Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 3/1/25**
(See policy history boxes for previous effective dates)

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)

Description/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 genes (BR*CA1*, *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).

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.[5] 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.

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.

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).[3]

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.

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.

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).[4] 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.

Regulatory Status

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 September 19, 2024. An up-to-date list of FDA cleared or approved companion diagnostics devices in vitro and imaging tools website**.**

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.	Foundation One CDx (Foundation Medicine, Inc.) 2023	*BRCA1 and BRCA2 alterations*	MAGNITUDE NCT03748641 Chi et al (2023)[6]	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)[7]	2A/ Prostate Cancer[3].
		Foundation One Liquid CDx (Foundation Medicine, Inc.) 2020	*BRCA1*, *BRCA2*, and *ATM* alterations	PROpel NCT03732820 Clarke et al (2022)[8]	
	Adults with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone.	Foundation One 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)[7,]	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	Foundation One Liquid CDx (Foundation Medicine, Inc.) 2020	*BRCA1* and *BRCA2* alterations	TRITON2 NCT02952534 Abida et al (2020)[9] TRITON 3 NCT02975934 Fizazi et al (2023)[10]	2A/ Prostate Cancer[3].

	therapy and a taxane-based chemotherapy.				
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) [11]	2A/ Prostate Cancer[16]
Immunotherapy for Solid Tumors[a]					
Larotrectinib (VITRAKVI)	• Adult and pediatric patients with solid tumors that: • 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.	Foundation One Liquid CDx (Foundation Medicine, Inc.) 2020	NTRK1, NTRK2 and NTRK3 fusions	Hong et al (2020)[12] - Pooled analysis of 3 studies: • LOXO-TRK-14001 NCT02122913 • SCOUT NCT02637687 • NAVIGATE NCT02576431	None
Entrectinib (ROZLYTREK)	Adult and pediatric patients 12 years of age and older with solid tumors that: • have a neurotrophic tyrosine receptor 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 either progressed	Foundation One Liquid CDx (Foundation Medicine, Inc.) 2022	NTRK1, NTRK2 and NTRK3 fusions	STARTRK-2 NCT02568267 Doebele et al (2020)[13] STARTRK-1 NCT02097810 Drilon et al (2017)[14] Doebele et al (2020)[12.] ALKA-372-001 Doebele et al (2020)[13.] STARTRK-NG NCT02650401 Desai et al (2022)[15.]	None

	following treatment or have no satisfactory alternative therapy.				

[a] Indications not specific to prostate cancer.

NCCN: National Comprehensive Cancer Network.

Sources: Food and Drug Administration (2024);[17] Drugs@FDA(2024)[18]

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.

Medical Policy Statement

The clinical utility of germline *BRCA1/2* variant analysis using tissue biopsy or circulating tumor DNA testing (liquid biopsy) for individuals with metastatic castrate-resistant prostate cancer (mCRPC) to select treatment with FDA-approved targeted therapies is **established** when criteria are met**.**

The clinical utility of somatic testing using tissue biopsy or circulating tumor DNA testing (liquid 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 is **established** when criteria are met.

The clinical utility of 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 is **established** when criteria are met.

The clinical utility of testing of *NTRK* gene fusions using tissue biopsy or circulating tumor DNA testing (liquid biopsy) in individuals with mCRPC to select treatment with FDA-approved targeted therapies is **established** when criteria are met.

Inclusionary and Exclusionary Guidelines

Inclusions (for all FDA-approved therapies, please check the FDA site):

The clinical utility of Germline and Somatic Biomarker Testing using tumor tissue or circulating tumor DNA (Liquid Biopsy) for Targeted Treatment in Prostate Cancer (*BRCA1/2,* Homologous

Recombination Repair Gene Alterations) has been established when any of the following criteria are met.

