MEDICAL POLICY

POLICY TITLE	GENE EXPRESSION PROFILING, PROTEIN BIOMARKERS, AND MULTIMODAL ARTIFICIAL INTELLIGENCE FOR PROSTATE CANCER MANAGEMENT
POLICY NUMBER	MP 2.263

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**4/1/2026**

POLICY

Use of gene expression analysis, protein biomarkers, and multimodal artificial intelligence (MMAI) 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

PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

DESCRIPTION/BACKGROUND

PROSTATE CANCER

Prostate cancer is the most common cancer diagnosed among men in the U. S, and the second most common cancer overall. 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 (e.g., 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 (aged >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 (NCCN) 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.

Principles of Risk Stratification and Biomarkers for Prostate Cancer

Predictive biomarkers and risk stratification methods are the primary tools within clinical practice that may aid in the treatment of individuals with localized and advanced prostate cancer. The NCCN uses multiple categories and subgroupings to capture prognostic risk and provide a method for risk-stratification to allow standardized treatment recommendations for individuals with localized and advanced prostate cancer. These tools are separated by type and category:

Type:

- "Standard Tools: These include clinical and/or pathologic variables routinely collected to assign a patient to an NCCN category and/or subgroup. Examples include TNM stage, Grade Group, PSA, and metastatic volume of disease."
- "Clinical and Pathologic Tools: These include clinical and/or pathologic tools that are generally derived from standard tools. Examples include multivariable models or nomograms, histologic variants, and PSA kinetics."
- "Advanced Tools: These involve an additional test above what is collected to assign an NCCN category or subgroup. These may include, but are not limited to, germline or somatic tests, gene expression tests, digital histopathology-based tests, imaging, and circulating markers."

Category:

- "Prognostic: Discriminates the risk of developing an oncologic endpoint (e.g., distant metastasis). The relative benefit of a treatment (i.e., the treatment effect or hazard ratio) is generally similar across a prognostic spectrum, although the absolute benefit of an intervention may vary by risk (i.e., number needed to treat [NNT])."
    - "Prognostic biomarkers independently discriminate and are associated with a clinically meaningful endpoint above and beyond standard tools relevant to that disease setting that ultimately helps guide a therapeutic decision."
- "Predictive: Discriminates a difference in the relative benefit of a specific treatment for an oncologic endpoint."
    - "Predictive biomarkers have been demonstrated to measure a biomarker-treatment interaction that ultimately helps guide a therapeutic decision in the context of a randomized trial, specifically randomizing the treatment of interest."

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. Prostate-specific antigen 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 recommends 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. Androgen deprivation therapy 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.

Decision Framework for Evaluation Prostate Cancer Biomarkers

Simon et al Framework

Many studies have investigated individual biomarkers or combinations of biomarkers associated with prostate cancer outcomes. Determining which studies constitute sufficient evidence that the test or biomarker is likely to be clinically useful depends on attributes of the test such as its performance and the quality of the study generating the results. Simon et al (2009) have

described a framework to evaluate prognostic biomarker evidence. Study designs, such as prospective clinical trials or previously conducted clinical trials with archived tumor samples, constitute stronger evidence than studies with less planned and systematic patient recruitment and data collection. Randomized trials allow the determination of treatment-biomarker interactions that may be clinically important. In some clinical scenarios, demonstration of a treatment-biomarker interaction is not critical, because the decision to withhold chemotherapy in a low-risk group (to avoid chemotherapy-related morbidity) does not require the presence of a biomarker-treatment interaction. The study must generate an absolute estimate of outcomes in the patient group of interest that would result in a change in management (e.g., withholding of chemotherapy), and the study must have sufficient precision (narrow confidence intervals). Results of the same test across studies should show the consistency of results and more than 1 study demonstrating the desired result should be available. Simon et al (2009) have proposed that at least 2 Simon et al (2009) category B studies showing results consistent with clinical utility are necessary to demonstrate adequate evidence of a biomarker. Simon et al (2009) also proposed that while "further confirmation in a separate trial of the results gained from a category A prospective trial is always welcome, compelling results from such a trial would be considered definitive and no other validating trial would be required."

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 (Decipher Corp), the ProMark™ protein biomarker test (Metamark Genetics), and Artera® Prostate Test 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 these tests.

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

SUMMARY OF EVIDENCE

Initial Management Decision: Active Surveillance vs Therapeutic Intervention

For individuals who have 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. 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 that the technology results in an improvement in the net health outcome.

For individuals who have 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 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 that the technology results in an improvement in the net health outcome.

For individuals who have clinically localized untreated prostate cancer who receive Decipher Biopsy, the evidence includes retrospective cohort studies of clinical validity using archived samples in intermediate- and high-risk patients and no studies of clinical utility. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. A test designed to identify intermediate-risk men who can receive active surveillance instead of RP or radiotherapy (RT) or high-risk men who can forego androgen deprivation therapy would need to show very high negative predictive value for disease-specific mortality at 10 years and improvement in prediction compared with existing tools used to select such men. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have 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 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 that the technology results in an improvement in the net health outcome.

