia |
| Palmetto GBA | A and B and HHH MAC | 11501 - MAC A | J - M | North Carolina |
| Palmetto GBA | A and B and HHH MAC | 11502 - MAC B | J - M | North Carolina |

# LCD Information

## Document Information

**LCD ID**
L38292

**LCD Title**
MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease

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N/A

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**AMA CPT / ADA CDT / AHA NUBC Copyright Statement**



## CMS National Coverage Policy

Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), states that no Medicare payment shall be made for items or services that are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

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

CMS Internet-Only Manual, Pub. 100-02, Medicare Benefit Policy Manual, Chapter 15, §§80, 80.1.1, 80.2 Clinical Laboratory services

## Coverage Guidance

**Coverage Indications, Limitations, and/or Medical Necessity**

This is a limited coverage policy for Genomic derived tests that assess risk in localized (non-metastatic) prostate cancer. The review is focused on the Decipher® Prostate Cancer Classifier Assay (identified as Decipher® to follow). The test is considered reasonable and necessary to help identify men with localized Prostate Cancer and a life expectancy of at least 10 years who are good candidates for active surveillance according to the most recent National Comprehensive Cancer Network (NCCN) guidelines.

Decipher® is covered for men with prostate cancer:

With localized or biochemically recurrent adenocarcinoma of the prostate (i.e., no clinical evidence of metastasis) who have a life expectancy of greater than or equal to 10 years if they are a candidate for and are considering (or being considered for) at least 1 of the following:

- Conservative management and yet would be eligible for definitive therapy (radical prostatectomy (RP), radiation or brachytherapy), or;
- Radiation therapy and yet would be eligible for the addition of a brachytherapy boost, or;
- Radiation therapy and yet would be eligible for the addition of short-term androgen deprivation therapy (ADT), or;
- Radiation therapy with short-term ADT yet would be eligible for the use of long-term ADT, or;
- Radiation with standard ADT yet would be eligible for systemic therapy intensification using next generation androgen signaling inhibitors or chemotherapy, or;
- Observation post-prostatectomy yet would be eligible for the addition of post-operative adjuvant radiotherapy, or;
- Salvage radiotherapy post-prostatectomy yet would be eligible for the addition of ADT.

The following criteria must also be met for coverage:

- The assay is performed on formalin-fixed paraffin embedded (FFPE) prostate biopsy tissue with at least 0.5 mm of linear tumor diameter or FFPE tissue from a prostate resection specimen, and;
- Result will be used to determine treatment according to established practice guidelines, and;
- Patient has not received pelvic radiation or ADT prior to the biopsy or prostate resection specimen, and;
- Patient is monitored for disease progression according to established standards of care.

Other genomic tests that demonstrate an equivalent analytical validity and clinical validity will be considered reasonable and necessary for the same indications. Analytical and clinical validity will be assessed as part of a thorough and comprehensive technical assessment (TA) by the MolDX program and will similarly attain coverage for indications that are supported by the evidence and intended use within the scope of this policy.

**Summary of Evidence**

**Background**

In 2017, over 160,000 men in the United States (U.S.) were diagnosed with prostate cancer, which accounted for 9.6% of all new cancer diagnoses.[1] Clinically localized prostate cancer accounts for ~80% of newly diagnosed cases.[1] The NCCN, classifies these men into risk groups based on clinical and pathological features, which are intended to be used in conjunction with life expectancy estimates to select optimal treatment approaches.[2] Prostate cancer is a heterogeneous disease, which to better risk stratify this patient cohort was the creation of favorable and unfavorable intermediate risk disease groups developed by Zumsteg and Spratt at Memorial Sloan Kettering, now adopted by NCCN guidelines.[3] Recommendations for the treatment of prostate cancer are made based on the risk category of the cancer and additional considerations as noted in Table 1 below.

