2.04.155	Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, NTRK Gene Fusion)		
Original Policy Date:	December 1, 2022	**Effective Date:**	October 1, 2025
Section:	2.0 Medicine	**Page:**	Page 1 of 21

Policy Statement

I. 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**.

II. All other uses of germline *BRCA1/2* variant analysis to guide prostate cancer targeted therapy are considered **investigational**.

III. 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**.

IV. All other uses of somatic testing using tissue biopsy for HRR gene alterations to guide prostate cancer targeted therapy are considered **investigational**.

V. 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**.

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

VII. 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).

VIII. 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.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

Testing for other variants may become available between policy updates.
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 , Blue Shield of California Medical Policy: Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

Note that TMB is often included in panel tests and might not have separate coding; Plans with coverage for panels might consider local decision for TMB.

FDA approves tests in between policy review cycles. As such, newly approved tests might need to be considered per local Plan discretion. 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. The pivotal evidence is included in Table 1 for informational purposes. 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 Blue Shield of California Medical Policy: related to inherited cancer syndromes, Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2) Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes, Genetic Testing for PTEN Hamartoma Tumor Syndrome Genetic Testing for Li-Fraumeni Syndrome).

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 Blue Shield of California Medical Policy: Genetic Cancer Susceptibility Panels Using Next Generation Sequencing for germline panel, and see Blue Shield of California Medical Policy: 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.

Coding

See the Codes table for details.

Description

Biomarker-targeted therapy has shown a clear survival benefit in individuals with metastatic prostate cancer. Typically, the evaluation of biomarker status requires tissue biopsy. Circulating tumor DNA (ctDNA) (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 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.

Additional Information

Not applicable.

Related Policies

- Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2) **(to be published)**
- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
- Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
- Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer (BRCA1, BRCA2, PIK3CA, Ki-67, RET, BRAF, ESR1, NTRK)
- Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
- Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, NTRK) **(to be published)**
- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

SB 535

Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

SB 496

SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

FDA-Approved Targeted Treatments and Companion Diagnostic Tests for Prostate Cancer

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.

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	
Targeted Treatment for Prostate Cancer						
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)[5]	None	
Olaparib (Lynparza)	In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated mCRPC.	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.) 2020	*BRCA1* and *BRCA2* alterations	PROfound NCT02987543 Hussain et al (2020)[6]	2A/Prostate Cancer[3]	
		FoundationOne Liquid CDx (Foundation	*BRCA1*, *BRCA2*, and *ATM* alterations	PROpel NCT03732820		

Treatment	Indications in Prostate Cancer	Companion Diagnostics Date	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline	
			Medicine, Inc.) 2020		Clarke et al (2022)[7,]	
	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)[6,]	2A/Prostate Cancer[3,]
Rucaparib (Rubraca)	Adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.	*BRCA1* and *BRCA2* alterations			TRITON2 NCT02952534 Abida et al (2020)[8,] TRITON 3 NCT02975934 Fizazi et al (2023)[9,]	2A/Prostate Cancer[3,]
Talazoparib (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)[10,]	2A/Prostate Cancer[3,]
Immunotherapy for Solid Tumors[a]						
Larotrectinib (VITRAKVI)	Adult and pediatric patients with solid tumors that:				Hong et al (2020)[11,] - Pooled analysis of 3 studies:	None

Treatment	Indications in Prostate Cancer	Companion Diagnostics Date	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
	have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.				LOXO-TRK-14001 NCT02122913 SCOUT NCT02637687 NAVIGATE NCT02576431
Entrectinib (ROZLYTREK)		NTRK1, NTRK2 and NTRK3 fusions	STARTRK-2 NCT02568267 Doebele et al (2020)[12,] STARTRK-1 NCT02097810 Drilon et al (2017)[13,] Doebele et al (2020)[12,] ALKA-372-001 Doebele et al (2020)[12,] STARTRK-NG NCT02650401 Desai et al (2022)[14,]		None

[a] Indications not specific to prostate cancer.
NCCN: National Comprehensive Cancer Network.
Sources: Food and Drug Administration (2023);[15,] Drugs@FDA (2023)[16,]

Rationale

Background

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.[1,]

Friends of Cancer Research convened a consortium addressing the lack of consistency in the way HRD is defined and measurement methods.[2,] 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..[3,]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.[4,] 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.