For individuals who have clinically localized untreated prostate cancer who receive ArteraAI Prostate Test, the evidence includes 1 meta-analysis and 5 retrospective analyses on archived samples from randomized clinical trials on prostate cancer patients of mixed risk categories to

assess clinical validity and utility. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. Evidence for clinical validity and potential clinical utility of ArteraAI Prostate Test in patients with clinically localized prostate cancer derives from a handful of studies comparing relevant outcomes against comparators like National Comprehensive Cancer Network (NCCN) and standard clinicopathologic risk-stratification tools. Multimodal artificial intelligence (MMAI) algorithms, that form the foundation of ArteraAI, have shown they can outperform comparators at prognosticating 10-year outcomes of interest (OS, distant metastasis [DM], biochemical failure [BF], and prostate cancer-specific survival [PCSS]). Additionally, MMAI was able to demonstrate it is predictive for short-term androgen deprivation therapy (ST-ADT) and can determine if prostate cancer patients would have a better net health outcome on RT alone or RT plus ST-ADT. Limitations of these studies are synonymous with retrospective analysis, including but not limited to, clinical heterogeneity of study populations, variability in data recording, and different conditions under which measurements occurred. No study reported management changes made in response to ArteraAI Prostate Test results, but current NCCN management algorithms recommend MMAI testing with ArteraAI for prostate cancer patients with NCCN intermediate-risk scores to indicate patients that should undergo ST-ADT regardless of RT dose or type. Moreover, NCCN notes that MMAI testing with ArteraAI may provide more accurate risk stratification to enable better management of cancer patients; however, it remains unclear on how this could be used in clinical practice as specific MMAI cutoff values have not been published. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 OS, disease-specific survival, QOL, and treatment-related morbidity. No direct evidence is available to support the clinical utility of Prolaris for improving net outcomes of patients with localized prostate cancer following RP. The chain of evidence is also incomplete. Decision-curve analysis did not provide convincing evidence of meaningful improvement in net benefit by incorporating the cell cycle progression (CCP) score. 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. Although Prolaris CCP score may have an association with biochemical recurrence (BCR), disease-specific survival outcomes were reported in only 1 analysis. A larger number of disease-specific survival events and precision estimates for discrimination measures are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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. 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 RT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have localized prostate cancer treated with RP who receive ArteraAI Prostate Test, the evidence includes 2 retrospective cohort studies of clinical validity using archived samples. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. ArteraAI proved to be prognostic for RP-specific endpoints of BCR and adverse pathology given the statistically significant association. Disease-specific survival outcomes were reported in both studies and the evidence of clinical validity and prognostic accuracy for MMAI scores via ArteraAI testing in patients after RP demonstrated statistically improved PCSM and OS when compared to standard clinicopathologic risk stratification tools. Limitations of these studies are synonymous with retrospective analysis, including but not limited to, clinical heterogeneity of study populations, variability in data recording, and different conditions under which measurements occurred. No study reported management changes made in response to ArteraAI Prostate Test results. Overall, ArteraAI Prostate Test is validated for disease-specific outcomes for prostate cancer patients who underwent RP and can provide additional prognostic information that may guide postoperative management, but further studies are needed to determine if MMAI can be used to decide specific treatment regimens that improve health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 1 prospective cohort study, 1 retrospective cohort study of clinical validity using archived samples, and no studies of clinical utility. 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 2 clinical validity studies meeting inclusion criteria were available. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Management Decision in Castration-Sensitive Prostate Cancer

For individuals who have metastatic castration-sensitive prostate cancer (mCSPC) who receive ArteraAI Prostate Test, the evidence includes 2 retrospective cohort studies of clinical validity using archived samples. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. MMAI was able to estimate treatment effects and determine that MMAI high-risk mCRPC patients would derive benefit from metastasis-directed therapy (MDT) when compared to observation. Limitations of these studies are synonymous with retrospective analysis, including but not limited to, clinical heterogeneity of study populations, variability in data recording, and different conditions under which measurements occurred. No study reported management changes made in response to ArteraAI Prostate Test results. Overall, ArteraAI

Prostate Test is prognostic for mCSPC patients and has the potential to guide treatment management, but further studies are needed to determine if MMAI can be used to decide specific treatment regimens that improve net health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

DEFINITIONS

N/A

DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as permitted by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

CODING INFORMATION

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:

Procedure Codes								
81541	81542	81479	0047U	0376U	0512U	0513U		

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POLICY HISTORY

MP 2.263	**01/01/2020 Administrative Update.** Added new code 81542.
	08/19/20 Consensus Review. Policy statement unchanged. References and Rationale updated.
	12/30/2020 Retirement Review. Policy will now be managed on 2.280
	10/09/2025 Major Review. Policy to be reinstated as INV only policy.

POLICY TITLE	GENE EXPRESSION PROFILING, PROTEIN BIOMARKERS, AND MULTIMODAL ARTIFICIAL INTELLIGENCE FOR PROSTATE CANCER MANAGEMENT
POLICY NUMBER	MP 2.263

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