Genetic testing for prostate cancer prognosis

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Next review date: 3/2024

Policy contains: Decipher; inherited cancer syndromes; Oncotype; Prolaris; Promark; prostate cancer; risk assessment.

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Coverage policy

Germline genetic testing for prostate cancer is clinically proven and, therefore, medically necessary for members with any of the following clinical criteria and when the testing outcomes will impact care management (National Comprehensive Cancer Network, 2022):

- Very low risk, low risk, or intermediate risk prostate cancer (defined as clinical or pathological features T2c or lower, Grade Group 3 or lower [Gleason score 7 or lower], and prostate-specific antigen ≤ 20 ng/ml) and a positive family history defined as either:
  - Brother, father, or multiple family members who were diagnosed with prostate cancer (but not clinically localized Grade Group 1) at younger than age 60 years or who died from prostate cancer.
  - Three or more cancers on the same side of family, especially diagnoses at age 50 years or younger: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial cancer.
- High risk, very high risk, regional, or metastatic prostate cancer, regardless of family history:
  - High risk defined as T3a, Grade Group 4 or 5 (Gleason score 8-10), or prostate-specific antigen > 20 ng/ml.
  - Very high risk defined as T3b-T4, primary Gleason pattern 5, or > four cores Grade Group 4 or 5.
- Ashkenazi Jewish ancestry.
- Prostate cancers with cribiform architecture, ductal histology, or intraductal histology.
- Suspected germline findings on somatic tumor sequencing.
Somatic tumor testing is clinically proven and, therefore, medically necessary for risk stratification and prognosis to inform treatment choice in members with prostate cancer classified as low, intermediate, or high risk and with an estimated life expectancy at least 10 years, if the additional risk stratification information from genetic testing will affect treatment choice (National Comprehensive Cancer Network, 2022).

- Plasma circulating cell-free deoxyribonucleic acid concentration may be indicated for somatic tumor testing when a metastatic biopsy for molecular and histologic evaluation is not possible, preferably at the time of biochemical or radiographic progression in order to maximize yield.

Genetic testing recommendations (National Comprehensive Cancer Network, 2022):

- Germline testing should include the homologous recombination genes breast cancer 1 (BRCA1), breast cancer 2 (BRCA2), ATM, PALB2, and CHEK2 involved in the deoxyribonucleic acid repair pathway in members meeting any of the above clinical criteria. A cancer predisposition next-generation sequencing panel testing, at a minimum including BRCA2, BRCA1, ATM, CHEK2, homeobox B13, PALB2, MLH1, MSH2, MSH6, and PMS2, can be considered.
- Tumor testing for somatic homologous recombination gene mutations (e.g., BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, and CHEK2) in members with regional or metastatic prostate cancer.
- Tumor testing for deoxyribonucleic acid mismatched repair genes MLH1, MSH2, MSH6, and PMS2 in members with regional or metastatic prostate cancer.
- Multigene tumor testing assays:
  - Decipher® Prostate (GenomeDx Biosciences Inc., San Diego, California), Oncotype DX® Genomic Prostate Score (Genomic Health, Inc., Redwood City, California), Prolaris® (Myriad Genetic Laboratories, Inc., Salt Lake City, Utah), or ProMark® Proteomic Prognostic test (Metamark Genetics, Inc., Waltham, Massachusetts) for members with either low or favorable-intermediate risk prostate cancer and life expectancy at least 10 years.
  - Prolaris or Decipher for members with unfavorable intermediate- and high-risk disease and a life expectancy of at least 10 years.
  - Decipher as part of counseling for risk stratification for members with prostate-specific antigen resistance/recurrence after radical prostatectomy.
- Members with a personal history of prostate cancer and 1) intermediate-risk prostate cancer and intraductal/cribiform histology or 2) a personal history of exocrine pancreatic cancer, breast cancer, colorectal, gastric, melanoma, pancreatic cancer, upper tract urothelial cancer, glioblastoma, biliary tract cancer, and small intestinal cancer.

- Limitations

Genetic testing for a specific gene mutation is limited to once per lifetime.

Genetic testing for prostate cancer is not medically necessary for individuals who are not Plan members.