Literature Review

Testing for individual genes (not gene panels) associated with Food and Drug Administration (FDA)-approved therapeutics for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. The pivotal evidence is included in Table 1 for informational purposes. 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.

Germline *BRCA1/2* Variant Testing to Select Targeted Treatment in Prostate Cancer

For individuals with metastatic castration-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.

Somatic Testing for Homologous Recombination Repair Gene Alterations Using Tissue Biopsy to Select Targeted Treatment in Prostate Cancer

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.

Somatic Testing for *BRCA1*, *BRCA2*, and *ATM* Alterations Using Liquid Biopsy to Select Targeted Treatment in Prostate Cancer

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.

Neurotrophic Receptor Tyrosine Kinase (*NTRK)* Gene Fusion Testing to Select Targeted Treatment

Clinical Context and Test Purpose

The purpose of tropomyosin receptor kinase (TRK) inhibitors such as larotrectinib and entrectinib for individuals with locally advanced or metastatic solid tumors that 1) have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation, 2) are metastatic or where surgical resection is likely to result in severe morbidity, and 3) have no satisfactory alternative treatments or have progressed following treatment, is to provide a treatment option that is an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with mCRPC to select treatment with FDA-approved therapies.

Interventions

The test being considered in this review is *NTRK* gene fusion testing.

Comparators

The comparator of interest is no *NTRK* gene fusion testing to guide treatment.

Outcomes

The overall outcomes of interest are overall survival (OS), disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity.

Study Selection Criteria

For the evaluation of clinical validity of the *NTRK* gene fusion test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (ie, as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (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.

Clinically Valid and Clinically Useful

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Review of Evidence

Clinical trials have evaluated the effectiveness of using *NTRK* gene fusion testing to identify individuals with solid tumors for treatment with FDA-approved therapies. The incidence of *NTRK* fusions is below 1% for most common cancers such as lung, prostate, and colon cancer. *NTRK* fusion cancers are rare and therefore conducting randomized trials would be challenging. A limitation in relevance is related to the generalizability of its results to populations that were not well represented in the pivotal study due to the small numbers of patients. Although the efficacy of larotrectinib and entrectinib is largely unknown in such cases, in settings where no treatment is available or where available treatment would result in significant morbidity or where the clinical effects of available treatments are modest, it is plausible to assume that larotrectinib or entrectinib may provide an advantage over available therapy for patients with *NTRK* fusion solid tumors. As per the FDA review, there was strong nonclinical support of the antitumor activity of larotrectinib across multiple cell lines and *NTRK* fusion partners, and clinically, durable tumor shrinkage occurred in a consistent fashion in patients with a variety of tumors harboring a diverse array of *NTRK* fusions. In light of these factors, the FDA review teams concluded that pooling of results from patients with *NTRK* fusion-solid tumors was warranted and supported a tissue agnostic indication.

Currently, the only FDA approved companion diagnostic test for larotrectinib and entrectinib is the FoundationOne® CDx (Foundation Medicine).[15,] Multiple commercial laboratories currently offer testing for *NTRK1*, *NTRK2*, and *NTRK3* gene fusions.[4,]

Larotrectinib

FoundationOne Liquid is an FDA-approved companion diagnostic to detect *NTRK* gene fusion in patients who may benefit from treatment with laratrectinib.[15,] Approval was based on pooled results of 3, single-arm prospective studies.[11,] The ORR was 79% (95% confidence interval [CI], 72% to 85%). At the time of data cutoff (February 19, 2019), in 108 participants with confirmed response, the median duration of response (DOR) was 35.2 months (95% CI, 22.8 months to not estimable).

Depending on the cancer site, ORR ranged widely from 0 to 100%. The safety population included 260 patients treated with larotrectinib. regardless of *NTRK*fusion status. Adverse event were primarily Grade 1 or 2, and were similar in pediatric and adult patients. Grade 3 adverse events occurred in 39% of patients, and Grade 4 events occurred in 17% of patients. Serious adverse events included pneumonia, pyrexia, abdominal pain and diarrhea, all occurring in 2% of included patients. Assessment of a causal relationship between larotrectinib and adverse events is limited due to the single-arm design of the study.

