2.04.155	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)		
Original Policy Date:	December 1, 2022	**Effective Date:**	December 1, 2022
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Policy Statement

I. Germline *BRCA1/2* variant analysis for individuals with metastatic castrate-resistant prostate cancer (mCRPC; See Policy Guidelines) to select treatment with FDA-approved targeted therapies or immunotherapy may be considered **medically necessary**.
II. All other uses of germline *BRCA1/2* variant analysis to guide prostate cancer targeted therapy or immunotherapy 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 or immunotherapy may be considered **medically necessary**. (Note: Testing for HRR gene mutations is not the same as HRD-Homologous Recombination Deficiency-associated with ovarian cancer) See Policy Guidelines.
IV. All other uses of somatic testing for HRR gene alterations to guide prostate cancer targeted therapy or immunotherapy are considered **investigational**.
V. Tumor testing for microsatellite instability(MSI) or deficient mismatch repair (dMMR; MSH 2, MSH 6, PMS 2 and MLH 1)) to select treatment for unresectable or metastatic prostate cancer with FDA-approved targeted therapies or immunotherapy (e.g., pembrolizumab/Keytruda). may be considered **medically necessary**. See Policy Guidelines.
VI. All other uses of tumor testing for MSI or dMMR to guide prostate cancer targeted therapy or immunotherapy are considered **investigational**.
VII. *BRCA1/2* and *ATM* variant analysis using ctDNA (liquid biopsy) for individuals with mCRPC to select treatment with FDA-approved targeted therapies may be considered **medically necessary**. (Note: most liquid biopsies are larger panels and individual gene testing is not available, so a panel including these 3 genes can be approved for this purpose).
VIII. All other uses of biomarker testing with ctDNA (liquid biopsy) to guide prostate cancer targeted therapy or immunotherapy is considered **investigational** (see Policy Guidelines). 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

Androgen deprivation therapy (ADT) is usually the initial treatment for patients with advanced prostate cancer. Disease that progresses white the patient is on ADT is referred to a castration-resistant prostate cancer.

HRR testing vs. HRD: Homologous recombination occurs in early cell division when homologous chromosomes pair up. There are a lot of DNA breaks during this process, which HRR fixes similar to the MisMatch Repair (MMR) genes. MMR has to do with smaller breaks or changes with nucleotides. Both repair the normally occurring DNA breaks that minimize mutations. When absent or deficient, more mutations occur which can lead to cancer. HRR gene mutations (beyond BRCA) are not interchangeable with genomic instability. There are about 14 HRR genes, and 4 common MMR genes. The HRR pathway is sometimes referred to as the PARP pathway. HRR mutations are an indication for PARP inhibitor (e.g., Olaparib/Lynparza) treatment.

Homologous recombination deficiency (HRD) is a similar tumor characteristic that is defined by the inability to accurately repair double-strand breaks (DSBs) in DNA via homologous

recombination. HRD can be accessed via 2 different types of biomarkers. In ovarian cancers, these include individual mutations in BRCA1 or BRCA2 and the assessment of genomic instability (Loss of Heterozygosity or LOH, Large-scale State Transitions or LST and Telomeric Allelic Imbalance or TAI). Genomic instability, or large-scale structural rearrangements to chromosomes, results in specific measurable genomic aberrations and serves as the "collateral damage" that can occur to the genome as a result of HRD. Tumor samples that have individual *BRCA1/2* mutations or markers of genomic instability are characterized as HRD positive. HRD testing is done routinely for ovarian cancer.

MSI/dMMR: Microsatellites are small repeat sequences in non-coding DNA, usually 2-7 nucleotides. A simple PCR test can identify them. MMR genes (e.g., MSH2, MSH6, PMS2, and MH1) function to repair these insertions and deletions (indels). When MMR genes are deficient (dMMR), the microsatellites become more frequent or unstable (MSI-H). dMMR can be checked using IHC (ImmunoHisto Chemistry) that looks for absence of the normal proteins produced by the MMR genes, or by looking for mutations in the genes. dMMR usually leads to MSI-H.

This policy does not address NTRK testing. The use of tropomyosin receptor kinase (TRK) inhibitors for individuals with neurotrophic tyrosine receptor kinase (NTRK) gene fusion-positive solid tumors is addressed separately in evidence review 5.01.31.

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., 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.