All other genetic testing for prostate cancer prognosis is not medically necessary, including but not limited to (National Comprehensive Cancer Network, 2022):

- Genetic screening in the general population.
- Members with no personal history of prostate cancer.
- Members younger than age 18 years.

Genetic counseling must be accompanied with a care-coordinating, multidisciplinary team available for genetic and behavioral counseling, which includes a primary care provider and a geneticist (who is a physician or a
licensed genetic counselor). If access to a genetic counselor or medical geneticist is not possible, genetic counseling may be initiated by a physician with relevant genetic expertise.

- Alternative covered services
- Standard diagnostic and radiographic tests for prostate cancer (e.g., prostate-specific antigen and radionuclide bone scan).
- Genetic counseling.

**Background**

Prostate cancer is the most common noncutaneous malignancy and the second-leading cancer cause of death in men (National Cancer Institute, 2022). Prostate cancer is usually slow-growing, and most cases will never become symptomatic during the patients’ lifetimes. Efforts at early detection with prostate-specific antigen or digital rectal exam and consequent earlier treatment have not resulted in improved health or longevity, and may be harmful. Factors that may increase the risk of prostate cancer include older age (> 50 years), a family history of prostate cancer, race (e.g., African American), hormones (dihydrotestosterone), and certain dietary factors (vitamin E, folic acid, dairy, and calcium).

Current strategies used to establish prostate cancer prognosis are tumor stage, Gleason grade, and prostate-specific antigen level to define risk groups. In 2014, the International Society of Urological Pathology (Epstein, 2016) revised the Gleason scoring system into five risk groups based on pathology, and the National Comprehensive Cancer Network (2022) has accepted this new system to better inform treatment decisions, yet heterogeneity within each group exists. Few long-term prognostic models are available to inform decision-making in these patients (Thurtle, 2019). Genetic testing may provide more individualized risk assessment information, particularly on tumor aggressiveness.

Prostate cancer is associated with several genes and more than 100 single nucleotide polymorphisms (National Cancer Institute, 2022). The *BRCA1* gene, *BRCA2* gene, deoxyribonucleic acid mismatch repair genes, and homeobox B13 confer modest to high lifetime risk of prostate cancer. Germline genetic risk markers are appealing as screening biomarkers for their accessibility at any age and their stability over time and in the setting of particular conditions. Men genetically predisposed to developing prostate cancer may benefit from targeted surveillance and targeted gene therapies.

Knowledge of inherited variants from tumor genetic testing may differentiate indolent disease that could be observed safely from aggressive disease that would require treatment. Biomarker testing of blood, urine, and prostate tissue-based molecular assays are commercially available for managing patients with localized prostate cancer (Lamy, 2018). Tumor-based molecular assays for prognosis encompass immunohistochemistry, fluorescence in situ hybridization, enzyme-linked immunosorbent assay, and sequencing methods. Examples of tumor molecular assays available for clinical use in the United States include (Lamy, 2018):

- **Decipher** – predicts the likelihood that the cancer will metastasize within 5 years.
- **Oncotype DX Genetic Prostate Score** – measures tumor aggressiveness and predicts the risk for metastasis and death at 10 years.
- **Prolaris** – measures tumor aggressiveness and predicts risk of recurrence, metastasis, and death.
- **ProMark** – measures tumor proteins to provide a personalized prediction that aids in decision to manage cancer with or without aggressive treatment.
Findings

Evaluating the clinical value of a test for screening or diagnosis is the subject of much methodological discussion. The rationale for genetic testing is to provide information that history, physical examination, and any previous testing is considered insufficient to address. The information should be useful to the clinician and to the patient in terms of improving diagnostic certainty, supporting efficacious treatment, and, ultimately, leading to a better clinical outcome.

Available reviews focus on pre-clinical (laboratory) or observational research, which is still in the process of identifying optimal genetic or molecular markers to identify those men receiving active surveillance who are likely to die from, rather than with, their cancers (Choudhury, 2012; Guo, 2013; Li, 2013; Little, 2012; Yao, 2014). In other words, risk assessment for prostate cancer remains at the hypothesis-generating level (cross-sectional associations of marker concentrations with tumor volume or other intermediate/surrogate endpoints) rather than hypothesis-testing level (trials or cohort studies following tested patients forward in time to assess outcomes). Research confirming that any currently available tests, or those under development, actually impact therapeutic decisions or health outcomes has yet to be published or addressed in systematic reviews.