Entrectinib

FoundationOne Liquid is an FDA-approved companion diagnostic to detect *NTRK* gene fusion in patients who may benefit from treatment with entrectinib.[15,] In the integrated analysis of STARTRK-1, STARTRK-2, and ALKA-372-001 data,the median age was 58 years (range, 21 to 83 years), 89% had an ECOG performance score of 0 or 1, 63% had received prior anticancer therapy (20% received 1, 43% received ≥2) and 22% had CNS disease at baseline.[12,] Median duration of follow-up was 12.9 months (interquartile range, 8.8 to 18.8 months). In 54 adult patients with *NTRK* fusion-positive solid tumors, the objective response rate was 57% and median DOR was 10.4 months. The safety population included 68 patients with *NTRK* fusion-positive solid tumors who had received any dose of entrectinib; median treatment duration for the safety evaluation was 7.9 months. Adverse events

were graded using the National Cancer Institute Common Toxicity Criteria. Serious treatment-related adverse reactions were reported in 10% of patients. Permanent discontinuation due to treatment-related adverse events occurred in 4% of patients. Assessment of a causal relationship between entrectinib and adverse events is limited due to the single-arm design of the study.

Phase 2 results from the STARTRK-NG trial included 27 children and adolescents, 15 of whom had *NTRK* fusion-positive solid tumors.[14,] The cut-off date for data analysis was September 2020. The objective response rate was 60% after a median duration of 11 months follow-up. Among the total Phase 2 population, 85% (23/27) had a Grade 3 or higher adverse event, most commonly weight gain (33% [9/27]) and a decrease in neutrophil count (22% [6/27]). The STARTRK-NG trial is ongoing, with expected completion in 2027.

Section Summary:
Clinical trials have demonstrated clinical benefit when testing was used to identify individuals for treatment with FDA-approved therapies. 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%.

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 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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 Assocation/Society of Urologic Oncology

In 2023, the American Urological Assocation and the Society of Urologic Oncology published amended guidelines on advanced prostate cancer.[17,] 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 4.2024.[3,] Guidelines are updated frequently; refer to the source for the most current recommendations.

The guidelines include the following relevant recommendations:

Targeted Therapy

- "Olaparib is an option for patients with mCRPC who have an HRR mutation and whose cancer has progressed on prior treatment with androgen receptor-directed therapy regardless of prior docetaxel therapy based on results of a randomized phase 3 study in patients with HRR mutations. Radiographic PFS was improved over physician's choice of abiraterone or enzalutamide. In the pre-docetaxel setting, olaparib is a preferred treatment option for patients with a pathogenic mutation (germline and/or somatic) in BRCA1 or BRCA2, and is also an option in this setting for patients with other HRR gene alterations (ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L)."
- "Rucaparib is an option 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 based on results from a phase 2 trial."

- "Olaparib with abiraterone is an option for certain patients with mCRPC (PROS-16) and a pathogenic BRCA1 or BRCA2 mutation (germline and/or somatic) who have not yet received a novel hormone therapy and who have not yet had treatment in the setting of CRPC based on results of an international, doubleblind, phase 3 trial."
- "Talazoparib plus enzalutamide is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in an HRR 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, depending on prior treatment in other disease settings (PROS-16) based on results from a randomized, double-blind, phase 3 trial."

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 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 (e.g., *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*).

U.S. Preventive Services Task Force Recommendations

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."[18,]

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 2024
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)	696 (actual)	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.

References

1. Mateo J, Boysen G, Barbieri CE, et al. DNA Repair in Prostate Cancer: Biology and Clinical Implications. Eur Urol. Mar 2017; 71(3): 417-425. PMID 27590317
2. Stewart MD, Merino Vega D, Arend RC, et al. Homologous Recombination Deficiency: Concepts, Definitions, and Assays. Oncologist. Mar 11 2022; 27(3): 167-174. PMID 35274707
3. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Prostate Cancer. Verson 4.2024. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed August 7, 2024.
4. TRK Fusion Cancer (Testing). https://trkcancer.com/testing. Accessed August 7, 2024.
5. Chi KN, Rathkopf D, Smith MR, et al. Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. J Clin Oncol. Jun 20 2023; 41(18): 3339-3351. PMID 36952634

