Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer is addressed separately in medical policy 00272.

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 Company considers gene expression analysis and protein biomarkers to guide management of prostate cancer in all situations to be **investigational.***

Background/Overview

Prostate Cancer

Prostate cancer is the second most common noncutaneous cancer diagnosed among men in the U. S. Autopsy studies in the era before the availability of prostate-specific antigen (PSA) screening have identified incidental cancerous foci in 30% of men 50 years of age, with incidence reaching 75% at age 80 years.

Localized prostate cancers may appear very similar clinically at diagnosis. However, they often exhibit diverse risk of progression that may not be captured by clinical risk categories (eg, D'Amico criteria) or prognostic tools 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 older men (ages ≥70 years) with low-risk disease, comorbidities typically supervene as a cause of death; these men will die with prostate cancer present, rather than from cancer itself. Other very similar appearing low-risk tumors may progress unexpectedly rapidly, quickly disseminating and becoming incurable.

Risk Stratification in Newly Diagnosed Disease
In the U. S., 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 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/Gleason 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 are 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 that biochemical recurrence be defined as a serum PSA of 0.2 ng/mL or higher, which is confirmed by the second determination with a PSA level of 0.2 ng/mL or higher.

Castration-Resistant Prostate Cancer
Androgen deprivation therapy (ADT) is generally the initial treatment for patients with advanced prostate cancer. ADT can produce tumor response and improve quality of life but most patients will eventually progress on ADT. Disease that progresses while the patient is on ADT is referred to as castration-resistant prostate cancer. After progression, continued ADT is generally used in conjunction with other treatments. Androgen pathways are important in the progression of castration-resistant prostate cancer. Several drugs have been developed that either inhibit enzymes

involved in androgen production or inhibit the androgen receptor, such as abiraterone and enzalutamide. Taxane chemotherapy with docetaxel or cabazitaxel may also be used after progression. Immunotherapy (sipuleucel-T) or radium 223 are options for select men.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Prolaris®‡ (Myriad Genetics), Oncotype DX®‡ Prostate and Oncotype DX AR-V7 Nuclear Detect (Genomic Health), Decipher gene expression profiling test (Decipher Corp), and the ProMark™‡ protein biomarker test (Metamark Genetics) are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In November 2015, the FDA's Office of Public Health Strategy and Analysis published a report suggesting FDA oversight of laboratory-developed tests. The FDA argued that many tests need more FDA oversight than the regulatory requirements of the CLIA. The 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 report asserted that patients are potentially receiving inappropriate prostate cancer care because there is no evidence that results from the test meaningfully improve clinical outcomes.

Rationale/Source

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 for active surveillance or therapeutic intervention, to guide radiotherapy use after radical prostatectomy (RP), or to guide medication selection after progression in metastatic castration-resistant prostate cancer.

Initial Management Decision: Active Surveillance vs Therapeutic Intervention

For individuals who have low- or intermediate-risk clinically localized untreated prostate cancer who receive Prolaris, the evidence includes retrospective cohort studies of clinical validity using

archived samples in patients of mixed risk categories. The relevant outcomes include overall survival (OS), disease-specific survival, quality of life (QOL), and treatment-related morbidity. For the low-risk group, the Prostate Testing for Cancer and Treatment trial showed 99% 10-year disease-specific survival in mostly low-risk patients receiving active surveillance. The low mortality rate estimated with tight precision makes 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 the intermediate-risk group, the evidence of improved clinical validity or prognostic accuracy for prostate cancer death using Prolaris Cell Cycle Progression score in patients managed conservatively after a needle biopsy has shown some improvement in areas under the receiver operating characteristic curve over clinicopathologic risk stratification tools. 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, the evidence includes case-cohort and retrospective cohort studies of clinical validity using archived samples in patients of mixed risk categories, and a decision-curve analysis examining indirect evidence of clinical utility. The relevant outcomes include OS, disease-specific survival, QOL, 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 after RP. The validity of using tumor pathology as a surrogate for the risk of progression and cancer-specific death is unclear. It is also unclear whether results from an RP population can be generalized to an active surveillance population. 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 Decipher Biopsy, the evidence includes retrospective cohort studies of clinical validity using archived samples in intermediate-risk patients and no studies of clinical utility. The relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. For intermediate-risk men, a test designed to identify men who can receive active surveillance instead of RP or RT would need to show very high negative predictive value for disease-specific mortality at ten years and improvement in prediction compared with existing tools used to select such men. Clinical validity studies of Decipher Biopsy reported prostate cancer metastases at five years but did