In 2018, we added one meta-analysis (Cui, 2017), one systematic review (Hamilton, 2017), two evidence-based guidelines from the National Comprehensive Cancer Network on prostate cancer (2018) and genetic and familial high-risk assessment for breast and ovarian cancers (2019), and evidence-based and consensus recommendations from the 2017 Philadelphia Prostate Cancer Consensus Conference on genetic testing for inherited prostate cancer risk (Giri, 2018).

Increasing evidence supports an inherited predisposition of prostate cancer with implications for cancer risk assessment for men and their families and targeted treatment of metastatic disease (e.g., early use of platinum chemotherapy). Higher prostate cancer risk is associated with BRCA 1/2 mutations (linked to hereditary breast and ovarian cancer syndrome) and homeobox B13 mutations (linked to hereditary prostate cancer), and other gene mutations may be involved. Men with germline BRCA 1/2 mutations appear to have more aggressive prostate cancers (e.g., Gleason score ≥ 8), nodal involvement, and distant metastasis compared with noncarriers.

Early studies and guidelines focused on BRCA 1/2 testing, but other genes implicated in prostate cancer predisposition are now available for testing through multigene panels (Giri, 2018). Genetic testing should be analytically and clinically valid, directly impact disease management, and incorporate a tiered panel or targeted test sequence for minimal number of genes needed to establish the diagnosis. The genetic test should incorporate the genetic spectrum associated with personal and family history of prostate cancer and inherited cancer syndromes, as well as tumor sequencing results. Changes to the coverage policy reflect recommendations on the expanding clinical role of genetic testing in inherited prostate cancer as a complement to current risk assessment strategies (Giri, 2018; National Comprehensive Cancer Network, 2018, 2019). The policy ID was changed from CP# 13.01.01 to CCP.1121.

In 2019, the National Comprehensive Cancer Network (2019) modified the indications for genetic testing in prostate cancer and expanded the list of genes recommended for germline testing and somatic tumor testing in newly diagnosed men considering active surveillance and in treated men considering adjuvant therapy or treatment of recurrence:

- Germline testing should include the homologous recombination genes BRCA1, BRCA2, ATM, PALB2, and CHEK2 involved in the deoxyribonucleic acid repair pathway. A cancer predisposition next-generation sequencing panel testing, at a minimum including BRCA2, BRCA1, ATM, CHEK2, PALB2, MLH1, MSH2, MSH6, and PMS2, can be considered. Additional genes may be appropriate depending on the clinical context.
Tumor testing for somatic homologous recombination gene mutations (e.g., \textit{BRCA1}, \textit{BRCA2}, \textit{ATM}, \textit{PALB2}, \textit{FANCA}, \textit{RAD51D}, and \textit{CHEK2}) can be considered in patients with regional or metastatic prostate cancer.

Tumor testing for deoxyribonucleic acid mismatched repair genes \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, and \textit{PMS2} in patients with regional or metastatic prostate cancer who meet characteristics for Lynch syndrome.

Multigene molecular testing using Decipher, Oncotype DX Prostate, or Prolaris can be considered for patients with either low or favorable-intermediate risk prostate cancer, and life expectancy at least 10 years.

The Decipher molecular assay can be considered as part of counseling for risk stratification in patients with prostate-specific antigen resistance/recurrence after radical prostatectomy.

Expanding the list of recommended genes was based in part on the results of a cross-sectional cohort study of 3,607 unselected men with prostate cancer, which highlighted the limitations of using previous versions of National Comprehensive Cancer Network genetic/familial breast and ovarian guidelines and Gleason scores to stratify patients with prostate cancer (Nicolosi, 2019). They identified 674 positive variants in 620 (17.2%) participants, of whom 558 (90%) participants had corresponding family histories. The most frequently detected mutated genes were \textit{BRCA2}, followed by \textit{ATM}, \textit{CHEK2}, and \textit{BRCA1}, representing 11.5% of germline mutations. Approximately 57% of the positive variants detected (386 of 674 variants) were identified in genes not recommended for genetic testing in the previous guidelines, and 229 patients (37%) with the positive variants would not have been referred for genetic testing based on Gleason scores or family history.

