Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Prostate Cancer

Policy # 00809
Original Effective Date: 01/01/2023
Current Effective Date: 01/01/2024

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: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers is addressed separately in medical policy 00047.

Note: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes is addressed separately in medical policy 00190.

Note: Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer is addressed separately in medical policy 00233.

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

Note: Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Melanoma or Glioma is addressed separately in medical policy 00320.

Note: Genetic Cancer Susceptibility Panels Using Next Generation Sequencing is addressed separately in medical policy 00382.

Note: Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management is addressed separately in medical policy 00403.

Note: Genetic Testing for PTEN Hamartoma Tumor Syndrome is addressed separately in medical policy 00417.

Note: Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies is addressed separately in medical policy 00423.

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Note: Genetic Testing for Li-Fraumeni Syndrome is addressed separately in medical policy 00424.

Note: Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer is addressed separately in medical policy 00452.

Note: Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) is addressed separately in medical policy 00497.

Note: Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer is addressed separately in medical policy 00731.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider germline *BRCA1/2* variant analysis (if not done before) for individuals with metastatic castrate-resistant prostate cancer (mCRPC) to select treatment with FDA-approved targeted therapies or immunotherapy to be **eligible for coverage.****

Based on review of available data, the Company may consider somatic testing using tissue biopsy for homologous recombination repair (HRR) gene alterations (i.e., using FoundationOne CDx for testing of *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L* genes) if not done before, to select treatment for mCRPC with FDA-approved targeted therapies or immunotherapy to be **eligible for coverage.****

Based on review of available data, the Company may consider tumor testing for microsatellite instability (MSI) using FoundationOne CDx or mismatch repair (MMR) if not done before, to select treatment for unresectable or metastatic prostate cancer with FDA-approved targeted therapies or immunotherapy to be **eligible for coverage.****

Based on review of available data, the Company may consider *BRCA1/2* and *ATM* variant analysis using ctDNA (i.e., using FoundationOne Liquid CDx for liquid biopsy testing) if not done before and when somatic testing is not safe or feasible, for individuals with mCRPC to select treatment with FDA-approved targeted therapies to be **eligible for coverage.****

Notes:
When feasible, molecular testing should be done on a metastatic biopsy. When unsafe or unfeasible, ctDNA assay is an option, preferably collected during biochemical (PSA) and/or radiographic progression in order to maximize diagnostic yield.

Panel testing performed on the same specimen and date of services needs to be reported with a single most appropriate procedure code rather than billing numerous procedure codes.

Per the AMA, when a PLA code is available to report a given proprietary laboratory service, the service should not be reported with any other CPT code(s).

Testing for other variants may become available between policy updates.

When 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 all other uses of germline *BRCA1/2* variant analysis to guide prostate cancer targeted therapy or immunotherapy to be **investigational.***

Based on review of available data, the Company considers all other uses of somatic testing for HRR gene alterations to guide prostate cancer targeted therapy or immunotherapy to be **investigational.***

Based on review of available data, the Company considers all other uses of tumor testing for MSI or MMR to guide prostate cancer targeted therapy or immunotherapy to be **investigational.***

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Based on review of available data, the Company considers tumor mutational burden (TMB) testing to guide prostate cancer targeted therapy or immunotherapy to be **investigational.***

Based on review of available data, the Company considers all other uses of biomarker testing with ctDNA (liquid biopsy) to guide prostate cancer targeted therapy or immunotherapy to be **investigational.***

Based on review of available data, the Company considers simultaneous testing using liquid and tumor biopsies (outside of concurrent somatic-germline testing) to guide treatment in individuals with prostate cancer to be **investigational.***

When Services Are Not Covered

Based on review of available data, the Company considers repeat germline testing to be **not covered****.

Note:
Repeat germline testing that investigates the same genetic information is not reasonable and necessary as it is duplicative and not required for medical treatment decisions. Examples of germline tests include, but are not limited to, single gene testing, gene panel tests, and whole exome or whole genome sequencing for inherited disorders.

Policy Guidelines

Testing for individual genes (not gene panels) associated with Food and Drug Administration (FDA)-approved therapeutics for therapies with NCCN recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel. The pivotal evidence is included in Table 1 for informational purposes.