The primary treatment decisions in localized prostate cancer that are guided by prognosis are the use of definitive therapy versus conservative management with active surveillance, the addition of ADT to radiotherapy, the addition of brachytherapy to external beam radiotherapy, the use of long versus short-term ADT with radiotherapy, and the incorporation of newer forms of more potent ADT such as abiraterone.[2] Similarly, the primary treatment decisions after a patient has undergone a RP include the addition of adjuvant radiotherapy and addition of ADT to post-operative salvage radiotherapy. These treatment recommendations are based on multiple trials, though these guidelines provide little guidance regarding how to select the optimal therapy including how best to personalize treatment intensification or de-escalation.

**Table 1: NCCN 2018 V4 - Localized Prostate Cancer Risk Stratification and Treatment**

| | **Risk Category** | | | | |
|---|---|---|---|---|---|
| | **Very Low** | **Low** | **Favorable Intermediate** | **Unfavorable Intermediate** | **High/V** |
| **Clinical/ pathologic features** | • T1c **AND**<br>• Gleason score ≤6/grade group 1 **AND**<br>• PSA <10 ng/mL **AND**<br>• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core **AND**<br>• PSA density <0.15 ng/mL/g | • T1-T2a **AND**<br>• Gleason score ≤6/grade group 1 **AND**<br>• PSA <10 ng/mL | • T2b-T2c **OR**<br>• Gleason score 3+4=7/grade group 2 **OR**<br>• PSA 10-20 ng/mL **AND**<br>• Percentage of positive biopsy cores <50% | • T2b-T2c **OR**<br>• Gleason score 3+4=7/grade group 2 or Gleason score 4+3=7/grade group 3 **OR**<br>• PSA 10-20 ng/mL | **High**<br>• T3a<br>• Glea 8/g 4 or scor 4+5 grou<br>• PSA ng/<br>**Very**<br>• T3b<br>• Prim Glea patt<br>• >4 Glea 8-1 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | grou |
| **Treatment Options** | | | | | |
| **≥20 y life expectancy** | • Active surveillance<br>• EBRT or brachytherapy<br>• RP ± PLND (if predicted probability of lymph node metastasis≥ 2%) | | | | |
| **≥10 y life expectancy** | • Active surveillance[a] | • Active surveillance<br>• EBRT or brachytherapy alone<br>• RP ± PLND (if predicted probability of lymph node metastasis≥ 2%) | • Active surveillance<br>• EBRT or brachytherapy alone<br>• RP ± PLND (if predicted probability of lymph node metastasis≥ 2%) | • RP ± PLND (if predicted probability of lymph node metastasis≥ 2%)<br>• EBRT +ADT (4-6 mo)<br>• EBRT +brachytherapy ± ADT (4-6 mo) | |
| **<10 y life expectancy** | • Observation | • Observation | • EBRT or brachytherapy<br>• Observation | • EBRT +brachytherapy ± ADT (4-6 mo)<br>• Observation | |
| **>5 y life expectancy** | | | | | • EBR (2-3<br>• EBR brac + A<br>• RP - |

[a]Active surveillance recommended for patients with 10-20 years life expectancy

PSA – Prostate Specific Antigen; EBRT – External Beam Radiation Therapy; RP – Radical Prostatectomy; PLND – Pelvic Lymph Node Dissection; ADT – Androgen Deprivation Therapy

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 Prostate Cancer Intervention Versus Observation (PIVOT) trial[4], men with early prostate cancer, initially randomized to RP 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 5,023 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 U.S.

