Genetic and Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer

Gene expression profile analysis and protein biomarkers have been proposed as a means to risk-stratify patients with prostate cancer to guide treatment decisions. These tests are intended to be used either on prostate needle biopsy tissue to guide management decisions regarding active surveillance versus therapeutic intervention, or after radical prostatectomy (RP) to guide radiotherapy use.

Prostate cancer is the second most common non-cutaneous cancer diagnosed among men in the United States. According to the National Cancer Institute (NCI) approximately 161,000 new cases are expected to be diagnosed in the United States in 2017 and more than 26,730 prostate cancer deaths will occur. Autopsy studies in the pre-PSA screening era have identified incidental cancerous foci in 30% of men 50 years of age, with incidence reaching 75% at age 80 years.

Grading
The most widely used grading scheme for prostate cancer is the Gleason system. It is an architectural grading system ranging from 1 (well differentiated) to 5 (poorly differentiated); the score is the sum of the primary and secondary patterns. A Gleason score of 6 is low-grade prostate cancer that usually grows slowly; 7 is an intermediate grade; 8 to 10 is high-grade cancer that grows more quickly. Ten-year survival rates stratified by Gleason score have been estimated from the Surveillance, Epidemiology, and End Results registry to be about 98% for scores 2 through 6, 92% for a score of 7 with primary pattern 3 and secondary pattern 4 (3+4), 77% for a score of 7 (4+3), and 70% for scores between 8 and 10. Numerous genetic alterations associated with development or progression of prostate cancer have been described, with the potential for the use of these molecular markers to improve the selection process of men who should undergo prostate biopsy or repeat biopsy after an initial negative biopsy.

Localized prostate cancers may appear very similar clinically at diagnosis. However, they often exhibit diverse risk of progression that may not be captured by accepted clinical risk categories (eg, D’Amico criteria) or prognostic tools that are based on clinical findings, including PSA titers, Gleason grade, or tumor stage. In studies of conservative management, the risk of localized disease progression based on prostate cancer specific survival rates at 10 years may range from 15% to 20% to perhaps 27% at 20-year follow-up. Among elderly men (>70 years) with low-risk disease, co-morbidities typically supervene as a cause of death; these men will die with prostate cancer present, rather than from the cancer. Other very similar-appearing low-risk tumors may progress unexpectedly rapidly, quickly disseminating and becoming incurable.

Risk Stratification in Newly Diagnosed Disease
In the United States, most prostate cancers are clinically localized at diagnosis due in part to the widespread use of PSA testing. Clinicopathologic characteristics are used to stratify patients by risk based on the extent of the primary tumor (T category), nearby lymph node involvement (N category), metastasis (M category), PSA level and Gleason score. The National Comprehensive Cancer Network
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and American Urological Association risk categories for clinically localized prostate cancer are similar, derived from the D’Amico criteria and broadly include low-, intermediate-, or high-risk as follows as well as subcategories within these groups:

- Low: T1-T2a and Gleason score ≤6 grade group 1 and PSA level ≤10 ng/mL;
- Intermediate: T2b-T2c or Gleason score 3+4=7/Gleason grade group 2 or Gleason score 4+3=7/Gleason grade group 3 or PSA level 10-20 ng/mL;
- High: T3a or Gleason score 8/Gleason grade group 4 or Gleason score 9-10/Gleason grade group 5 or PSA level >20 ng/mL.

Risk stratification is combined with patient age, life expectancy, and treatment preferences to make initial therapy decisions.

**Monitoring After Prostatectomy**

All normal prostate tissue and tumor tissue is theoretically removed during radical prostatectomy (RP), so the serum level of PSA should be undetectable following RP. Detectable PSA post-RP indicates residual prostate tissue and presumably persistent or recurrent disease. PSA is serially measured following RP to detect early disease recurrence. The National Comprehensive Cancer Network recommends monitoring serum PSA every 6 to 12 months for the first 5 years and annually thereafter. Many recurrences following RP can be successfully treated. The American Urological Association has recommended a biochemical recurrence be defined as a serum PSA of 0.2 ng/mL or higher, which is confirmed by a second determination with a PSA level of 0.2 ng/mL or higher.