6. Hussain M, Mateo J, Fizazi K, et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. Dec 10 2020; 383(24): 2345-2357. PMID 32955174
7. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, Oya M, Shore N, Loredo E, Procopio G, et al for the PROpel Investigators. 2022. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. NEJM Evid 2022;1(9). https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200043. Accessed August 7, 2024.
8. Abida W, Patnaik A, Campbell D, et al. Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration. J Clin Oncol. Nov 10 2020; 38(32): 3763-3772. PMID 32795228
9. Fizazi K, Piulats JM, Reaume MN, et al. Rucaparib or Physician's Choice in Metastatic Prostate Cancer. N Engl J Med. Feb 23 2023; 388(8): 719-732. PMID 36795891
10. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Lancet. Jul 22 2023; 402(10398): 291-303. PMID 37285865
11. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol. Apr 2020; 21(4): 531-540. PMID 32105622
12. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol. Feb 2020; 21(2): 271-282. PMID 31838007
13. Drilon A, Siena S, Ou SI, et al. Safety and Antitumor Activity of the Multitargeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib: Combined Results from Two Phase I Trials (ALKA-372-001 and STARTRK-1). Cancer Discov. Apr 2017; 7(4): 400-409. PMID 28183697
14. Desai AV, Robinson GW, Gauvain K, et al. Entrectinib in children and young adults with solid or primary CNS tumors harboring NTRK, ROS1, or ALK aberrations (STARTRK-NG). Neuro Oncol. Oct 03 2022; 24(10): 1776-1789. PMID 35395680
15. Food and Drug Administration. 2024. List of Cleared or Approved Companion Diagnostic Devices ((n 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. Accessed August 7, 2024.
16. Food and Drug Administration. 2024. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed August 7, 2024.
17. Lowrance W, Dreicer R, Jarrard DF, et al. Updates to Advanced Prostate Cancer: AUA/SUO Guideline (2023). J Urol. Jun 2023; 209(6): 1082-1090. PMID 37096583
18. Centers for Medicare & Medicaid Services. 2020. National Coverage Determination 90.2: Next Generation Sequencing. https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?NCDId=372&ncdver=2&NCAId=296&bc=ACAAAAAACAAA&. Accessed August 7, 2024.

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
- Clinical findings (i.e., pertinent symptoms and duration)
- Comorbidities
- Activity and functional limitations
- Family history, if applicable
- Reason for procedure/test/device, when applicable
- Pertinent past procedural and surgical history
- Pertinent past and present diagnostic testing and results
- Prior pertinent treatments, duration, and response
- Treatment plan (i.e., surgical or medication intervention)

- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, US)

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)
- New medications prescribed

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden (FoundationOne CDx™ (F1CDx)
	0129U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53) BRCAplus
	0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations (FoundationOne® Liquid CDx)
	81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (e.g., solid tumors) translocation analysis
	81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (e.g., solid tumors) translocation analysis

Type	Code	Description
	81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (e.g., solid tumors) translocation analysis
	81194	NTRK (neurotrophic receptor tyrosine kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis
	81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
	81215	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
	81216	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
	81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
	81307	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence
	81308	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant
	81408	Molecular pathology procedure, Level 9
	81432	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/01/2022	New policy.
06/01/2023	Annual review. Policy statement, guidelines and literature updated. Policy title changed from Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, Microsatellite Instability/Mismatch Repair, Tumor Mutational Burden) to current one. Coding update.
10/01/2025	Policy reactivated. Previously archived from 07/01/2024 to 09/30/2025

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) 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 the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** Blue font: Verbiage Changes/Additions
Reactivated Policy **Policy Statement:** N/A	**Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, NTRK Gene Fusion) 2.04.155** **Policy Statement:** I. 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**. II. All other uses of germline *BRCA1/2* variant analysis to guide prostate cancer targeted therapy are considered **investigational**. III. 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**. IV. All other uses of somatic testing using tissue biopsy for HRR gene alterations to guide prostate cancer targeted therapy are considered **investigational**. V. 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**. VI. All other uses of somatic testing using circulating tumor DNA testing (liquid biopsy) to guide prostate cancer targeted therapy are considered **investigational**.

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
	VII. 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). VIII. 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.