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

Repeat Genomic Testing

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

Paired Somatic-Germline Testing

Testing for genetic changes in tumor tissue assesses somatic changes. Some somatic testing involves a paired blood analysis in order to distinguish whether findings in tumor tissue are acquired somatic changes or germline changes. Some laboratories offer paired tumor sequencing and germline sequencing which is done at the same time and in the same laboratory. The goal of this paired testing is to identify truly somatic changes to guide treatment. However, paired testing can also identify potential germline changes that might indicate an inherited cancer syndrome. These results would need to be confirmed through germline testing if personal and family cancer history is consistent with an inherited cancer syndrome (see policies related to inherited cancer syndromes, 2.04.02, 2.04.08, 2.04.88, 2.04.101).

Paired genetic testing is different than concurrent somatic-germline testing. In concurrent testing, the germline results are not used to filter the somatic results. Rather, the laboratories perform large, separate panels of germline and somatic variants. The goal is to identify options for genome-informed treatment and to identify hereditary cancer risk. For concurrent panel testing, see evidence review 2.04.93 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing for germline panel, and see evidence review 2.04.115 - 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.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" - to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence

Variant Classification	Definition
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients 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.

Description

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

Related Policies

- 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
- Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management
- 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 and Immunotherapy in Breast Cancer
- Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
- Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer
- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the 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 mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Table 1 summarizes the targeted treatments approved by the FDA for patients with prostate cancer, along with the approved companion diagnostic tests. The information in Table 1 was current as of August 15, 2022. 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. The table does not include NTRK testing (Refer to policy 5.01.31).

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

Treatment	Indication in Prostate Cancer	Companion Diagnostic	Biomarkers
Targeted Treatment for Prostate Cancer			
Olaparib (Lynparza)	Adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	*BRCA1* and *BRCA2* Mutations
		FoundationOne CDx (Foundation Medicine, Inc.)	Homologous recombination repair (HRR) genes: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*,*CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*,*RAD51D,* and *RAD54L* alterations
		Foundation One Liquid CDx (Foundation Medicine, Inc.)	*BRCA1*, *BRCA2*, and *ATM* alterations

Treatment	Indication in Prostate Cancer	Companion Diagnostic	Biomarkers	
	for Lynparza.			
Rucaparib (Rubraca)	Adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca.	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations	
Immunotherapy for Solid Tumors				
Pembrolizumab(Keytruda)	Adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options	Foundation One CDx (Foundation Medicine, Inc.)	Microsatellite instability-High (MSI-H)	
	Adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (≥10 mutations/mega base) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative	Foundation One CDx (Foundation Medicine, Inc.)	TMB ≥ 10 mutations per megabase	

Treatment	Indication in Prostate Cancer	Companion Diagnostic	Biomarkers
	treatment options		

Sources: Food and Drug Administration (2022);[6] Drugs@FDA[7]

Rationale

Background

Homologous Recombination Repair (HRR) Gene Alterations (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D,* and *RAD54L*) to Guide Treatment

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 which are a subset of the 14 genes approved by the FDA (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D,* and *RAD54L)*, and acknowledges the 14 HRR genes for determining eligibility for olaparib.[3]

Mismatch Repair Deficiency/Microsatellite Instability

Mismatch repair deficiency (dMMR) and high levels of microsatellite instability (MSI-H) describe cells that have alterations in certain genes involved in correcting errors made when DNA is replicated. dMMR tumors are characterized by a high tumor mutational load and potential responsiveness to anti-PD-L1-immunotherapy. MMR deficiency is most common in colorectal cancer, other types of gastrointestinal cancer, and endometrial cancer, but it may also be found in other cancers including prostate cancer. Microsatellite instability testing is generally performed using polymerase chain reaction (PCR) for 5 biomarkers, although other biomarker panels and next generation sequencing (NGS) are sometimes performed. High microsatellite instability is defined as 2 or more of the 5 biomarkers showing instability or more than 30% of the tested biomarkers showing instability depending on what panel is used. Microsatellite instability testing is generally paired with immunohistochemistry (IHC) assessing lack of protein expression from 4 DNA mismatch repair genes thereby reflecting dMMR.[4]

Tumor Mutational Burden

Tumor mutational burden (TMB), a measure of gene mutations within cancer cells, is an emerging biomarker of outcomes with immunotherapy in multiple tumor types. Initially, assessments of TMB involved whole exome sequencing (WES). More recently, targeted NGS panels are being adapted to estimate TMB. Currently FoundationOne CDx is the only U.S. Food and Drug Administration (FDA)-approved panel for estimating TMB, but others are in development.[5,]

Detecting Circulating Tumor DNA and Circulating Tumor Cells (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.

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total ctDNA. Therefore, more sensitive methods than the standard sequencing approaches (e.g., Sanger sequencing) are needed.

