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 cancer diagnosed among men with a predicted 181,000 incidence cases and 26,100 deaths in the United States in 2016. According to the National Cancer Institute (NCI), 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. However, between 1975 and 1991 prostate cancer mortality rose and subsequently dropped by 39% in 2007. The rise in mortality is unexplained but suggested to be due to how cause of death was assigned. A number of potential explanations have been suggested underlying the decline; treatment and screening, changes in assigning causes of death, and risk of cardiovascular death among men with prostate cancer treated with hormonal therapy.

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.

The divergent behavior of localized prostate cancers creates uncertainty whether or not to treat immediately. A patient may choose potentially curative treatment upfront. Surgery (RP) or external beam radiotherapy (EBRT) are most commonly used to treat patients with localized prostate cancer. Complications most commonly reported with RP or EBRT and with the greatest variability are incontinence (0%-73%) and other genitourinary toxicities (irritative and obstructive symptoms); hematuria (typically ≤5%); gastrointestinal and bowel toxicity, including nausea and loose stools (25%-50%); proctopathy, including rectal pain and bleeding (10%-39%); and erectile dysfunction, including impotence (50%-90%).

American Urological Association (AUA) Guidelines suggest patients with low- and intermediate-risk disease have the option of “active surveillance”, taking into account patient age, patient preferences, and health conditions related to urinary, sexual, and bowel function. With this approach the patient will forgo immediate therapy and continue regular monitoring until signs or symptoms of disease progression are evident, at which point curative treatment is instituted.
Genetic and Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer

In the Prostate Testing for Cancer and Treatment (ProtecT) trial, active surveillance, RP, and EBRT for the treatment of clinically localized prostate cancer were compared in 1643 men who were identified through PSA testing. At a median of 10-year follow-up, prostate cancer–specific mortality was low and similar in the 3 treatment groups: 1.5 (95% confidence interval [CI], 0.7 to 3.0) deaths per 1000 person-years in active surveillance, 0.9 (95% CI, 0.4 to 2.2) per 1000 person-years in the surgery group, and 0.7 (95% CI, 0.3 to 2.0) per 1000 person-years in the radiotherapy (RT) group. Surgery and RT were associated with lower incidences of disease progression and metastases compared to active surveillance.

For individuals for whom an initial prostate biopsy or a re-biopsy is being considered 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, performance of biomarker testing for predicting biopsy 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, 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.

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

After radical prostatectomy (RP), accurate risk stratification could identify those patients at high risk of prostate cancer specific mortality who would most likely benefit from additional therapy versus those patients who may be cured by surgery alone and could be spared the potential impact of additional treatment.

The optimal timing of Radiation Therapy (RT) after RP is a debate. Adjuvant RT may maximize cancer control outcomes, however, salvage RT can minimize overtreatment and still lead to acceptable oncologic outcomes. Several analyses have shown conflicting conclusions as to whether adjuvant RT is favored over salvage RT (with salvage RT typically being initiated at a post-RP PSA level of 0.3 to 0.6ng/mL).

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.

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.29 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
Genetic and Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer

**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);
- Metabolomic profiles (eg, Prostarix™);
- 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:

- 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.

Two gene expression profiling tests, Prolaris® and Oncotype Dx® Prostate, are intended to be used in combination with accepted clinical criteria (Gleason score, prostate-specific antigen [PSA], clinical stage) to stratify biopsy-diagnosed localized prostate cancer according to biological aggressiveness, and direct initial patient management. The Promark™ protein biomarker test uses immunofluorescence and automated quantitative images in intact biopsy tissue to risk stratify patients to active surveillance or therapeutic intervention.

For individuals for whom an initial prostate biopsy or a rebiopsy is being considered 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, performance of biomarker testing for predicting biopsy 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, 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.

For individuals who have clinically localized prostate cancer who receive Prolaris, the evidence includes 1 study of analytic validity and retrospective cohort studies using archived samples examining clinical validity and decision curve analysis providing 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 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 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 clinically localized prostate cancer who receive Oncotype DX Prostate includes 2 studies of analytic validity, case-cohort and retrospective cohort studies using archived samples examining clinical validity, 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 clinically localized prostate cancer who receive ProMark protein biomarker tests, the evidence includes 1 study of analytic validity, 1 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.

For individuals who have intermediate- or low-risk prostate cancer after radical prostatectomy who receive Prolaris, the evidence includes 1 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 high-risk prostate cancer after post-radical prostatectomy who receive the Decipher prostate cancer classifier, the evidence includes 1 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.
Genetic and Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer

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 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, 81313, 81479, 81539, 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

Senar Medical Director - 2/2009
Medical Director – 8/2010
Medical Director – 4/2012
Senior Medical Director – 1/2014
Genetic and Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer


Medical Director review 10/2016

Specialty Matched Consultant Advisory Panel 8/2017

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

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

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”

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)

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.