Given the unpredictable behavior of early prostate cancer, additional prognostic methods to biologically stratify this disease are under investigation. These include microarray-based gene expression profiling, which refers to analysis of mRNA expression levels of many genes simultaneously in a tumor specimen, and protein biomarkers. Two microarray-based gene expression profiling tests and one protein biomarker test are now offered, intended to biologically stratify prostate cancers diagnosed on prostate needle biopsy: Prolaris® (Myriad Genetics, Salt Lake City, UT) and Oncotype Dx® Prostate Cancer Assay (Genomic Health, Redwood City, CA) are gene expression profiling tests which use archived tumor specimens as the mRNA source, reverse transcriptase polymerase chain reaction amplification, and the TaqMan low-density array platform (Applied Biosystems, Foster City, CA). Prolaris® is used to quantify expression levels of 31 cell cycle progression (CCP) genes and 15 housekeeper genes to generate a CCP score. Oncotype Dx® Prostate is used to quantify expression levels of 12 cancer-related and 5 reference genes to generate a Genomic Prostate Score (GPS). In the final analysis, the CCP score or GPS are combined in proprietary algorithms with clinical risk criteria (PSA, Gleason grade, tumor stage) to generate new risk categories (ie, reclassification) intended to reflect biological indolence or aggressiveness of individual lesions, and thus inform management decisions.

A protein biomarker test, Promark™ (Metamark Genetics, Cambridge, MA) is an automated quantitative imaging method to measure protein biomarkers by immunofluorescent staining in defined areas in intact formalin-fixed paraffin-embedded biopsy tissue, in order to provide independent prognostic information to aid in the stratification of patients with prostate cancer to active surveillance or therapy.

Decipher (GenomeDx Biosciences, Vancouver, BC, Canada) is a tissue-based tumor 22-biomarker gene expression profile test that is intended to guide the use of radiation after radical prostatectomy. The Decipher test classifies patients as low risk who can delay or defer radiation after prostatectomy, or high risk as those who would potentially benefit from early radiation. The gene expression classifier is a continuous risk score between 0 and 1, with high risk scores indicating greater probability of developing metastasis.
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**Regulatory Status**
In November 2015, the FDA’s Office of Public Health Strategy and Analysis published a document on public health evidence for FDA oversight of laboratory developed tests. The document argued that many tests need more FDA oversight than the regulatory requirements of CLIA. CLIA standards relate to laboratory operations, but do not address inaccuracies or unreliability of specific tests. Prolaris is among the 20 case studies in the document cited as needing FDA oversight. The document asserted that patients are potentially receiving inappropriate prostate cancer care because there is no evidence that results from the test meaningfully improved clinical outcomes.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Prolaris®, Oncotype Dx® Prostate and Decipher® gene expression profiling and the ProMark™ protein biomarker tests are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

**Policy**

Genetic tests for the screening, detection, and management of prostate cancer are considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

**Benefits Application**

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

**When Genetic and Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer are covered**

Not applicable

**When Gene and Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer are not covered**

Gene-based tests for screening, detection, and/or management of prostate cancer are considered investigational. These include, but are not limited to, the following:

- Single-nucleotide polymorphisms (SNPs) for risk assessment;
- PCA3 testing;
- TMPRSS fusion genes;
- Multiple gene tests (gene panels);
- Gene hypermethylation testing (eg, ConfirmMDx®);
- Kallikrein markers (eg, 4Kscore™ Test);
- Candidate gene panels;
- Mitochondrial DNA mutation testing (eg, Prostate Core Mitomics Test™);
- Prostate Health Index (phi)

Gene expression analysis to guide management of prostate cancer is considered investigational in all situations. These include, but are not limited to, the following:
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- Promark™
- Decipher ®
- Prolaris®
- Oncotype Dx® Prostate

Policy Guidelines

Gene expression profile analysis and protein biomarkers have been proposed as a means to risk-stratify patients with prostate cancer to guide treatment decisions. These tests are intended to be used either on prostate needle biopsy tissue to guide management decisions regarding active surveillance versus therapeutic intervention or post radical prostatectomy to guide radiation therapy use.

For individuals who are being considered for an initial prostate biopsy or a repeat biopsy who receive genetic and protein biomarker testing, the evidence includes systematic reviews and meta-analyses and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, other test performance measures, resource utilization, hospitalizations, quality of life, and treatment-related mortality and morbidity. The evidence supporting clinical utility varies by test but has not been directly shown for any biomarker test. In general, the performance of biomarker testing for predicting biopsy referrals compared with clinical examination, including the ratio of free or unbound prostate-specific antigen (PSA) to total PSA, is lacking. However, procedures for referrals for biopsy based on clinical examination vary, making it difficult to quantify performance characteristics for this comparator. There is considerable variability in biopsy referral practices based on clinical examination alone and many biomarker tests do not have standardized cutoffs to recommend biopsy. Therefore, having prospective, comparative information on how test results are expected to be used or actually being used in practice and the associated effects on outcomes will be needed to determine if the tests improve net health outcomes. Many of the test validation populations have included men with a positive digital rectal exam, prostate-specific antigen (PSA) level outside of the gray zone (between 3 or 4 ng/mL and 10 ng/mL), or older men for whom the information for test results are less likely to be informative. African Americans have a high burden of morbidity and mortality, but have not been well represented in these study populations. It is unclear how to monitor men with low biomarker risk scores who continue to have symptoms or high or rising PSA levels. Comparative studies of the many biomarkers are lacking and it is unclear how to use the tests in practice, particularly when test results are contradictory. The evidence is insufficient to determine the effects of the technology on health outcomes.