- Germline BRCA1/2 variant analysis for individuals with advanced for metastatic castrate-resistant prostate cancer (mCRPC) with FDA-approved targeted therapies.
- Somatic BRCA1/2 variant analysis using tumor tissue for individuals with advanced for metastatic castrate-resistant prostate cancer (mCRPC) with FDA-approved targeted therapies.
- Somatic testing using tissue biopsy or circulating tumor DNA testing (liquid biopsy) for homologous recombination repair (HRR) gene alterations (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51 B*, *RAD51C*, *RAD51D,* and *RAD54L*) to select treatment for metastatic castrate-resistant prostate cancer (mCRPC) with FDA-approved targeted therapies.
- 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.
- Somatic testing of *NTRK* gene fusions using tissue or circulating tumor DNA (Liquid Biopsy) in individuals with mCRPC to select treatment with FDA-approved targeted therapies. The following medications are FDA approved when NTRK mutation is identified: for example Repotrectinib, Larotrectinib, entrectinib.
- Repeated testing of gene variants using tissue biopsy or circulating tumor DNA (liquid biopsy) for determining targeted therapy or immunotherapy in individuals with prostate cancer with suspected acquired resistance at time of cancer progression for treatment decision-making.
- Paired somatic-germline testing in order to distinguish whether findings in tumor tissue are acquired somatic changes or germline changes. The goal of this paired testing is to identify truly somatic changes to guide treatment.
- Concurrent somatic liquid-based and tissue-based genomic testing. 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.

Exclusions:

- All other uses of germline *BRCA1/2* variant analysis to guide prostate cancer targeted therapy are considered investigational.
- All other uses of somatic testing using tissue biopsy or circulating tumor DNA (liquid biopsy) for HRR gene alterations to guide prostate cancer targeted therapy are considered investigational.
- All other uses of somatic testing using tissue biopsy or circulating tumor DNA testing (liquid biopsy) to guide prostate cancer targeted therapy are considered investigational.
- 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.
- All other uses of *NTRK* fusion not mentioned in the above inclusion criteria for mCRPC is considered investigational.

Circulating tumor DNA (Liquid Biopsy):

The clinical utility of circulating tumor DNA and circulating tumor cells for germline and somatic biomarker testing for targeted treatment in prostate cancer is established when there is clinical documentation that tissue-based testing cannot be performed (e.g., insufficient sample, inaccessible tumor or where there may be a delay in obtaining tumor

sample) OR tissue-based testing is not required when there is an FDA-approved companion diagnostic device that is a circulating tumor test (liquid biopsy).

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81162	81163	81164	81165	81166	81167
81191	81192	81193	81194		
81212	81215	81216	81217	81301	81307
81308	81408**	81432	81479*		
0037U	0172U	0239U			

** Policy criteria must be met. This code is subject to individual review.*
**(ataxia-telangiectasia mutated [ATM])

Other codes (investigational, not medically necessary, etc.):

0129U	0475U

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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 CRPC 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.

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

(B*RCA1*, *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.

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.

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 11arotrectinib. Regardless of NTRKfusion 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 arotrectinib, 3, single-arm studies evaluating the efficacy of arotrectinib 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. 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 (B*RCA1*, *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 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 Association/Society of Urologic Oncology
In 2023, the American Urological Association and the Society of Urologic Oncology published amended guidelines on advanced prostate cancer.[19] 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.[16] 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

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

U.S. Preventive Services Task Force Recommendations
Not applicable.

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	Sept 2025

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

Government Regulations
National:

Next Generation Sequencing (NGS)
90.2 Manual Section Title: Next Generation Sequencing (NGS) Effective Date 01/27/20 Implementation Date 11/13/2020

Indications and Limitations of Coverage

B. Nationally Covered Indications
1. Somatic (Acquired) Cancer
Effective for services performed on or after March 16, 2018, the Centers for Medicare & Medicaid Services (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.

2. Germline (Inherited) Cancer

Effective for services performed on or after January 27, 2020, CMS has determined that NGS as a diagnostic laboratory test is reasonable and necessary and covered nationally for patients with germline (inherited) cancer, when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

a. Patient has:

i. ovarian or breast cancer; and,
ii. a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer; and,
iii. a risk factor for germline (inherited) breast or ovarian cancer; and
iv. not been previously tested with the same germline test using NGS for the same germline genetic content.

b. The diagnostic laboratory test using NGS must have all of the following:

i. FDA-approval or clearance; and,
ii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

C. Nationally Non-Covered Indications

1. Somatic (Acquired) Cancer

Effective for services performed on or after March 16, 2018, NGS as a diagnostic laboratory test for patients with acquired (somatic) cancer are non-covered if the cancer patient does not meet the criteria noted in section B.1., above.

