MEDICAL POLICY

POLICY TITLE	**GERMLINE AND SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT IN PROSTATE CANCER (BRCA1/2, HOMOLOGOUS RECOMBINATION REPAIR GENE ALTERATIONS, NTRK GENE FUSION)**
POLICY NUMBER	**MP 2.394**

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:	**RETIRED 7/1/2026**

I. POLICY

Germline *BRCA1/2* variant analysis for individuals with metastatic castrate-resistant prostate cancer (mCRPC) to select treatment with FDA-approved targeted therapies may be considered **medically necessary**.

All other uses of germline *BRCA1/2* variant analysis to guide prostate cancer targeted therapy are considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Somatic testing using tissue biopsy for homologous recombination repair (HRR) gene alterations (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D,* and *RAD54L*) to select treatment for mCRPC with FDA-approved targeted therapies may be considered **medically necessary**.

All other uses of somatic testing using tissue biopsy for HRR gene alterations to guide prostate cancer targeted therapy are considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Somatic testing using circulating tumor DNA testing (liquid biopsy) for *BRCA1*, *BRCA2*, and *ATM* alterations to select treatment for mCRPC with FDA-approved targeted therapies may be considered **medically necessary**.

All other uses of somatic testing using circulating tumor DNA testing (liquid biopsy) to guide prostate cancer targeted therapy are considered **investigational**. There is insufficient evidence

to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Simultaneous testing using liquid and tumor biopsies (outside of paired or concurrent somatic-germline testing) to guide treatment in individuals with prostate cancer is considered **investigational** (see Policy Guidelines). There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Testing of *NTRK* gene fusions in individuals with mCRPC to select treatment with FDA-approved targeted therapies may be considered **medically necessary**.

Testing for other variants may become available between policy updates.

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.

For expanded panel testing, see **MP 2.259**.

For somatic biomarker testing related to use of immune checkpoint inhibitor therapy (*BRAF,* microsatellite instability/mismatch repair [MSI/MMR], PD-L1, tumor mutational burden [TMB]), see **MP 2.388**.

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

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) for an updated list of FDA-approved tumor markers and consult the most current version of NCCN management algorithms.

Note: Extensive evidence review is not included for somatic tests of individual genes (not gene panels) associated with FDA-approved therapies with NCCN recommendations of 2A or higher. Additionally, no evidence review is provided for somatic tests of individual genes that do not have associated FDA-approved therapies regardless of NCCN recommendations, as these off-label therapies are deemed investigational.

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-B 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 policies related to inherited cancer syndromes, **MP 2.211, MP 5.013, MP 2.255, MP 2.274**).

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 **MP 2.325 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing** for germline panel, and see **MP 2.259 – Molecular Panel Testing of Cancers to Identify Targeted 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.

Cross-References:

MP 2.211 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers
MP 2.255 Genetic Testing for PTEN Hamartoma Tumor Syndrome
MP 2.259 Molecular Panel Testing of Cancers to Identify Targeted Therapies
MP 2.274 Genetic Testing for Li-Fraumeni Syndrome
MP 2.325 Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
MP 2.388 Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy
MP 2.392 Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes
MP 2.393 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer
MP 2.395 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer
MP 5.013 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

II. PRODUCT VARIATIONS

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

POLICY TITLE	GERMLINE AND SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT IN PROSTATE CANCER (BRCA1/2, HOMOLOGOUS RECOMBINATION REPAIR GENE ALTERATIONS, NTRK GENE FUSION)
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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

III. DESCRIPTION/BACKGROUND

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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).

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.

Neurotrophic Receptor Tyrosine Kinase (*NTRK*) Gene Fusion Testing

The presence of *NTRK* gene fusion can be detected by multiple methods including next-generation sequencing, reverse transcription-polymerase chain reaction, fluorescence in situ hybridization and immunohistochemistry. Next-generation sequencing provides the most comprehensive view of a large number of genes and may identify *NTRK* gene fusions as well as other actionable alterations, with minimal tissue needed. The fluorescence in situ hybridization using break-apart probes can detect gene rearrangements in DNA that may generate a fusion transcript. The immunohistochemistry techniques have generally been used in the research setting. Reverse transcription-polymerase chain reaction is designed to identify only known translocation partners and breakpoints and cannot identify novel breakpoints or novel fusion partners.

Regulatory Status

Table 1 summarizes the targeted treatments approved by the FDA for individuals with prostate cancer, along with the approved companion diagnostic tests. 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.

Treatment	Companion Diagnostics
Niraparib + abiraterone acetate (AKEEGA)	FoundationOne CDx (Foundation Medicine, Inc.)
Olaparib (Lynparza)	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.) FoundationOne Liquid CDx (Foundation Medicine, Inc.) FoundationOne CDx (Foundation Medicine, Inc.)
Rucaparib (Rubraca)	FoundationOne Liquid CDx (Foundation Medicine, Inc.)
Talazoparib (Talzenna)	No FDA companion diagnostic for this indication

Larotrectinib (VITRAKVI) [a]	FoundationOne Liquid CDx (Foundation Medicine, Inc.)
Entrectinib (ROZLYTREK) [a]	FoundationOne Liquid CDx (Foundation Medicine, Inc.)

[a] Indications not specific to prostate cancer.

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.

IV. RATIONALE

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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 circulating tumor DNA (ctDNA; liquid 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 NTRK gene fusion testing to select treatment with FDA-approved therapies, the evidence includes pooled results from single-arm studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, medication use, and treatment-related morbidity. For larotrectinib, 3, single-arm studies evaluating the efficacy of larotrectinib in 159 pediatric and adult patients with unresectable or

metastatic solid tumors with an NTRK gene fusion are ongoing. Pooled results of the first 55 sequentially enrolled patients have been published. All patients were required to have progressed on systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease. The ORR by the Institutional Review Committee (primary study endpoint) was 79% (95% CI, 72% to 85%); complete response 16%; and partial response 63%. Responses observed were independent of age, tumor type, NTRK gene, or fusion partner. For entrectinib, integrated data from 54 adult patients with NTRK fusion-positive, locally advanced or metastatic solid tumors from 3, single-arm ongoing studies who had completed a minimum of 6 months of follow-up were reviewed. The ORR by blinded independent central review was 57.4% in patients with NTRK fusion-positive solid tumors. The median DOR was 10.4 months. Results were similar in a Phase 2 trial of children and adolescents with NTRK fusion-positive tumors, with an ORR of 60.0%. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS/BACKGROUND

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N/A

VI. DISCLAIMER

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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 required 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.

VII. 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. The codes need to be in numerical order.

Investigational; therefore, not covered:

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Procedure Codes							
81432	0129U						

Covered when medically necessary:

Procedure Codes							
81162	81163	81164	81165	81166	81167	81191	81192
81193	81194	81212	81215	81216	81217	81307	81308
81408	81479*	0037U	0239U				

*Could be used for liquid biopsy of individual medically necessary variants or used for somatic tissue testing of individual HRR genes

ICD-10-CM Diagnosis Code	Description
C61	Malignant neoplasm of prostate
C79.82	Secondary malignant neoplasm of genital organs
D07.5	Carcinoma in situ of prostate

VIII. REFERENCES

TOP

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IX. POLICY HISTORY

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MP 2.394	**01/17/2025 Major Review**. New Policy Adoption
	06/24/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	03/03/2026 Retirement Review. This service will be managed by the vendor Evicore.

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