Note that TMB is often included in panel tests and might not have separate coding;

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FDA approves tests in between policy review cycles. For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools) for an updated list of FDA-approved tumor markers and consult the most current version of NCCN management algorithms.

Repeat Genomic Testing
There may be utility in repeated testing of gene variants for determining targeted therapy or immunotherapy in individuals with prostate cancer, as tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making (See NCCN PROS-C 3 of 3). The American Society of Clinical Oncology (ASCO) currently suggests repeat genomic testing for individuals on targeted therapy with suspected acquired resistance, especially if choice of next-line therapy would be guided. The ASCO guidance is not tumor specific, and it cautions to consider clinical utility (Chakravarty et al, 2022; PMID 35175857).

Paired Somatic-Germline Testing
Testing for genetic changes in tumor tissue assesses somatic changes. Some somatic testing involves a paired blood analysis in order to distinguish whether findings in tumor tissue are acquired somatic changes or germline changes. Some laboratories offer paired tumor sequencing and germline sequencing which is done at the same time and in the same laboratory. The goal of this paired testing is to identify truly somatic changes to guide treatment. However, paired testing can also identify potential germline changes that might indicate an inherited cancer syndrome. These results would need to be confirmed through germline testing if personal and family cancer history is consistent with an inherited cancer syndrome (see evidence reviews related to inherited cancer syndromes, 00047, 00190, 00417, 00424).

Paired genetic testing is different than concurrent somatic-germline testing. In concurrent testing, the germline results are not used to filter the somatic results. Rather, the laboratories perform large, separate panels of germline and somatic variants. The goal is to identify options for genome-informed treatment and to identify hereditary cancer risk. For concurrent panel testing, see evidence review 00382 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing for

germline panel, and see evidence review 00423 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies for somatic panel.

Concurrent Somatic Liquid-based and Tissue-based Genomic Testing
Liquid biopsy testing uses blood samples and assesses cancer DNA and non-cancer DNA in the same blood sample. The goal is to identify options for genome-informed treatment. Some providers will order a liquid biopsy test and a tissue biopsy test at the same time, not for filtering or for comparison as in the paired genetic testing section above, but to hasten time to treatment. If the intent of concurrent testing is to follow an individual over time for resistance mutations/response to therapy, then consideration could be given to doing liquid biopsy at diagnosis with the tissue biopsy to make sure that whatever mutations are going to be followed longitudinally can be detected by the liquid biopsy. For example, monitoring of *BRCA* mutation evolution (reversion mutations) in individuals with prostate cancer during poly adenosine diphosphate-ribose polymerase (PARP) inhibitor therapy may be achieved with serial circulating tumor DNA (ctDNA) sampling, and allow for earlier detection of resistance and selection of alternative therapies to reduce the risk of resistance (Goodall et al, 2017; PMID 28450425). This testing strategy has not been fully studied, and is not yet discussed in the NCCN guidelines for prostate cancer.

Genetic Counseling
Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

Targeted Treatment in Metastatic Castrate Resistant Prostate Cancer
DNA damage happens daily, and most are repaired to allow normal cell functioning. Double strand breaks (DSB) in the DNA are particularly damaging. Repair of DSB utilizes the homologous

recombination repair (HRR) pathway. Many types of cancer, however, are unable to repair DNA damage. This leads to the accumulation of genetic errors, such as loss of DNA, rearrangements in the DNA, and loss of entire genes. The consequence of these errors is genomic instability. The loss of the HRR and associated genomic instability is called homologous recombination deficiency (HRD). HRD is associated with several types of cancer including prostate cancer, where estimates as high as 30% of metastatic castrate-resistant prostate cancer (mCRPC) tumors have genetic changes that result in the loss of DNA repair capacity.

Friends of Cancer Research convened a consortium addressing the lack of consistency in the way HRD is defined and measurement methods. They proposed the following definition: "HRD is a phenotype that is characterized by the inability of a cell to effectively repair DNA double-strand breaks using the HRR pathway." Additionally, they encourage the use of "HRD" and "HRP" to reflect homologous recombination deficiency and homologous recombination proficiency. While the consortium did not explicitly define how to measure homologous recombination repair status, they acknowledge that it might involve gene variant testing as well as genomic instability measurement and call for transparency and standardization.