Recent results from the Prostate Testing for Cancer and Treatment (ProtecT) trial of men with primarily low-risk prostate cancer randomized to active surveillance or intervention with local therapy also highlight risks for men deferring initial therapy. At a median of 10 years, death from prostate cancer was low irrespective of the treatment assigned. However, roughly 20% of men randomized to active surveillance experienced disease progression to an incurable state (including metastatic disease, locally advanced prostate cancer and need for long term chemical castration), a two-fold increase compared to men treated with local therapy.[5] In spite of the fact that a sizeable portion of men managed with active surveillance will experience disease progression to an incurable state, evidence also suggests that active surveillance is under used. Data from the U.S. National Cancer Data Base and the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) summarized prostate cancer diagnosis and

management in the U.S., 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.[6,7]

In summary, research shows refinement of the current risk stratification techniques, techniques based on clinical and pathologic variables, could potentially allow for a better assessment of a patient's risk of a poor outcome in the absence of treatment, thereby avoiding unnecessary treatment in men who are at a lower risk of disease progression to an incurable state. 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 refine risk stratification and may identify men who may safely pursue active surveillance and increase physician/patient confidence in that choice or pursue treatment intensification for those identified at elevated risk for disease progression. 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.

For men that progress beyond biochemically recurrent prostate cancer to non-metastatic castrate-resistant, there are multiple treatment options including standard ADT versus intensified next-generation ADT with enzalutamide or apalutamide with minimal guidance on who needs these expensive therapies. Finally for men with castration naïve metastatic prostate cancer, treatment options include observation, endocrine therapies, or orchiectomy.[2] While, consideration of the adverse effects associated with each of these therapies is a recommended consideration, there is limited data in existing guidelines to support a particular risk stratification approach based on clinical and pathological features. However, risk of metastatic progression or death from disease remain important considerations in decisions on treatment intensity.[2]

**Decipher® Prostate Cancer Classifier Assay**

**Test Description**

Decipher® Prostate is a 22 gene genomic classifier microarray assay, measuring the expression of over 1.4 million RNAs (from coding and non-coding genes). The assay is performed on FFPE prostate cancer tumor tissue from diagnostic biopsy needle cores or prostate resection tissue (Transurethral resection (TUR) or prostatectomy). The assay results are reported as a genomic classifier (GC) score based on gene expression using a machine-learning algorithm. The molecular pathways represented include proliferation/cell death, invasion & metastasis, androgen signaling, immune activity & response, growth & differentiation, angiogenesis and metabolism functions.

The test can be used to further risk stratify patients providing both a continuous score and a categorization of that score into low, average or high-risk with associated probabilities of high-grade disease, 5-year metastatic risk and 10-year prostate cancer specific mortality.

**Test Performance**

Several clinical studies of patients with NCCN very low, low, or intermediate risk prostate cancer who were potential candidates for active surveillance demonstrate:

- Decipher® is an independent and significant predictor of prostate cancer tumor aggressiveness. The assay was clinically validated as a biopsy-based predictor of adverse pathology at RP (high-grade disease, pT3b or higher, or lymph node invasion), metastasis, and prostate cancer-specific mortality.

- Decipher® outperforms clinical and pathological risk factors currently used in standard practice (including pre-treatment PSA, clinical stage, Gleason Score/grade group or nomograms) and assesses underlying biology from very small biopsy tumor volumes, while also addressing issues of biopsy under-sampling, to predict disease aggressiveness.
- In men with NCCN intermediate risk prostate cancer, Decipher® classified low-risk patients had a low rate of adverse pathology, similar to NCCN very low or low-risk. Decipher® high-risk patients, however, had a significantly higher rate of adverse pathology as compared to NCCN very low or low-risk.
- In addition, men with NCCN intermediate or high-risk prostate cancer and a Decipher® score of <0.45 have a low-risk of developing metastases and/or prostate cancer specific death at 10 years.
- Decipher® enables physicians to determine a) which patients with prostate cancer are candidates for active surveillance and are more likely to have a good outcome without immediate definitive treatment and b) which patients may receive the oncologic benefits of immediate or intensified treatment modalities.

**Clinical Validation for Adverse Pathology**

Three validation studies prospectively validated Decipher® as a significant predictor of adverse pathology at RP in men who were candidates for active surveillance. Patients with adverse pathology such as high-grade disease, pT3b or higher or lymph node invasion are at increased recurrence and metastasis risk, and not suitable for active surveillance candidates.