Initial Management Decision: Active Surveillance vs. Therapeutic Intervention

For individuals who have low-risk clinically localized untreated prostate cancer who receive Prolaris, Oncotype DX Prostate or ProMark protein biomarker test, the evidence includes studies of analytic validity and studies of clinical validity using archived samples from patients in mixed risk categories. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. The PROTECT trial showed 99% ten-year disease-specific survival in mostly low-risk patients receiving active surveillance. The low mortality rate estimated with tight precision make it unlikely that a test intended to identify a subgroup of low-risk men with a net benefit from immediate treatment instead of active surveillance would find such a group.

For individuals who have intermediate-risk clinically localized untreated prostate cancer who receive Prolaris, the evidence includes a study of analytic validity and retrospective cohort studies of clinical validity using archived samples in patients of mixed risk categories and a decision-curve analysis providing indirect evidence of clinical utility. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. Evidence of improved clinical validity or prognostic accuracy for prostate cancer death using Prolaris Cell Cycle Progression score in patients managed conservatively after needle biopsy shows some
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...improvement in areas under the receiver operator characteristic curve over clinic-pathologic risk stratification tools. All validation studies are Simon category C or D. There is limited indirect evidence for potential clinical utility. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have low-or intermediate-risk clinically localized untreated prostate cancer who receive Oncotype DX Prostate includes 2 studies of analytic validity, case-cohort and retrospective cohort studies of clinical validity using archived samples in patients of mixed risk categories, and a decision curve analysis from 1 study examining indirect evidence for clinical utility. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. Evidence for clinical validity and potential clinical utility of Oncotype Dx® Prostate in patients with clinically localized prostate cancer derives from a study predicting adverse pathology following radical prostatectomy. Although a relevant intermediate outcome, it is necessary to establish generalizability to an active surveillance population. All validation studies are Simon category C or D. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have low- or intermediate-risk clinically localized untreated prostate cancer who receive ProMark protein biomarker tests, the evidence includes a study of analytic validity, a retrospective cohort study using archived samples examining clinical validity, and no studies of clinical validity. Relevant outcomes include overall survival, disease-specific survival, test accuracy, and validity, quality of life and treatment-related morbidity. There is insufficient evidence to support improved outcomes with ProMark™ given that only a single clinical validity study was available. The evidence is insufficient to determine the effects of the technology on health outcomes.

Management Decision After Radical Prostatectomy
For individuals who have localized prostate cancer who are treated with radical prostatectomy who receive Prolaris, the evidence includes a study of analytic validity and retrospective cohort studies using archived samples examining clinical validity. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. Evidence of improved clinical validity or prognostic accuracy for prostate cancer death using Prolaris Cell Cycle Progression score in patients postprostatectomy shows some improvement in areas under the receiver operator characteristic curve over clinicopathologic risk stratification tools. All validation studies are Simon category C or D. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have localized prostate cancer who are treated with radical prostatectomy and who receive the Decipher prostate cancer classifier, the evidence includes a study of analytic validity, prospective and retrospective studies with overlapping patients using archived samples examining clinical validity, and decision curve analyses examining indirect evidence for clinical utility, and prospective decision impact studies without pathology or clinical outcomes. Relevant outcomes include overall survival, disease-specific survival, test accuracy, test validity, quality of life and treatment-related morbidity. The clinical validity of the Decipher® genomic classifier has been evaluated in samples of patients with high-risk prostate cancer undergoing different interventions following radical prostatectomy. Studies reported some incremental improvement in discrimination. However, it is unclear whether there is consistent improved reclassification—particularly to higher risk categories—or whether the test could be used to predict which men will benefit from radiotherapy. All validation studies are Simon category C/D. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative
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Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0005U, 0047U, 0053U, 81313, 81479, 81539, 81541, 81551, 81599, 84999

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**


Senior Medical Director - 2/2009


Medical Director – 8/2010


Medical Director – 4/2012


Senior Medical Director – 1/2014


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Medical Director review 10/2016

Specialty Matched Consultant Advisory Panel 8/2017


Specialty Matched Consultant Advisory Panel 8/2018

Policy Implementation/Update Information

For Policy Titled: “Gene Based Tests for Screening, Detection, and/or Management of Prostate Cancer”