not report survival outcomes. 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 the ProMark protein biomarker test, the evidence includes a retrospective cohort study of clinical validity using archived samples and no studies of clinical utility. The relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. Current evidence does not support improved outcomes with ProMark given that only a single clinical validity study is 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 treated with RP who receive Prolaris, the evidence includes retrospective cohort studies of clinical validity using archived samples. The relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. Evidence of improved clinical validity or prognostic accuracy for prostate cancer death using the Prolaris Cell Cycle Progression score in patients after prostatectomy has shown some improvement in areas under the receiver operating characteristic curve over clinicopathologic risk stratification tools. 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 RP and who receive the Decipher RP prostate cancer classifier, the evidence includes a study of analytic validity, prospective and retrospective studies of clinical validity using overlapping archived samples, decision-curve analyses examining indirect evidence of clinical utility, and prospective decision-impact studies without pathology or clinical outcomes.

The relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. The clinical validity of the Decipher RP genomic classifier has been evaluated in samples of patients with high-risk prostate cancer undergoing different interventions following RP. Studies reported some incremental improvement in discrimination. However, it is unclear whether there is consistently improved reclassification-particularly to higher risk categories-or whether the test could be used to predict which men will benefit from radiotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Management Decision in Castration-Resistant Prostate Cancer
For individuals who have metastatic castration-resistant prostate cancer who receive the Oncotype DX AR-V7 Nuclear Detect, the evidence includes one prospective cohort study, one retrospective cohort study of clinical validity using archived samples, and no studies of clinical utility. The relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. Current evidence does not support improved outcomes with Oncotype DX AR-V7 Nuclear Detect, given that only two clinical validity studies meeting inclusion criteria were available. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

American Society of Clinical Oncology
In 2020, the American Society of Clinical Oncology (ASCO) published a guideline on molecular biomarkers in localized prostate cancer. The guidelines state, "Currently, there are no strong data or expert guidelines to support active surveillance in otherwise healthy men with Grade Group 3 or higher cancer; therefore, we would consider the use of genomic biomarkers only in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect a physician's recommendation or a patient's choice for surveillance versus treatment, but they should not be used routinely."

Specific recommendations included the following:
Molecular biomarkers to identify patients with prostate cancer who are most likely to benefit from active surveillance:

- Recommendation 1.1. Commercially available molecular biomarkers (i.e. Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
- Recommendation 1.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Molecular biomarkers to diagnose clinically significant prostate cancer:

- Recommendation 2.1. Commercially available molecular biomarkers (i.e. Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate).
- Recommendation 2.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Molecular biomarkers to guide the decision of post prostatectomy adjuvant versus salvage radiation:

- Recommendation 3.1. The Expert Panel recommends consideration of a commercially available molecular biomarker (eg, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
- Recommendation 3.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

American Urological Association et al

The American Urological Association, American Society for Radiation Oncology, and the Society of Urologic Oncology (2017, 2018) published joint guidelines on the management of clinically localized prostate cancer. The guidelines stated that among most low-risk localized prostate cancer patients, genomic biomarkers have not demonstrated a clear role in the selection of active surveillance or in the follow-up of patients on active surveillance.

The American Urological Association (2018) published guidelines for castration-resistant prostate cancer. The guidelines do not mention AR-V7 assays.

National Comprehensive Cancer Network
The National Comprehensive Cancer Network guidelines for prostate cancer (v.2.2020) provide a table of tissue-based tests for prostate cancer prognosis. The Network panel suggested that men with low or favorable intermediate clinically localized disease may consider Decipher, Oncotype DX Prostate, Prolaris, or ProMark during initial risk stratification and Decipher may be considered during workup for radical prostatectomy, although the panel warned that the utility of these assays has not been fully assessed in randomized controlled trials.

The panel also recommended that "the use of AR-V7 tests in circulating tumor cells can be considered to help guide selection of therapy in the post-abiraterone/enzalutamide metastatic castration-resistant prostate cancer setting."

