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

Medicare Advantage Medical Policy No.: MNG-027

The Health Plan reserves the right to amend this policy and procedure at any time. Exceptions to this policy and procedure will be made on a case-by-case basis at the total discretion of the Health Plan.

Effective Date: August 22, 2024

Instructions for use

This policy serves to provide guidance in determining coverage based on medical necessity. It also gives a list of resources used to create these guidelines. Medical necessity determinations will be made in accordance with generally accepted standards of medical practice, taking into account credible scientific evidence published in peer reviewed medical literature generally recognized by the relevant medical community, physician specialty society recommendations, and the views of the physicians practicing in relevant clinical areas, and other relevant factors, as they relate to the member's clinical circumstances.

Medicare Advantage Members

Coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria will be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of the coverage criteria and is to be used by all plans and lines of business unless Federal or State law, contract language, including member or provider contracts, take precedence over the policy.

Basic Requirements for Clinical Appropriateness:

1. Before diagnostic or therapeutic intervention, a clinician must confirm the diagnosis or establish the likelihood based on a history and physical exam and, when appropriate, a review of laboratory studies, previous diagnostic testing and response to any prior interventions, specifically relevant to the clinical situation.
2. An alternative treatment or other appropriate intervention should not offer any greater benefit based on standards of medical practice and/or current literature.
3. The potential benefit to the patient should outweigh the risk of the diagnostic or therapeutic intervention.
4. A reasonable likelihood of the intervention changing management and/or leading to an improved outcome for the patient must exist, based on the clinical evaluation, current literature and standards of medical practice.

If these requirements are not apparent in the request for authorization, including the clinical documentation provided, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

Simultaneous ordering of multiple diagnostic or therapeutic interventions and/or repeated diagnostic or therapeutic interventions in the same anatomic area may be denied, unless individual circumstances support the medical necessity of performing interventions simultaneously or repeatedly. This should be apparent in clinical documentation or in peer-to-peer conversations.

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When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider the Decipher® Prostate Cancer Classifier Assay (Decipher®) to be eligible for coverage 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.**

When Services are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan may consider Decipher® when the coverage criteria are not met and for all other indications to be investigational*.

Coverage Indications, Limitations, and/or Medical Necessity

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 Molecular Diagnostic Services Program (MolDX®) and will similarly attain coverage for indications that are supported by the evidence and intended use within the scope of this policy.

Background/Overview

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. Clinically localized prostate cancer accounts for ~80% of newly diagnosed cases. 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. 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.

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. 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.

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, 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 prostate specific antigen (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. 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.

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.

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.

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 al10 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 subsequent68 Ga-Prostate Specific Membrane Antigen (PSMA)-11 PET scan.10

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 al14 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

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 Thornbury15 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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Policy History

Chief Medical Officer Review: 08/22/2024

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Utilization Management Committee Review and Approval: 08/22/2024

Coding

The five-character codes included in this medical policy are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81541, 81542, 0047U
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

    1. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

    2. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient’s health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.