4/13/09 Evidence based guideline adopted from the BCBS Association. Reviewed with the Senior Medical Director 3/16/2009. "The available evidence does not permit conclusions regarding the clinical utility of gene-based tests for the screening, detection, and management of prostate cancer, therefore this test is not recommended." (btw)

10/12/09 Specialty Matched Consultant Advisory Panel review 8/28/09. No changes to evidence based guideline. (btw)

6/22/10 Policy Guideline Number(s) removed (amw)

9/14/10 “Description” section rewritten. Added examples of tests under the “Not Recommended” section to include; single-nucleotide polymorphisms (SNPs) for risk assessment, PCA3 for disease diagnosis, TMPRSS fusion genes for diagnosis and prognosis, multiple gene tests (gene panels) for prostate cancer diagnosis, gene hypermethylation for
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diagnosis and prognosis”. Updated the rationale. Reviewed by Medical Director 8/10/2010. References added. (btw)

9/30/11 Evidence Based Guideline converted to Corporate Medical Policy. “Description” section updated. “Policy” statement added indicating “Genetic tests for the screening, detection, and management of prostate cancer are considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.” Specialty Matched Consultant Advisory Panel review 8/31/2011. References added. Notification given 9/30/2011 Policy effective 1/1/2012. (btw)

3/30/12 Added HCPCS code S3721 to the Billing/Coding section. (btw)

5/1/12 Revised “Description” section. Added “and prognosis” to the second bullet under the “When Not Covered” section. No change to policy intent. Policy Guidelines updated. Reference added. Medical Director review 4/18/2012. (btw)

9/4/12 Specialty Matched Consultant Advisory Panel review 8/15/2012. No change to policy intent. (btw)

5/14/13 Added the following to the description section; “There are a variety of gene-based biomarkers that have been associated with prostate cancer. These tests have the potential to improve the accuracy of risk prediction, diagnosis, staging, or prognosis of prostate cancer.” Reference added. (btw)

9/10/13 Specialty Matched Consultant Advisory Panel review 8/21/2013. No change to policy. (btw)

1/28/14 Added information regarding microarray-based gene expression analysis to the Description and Policy Guidelines sections. The statement; “Gene expression analysis to guide management of prostate cancer is considered investigational in all situations.” was added to the When Not Covered section. Added CPT code 81479, 81599 and 84999 to Billing/Coding section. Senior Medical Director review 1/13/2014. Reference added. (btw)

5/27/14 References updated. Description section updated. No changes to Policy Statements. (mco)

9/9/14 Specialty matched consultant advisory panel review 8/26/2014. No changes to policy statement. (lpr)

12/30/14 Added CPT code 81313 to the Billing/Coding section for effective date 1/1/2015. (lpr)

10/1/15 Reference added. Description section extensively revised. Policy Guidelines section updated. Under “When Not Covered” section added the following investigational tests: Kallikrein Markers (4k score), Metabolomic profiles(Prostarix), Candidate gene panels, Mitochondrial DNA mutation testing (Prostate Core Mitomics Test), Promark, and Decipher. Added CPT code 0010M to “Billing/Coding” section. Specialty Matched Consultant Advisory Panel review 8/26/2015. No change to policy statement. (lpr)

12/30/15 Extensive updates to Description and Policy Guidelines sections. Added investigational tests Prolaris® and Oncotype Dx® Prostate to the “When Not Covered” section. Reference added. Deleted HCPCS code S3721 from Billing/Coding section effective 1/1/2016. (lpr)

9/30/16 Updated Policy Guidelines section. References added. Specialty Matched Consultant Advisory Panel review 8/31/2016. No change to policy statement. (lpr)

For Policy Re-titled: “Genetic and Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer”
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11/22/16  Policy title revised. Under “When Not Covered” section: added Prostate Health Index (phi) test as investigational indication. Policy Guidelines and Description sections updated and revised. Added CPT 81539 to the Billing/Coding section. Medical Director review 10/2016. References added. (lpr)

3/31/17  Added CPT code 0005U to the Billing/Coding section for effective date 4/1/17. (lpr)

9/15/17  Specialty Matched Consultant Advisory Panel review 8/30/2017. No change to policy statement. (lpr)

10/13/17 Deleted CPT 0010M from the Billing/Coding section. (lpr)

12/29/17 Updated Description and Policy Guidelines sections. Removed Prostarix test from policy. Added CPT codes 81541, 81551 to the Billing/Coding section. References added. No change to policy statement. (lpr)

7/13/18  Added codes 0047U and 0053U to Billing/Coding section effective 7/1/18. (lpr)

9/28/18  Specialty Matched Consultant Advisory Panel review 8/2018. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.