Specific to prostate cancer, the National Comprehensive Cancer Network (NCCN) prostate cancer guideline gives examples of HRR genes (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L).* Germline and somatic alterations in these genes may be predictive of the clinical benefit of PARP inhibitors in mCRPC..Olaparib (Lynparza) and rucaparib (Rubraca) were the first PARP inhibitors to receive FDA approval for the treatment of mCRPC. In 2023, niraparib in combination with abiraterone acetate (marketed as Akeega) and talazoparib (Talzenna) were also approved for use in mCRPC (see Table 1).

Mismatch Repair Deficiency/Microsatellite Instability

Mismatch repair deficiency (dMMR) and high levels of microsatellite instability (MSI-H) describe cells that have alterations in certain genes involved in correcting errors made when DNA is replicated. dMMR tumors are characterized by a high tumor mutational load and potential responsiveness to anti-PD-L1-immunotherapy. MMR deficiency is most common in colorectal cancer, other types of gastrointestinal cancer, and endometrial cancer, but it may also be found in other cancers including prostate cancer. Microsatellite instability testing is generally performed

using polymerase chain reaction (PCR) for 5 biomarkers, although other biomarker panels and next generation sequencing (NGS) are sometimes performed. High microsatellite instability is defined as 2 or more of the 5 biomarkers showing instability or more than 30% of the tested biomarkers showing instability depending on what panel is used. Microsatellite instability testing is generally paired with immunohistochemistry (IHC) assessing lack of protein expression from 4 DNA mismatch repair genes thereby reflecting dMMR.

Tumor Mutational Burden
Tumor mutational burden (TMB), a measure of gene mutations within cancer cells, is an emerging biomarker of outcomes with immunotherapy in multiple tumor types. Initially, assessments of TMB involved whole exome sequencing (WES). More recently, targeted NGS panels are being adapted to estimate TMB. Currently FoundationOne CDx is the only U.S. Food and Drug Administration (FDA)-approved panel for estimating TMB, but others are in development.

Circulating Tumor DNA (Liquid Biopsy)
Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA. Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or circulating tumor cells. Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA (ctDNA) can be used for genomic characterization of the tumor.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Table 1 summarizes the targeted treatments approved by the FDA for individuals with prostate cancer, along with the approved companion diagnostic tests. The information in Table 1 was current as of August 21, 2023. An up-to-date list of FDA cleared or approved companion diagnostics is available at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

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Table 1. Targeted Treatments for Metastatic Prostate Cancer and FDA Approved Companion Diagnostic Tests

Treatment	Indications in Prostate Cancer	Companion Diagnostics Date	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
Niraparib + abiraterone acetate (AKEEGA)	With prednisone, for the treatment of adult patients with deleterious or suspected deleterious*BRCA*-mutated metastatic castration-resistant prostate cancer.	FoundationOne CDx (Foundation Medicine, Inc.) 2023	*BRCA1 and BRCA2 alterations*	MAGNITUDE NCT03748641 Chi et al (2023)'	None
Olaparib (Lynparza)	In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.) 2020	*BRCA1* and *BRCA2* alterations	PROfound NCT02987543 Hussain et al (2020)	2A/Prostate Cancer
		FoundationOne Liquid CDx	*BRCA1*, *BRCA2*, and *ATM* alterations	PROpel	

	with deleterious or suspected deleterious BRCA-mutated mCRPC.	(Foundation Medicine, Inc.) 2020		NCT03732820 Clarke et al (2022)	
	Adults with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone.	FoundationOne CDx (Foundation Medicine, Inc.) 2020	Homologous recombination repair (HRR) genes: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*,*CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*,*RAD51D*, and *RAD54L* alterations	PROfound NCT02987543 Hussain et al (2020)[,]	2A/ Prostate Cancer[,]
Rucaparib (Rubraca)	Adult patients with a deleterious BRCA mutation (germline and/or somatic)-	FoundationOne Liquid CDx (Foundation Medicine, Inc.) 2020	*BRCA1* and *BRCA2* alterations	TRITON2 NCT02952534 Abida et al (2020)[,] TRITON 3 NCT02975934 Fizazi et al (2023)[,]	2A/Prostate Cancer[,]

	associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemo-therapy.				
Tala-zoparib (Talzenna)	In combination with enzalutamide for the treatment of adult patients with HRR gene-mutated metastatic castration-resistant prostate cancer.	No FDA companion diagnostic for this indication	HRR genes	TALAPRO-2 NCT03395197 Agarwal et al (2023)[,]	2A/ Prostate Cancer

NCCN: National Comprehensive Cancer Network.
Sources: Food and Drug Administration (2023); Drugs@FDA (2023)

Laboratory-Developed Tests

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). Laboratories that offer laboratory-developed tests

must be licensed under CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Description

Biomarker-targeted therapy has shown a clear survival benefit in individuals with metastatic prostate cancer. More recently, testing for tumor mutational burden (TMB) status to select individuals for immunotherapy has been proposed. Typically, the evaluation of biomarker status requires tissue biopsy. Circulating tumor DNA (ctDNA) or circulating tumor cell testing (also known as liquid biopsy) is proposed as a non-invasive alternative.

Summary of Evidence

For individuals with metastatic castrate-resistant prostate cancer (mCRPC) who receive germline BRCA1/2 variant testing to guide treatment with a poly adenosine diphosphate-ribose polymerase (PARP) inhibitor, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and National Comprehensive Cancer Network (NCCN) recommendations.

For individuals with mCRPC who receive somatic testing for homologous recombination repair (HRR) gene alterations (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L) using tissue biopsy to guide treatment with a PARP inhibitor, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with mCRPC who receive somatic testing for BRCA1, BRCA2, and ATM alterations using ctDNA (liquid biopsy) to guide treatment with a PARP inhibitor, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and National Comprehensive Cancer Network (NCCN) recommendations.

For individuals with prostate cancer who receive TMB testing to select treatment with immunotherapy, the evidence includes a prespecified retrospective subgroup analysis of a nonrandomized phase 2 trial. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Objective responses were observed in 35% of participants who had both TMB-high status and programmed death ligand-1 (PD-L1)-positive tumors and in 21% of participants who had TMB-high status and PD-L1-negative tumors. High TMB status was associated with improved response irrespective of PD-L1 status. Median OS and progression-free survival were not significantly different between TMB groups. Because no patients with prostate cancer were included in these analyses, it is not possible to draw conclusions about the clinical validity and utility of TMB in this group of patients. Well-designed prospective studies enrolling patients in the population of interest are required. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Urological Association/Society of Urologic Oncology

In 2023, the American Urological Association and the Society of Urologic Oncology published amended guidelines on advanced prostate cancer. The guidelines included the following relevant recommendation (level of evidence) on the treatment of mCRPC:

- In patients with mCRPC, clinicians should offer germline (if not already performed) and somatic genetic testing to identify DNA repair deficiency, microsatellite instability (MSI) status, tumor mutational burden, and other potential mutations that may inform prognosis and familial cancer risk, as well as direct potential targeted therapies.(Clinical Principle)

National Comprehensive Cancer Network
The current National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer are version 4.2023. Guidelines are updated frequently; refer to the source for the most current recommendations.

The guidelines include the following relevant recommendations:

Targeted Therapy

- "Consider inclusion of olaparib in patients who have an HRR mutation and whose cancer has progressed on prior treatment with androgen receptor-directed therapy regardless of prior docetaxel therapy. Olaparib is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*) who have been treated previously with androgen receptor-directed therapy."
- "Consider inclusion of rucaparib for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. If the patient is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given."
- "Olaparib with abiraterone is an option for patients with a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet received a novel hormone therapy or docetaxel."
- "Talazoparib plus enzalutamide is a treatment option for patients with metastatic CRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (*BRCA1*, *BRCA2*, *ATM*, *ATR*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, or *RAD51C*) who have not yet had treatment in the setting of CRPC."