Kim, et al. (2018) examined the ability of Decipher® to predict adverse pathology in 266 men with NCCN very low, low and favorable intermediate risk patients.[8] Decipher® was an independent predictor of adverse pathology (OR, 1.29; 95% confidence interval [CI], 1.03-1.61; p=0.025) in multivariable analysis (MVA). Decipher® risk group was associated with adverse pathology rate; 10.5% in Decipher® low-risk men and 19.1% in Decipher® intermediate/high-risk men. The authors also showed that a Decipher® score below the threshold of 0.45 (upper-bound of the Decipher® low-risk) had a negative predictive value (NPV) of 91%, and a Decipher® score below the threshold of 0.2 had an NPV of 96%.

Klein, et al. (2016) clinically validated Decipher® as a significant predictor of adverse pathology at RP (OR, 1.52; 95% CI, 1.06–2.32; p=0.02) in a cohort (n=57) balanced for NCCN low-risk (40%), intermediate risk (47%) and high/unknown risk (13%) patients.[9] The study also showed that Decipher® has a c-index of 0.71 (95% CI, 0.56-0.86) for predicting adverse pathology at RP.

**Clinical Validation for Metastasis**

Several clinical validation studies demonstrated the high discrimination of Decipher® for predicting lymph node involvement or metastasis. Recently, a study led by investigators at the University of California San Francisco (Xu, et al. 2018) confirmed the ability of Decipher® to predict metastatic lymph node involvement in a cohort of 91 NCCN intermediate and high-risk disease patients. In MVA adjusting for clinical risk factors, the study showed that for every 10% increase in Decipher® score was associated with an approximate 33-35% increase in the odds of harboring lymph node involvement as assessed on subsequent $^{68}$Ga-Prostate Specific Membrane Antigen (PSMA)-11 PET scan.[10]

Berlin, et al. (2018) investigated Decipher® in an intermediate risk prostate cancer cohort (n=121) treated uniformly with 78 Gy image-guided intensity-modulated radiotherapy but without use of any neoadjuvant or adjuvant hormone therapy or brachytherapy boost. The cohort consisted primarily of NCCN favorable (27%) and unfavorable (72%) intermediate risk disease patients. Decipher® reclassified 72% of the cohort as low genomic risk. Berlin, et al. (2018) reported that Decipher® was a significant predictor of 5-year metastasis (HR, 2.05; 95% CI, 1.24-4.24;

p=0.004) in multivariable models adjusting for NCCN risk groups. Also, the authors demonstrated that Decipher® was significantly more accurate than existing NCCN clinical criteria to predict metastasis (Decipher® AUC 0.86 vs. NCCN AUC 0.54). Finally, the study showed a 0% 5-year cumulative incidence of metastasis in Decipher® low-risk men but 14.3% in Decipher® high-risk men.[11]

Spratt, et al. (2018) demonstrated how the combination of NCCN and Decipher® risk groups using a simple summation method to create a novel clinical-genomic risk system can dramatically improve risk stratification for clinically localized prostate cancer patients. In the biopsy cohort (n=235) consisting primarily of unfavorable intermediate (40%) and high (35%) risk patients, the clinical-genomic model had an AUC of 0.84 (95% CI, 0.61-0.93) compared to 0.74 (95% CI, 0.65-0.84) with CAPRA alone for prediction of metastasis at 10 years post definitive treatment. Compared with clinical-genomic low-risk group, the hazard ratio for metastasis was 21.3 (95% CI, 2.8-2728; p<0.001) and 62.5 (95% CI, 8.5-7970; p<0.001) for clinical-genomic intermediate and high-risk groups, respectively. In combination with NCCN, men with low clinical-genomic risk had 10-year cumulative incidence of metastasis of 0% compared to 25.9% and 55.2% for clinical-genomic intermediate and high-risk groups, respectively (p<0.001). Further in a subset analysis, men with both Decipher® low and NCCN low or favorable intermediate risk disease had 100% metastasis free survival at 10 years.[12]

