

# Local Coverage Determination (LCD): MolDX: Genomic Health™ Oncotype DX® Prostate Cancer Assay (L36364)

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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

**LCD ID**

L36364

**LCD Title**

MolDX: Genomic Health™ Oncotype DX® Prostate Cancer Assay

**Proposed LCD in Comment Period**

N/A

**Source Proposed LCD**

DL36364

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**Original Effective Date**

For services performed on or after 07/05/2016

**Revision Effective Date**

For services performed on or after 11/01/2019

**Revision Ending Date**

N/A

**Retirement Date**

N/A

**Notice Period Start Date**

05/19/2016

**Notice Period End Date**

07/04/2016

**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.

## Coverage Guidance

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

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

Noridian will provide limited coverage for the Oncotype DX<sup>®</sup> Prostate Cancer Assay (Genomic Health<sup>™</sup>) 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.

### Background

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).

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			
	Very Low	Low	Intermediate	High
Clinicopathologic Findings	<ul style="list-style-type: none"><li>• T1c <b>AND</b></li><li>• Gleason score ≤ 6 <b>AND</b></li><li>• PSA ≤ 10 ng/mL <b>AND</b></li><li>• &lt; 3 prostate cores with tumor <b>AND</b></li><li>• ≤ 50% tumor in</li></ul>	<ul style="list-style-type: none"><li>• T1-T2a <b>AND</b></li><li>• Gleason score ≤ 6/Gleason grade group 1 <b>AND</b></li><li>• PSA ≤ 10 ng/mL</li></ul>	<ul style="list-style-type: none"><li>• T2b-T2c <b>OR</b></li><li>• Gleason score 3+4=7/Gleason grade group 2 <b>OR</b></li><li>• Gleason score 4+3=7/Gleason grade group 3</li></ul>	



- any core **AND**
- PSA density of < 0.15 ng/mL/g
- OR**
- PSA 10-20 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 or Brachy ± Adj Horm

**< 10 y life expectancy**

- Observation
- Observation
- RT or Brachy ± Adj Horm
- Observation

**Table 1: NCCN 2018 V4 - 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) (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 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 = 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 participants to eligible study patients, and the high rate of crossover (both initially and subsequently) demonstrate 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  $\geq 10$  years as a category 1 recommendation.

## **Oncotype DX<sup>®</sup> Prostate Cancer Assay Prostate Cancer Assay**

### **Test Description**

Oncotype DX<sup>®</sup> Prostate Cancer Assay is prostate biopsy-based 17-gene RT-PCR assay, representing four molecular pathways (androgen signaling, cellular organization, stromal response and proliferation), that provides a biologic measure of cancer aggressiveness. The assay is indicated for men who are considered candidates for active surveillance (AS) (those with NCCN<sup>®</sup> very low- and low-risk prostate cancer). The assay is designed to inform decisions between AS and immediate treatment.

### **Test Performance**

The clinical performance of this assay was assessed in several validation studies. The first was a prospective-retrospective study conducted in a contemporary fit-for-purpose cohort of 395 prostate cancer patient with NCCN very low-, low- and intermediate-risk disease who were considered candidates for AS but who had opted to have radical prostatectomy at a university center from 1997-2011. The objectives were to validate the Genomic Prostate Score (GPS) as a predictor of adverse pathology (AP) at radical prostatectomy, a hallmark of aggressive disease, and to determine whether the GPS added independent predictive information beyond standard clinical and pathologic data. The assay was successfully performed in 96% of needle biopsy specimens. Ninety-nine point five percent (99.5%) of samples with  $\geq 10$  ng/ml RNA yielded a GPS result. Per the pre-specified primary analysis, the GPS was a significant predictor of AP ( $p=0.002$ ). While conventional clinical risk assessment tools stratified risk, the incorporation of the GPS identified the wide range of biologic risk within each conventional (NCCN and CAPRA) risk group. In multivariable analysis, the GPS was found to predict AP at radical prostatectomy (RP), even after accounting for several standard clinical risk factors (biopsy GS, clinical T-stage, baseline PSA and age). Further analyses showed that by incorporating the GPS results with previously defined clinical risk assessment tools (NCCN, CAPRA), more patient were identified with very low- and low-risk biologic potential and as appropriate candidates for AS. Together, the GPS and the NCCN risk group provide a more accurate prediction of AP.