Intact circulating tumor cells (CTCs) are released from a primary tumor and/or a metastatic site into the bloodstream. The half-life of a CTC in the bloodstream is short (1-2 hours), and CTCs are cleared through extravasation into secondary organs. Most assays detect CTCs through the use of surface epithelial markers such as EpCAM and cytokeratins. The primary reason for detecting CTCs is prognostic, through quantification of circulating levels.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Biomarker Testing Using Tissue Biopsy to Select Targeted Treatment

Clinical Context and Test Purpose

Prostate cancer treatment selection is informed by tumor type, grade, stage, patient performance status and preference, prior treatments, and the molecular characteristics of the tumor such as the presence of driver mutations. One purpose of biomarker testing of patients who have advanced cancer is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment).
The question addressed in this evidence review is: Does biomarker testing of tumor tissue for *BRCA1/2* or homologous repair deficiency, or germline testing for *BRCA 1/2* variants improve the net health outcome in individuals with prostate cancer?

Note that this policy does not review NTRK gene fusions; The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with prostate cancer for whom the selection of targeted treatment depends on the molecular characterization of the tumor.

Interventions
The technologies being considered are germline *BRCA1/2* variant testing, or somatic testing for homologous recombination repair (HRR) gene alterations (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D,* and *RAD54L*), and tumor testing for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) to guide treatment.

Comparators
Decisions about treatment in prostate cancer are based on clinical characteristics. The comparator would be no variant testing to guide treatment.

Outcomes
The general outcomes of interest in oncology are overall survival (OS), disease-specific survival, quality of life (QOL), treatment-related mortality and morbidity.

Beneficial outcomes resulting from a true-positive test result are prolonged survival, reduced toxicity, and improved QOL associated with receiving a more effective targeted therapy. Beneficial outcomes from a true negative result are prolonged survival associated with receiving chemotherapy in those without driver mutations.

Harmful outcomes resulting from a false-negative test result include shorter survival from receiving less effective and more cytotoxic chemotherapy in those with driver mutations; possible harmful outcomes resulting from a false-positive test result are a shorter survival from receiving potentially ineffective targeted treatment and delay in initiation of chemotherapy in those without driver mutations.

The overall response rate (ORR) may be used as a surrogate endpoint reasonably likely to predict clinical benefit in patients with refractory solid tumors. ORR can be measured by the proportion of patients with best overall confirmed response of complete response) or partial response by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1),[8,] or Response Assessment in Neuro-Oncology criteria,[9,] as appropriate by a blinded and independent adjudication committee. There are clearly defined quantitative thresholds for the follow-up of patients in oncology trials. A general rule is a continuation of treatment until disease progression or unacceptable toxicity. Long-term follow-up outside of a study setting is conducted to determine survival status. The duration of follow-up for the outcomes of interest is 6 months and 1 year.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for randomized controlled trials (RCTs);
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

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 poly adenosine diphosphate-ribose polymerase (PARP) inhibitor drugs in individuals with prostate cancer confirmed to have a *BRCA1*, *BRCA2*, or *ATM alteration*. Summarized below are the pivotal trials that supported the *BRCA* variant-related FDA-approved indications in prostate cancer.

Olaparib

Hussain et al (2020) published results from the open-label, multicenter, phase 3 PROfound trial (NCT02987543), which randomized individuals with metastatic castration-resistant prostate cancer (mCRPC) and disease progression following prior treatment with a next-generation hormonal agent to treatment with olaparib 300 mg twice daily (n=256) or investigator's choice of enzalutamide or abiraterone acetate plus prednisone (n=131).[10,] Study participants were divided into 2 cohorts based on their HRR gene mutation status. Specifically, individuals with mutations in *BRCA1*, *BRCA2*, or *ATM* were randomized to cohort A (n=245) and those with mutations in 12 other HRR pathway genes (*BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L)* were randomized to cohort B (n=142). Participants with co-mutations were assigned to cohort A. The primary efficacy outcome was radiological progression-free survival (rPFS) in cohort A, which demonstrated a statistically significant improvement for olaparib compared to control with a median rPFS of 7.4 months versus 3.6 months (hazard ratio [HR], 0.34; 95% confidence interval [CI], 0.25 to 0.47; p <.0001). The median duration of OS in cohort A was 19.1 months with olaparib and 14.7 months with control therapy (HR, 0.69; 95% CI, 0.50 to 0.97; p =.02). In cohort B, the median duration of OS was 14.1 months with olaparib and 11.5 months with control therapy. In the overall population (cohorts A and B), the corresponding durations were 17.3 months and 14.0 months.