Nguyen, et al. (2017a) studied the validity of Decipher® for predicting metastasis for men treated with definitive radiation (i.e., external beam radiation therapy and/or brachytherapy with neoadjuvant ADT). The cohort (n=100) consisted of NCCN intermediate (55%) and high (45%) risk group patients. In MVA, each 0.1 unit increase in Decipher® score was significantly associated with time to distant metastasis (HR, 1.37; 95% CI, 1.06-1.78, p=0.014). Decipher® had a c-index of 0.76 (95% CI, 0.57-0.89) for predicting metastasis at 5 years post definitive radiation, greater than NCCN risk groups and CAPRA clinical risk model alone. Finally, the authors performed a sensitivity analysis and found in survival analysis that for patients with a Decipher® score <0.2, there were no metastatic events at 10 years post definitive radiation and suggested that these men may be candidates for de-intensification of therapy. Furthermore, the study showed Decipher® classified 26% of NCCN intermediate and high-risk men to Decipher® high-risk with a resulting 19.5% 5-year cumulative incidence of metastasis compared to 6.3% for Decipher® low-risk patients. The authors concluded that the Decipher® high-risk men would be good candidates for more potent systemic therapies and further that a significant portion of men in this cohort perhaps were over treated with hormone therapy.[13]

In a follow-on study led by the Dana-Farber group, Nguyen, et al. (2017b) further demonstrated the ability of Decipher® to predict metastasis after definitive therapy. The cohort consisted primarily of 54% NCCN intermediate and 32% NCCN high-risk treated with either definitive surgery (n=105) or radiation (n=130). Decipher® reclassified 60% of these patients to low genomic risk, 18% as intermediate and 23% classified as high-risk. In MVA, Decipher® was a significant predictor of metastasis (HR, 1.39; 95% CI, 1.15-1.69; p=0.001) after adjusting for NCCN risk groups. The c-index for predicting 5-year metastasis was 0.74 (95% CI, 0.63-0.83) for Decipher®, which was substantially better than 0.60 (95% CI, 0.50-0.69) for the CAPRA clinical risk model and 0.66 (95% CI, 0.53-0.77) for NCCN risk groups. In this study, the Decipher® low-risk group had favorable outcomes with 5-year metastasis rate of only 4.1% compared to 21.0% in those with Decipher® high-risk.[14]

Klein, et al. (2016) found similar performance of Decipher® for predicting short and long-term oncological outcomes when measured in tumor tissue from diagnostic biopsy as compared to their original study in RP tissue. In MVA, Decipher® was shown to be a significant predictor of metastasis (HR, 1.66; 95% CI, 1.09-2.55; p=0.01) after adjusting for NCCN risk groups. Decipher® alone had an improved c-index for 10-year metastasis risk post RP of 0.80 (95% CI, 0.63-0.94) compared to NCCN model alone (c-index, 0.75; 95% CI, 0.64-0.87). The c-index for Decipher® plus NCCN model was much higher at 0.88 (95% CI, 0.77-0.96). Additionally, Decipher® was a significant predictor of 5-year metastasis post RP with c-index of 0.87 (95% CI, 0.76-0.97). Decipher® reclassified 48% of NCCN intermediate clinical risk men as low genomic risk and none of these patients developed metastasis on study follow-up.[9]