For the second clinical validation study, a large cohort with a high proportion of African-American men (20%) in the Center for Prostate Disease Research (CPDR) multi-center longitudinal study was identified to test the association of GPS with tumor aggressiveness. Three endpoints for tumor aggressiveness were measured: AP at surgery (actionable); biochemical recurrence (BCR), longer-term; and metastasis (longer-term). This prospective-retrospective study included 402 men with NCCN very low-, low- and intermediate-risk prostate cancer treated with RP at two US military medical centers between 2007-2011. In pre-planned, univariate analyses, GPS was validated as a significant predictor of BCR (primary objective) and confirmed as a significant predictor of AP (first secondary objective) after adjustment for biopsy GS. In addition, while there were very few metastatic events in this low- to intermediate-risk population ( $n=5$  events), there was a strong association of GPS with metastatic recurrence. In multivariable analyses, GPS continued to be strongly associated with BCR and AP after adjustment for NCCN risk group, indicating that GPS adds value beyond standard clinico-pathologic features. A broad and overlapping range of GPS values was observed within each NCCN risk group, age quartile, and racial group. Importantly, GPS distribution, median values, and association of GPS with aggressive prostate cancer outcomes were similar between African-American and Caucasian men. The incorporation of GPS into risk assessment for AP improved the AUC from 0.63 (NCCN alone) to 0.72 (GPS and NCCN) within the subset with biopsy GS  $3+3$  and low-volume  $3+4$  disease, and the AUC for NCCN alone was 0.60 compared with 0.69 by adding GPS ( $p=0.001$ ). For BCR, the risk profile curve demonstrates a wide range of five-year risk of BCR as GPS increases.

The incorporation of GPS improved the c-statistic for NCCN from 0.59 (NCCN alone) to 0.68. The AUC with the use of NCCN risk stratification alone ranges between 0.09 and 0.13. The additional improvement in AUC when GPS is used together with NCCN is 0.09 in all of the above comparisons. Thus, when GPS is combined with NCCN, the AUC, or c-statistics, are improved by a comparable amount to the improvement observed with NCCN alone.

The potential usefulness of this test is that it allows physicians to determine which patients with early prostate cancer are candidates for active surveillance and are more likely to have a good outcome without needing to receive definitive treatment.

## Criteria for Coverage

The Oncotype DX<sup>®</sup> Prostate Cancer 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
  - Low Risk Disease (T1-T2a AND Gleason Score = 6 AND PSA = 10 ng/mL), Patient has an estimated life expectancy of  $\geq 10$  years, and
- Patient has a life expectancy of 10-20 years,
- 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 Genomic Health<sup>™</sup> Oncotype DX<sup>®</sup> Prostate Cancer Assay 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 Oncotype DX<sup>®</sup> Prostate Cancer 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 MolDX approved Genomic Health<sup>™</sup> Oncotype DX<sup>®</sup> Prostate Cancer Assay 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 Genomic Health<sup>™</sup> will provide to Palmetto GBA reports every 6 months in a mutually agreed upon format. The goals of the Genomic Health<sup>™</sup> Oncotype DX<sup>®</sup> Prostate Cancer Assay CTR program are as follows:

- To ensure that physicians understand the limitation of the test based on its validation , , and
- To inform prescribers and patients on the safe-use conditions for Oncotype DX<sup>®</sup> Prostate Cancer Assay<sup>™</sup>, and
- Make a good faith effort to identify any safety concerns from the use of the test, and
- Facilitate understanding of the incremental clinical utility of the test versus adherence to current NCCN guidelines.