A systematic review (Olleik, 2018) of 46 studies examined the clinical utility of current risk assessment tools supports the clinical utility of the three National Comprehensive Cancer Network-chosen molecular assays to aid in diagnosing prostate cancer and distinguishing indolent from aggressive disease (Oncotype DX, Decipher test, and Prolaris). At diagnosis after a positive biopsy, Decipher and Prolaris aided in the decision to add adjuvant therapy post-prostatectomy. We changed the policy testing criteria and added criteria for molecular testing assays to align with National Comprehensive Cancer Network recommendations.

In 2020, we updated the references, deleted the appendix, deleted the Medicare section, and modified coverage to align with changes in the National Comprehensive Cancer Network (2020) guideline, as follows:

- We separated recommendations for germline and tumor molecular testing. In general, genetic testing is recommended for risk categories in which the results will impact treatment decisions.
- We added the ProMark molecular testing assay to the list of tumor-based molecular testing assays for men with low or favorable intermediate risk disease and life expectancy at least 10 years.
- We added Prolaris to the list of tumor-based molecular assays for men with unfavorable intermediate and high-risk disease and a life expectancy of at least 10 years.
- For tumor testing for deoxyribonucleic acid mismatched repair genes \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, and \textit{PMS2}, we removed the requirement for meeting the characteristics of Lynch Syndrome in members with regional or metastatic prostate cancer.

In 2021, we added four systematic reviews to the policy. The systematic review findings from 42 studies (n = 30,407 patients) confirmed the clinical utility of the Decipher genomic classifier in identifying the aggressiveness of prostate cancer, particularly for men with intermediate-risk prostate cancer and post-prostatectomy decision-making (Jairath, 2021). Two systematic reviews examined the prognostic value of androgen receptor splicing variant 7 expression in prostate cancer, but differences in sample sizes and designs, testing assays, and disease characteristics across studies limited the findings (Li, 2021, n = 24 studies; Liu, 2021b, n = 21 studies).

The results of the fourth systematic review (Liu, 2021a, n = 23 studies) suggest plasma cell-free deoxyribonucleic acid concentration may have prognostic value in castration resistant prostate cancer, but confirmation in larger studies is needed. National Comprehensive Cancer Network (2021) guidance does recommend plasma cell-free
deoxyribonucleic acid concentration for somatic tumor testing when a metastatic biopsy for molecular and histologic evaluation is not possible, preferably at the time of biochemical or radiographic progression in order to maximize yield.

In addition, we removed two references, updated the reference list, and added the following indications for germline testing to coverage based on updated National Comprehensive Cancer Network (2021) guidance:

- Prostate cancers with cribiform architecture, ductal histology, or intraductal histology.
- Suspected germline findings on somatic tumor sequencing.

In 2022, we modified coverage from the latest version of the National Comprehensive Cancer Network guidelines (2022). We added a meta-analysis of 11 studies that compared mutation carrier rates for 11 genes in prostate cancer progressors (n = 3,944) and non-progressors (n = 20,054); the rate for progressors was significantly higher in 5 of 11 mutations (Shi, 2022). A review of 11 studies of hormone-sensitive prostate cancer patients (n = 1,682) found those with genomic alterations in AR, TP53, cell cycle signaling, and MYC were more likely to have a poorer clinical outcome (Van der Eecken, 2021).

References

On August 1, 2022, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “Prostate cancer, familial” [Supplementary Concept], “prostate cancer,” “risk stratification,” and “genetic tests.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.


Centers for Medicare & Medicaid Services. Local Coverage Determination L35869 MolDX: Prolaris™ Prostate Cancer Genomic Assay. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?lcdid=35869&ver=32&keyword=prostate%20prolaris&keywordType=all&areald=s11,s10,s12,s23,s25,s27,s37,s34,s45,s48&docType=NCD,MCD,F&contractOption=all&sortBy=relevance&bc=AAAAAAQAAAAA&KeyWordLookUp=Doc&KeyWordSearchType=And. Effective October 31, 2019


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**Policy updates**

7/2014: initial review date and clinical policy effective date: 1/2015

7/2015: Policy references updated.

7/2016: Policy references updated.

7/2017: Policy references updated.