**Clinical Validation for Prostate Cancer-Specific Mortality**

Decipher® was also validated as a significant predictor of prostate cancer-specific mortality. Using univariable analysis, Nguyen, et al. (2017b) showed that Decipher® was a significant predictor of prostate cancer-specific mortality (HR, 1.57; 95% CI, 1.03–2.48; p=0.037). Decipher® risk group was associated with 10-year cumulative incidence of prostate cancer-specific mortality—0% in men with Decipher® low-risk vs. 9.4% in those with Decipher ® high-risk.[14]

| End Point | Description | Results | | | |
|---|---|---|---|---|---|
| | | MVA Effect Size (95% CI, p-value) | AUC (95% CI)[a] | | |
| | | Decipher®[b] | Clinical Risk[c] | Decipher® | Clinical Risk[c] + Decipher® |
| Adverse pathology[d] | Kim (2018) *Prostate Cancer Prostatic Disease* N=266 | OR 1.29 (1.03-1.61, p=0.025) | 0.57 (0.47-0.68) [CAPRA] | 0.65 (0.56-0.74) | 0.65 (0.58-0.70)[e] |
| | Klein (2016) *Urology* N=57 | OR 1.52 (1.06-2.32, p=0.02) | NR | 0.71 (0.56-0.86) | NR |
| Biochemical Failure | Berlin (2018) *Int J Radiat Oncol Biol Phys* N=121 | HR 1.36 (1.09-1.71, p=0.007) | 0.56 (0.43-0.66) [NCCN, 5yr] | 0.78 (0.59-0.91) [5yr] | 0.85 (0.73-1.00)[f] [5yr] |
| | Xu (2018) *Eur Urol Oncol*[h] | OR 1.33 (1.04-1.71, p=0.02) | NR | NR | NR |
| | Berlin (2018) *Int J Radiat Oncol Biol Phys* N=121 | HR 2.05 (1.24-4.24, p=0.004) | 0.54 (0.32-0.67) [NCCN, 5yr] | 0.86 (0.79-0.94) [5yr] | 0.89 (0.68-1.00) [5yr] |
| | Spratt (2018) *J Clin Onc* | HR 21.3 (2.8-2728, p<0.001) | 0.74 (0.65-0.84) | NR | 0.84 (0.61-0.93)[i] |

| | | | | | |
|---|---|---|---|---|---|
| Metastasis | N= 235 | 62.5<br>(8.5-7970, p<0.001)[j]<br>[CGRG Int, High ref: Low] | [CAPRA, 10yr] | | [10yr] |
| | Nguyen (2017)<br>*Prostate Cancer Prostatic Disease*<br>N=100 | HR 1.37<br>(1.06-1.78, p=0.014) | 0.63<br>(0.40-0.78)<br>[NCCN, 5yr] | 0.76<br>(0.57-0.89)<br>[5yr] | NR |
| | Nguyen (2017)<br>*Eur Urol*<br>N=235 | HR 1.39<br>(1.15-1.69, p=0.001) | 0.66<br>(0.53–0.77)<br>[NCCN, 5yr] | 0.74<br>(0.63- 0.83)<br>[5yr] | 0.74<br>(0.66-0.82)[f]<br>[5yr] |
| | Klein (2016)<br>*Urology*<br>N=57 | HR 1.66<br>(1.09-2.55, p=0.01) | 0.75<br>(0.64-0.87)<br>[NCCN, 10yr] | 0.80<br>(0.63-0.94)<br>[10yr] | 0.88<br>(0.77-0.96)<br>[10yr] |
| | Klein (2016)<br>*Urology*[j]<br>N=57 | OR 1.93<br>(1.10-3.91, p=0.02) | NR | 0.87<br>(0.76-0.97)<br>[5 yr] | NR |
| Prostate Cancer-Specific Mortality | Nguyen (2017)<br>*Eur Urol*<br>N=235 | HR 1.57<br>(1.03-2.48, p=0.037)[l] | NR | 0.73<br>(0.54-0.85)[g]<br>[10 yr] | NR |

*MVA = multivariable analysis; CI = confidence interval; HR = hazard ratio; OR = odds ratio; ref = reference group; NR = not reported; CGRG = Clinical Genomic Risk Groups.*

*a Time is specified in square bracket if time-dependent AUC is reported.*

*b Hazard ratios or odds ratios of Decipher® were reported per 10% increase in score.*

*c Clinical risk model (indicated in square bracket) selected was the best reported comparator (highest AUC).*

*d Klein (2016) Urology: primary Gleason pattern 4 or 5 (high grade disease); Kim (2018) Prostate Cancer Prostatic Disease: primary Gleason pattern 4 or 5, pT3b or higher, or LNI.*

*e The result reported is based on the OR of NCCN favorable intermediate and Decipher® high-risk group compared to NCCN very low/low.*

*f AUCs of MVA models were corrected for optimism.*

*g 10 year mortality prediction*.