National Institute for Health and Care Excellence
In 2019, the National Institute for Health and Care Excellence updated its guidance on the diagnosis and management of prostate cancer. The guidance did not address gene expression profile testing.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Prolaris			
NCT03152448[a]	Two-Part Prospective Study to Measure Impact of Prolaris Testing Added to Treatment Decision Following Biopsy in Newly Diagnosed Prostate Cancer Patients to Measure Prediction of Progression/Recurrence in Men Treated at VAMC	1509	Jan 2024
NCT03290508[a]	Long-Term Prospective Registry to Evaluate Treatment Decisions and Clinical Outcomes in Patients With Favorable Intermediate-Risk Localized Prostate Cancer Following Cell Cycle Progression (CCP) Testing (Prolaris Test)	6000	Sep 2027
NCT02668276[a]	The Impact of a Gene Expression Profile on Treatment Choice and Outcome Among Minority Men Newly Diagnosed With Prostate Cancer: A Randomized Trial	300	Aug 2022
Decipher			
NCT02609269	Decipher Genomics Resource Information Database (GIRD)	10,000	Dec 2020
NCT02723734	Validation Study on the Impact of Decipher Testing - VANDAAM Study	250	May 2022
NCT04396808	Genomics in Michigan to AdJust Outcomes in Prostate canceR (G-MAJOR): A Randomized Multi-center Study for Men With Newly Diagnosed Favorable Risk Prostate Cancer	900	Sep 2023
Unpublished			
Prolaris			
NCT03511235[a]	Clinical Outcomes in Men With Prostate Cancer Who Selected Active Surveillance Using Prolaris Testing	850	Aug 2018 (completed)

NCT No.	Trial Name	Planned Enrollment	Completion Date
			last update Oct 2020)
Oncotype DX			
NCT02668276[a]	The Impact of a Gene Expression Profile on Treatment Choice and Outcome Among Minority Men Newly Diagnosed With Prostate Cancer: A Randomized Trial	200	Aug 2019

NCT: national clinical trial; PTEN: phosphatase and tensin homolog.
[a] Denotes industry-sponsored or cosponsored trial.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management", 2.04.111, December 2020.
2. Dall'Era MA, Cooperberg MR, Chan JM, et al. Active surveillance for early-stage prostate cancer: review of the current literature. Cancer. Apr 15 2008; 112(8): 1650-9. PMID 18306379
3. Bangma CH, Roemeling S, Schroder FH. Overdiagnosis and overtreatment of early detected prostate cancer. World J Urol. Mar 2007; 25(1): 3-9. PMID 17364211
4. Johansson JE, Andren O, Andersson SO, et al. Natural history of early, localized prostate cancer. JAMA. Jun 09 2004; 291(22): 2713-9. PMID 15187052
5. Ploussard G, Epstein JI, Montironi R, et al. The contemporary concept of significant versus insignificant prostate cancer. Eur Urol. Aug 2011; 60(2): 291-303. PMID 21601982
6. Harnden P, Naylor B, Shelley MD, et al. The clinical management of patients with a small volume of prostatic cancer on biopsy: what are the risks of progression? A systematic review and meta-analysis. Cancer. Mar 01 2008; 112(5): 971-81. PMID 18186496
7. Brimo F, Montironi R, Egevad L, et al. Contemporary grading for prostate cancer: implications for patient care. Eur Urol. May 2013; 63(5): 892-901. PMID 23092544
8. Eylert MF, Persad R. Management of prostate cancer. Br J Hosp Med (Lond). Feb 2012; 73(2): 95-9. PMID 22504752
9. Eastham JA, Kattan MW, Fearn P, et al. Local progression among men with conservatively treated localized prostate cancer: results from the Transatlantic Prostate Group. Eur Urol. Feb 2008; 53(2): 347-54. PMID 17544572

10. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. May 12 2005; 352(19): 1977-84. PMID 15888698
11. Thompson IM, Goodman PJ, Tangen CM, et al. Long-term survival of participants in the prostate cancer prevention trial. N Engl J Med. Aug 15 2013; 369(7): 603-10. PMID 23944298
12. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA. May 04 2005; 293(17): 2095-101. PMID 15870412
13. National Comprehensive Cancer Network (NCCN). NCCN Clincal Practice Guidelines in Oncology: Prostate Cancer. Version 2.2020. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
14. American Urological Association (AUA). Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. 2017; http://www.auanet.org/guidelines/clinically-localized-prostate-cancer-new-(aua/astro/suo-guideline-2017).
15. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol. Aug 2013; 190(2): 441-9. PMID 23707439
16. Food and Drug Administration (FDA). The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies. 2015; http://www.nila-usa.org/images/nila/The%20Public%20Health%20Case%20for%20FDA%20Oversight%20of%20LDTs%20110915(2)_508ed%20(1).pdf.
17. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Gene Expression Analysis for Prostate Cancer Management. TEC Assessments. 2014;Volume 28:Tab 11.
18. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Gene Expression Profiling for Prostate Cancer Management. TEC Assessments. 2015;Volume 29:Tab 9.
19. Borley N, Feneley MR. Prostate cancer: diagnosis and staging. Asian J Androl. Jan 2009; 11(1): 74-80. PMID 19050692
20. Freedland SJ. Screening, risk assessment, and the approach to therapy in patients with prostate cancer. Cancer. Mar 15 2011; 117(6): 1123-35. PMID 20960523
21. Whitson JM, Carroll PR. Active surveillance for early-stage prostate cancer: defining the triggers for intervention. J Clin Oncol. Jun 10 2010; 28(17): 2807-9. PMID 20439633
22. Albertsen PC. Treatment of localized prostate cancer: when is active surveillance appropriate?. Nat Rev Clin Oncol. Jul 2010; 7(7): 394-400. PMID 20440282
23. Ip S, Dahabreh IJ, Chung M, et al. An evidence review of active surveillance in men with localized prostate cancer. Evid Rep Technol Assess (Full Rep). Dec 2011; (204): 1-341. PMID 23126653

24. Nam RK, Cheung P, Herschorn S, et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. Lancet Oncol. Feb 2014; 15(2): 223-31. PMID 24440474
25. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. Oct 13 2016; 375(15): 1415-1424. PMID 27626136
26. Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and Longer-Term Outcomes From a Prospective Active-Surveillance Program for Favorable-Risk Prostate Cancer. J Clin Oncol. Oct 20 2015; 33(30): 3379-85. PMID 26324359
27. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol. Jan 20 2015; 33(3): 272-7. PMID 25512465
28. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. Jul 19 2012; 367(3): 203-13. PMID 22808955
29. Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. N Engl J Med. Jul 13 2017; 377(2): 132-142. PMID 28700844
30. van den Bergh RC, Korfage IJ, Roobol MJ, et al. Sexual function with localized prostate cancer: active surveillance vs radical therapy. BJU Int. Oct 2012; 110(7): 1032-9. PMID 22260273
31. Johansson E, Steineck G, Holmberg L, et al. Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian Prostate Cancer Group-4 randomised trial. Lancet Oncol. Sep 2011; 12(9): 891-9. PMID 21821474
32. Wu CL, Schroeder BE, Ma XJ, et al. Development and validation of a 32-gene prognostic index for prostate cancer progression. Proc Natl Acad Sci U S A. Apr 09 2013; 110(15): 6121-6. PMID 23533275
33. Spans L, Clinckemalie L, Helsen C, et al. The genomic landscape of prostate cancer. Int J Mol Sci. May 24 2013; 14(6): 10822-51. PMID 23708091
34. Schoenborn JR, Nelson P, Fang M. Genomic profiling defines subtypes of prostate cancer with the potential for therapeutic stratification. Clin Cancer Res. Aug 01 2013; 19(15): 4058-66. PMID 23704282
35. Huang J, Wang JK, Sun Y. Molecular pathology of prostate cancer revealed by next-generation sequencing: opportunities for genome-based personalized therapy. Curr Opin Urol. May 2013; 23(3): 189-93. PMID 23385974
36. Yu YP, Song C, Tseng G, et al. Genome abnormalities precede prostate cancer and predict clinical relapse. Am J Pathol. Jun 2012; 180(6): 2240-8. PMID 22569189