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Germline Testing
The Principles of Genetics section (PROS-B) provides appropriate scenarios for germline genetic testing in individuals with a personal history of prostate cancer.

Germline testing is recommended in patients with a personal history of prostate cancer in the following scenarios related to the tumor: metastatic, regional (node-positive), very-high risk localized, high-risk localized prostate cancer.

Germline testing may be considered in patients with a personal history of prostate cancer in the following scenarios related to the tumor: intermediate-risk prostate cancer with intraductal/cribriform histology; or a prior personal history any of the following cancers: of exocrine pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, and small intestinal.

Somatic Testing
Tumor testing for alterations in homologous recombination DNA repair genes, such as *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and *CDK12*, is recommended in patients with metastatic prostate cancer. This testing can be considered in patients with regional prostate cancer.

Tumor testing for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR), if previously not performed, is recommended in patients with metastatic castration-resistant prostate cancer and may be considered in patients with regional or castration *sensitive* metastatic prostate cancer.

TMB testing may be considered in patients with metastatic castration-resistant prostate cancer.

Tumor Specimen and Assay Considerations
The panel strongly recommends a metastatic biopsy for histologic and molecular evaluation. When unsafe or unfeasible, plasma ctDNA assay is an option, preferably collected during biochemical (PSA) and/or radiographic progression in order to maximize diagnostic yield.

Caution is needed when interpreting ctDNA-only evaluation due to potential interference from clonal hematopoiesis of indeterminate potential (CHIP), which can result in a false-positive biomarker signal.

The preferred method of selecting patients for rucaparib treatment is somatic analysis of *BRCA1* and *BRCA2* using a ctDNA sample.

Post-Test Considerations
Post-test genetic counseling is recommended if pathogenic/likely pathogenic variant (mutation) identified in any gene that has clinical implications if also identified in germline (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*).

U.S. Preventive Services Task Force Recommendations1.2023
Not applicable.

Medicare National Coverage
The Centers for Medicare & Medicaid Services (CMS) National Coverage Determination on Next Generation Sequencing (90.2) states:

> "Effective for services performed on or after March 16, 2018, [CMS] has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:
>
> a. Patient has:
> i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
> ii. not been previously tested with the same test using NGS for the same cancer genetic content; and
> iii. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
>
> b. The diagnostic laboratory test using NGS must have:
> i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,

ii. an FDA-approved or -cleared indication for use in that patient's cancer; and,
iii. results provided to the treating physician for management of the patient using a report template to specify treatment options."[,]

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04550494	Measuring the Effects of Talazoparib in Patients With Advanced Cancer and DNA Repair Variations	36	Dec 2023
NCT04038502	Carboplatin or Olaparib for BRcA Deficient Prostate Cancer (COBRA)	100	Aug 2025
NCT04497844[a]	A Study of Niraparib in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for the Treatment of Participants With Deleterious Germline or Somatic Homologous Recombination Repair (HRR) Gene-Mutated Metastatic Castration-Sensitive Prostate Cancer (mCSPC) (AMPLITUDE)	692	May 2027
NCT05689021	CJNJ-67652000 and Prednisone for Treatment of Metastatic Castration-Resistant Prostate Cancer and SPOP Gene Mutations	30	Sep 2025

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 01/01/2023
Current Effective Date: 01/01/2024

12/01/2022	Medical Policy Committee review
12/14/2022	Medical Policy Implementation Committee approval. New policy.
01/13/2023	Coding update
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. Added a "When Services Are Not Covered" section for repeat germline testing. Revised the Policy Guidelines, Rationale and Supplemental Information sections. New codes effective 01/01/2024 added to policy.

Next Scheduled Review Date: 12/2024

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 2022 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.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice

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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	0037U, 0129U, 0239U, 81162, 81301 Add codes effective 03/01/2023: 0242U, 0326U Add code effective 01/01/2024: 81307, 81457, 81458, 81459
HCPCS	No codes
ICD-10 Diagnosis	C61, C7982, D075

*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 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.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ 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.

Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Prostate Cancer

Policy # 00809
Original Effective Date: 01/01/2023
Current Effective Date: 01/01/2024

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.