MEDICAL POLICY

POLICY TITLE	GENE EXPRESSION PROFILING AND PROTEIN BIOMARKERS FOR PROSTATE CANCER MANAGEMENT
POLICY NUMBER	MP-2.263

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I. POLICY

Use of gene expression analysis and protein biomarkers to guide management of prostate cancer are considered **investigational** in all situations. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-reference:

MP-2.280 Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

II. PRODUCT VARIATIONS

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This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO - Refer to FEP Medical Policy Manual MP-2.04.111, Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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PROSTATE CANCER

Prostate cancer is the second most common noncutaneous cancer diagnosed among men in the United States. 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.[1]

Localized prostate cancers may appear very similar clinically at diagnosis.[3] However, they often exhibit diverse risk of progression that may not be captured by clinical risk categories (e.g., D'Amico criteria) or prognostic tools based on clinical findings, including PSA titers, Gleason grade, or tumor stage.[4-8] 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%[9,10] to 20%[11] to perhaps 27% at 20-year follow-up.[12] 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 the 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 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 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[13,14]:

- 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.[13] 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.[15]

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.

REGULATORY STATUS
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 (GenomeDx Biosciences), and the ProMark™ protein biomarker test (Metamark Genetics) are available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by 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.[15] FDA 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 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.

IV. RATIONALE

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SUMMARY OF EVIDENCE

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 studies includes retrospective cohort studies of clinical validity using archived samples in patients of mixed risk categories. Relevant outcomes include overall survival, disease-specific survival, quality of life, and treatment-related

morbidity. For the low-risk group, 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 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 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. Relevant outcomes include overall survival, disease-specific survival, 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 after RP. The validity of using tumor pathology as a surrogate for 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 the ProMark protein biomarker test, the evidence includes a retrospective cohort study of clinical validity using archived samples and no studies of clinical utility. Relevant outcomes include overall survival, disease-specific survival, quality of life, 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. Relevant outcomes include overall survival, disease-specific survival, quality of life, 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 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. Relevant outcomes include overall survival, disease-specific survival, 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 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 a retrospective cohort study of clinical validity using archived samples, and no studies of clinical utility. Relevant outcomes include overall survival, disease-specific survival, quality of life, and treatment-related morbidity. Current evidence does not support improved outcomes with Oncotype DX AR-V7 Nuclear Detect, given that only a single clinical validity study, meeting inclusion criteria was available. The evidence is insufficient to determine the effects of the technology on health outcomes.

V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition

with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered for Prolaris:

CPT Codes®								
81541								

Investigational; therefore, not covered for gene expression profiling and protein biomarkers for prostate cancer management*:

CPT Codes®								
81479	81599	0047U						

**There is no specific CPT code(s) for this testing, other than Prolaris. If the test uses an algorithm for analysis of the results of testing for multiple genes and the results are reported as a type of score, CPT code 81599 may be reported. If no algorithm is performed and the results are not reported as a score, CPT code 81479 may be reported.*

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X. POLICY HISTORY

TOP

MP -2.263	**CAC 5/20/14** New policy. BCBSA adopted. Gene expression analysis to guide management of prostate cancer is considered investigational in all situations. Policy coded.
	CAC 6/2/15 Consensus review. No changes to the policy statements. References and rationale updated. FEP variation added. No coding changes.
	CAC 11/24/15 Minor review. Promark and Decipher tests added to investigational policy statement. Changed title to Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management (formerly Gene Expression Profile Analysis for Prostate Cancer Management). Changed Medicare variation to reference Palmetto GBA Local Coverage Determination (LCD) L35869 MolDX: Prolaris™ Prostate Cancer Genomic Assay, L35868 MolDX: Decipher® Prostate Cancer Classifier Assay and L36153 MolDX: Genomic Health™ Oncotype DX® Prostate Cancer Assay. This testing is covered with criteria for Senior Blue products. Coding reviewed/updated.
	Admin update 1/1/17: Product variation section updated.
	CAC 1/31/17 Consensus review. No changes to the policy statement. Background, rationale, and reference update**.** Coding reviewed.
	12/19/17 Consensus review. Clarification added to the policy statement language, but the intent is unchanged. Product Variations, Description/Background, Rationale and Reference sections updated. Added new code 81541for Prolaris, effective 1/1/18
	Admin update 7/1/18: New Code 0047U added; effective 7/1/18. Updated rationale to Summary of Evidence only.
	12/10/18 Consensus. No change to policy statements. Background, rationale summary and references updated.

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