37. Agell L, Hernandez S, Nonell L, et al. A 12-gene expression signature is associated with aggressive histological in prostate cancer: SEC14L1 and TCEB1 genes are potential markers of progression. Am J Pathol. Nov 2012; 181(5): 1585-94. PMID 23083832
38. Thompson I, Thrasher JB, Aus G, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. J Urol. Jun 2007; 177(6): 2106-31. PMID 17509297
39. Kattan MW, Eastham JA, Wheeler TM, et al. Counseling men with prostate cancer: a nomogram for predicting the presence of small, moderately differentiated, confined tumors. J Urol. Nov 2003; 170(5): 1792-7. PMID 14532778
40. Cooperberg MR, Freedland SJ, Pasta DJ, et al. Multiinstitutional validation of the UCSF cancer of the prostate risk assessment for prediction of recurrence after radical prostatectomy. Cancer. Nov 15 2006; 107(10): 2384-91. PMID 17039503
41. Chen RC, Chang P, Vetter RJ, et al. Recommended patient-reported core set of symptoms to measure in prostate cancer treatment trials. J Natl Cancer Inst. Jul 2014; 106(7). PMID 25006192
42. Cuzick J, Berney DM, Fisher G, et al. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. Br J Cancer. Mar 13 2012; 106(6): 1095-9. PMID 22361632
43. Cuzick J, Stone S, Fisher G, et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. Br J Cancer. Jul 28 2015; 113(3): 382-9. PMID 26103570
44. Lin DW, Crawford ED, Keane T, et al. Identification of men with low-risk biopsy-confirmed prostate cancer as candidates for active surveillance. Urol Oncol. Jun 2018; 36(6): 310.e7-310.e13. PMID 29655620
45. Montironi R, Mazzuccheli R, Scarpelli M, et al. Gleason grading of prostate cancer in needle biopsies or radical prostatectomy specimens: contemporary approach, current clinical significance and sources of pathology discrepancies. BJU Int. Jun 2005; 95(8): 1146-52. PMID 15877724
46. Sommariva S, Tarricone R, Lazzeri M, et al. Prognostic Value of the Cell Cycle Progression Score in Patients with Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol. Jan 2016; 69(1): 107-15. PMID 25481455
47. Crawford ED, Scholz MC, Kar AJ, et al. Cell cycle progression score and treatment decisions in prostate cancer: results from an ongoing registry. Curr Med Res Opin. Jun 2014; 30(6): 1025-31. PMID 24576172

48. Shore N, Concepcion R, Saltzstein D, et al. Clinical utility of a biopsy-based cell cycle gene expression assay in localized prostate cancer. Curr Med Res Opin. Apr 2014; 30(4): 547-53. PMID 24320750
49. Shore ND, Kella N, Moran B, et al. Impact of the Cell Cycle Progression Test on Physician and Patient Treatment Selection for Localized Prostate Cancer. J Urol. Mar 2016; 195(3): 612-8. PMID 26403586
50. Schaink A, Li C, Wells D, et al. Prolaris Cell Cycle Progression Test for Localized Prostate Cancer: A Health Technology Assessment. Ont Health Technol Assess Ser. 2017; 17(6): 1-75. PMID 28572867
51. Klein EA, Cooperberg MR, Magi-Galluzzi C, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur Urol. Sep 2014; 66(3): 550-60. PMID 24836057
52. Cullen J, Rosner IL, Brand TC, et al. A Biopsy-based 17-gene Genomic Prostate Score Predicts Recurrence After Radical Prostatectomy and Adverse Surgical Pathology in a Racially Diverse Population of Men with Clinically Low- and Intermediate-risk Prostate Cancer. Eur Urol. Jul 2015; 68(1): 123-31. PMID 25465337
53. Whalen MJ, Hackert V, Rothberg MB, et al. Prospective correlation between likelihood of favorable pathology on the 17-Gene Genomic Prostate Score and actual pathological outcomes at radical prostatectomy. Urol Pract. Sep 2016;3(5):379-386. https://www.sciencedirect.com/science/article/abs/pii/S2352077915002411.
54. Van Den Eeden SK, Lu R, Zhang N, et al. A Biopsy-based 17-gene Genomic Prostate Score as a Predictor of Metastases and Prostate Cancer Death in Surgically Treated Men with Clinically Localized Disease. Eur Urol. Jan 2018; 73(1): 129-138. PMID 28988753
55. Salmasi A, Said J, Shindel AW, et al. A 17-Gene Genomic Prostate Score Assay Provides Independent Information on Adverse Pathology in the Setting of Combined Multiparametric Magnetic Resonance Imaging Fusion Targeted and Systematic Prostate Biopsy. J Urol. Sep 2018; 200(3): 564-572. PMID 29524506
56. Cooperberg MR, Simko JP, Cowan JE, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. J Clin Oncol. Apr 10 2013; 31(11): 1428-34. PMID 23460710
57. McShane LM, Altman DG, Sauerbrei W, et al. Reporting recommendations for tumor marker prognostic studies. J Clin Oncol. Dec 20 2005; 23(36): 9067-72. PMID 16172462