*h The end point reported was lymph node involvement defined as PSMA-avid pelvic nodal involvement.*

*i The results reported are based on a clinical genomic point-based system that combines NCCN and Decipher® risk groups.*

*j The end point reported was metastasis within 5 years.*

**Guideline Review**

The NCCN Clinical Practice Guideline in Oncology for Prostate Cancer notes that molecular assays may be able to reduce the uncertainty about the risk of disease progression, but no tests have been studied with randomized controlled trials.

**Analysis of Evidence**
**(Rationale for Determination)**

Numerous prior Medicare coverage decisions have considered the evidence in the hierarchical framework of Fryback and Thornbury[15] where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. To apply this same hierarchical framework to analyze an in vitro diagnostic test, we utilized the ACCE Model Process for Evaluating Genetic Tests.[16] The practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes. When a proven, well established association or pathway is available, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

In the treatment of prostate cancer, a number of treatment approaches have shown potential benefits for survival, but also significant adverse events. Therefore, the risk of a patient having an unfavorable outcome due to prostate cancer within the patient's expected lifetime is at the core of the management of prostate cancer. Patients at a higher risk are recommended to have a greater intensity of treatment. For the treatment of localized prostate cancer there is a well-established risk stratification scheme based on clinical and pathological factors, though even within a single risk stratum there is significant variability, which Decipher® has shown the ability to further stratify. There are also numerous potential treatment options of varying levels of intensity with varying severities of side effects, so the potential benefit of treatment, which is heavily driven by risk stratum, must be weighed against the downsides of therapy. For patients with recurrent or metastatic disease there are also a number of effective treatment options of varying intensity, also associated with varying severities of adverse events. While there are no randomized controlled trials of outcomes using the Decipher® test, numerous studies from different institutions have all had similar and consistent findings, providing evidence that this test accurately risk stratifies patients based on genetic information and accurately predicts risk of biochemical recurrence, metastatic disease, or prostate-cancer specific mortality. Given that existing treatment paradigms are heavily reliant upon risk assessment, the ability to accurately risk

stratify has potential utility in the management of prostate cancer. As such, this test provides clinically actionable incremental information that fits into existing evidence-based or consensus-recommended prostate cancer treatment paradigms.

Since this test helps inform clinicians at a decision point regarding the need for treatment in the existing consensus treatment guidelines, the clinical utility of this test hinges on both the framework's treatment recommendations, and a certain level of decision uncertainty that accompanies treatment decisions within this framework. As such, this contractor will continue to monitor evidence and consensus recommendations regarding optimal selection of treatment intensity, and coverage may be re-evaluated following any substantial new evidentiary developments or guideline changes regarding the treatment of patients who are currently considered to have unfavorable intermediate risk prostate cancer. Such changes may include a new treatment paradigm or the development of a risk-stratification tool for which high quality, strength, and weight evidence shows improved outcomes and obviates the need for previously developed tests.

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# General Information

**Associated Information**

N/A

**Sources of Information**

N/A

**Bibliography**


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# Revision History Information

N/A

# Associated Documents

**Attachments**

N/A

**Related Local Coverage Documents**

Article(s)

A58343 - Billing and Coding: MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease

A58344 - Response to Comments: MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease LCD(s)
DL38292 - MolDX: Decipher® Biopsy Prostate Cancer Classifier Assay for Men with Favorable Intermediate Risk Disease

**Related National Coverage Documents**

N/A

**Public Version(s)**

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# Keywords

- Decipher
- Prostate Cancer