D. Other

1. Somatic (Acquired) Cancer

Effective for services performed on or after March 16, 2018, Medicare Administrative Contractors (MACs) may determine coverage of NGS as a diagnostic laboratory test for patients with advanced cancer only when the test is performed in a CLIA-certified laboratory, when ordered by a treating physician, and when the patient has:

a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and,
b. not been previously tested with the same test using NGS for the same cancer genetic content, and
c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

2. Germline (Inherited) Cancer

Effective for services performed on or after January 27, 2020, MACs may determine coverage of NGS as a diagnostic laboratory test for patients with germline (inherited) cancer only when the test is performed in a CLIA-certified laboratory, when ordered by a treating physician, when results are provided to the treating physician for management of the patient and when the patient has:

a. any cancer diagnosis; and,
b. a clinical indication for germline (inherited) testing of hereditary cancers; and,
c. a risk factor for germline (inherited) cancer; and,
d. not been previously tested with the same germline test using NGS for the same germline genetic content.

Local:

NA

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Germline and Somatic Biomarker Testing (Including Liquid Biopsy) For Targeted Treatment in Ovarian Cancer (BRCA 1, BRCA2, Homologous Recombination Deficiency, NTRK)
- Circulating Tumor DNA and Circulating Tumor Cells for Selecting targeted therapy for advanced solid Cancers (Liquid Biopsy)
- Genetic Testing-Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB)
- Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)
- Genetic Testing—BRAF/NTRK Mutation in Selecting Melanoma Patients for Targeted Therapy Including Liquid Biopsy (MXD)
- Somatic Biomarker Testing (including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, NTRK and HER2 (EST)
- Genetic Testing – NGS (NEXT-GENERATION SEQUENCING) Testing of Multiple Genes (Panel) for Solid and Hematolymphoid Malignant Conditions

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 9/19/24 the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/24	12/20/23		Joint policy established (jf) Vendor Managed: NA
7/1/24	4/16/24		Coming early for Minor Edits (jf): • Medical policy received an inquiry from the UM team. They had questions on the MPS and inclusions. Edits made to the MPS and inclusions for clarity. • Added in first paragraph of inclusions “using tumor tissue or circulating tumor DNA” • Removed “may be” from MPS and added “is” Added 2 bullets under inclusions: • Germline BRCA1/2 variant analysis for individuals with advanced for metastatic castrate-resistant prostate cancer (mCRPC) with FDA-approved targeted therapies. • Somatic BRCA1/2 variant analysis using tumor tissue for individuals with advanced for metastatic castrate-resistant prostate cancer (mCRPC) with FDA-approved targeted therapies. • Received email from MPC on 2/29/24 that Myriad genetics verified that BRACAnalysis CDX is represented code with 88162. Edit made to the nomenclature and BRACAnalysis CDx removed from code 81479. • Removal of * on code 81479
11/1/24	8/20/24		• PLA 2024 Code Update Effective 7/1/24 (jf)

			• Add 0475U as E/I Vendor Managed: NA
3/1/25	12/17/24		Routine maintenance (jf) Vendor Managed: NA **Title Change 12/24:** per BCBSA added “NTRK Gene Fusion”. **Current 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) ○ Testing of *NTRK* gene fusions in individuals with mCRPC to select treatment with FDA-approved targeted therapies is **established.** ○ Edits to the title, rationale, MPS, inclusions,exclusions and summary of evidence ○ Added NTRK Gene Fusion in title. New 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) ○ Added Ref: 3,4,5,12,13,14,15 ○ Added Codes as Established 81191-81194 NTRK translocation analysis code range ○ Code 81432 revised Effective Date 1/1/25

Next Review Date: 4th Qtr, 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GERMLINE AND SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT IN PROSTATE CANCER (*BRCA1/2,* HOMOLOGOUS RECOMBINATION REPAIR GENE ALTERATIONS, *NTRK* GENE FUSION)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered if criteria is met
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.