58. Epstein JI, Allsbrook WC, Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol. Sep 2005; 29(9): 1228-42. PMID 16096414
59. Brand TC, Zhang N, Crager MR, et al. Patient-specific Meta-analysis of 2 Clinical Validation Studies to Predict Pathologic Outcomes in Prostate Cancer Using the 17-Gene Genomic Prostate Score. Urology. Mar 2016; 89: 69-75. PMID 26723180
60. Albala D, Kemeter MJ, Febbo PG, et al. Health Economic Impact and Prospective Clinical Utility of Oncotype DX(R) Genomic Prostate Score. Rev Urol. 2016; 18(3): 123-132. PMID 27833462
61. Eure G, Germany R, Given R, et al. Use of a 17-Gene Prognostic Assay in Contemporary Urologic Practice: Results of an Interim Analysis in an Observational Cohort. Urology. Sep 2017; 107: 67-75. PMID 28454985
62. Badani KK, Kemeter MJ, Febbo PG, et al. The impact of a biopsy based 17-Gene Genomic Prostate Score on treatment recommendations in men with newly diagnosed clinically prostate cancer who are candidates for active surveillance. Urol Pract. 2015;2(4):181-189. PMID not Indexed in Pubmed
63. Canfield SK, M.J.; Febbo, P.G.; Hornberger, J. Balancing confounding and generalizability using observational, real-world data: 17-gene genomic prostate score assay effect on active surveillance. Rev Urol. 2018;20(2):69-76.
64. Canfield S, Kemeter MJ, Hornberger J, et al. Active Surveillance Use Among a Low-risk Prostate Cancer Population in a Large US Payer System: 17-Gene Genomic Prostate Score Versus Other Risk Stratification Methods. Rev Urol. 2017; 19(4): 203-212. PMID 29472824
65. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making. Nov-Dec 2006; 26(6): 565-74. PMID 17099194
66. Cooperberg MR, Broering JM, Carroll PR. Risk assessment for prostate cancer metastasis and mortality at the time of diagnosis. J Natl Cancer Inst. Jun 16 2009; 101(12): 878-87. PMID 19509351
67. Berlin A, Murgic J, Hosni A, et al. Genomic Classifier for Guiding Treatment of Intermediate-Risk Prostate Cancers to Dose-Escalated Image Guided Radiation Therapy Without Hormone Therapy. Int J Radiat Oncol Biol Phys. Jan 01 2019; 103(1): 84-91. PMID 30170099
68. Nguyen PL, Shin H, Yousefi K, et al. Impact of a Genomic Classifier of Metastatic Risk on Postprostatectomy Treatment Recommendations by Radiation Oncologists and Urologists. Urology. Jul 2015; 86(1): 35-40. PMID 26142578