Noridian expects Genomic Health<sup>™</sup> to:

- Establish and maintain the Oncotype DX<sup>®</sup> Prostate Cancer Assay Certification and Training Registry (CTR);
- Ensure that healthcare providers who order the Oncotype DX<sup>®</sup> Prostate Cancer Assay score are registered and certified in the Oncotype DX<sup>®</sup> Prostate Cancer Assay CTR program and that the Oncotype DX Prostate Cancer Assay is available only through these providers;
- Maintain a secure registry database of Genomic Health<sup>™</sup> Oncotype DX<sup>®</sup> Prostate Cancer Assay 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., GPS + NCCN risk group), and
    - Treatment recommendation based on test results, and
    - Physician-patient treatment decision, and
    - Report utilization data by clinico-pathologic staging;
    - Any subsequent change in patient or physician 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 complaint fashion.

## Summary of Evidence

N/A

## Analysis of Evidence (Rationale for Determination)

N/A

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# General Information

## Associated Information

### Documentation Requirements

The patient's medical record must contain documentation that fully supports the medical necessity for services included within this LCD. (See "Coverage Indications, Limitations, and/or Medical Necessity") This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures.

Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and

must be made available to the MAC upon request.

## Sources of Information

### References

1. Cullen J, Rosner IL, Brand TC, et al. A Biopsy-based 17-gene Genomic Prostate Score Predicts Recurrence After Radical Prostatectomy and Adverse Surgical Pathology in a Racially Diverse Population of Men with Clinically Low- and Intermediate-risk Prostate Cancer. *Eur Urol.* 2014. doi: 10.1016/j.eururo.2014.11.030.
2. Klein EA, Cooperberg MR, Magi-Galuzzi C, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur Urol.* 2014; 66:1: 550-60.
3. Knezevic D, Goddard AD, Natraj N, et al. Analytical validation of the Oncotype DX® prostate cancer assay a clinical RT-PCR assay optimized for prostate needle biopsies. *BMC Genomics.* 2013;14:690
4. National Cancer Institute (U.S.), Surveillance and Epidemiology End Results (SEER), 2010. <http://seer.cancer.gov/statfacts/html/>
5. NCCN Prostate Cancer Guideline 2018, V4
6. Resnick MJ et al. Long-Term Functional Outcomes after Treatment for Localized Prostate Cancer. *N Engl J Med* 2013;368:436-445.
7. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367:203-13

## Bibliography

N/A

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## Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
11/01/2019	R4	<p>The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.</p> <p>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"><li>• Other (The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD. )</li></ul>
11/01/2019	R3	CMS references are revised.	<ul style="list-style-type: none"><li>• Creation of Uniform LCDs With Other MAC</li></ul>

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.	Jurisdiction
11/01/2019	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.	<ul style="list-style-type: none"> <li>• Revisions Due To Code Removal</li> </ul>
07/01/2018	R1	<p>Replaced CPT/HCPCS Code 81479 with 0047U per the CPT/HCPCS Q3 Update, effective July 1, 2018.</p> <p>The procedure code 0047U will not go into the system until 10/1/18, though claims are retro-effective to 7/1/18. <b>Providers must use 81479 until 10/1/18.</b></p> <p>Removed CDD from title.</p> <p>(10/01/2018): 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"> <li>• Creation of Uniform LCDs With Other MAC Jurisdiction</li> <li>• Revisions Due To CPT/HCPCS Code Changes</li> </ul>

## Associated Documents

### Attachments

N/A

### Related Local Coverage Documents

Article(s)

A56371 - Billing and Coding: MoIDX: Genomic Health™ Oncotype DX® Prostate Cancer Assay

A55033 - Response to Comments: MoIDX-CDD: Genomic Health™ Oncotype DX® Prostate Cancer Assay

LCD(s)

DL36333

- (MCD Archive Site)DL36364

- (MCD Archive Site)

### Related National Coverage Documents

N/A

## Public Version(s)

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

Updated on 12/09/2019 with effective dates 11/01/2019 - N/A

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Updated on 05/02/2016 with effective dates 07/05/2016 - N/A

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## Keywords

- MolDX
- genomic
- oncotype
- prostate
- cancer
- assay