Rucaparib

Abida et al (2020) published results from the phase 2, multi-center, single-arm clinical trial of rucaparib in individuals with *BRCA*-mutated mCRPC that supported its accelerated FDA approval in 2020 (TRITON2).[11,] This trial enrolled 115 participants who were treated with rucaparib 600 mg twice daily. For the efficacy population, median treatment duration was 8.1 months and median follow-up was 17.1 months. The primary endpoint of objective response rate, which was rated by blinded, independent radiology review, was 43.5% (95% CI, 31.0% to 56.7%). Median rPFS duration was 9.0 months (95% CI, 8.3 to 13.5). Anemia was the most frequent grade 3 or higher adverse event (25.2%). A key limitation of this trial is its lack of a control group. Continued approval for this indication for rucaparib may be contingent upon verification of progression-free survival in the ongoing confirmatory TRITON3 trial (NCT02975934), which is a randomized, controlled phase 3 trial evaluating rucaparib 600 mg twice daily versus physician’s choice of treatment in patients with mCRPC and a deleterious germline or somatic *BRCA1*, *BRCA2*, or *ATM* mutation.

Pembrolizumab

FDA approval of pembrolizumab was supported by the Phase 2 KEYNOTE-158 study. The trial included a total of 233 previously treated participants with MSI-H solid tumors, 6 of whom had prostate cancer. In the full cohort, the ORR was 34.3% (95% CI, 28.3% to 40.8%). Median progression-

free survival (PFS) was 4.1 months (95% CI, 2.4 to 4.9 months) and median OS was 23.5 months (95% CI, 13.5 months to not reached). Treatment-related adverse events occurred in 151 patients (64.8%).[12,]

Section Summary: Biomarker Testing Using Tissue Biopsy to Select Targeted Treatment

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

Tumor Mutational Burden Testing to Guide Treatment for Metastatic Prostate Cancer

Clinical Context and Test Purpose

The purpose of tumor mutational burden (TMB) testing in individuals with advanced prostate cancer is to inform a decision on whether patients should receive immunotherapy versus another systemic therapy. The goal of immunotherapy is to preferentially kill malignant cells without significant damage to normal cells so that there is improved therapeutic efficacy along with decreased toxicity. The question addressed in this evidence review is: In individuals with metastatic prostate cancer, does the use of TMB testing improve the net health outcome?

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

Populations

The relevant population of interest is individuals with metastatic prostate cancer.

Interventions

Tumor mutational burden, a measure of gene mutations within cancer cells, is proposed as a biomarker for response to immunotherapy.

Comparators

The comparator is treatment as usual without TMB testing.

Outcomes

The general outcomes of interest in oncology are OS, disease-specific survival, QOL, treatment-related mortality and morbidity.

Beneficial outcomes resulting from a true-positive test result are prolonged survival, reduced toxicity, and improved QOL associated with receiving a more effective targeted therapy. Beneficial outcomes from a true negative result are prolonged survival associated with receiving chemotherapy in those without driver mutations.

Harmful outcomes resulting from a false-negative test result include shorter survival from receiving less effective and more cytotoxic chemotherapy in those with driver mutations; possible harmful outcomes resulting from a false-positive test result are a shorter survival from receiving potentially ineffective targeted treatment and delay in initiation of chemotherapy in those without driver mutations.

The ORR may be used as a surrogate endpoint reasonably likely to predict clinical benefit in patients with refractory solid tumors. ORR can be measured by the proportion of patients with best overall confirmed response of complete response) or partial response by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1),[8,] or Response Assessment in Neuro-Oncology criteria, [9,]as appropriate by a blinded and independent adjudication committee.

There are clearly defined quantitative thresholds for the follow-up of patients in oncology trials. A general rule is a continuation of treatment until disease progression or unacceptable toxicity. Long-term follow-up outside of a study setting is conducted to determine survival status. The duration of follow-up for the outcomes of interest is 6 months and 1 year.

Study Selection Criteria

For the evaluation of clinical validity, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology;
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid

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).

Review of Evidence

FDA-Approved Companion Diagnostic Test

FoundationOne CDx is FDA approved as a companion diagnostic for use with pembrolizumab in patients with TMB-high (≥ 10 mutations per megabase) solid tumors. Approval was based on results of the KEYNOTE-158 study that enrolled patients with solid tumors, but none of the patients evaluated had prostate cancer.