69. Blume-Jensen P, Berman DM, Rimm DL, et al. Development and clinical validation of an in situ biopsy-based multimarker assay for risk stratification in prostate cancer. Clin Cancer Res. Jun 01 2015; 21(11): 2591-600. PMID 25733599
70. Fossati N, Karnes RJ, Boorjian SA, et al. Long-term Impact of Adjuvant Versus Early Salvage Radiation Therapy in pT3N0 Prostate Cancer Patients Treated with Radical Prostatectomy: Results from a Multi-institutional Series. Eur Urol. Jun 2017; 71(6): 886-893. PMID 27484843
71. Hwang WL, Tendulkar RD, Niemierko A, et al. Comparison Between Adjuvant and Early-Salvage Postprostatectomy Radiotherapy for Prostate Cancer With Adverse Pathological Features. JAMA Oncol. May 10 2018; 4(5): e175230. PMID 29372236
72. Buscariollo DL, Drumm M, Niemierko A, et al. Long-term results of adjuvant versus early salvage postprostatectomy radiation: A large single-institutional experience. Pract Radiat Oncol. Mar 2017; 7(2): e125-e133. PMID 28274403
73. Freedland SJ, Rumble RB, Finelli A, et al. Adjuvant and salvage radiotherapy after prostatectomy: American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol. Dec 01 2014; 32(34): 3892-8. PMID 25366677
74. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol. May 20 2007; 25(15): 2035-41. PMID 17513807
75. Stephenson AJ, Scardino PT, Eastham JA, et al. Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Clin Oncol. Oct 01 2005; 23(28): 7005-12. PMID 16192588
76. Cooperberg MR, Hilton JF, Carroll PR. The CAPRA-S score: A straightforward tool for improved prediction of outcomes after radical prostatectomy. Cancer. Nov 15 2011; 117(22): 5039-46. PMID 21647869
77. Cuzick J, Swanson GP, Fisher G, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. Lancet Oncol. Mar 2011; 12(3): 245-55. PMID 21310658
78. Bishoff JT, Freedland SJ, Gerber L, et al. Prognostic utility of the cell cycle progression score generated from biopsy in men treated with prostatectomy. J Urol. Aug 2014; 192(2): 409-14. PMID 24508632
79. Koch MO, Cho JS, Kaimakliotis HZ, et al. Use of the cell cycle progression (CCP) score for predicting systemic disease and response to radiation of biochemical recurrence. Cancer Biomark. Jun 07 2016; 17(1): 83-8. PMID 27314296

80. Freedland SJ, Gerber L, Reid J, et al. Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. Int J Radiat Oncol Biol Phys. Aug 01 2013; 86(5): 848-53. PMID 23755923
81. Klein EA, Yousefi K, Haddad Z, et al. A genomic classifier improves prediction of metastatic disease within 5 years after surgery in node-negative high-risk prostate cancer patients managed by radical prostatectomy without adjuvant therapy. Eur Urol. Apr 2015; 67(4): 778-86. PMID 25466945
82. Den RB, Yousefi K, Trabulsi EJ, et al. Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. J Clin Oncol. Mar 10 2015; 33(8): 944-51. PMID 25667284
83. Den RB, Feng FY, Showalter TN, et al. Genomic prostate cancer classifier predicts biochemical failure and metastases in patients after postoperative radiation therapy. Int J Radiat Oncol Biol Phys. Aug 01 2014; 89(5): 1038-1046. PMID 25035207
84. Cooperberg MR, Davicioni E, Crisan A, et al. Combined value of validated clinical and genomic risk stratification tools for predicting prostate cancer mortality in a high-risk prostatectomy cohort. Eur Urol. Feb 2015; 67(2): 326-33. PMID 24998118
85. Ross AE, Feng FY, Ghadessi M, et al. A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy. Prostate Cancer Prostatic Dis. Mar 2014; 17(1): 64-9. PMID 24145624
86. Karnes RJ, Bergstralh EJ, Davicioni E, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. J Urol. Dec 2013; 190(6): 2047-53. PMID 23770138
87. Erho N, Crisan A, Vergara IA, et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. PLoS One. 2013; 8(6): e66855. PMID 23826159
88. Ross AE, Johnson MH, Yousefi K, et al. Tissue-based Genomics Augments Post-prostatectomy Risk Stratification in a Natural History Cohort of Intermediate- and High-Risk Men. Eur Urol. Jan 2016; 69(1): 157-65. PMID 26058959
89. Freedland SJ, Choeurng V, Howard L, et al. Utilization of a Genomic Classifier for Prediction of Metastasis Following Salvage Radiation Therapy after Radical Prostatectomy. Eur Urol. Oct 2016; 70(4): 588-596. PMID 26806658
90. Glass AG, Leo MC, Haddad Z, et al. Validation of a Genomic Classifier for Predicting Post-Prostatectomy Recurrence in a Community Based Health Care Setting. J Urol. Jun 2016; 195(6): 1748-53. PMID 26626216

91. Klein EA, Haddad Z, Yousefi K, et al. Decipher Genomic Classifier Measured on Prostate Biopsy Predicts Metastasis Risk. Urology. Apr 2016; 90: 148-52. PMID 26809071
92. Spratt DE, Dai DLY, Den RB, et al. Performance of a Prostate Cancer Genomic Classifier in Predicting Metastasis in Men with Prostate-specific Antigen Persistence Postprostatectomy. Eur Urol. Jul 2018; 74(1): 107-114. PMID 29233664
93. Karnes RJ, Choeurng V, Ross AE, et al. Validation of a Genomic Risk Classifier to Predict Prostate Cancer-specific Mortality in Men with Adverse Pathologic Features. Eur Urol. Feb 2018; 73(2): 168-175. PMID 28400167
94. Ross AE, Den RB, Yousefi K, et al. Efficacy of post-operative radiation in a prostatectomy cohort adjusted for clinical and genomic risk. Prostate Cancer Prostatic Dis. Sep 2016; 19(3): 277-82. PMID 27136742
95. Spratt DE, Yousefi K, Deheshi S, et al. Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease. J Clin Oncol. Jun 20 2017; 35(18): 1991-1998. PMID 28358655
96. Lobo JM, Dicker AP, Buerki C, et al. Evaluating the clinical impact of a genomic classifier in prostate cancer using individualized decision analysis. PLoS One. 2015; 10(3): e0116866. PMID 25837660
97. West TA, Kiely BE, Stockler MR. Estimating scenarios for survival time in men starting systemic therapies for castration-resistant prostate cancer: a systematic review of randomised trials. Eur J Cancer. Jul 2014; 50(11): 1916-24. PMID 24825113
98. Scher HI, Graf RP, Schreiber NA, et al. Nuclear-specific AR-V7 Protein Localization is Necessary to Guide Treatment Selection in Metastatic Castration-resistant Prostate Cancer. Eur Urol. Jun 2017; 71(6): 874-882. PMID 27979426
99. Armstrong AJ, Halabi S, Luo J, et al. Prospective Multicenter Validation of Androgen Receptor Splice Variant 7 and Hormone Therapy Resistance in High-Risk Castration-Resistant Prostate Cancer: The PROPHECY Study. J Clin Oncol. May 01 2019; 37(13): 1120-1129. PMID 30865549
100. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. J Urol. Mar 2018; 199(3): 683-690. PMID 29203269
101. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part II: Recommended Approaches and Details of Specific Care Options. J Urol. Apr 2018; 199(4): 990-997. PMID 29331546

102. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med. Sep 11 2014; 371(11): 1028-38. PMID 25184630
103. Scher HI, Lu D, Schreiber NA, et al. Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer. JAMA Oncol. Nov 01 2016; 2(11): 1441-1449. PMID 27262168
104. Scher HI, Graf RP, Schreiber NA, et al. Assessment of the Validity of Nuclear-Localized Androgen Receptor Splice Variant 7 in Circulating Tumor Cells as a Predictive Biomarker for Castration-Resistant Prostate Cancer. JAMA Oncol. Sep 01 2018; 4(9): 1179-1186. PMID 29955787
105. Eggener SE, Rumble RB, Armstrong AJ, et al. Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline. J Clin Oncol. May 01 2020; 38(13): 1474-1494. PMID 31829902
106. Lowrance WT, Murad MH, Oh WK, et al. Castration-Resistant Prostate Cancer: AUA Guideline Amendment 2018. J Urol. Dec 2018; 200(6): 1264-1272. PMID 30086276
107. National Institute for Health and Care Excellence (NICE). Prostate cancer: diagnosis and management [NG131]. 2019; https://www.nice.org.uk/guidance/ng131.

Policy History

Original Effective Date: 02/19/2014
Current Effective Date: 07/12/2021

02/06/2014	Medical Policy Committee review
02/19/2014	Medical Policy Implementation Committee approval. New policy.
06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Implementation Committee approval. Policy statement unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Promark and Decipher tests added to the policy. Policy statement updated by adding "protein biomarkers". Title change.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Extensive updates to rationale and references.

08/01/2017	Coding update
06/07/2018	Medical Policy Committee review
06/20/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/01/2018	Coding update
08/07/2018	Coding update
06/06/2019	Medical Policy Committee review
06/19/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/11/2019	Coding update
06/04/2020	Medical Policy Committee review
06/10/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/08/2020	Coding update
03/24/2021	Coding update
06/03/2021	Medical Policy Committee review
06/09/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 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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CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	0047U, 81479, 81541, 81542, 81599, 84999
HCPCS	No codes
ICD-10 Diagnosis	C61

*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. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA 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 Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.