Nonrandomized Trials

Marabelle et al (2020) reported the association of high TMB to response to pembrolizumab in patients with solid tumors enrolled in a prespecified exploratory analysis of the KEYNOTE-158 study.[13,] High TMB was defined as >10 mutations per megabase according to the FoundationOne CDx panel. The proportion of patients with an objective response in the TMB-high group was 29%. At a median follow-up of approximately 3 years, the median duration of response was not reached in the TMB-high group and was 33.1 months in the non-TMB-high group. Notably, TMB-high status was associated with improved response irrespective of programmed death-ligand 1 (PD-L1). Median PFS and OS did not differ between the high and non-high TMB groups. Objective responses were observed in 24 (35%; 95% CI 24 to 48) of 68 participants who had both TMB-high status and PD-L1-positive tumors (ie, PD-L1 combined positive score of ≥1) and in 6 (21%; 8 to 40) of 29 participants who had TMB-high status and PD-L1-negative tumors. Study-eligible cancers were limited to anal, biliary, cervical, endometrial, mesothelioma, neuroendocrine, salivary, small-cell lung, thyroid, and vulvar. Because no patients with prostate cancer were included in these analyses, it is not possible to draw conclusions about the clinical validity and utility of TMB in this group of patients.

Clinically Useful

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.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. There is no direct evidence of clinical utility of TMB testing to guide prostate cancer treatment.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. Because the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Tumor Mutational Burden Testing to Guide Treatment for Metastatic Prostate Cancer

In a prespecified exploratory analysis of a nonrandomized trial of pembrolizumab in patients with various solid tumors, objective responses were observed in 35% of participants who had both TMB-high status and PD-L1-positive tumors and in 21% of participants who had TMB-high status and PD-L1-negative tumors. A TMB-high status was associated with improved response irrespective of PD-L1 status. Median OS and PFS survival were not significantly different between TMB groups. Because no patients with prostate cancer were included in these analyses, it is not possible to draw conclusions about the clinical validity and utility of TMB in this group of patients. These results need to be confirmed in well-designed prospective studies enrolling patients with prostate cancer.

Biomarker Testing with Circulating Tumor DNA (Liquid Biopsy) to Guide Treatment in Prostate Cancer

Clinical Context and Test Purpose

One purpose of liquid biopsy testing of patients who have advanced prostate cancer is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment). Treatment selection is informed by tumor type, grade, stage, patient performance status and preference, prior treatments, and the molecular characteristics of the tumor such as the presence of driver mutations.

The question addressed in this evidence review is: Does use of circulating tumor DNA (ctDNA) testing (liquid biopsy) to select treatment in patients with prostate cancer improve the net health outcome? The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are patients with advanced prostate cancer for whom the selection of treatment depends on the molecular characterization of the tumor(s).

Interventions

The test being considered is liquid biopsy using ctDNA. Both targeted polymerase chain reaction-based assays and broad next-generation sequencing-based approaches are available.

Comparators

For patients who are able to undergo a biopsy, molecular characterization of the tumor is performed using standard tissue biopsy samples. Patients unable to undergo a biopsy generally receive standard therapy.

Outcomes

Liquid biopsies are easier to obtain and less invasive than tissue biopsies. True-positive liquid biopsy test results lead to the initiation of appropriate treatment (e.g., targeted therapy) without a tissue biopsy. False-positive liquid biopsy test results lead to the initiation of inappropriate therapy, which could shorten progression-free survival.

In patients able to undergo a tissue biopsy, negative liquid biopsies reflex to tissue testing. In patients unable to undergo a tissue biopsy, a negative liquid biopsy result would not change empirical treatment. Therefore, health outcomes related to negative test results do not differ between liquid biopsy and tissue biopsy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for randomized controlled trials (RCTs);

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

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

Olaparib

FoundationOne Liquid is an FDA-approved companion diagnostic to detect *BRCA1*, *BRCA2*, or *ATM* alterations in mCRPC patients who may benefit from treatment with olaparib.[14,] Approval was based on a retrospective analysis of data from participants enrolled in cohort A of the PROfound trial (i.e., patients who had a *BRCA2*, *BRCA2*, or *ATM* tumor variant). The sponsor conducted a clinical bridging study to demonstrate the concordance between variant status by the clinical trial assay used for enrollment and the FoundationOne Liquid CDx, and the effectiveness of olaparib in patients identified with a variant by the liquid test. The point estimates of PPA and NPA between FoundationOne® Liquid CDx and the F1 LDT CTA assay and the corresponding 95% confidence intervals were: PPA, 79.9% (72.2% to 86.2%); NPA, 91.8% (87.0, 95.2). Estimated radiological PFS HR and the corresponding 95% confidence intervals were 0.33 [0.21, 0.53] for the FoundationOne Liquid CDx ATM/BRCA1/BRCA2 positive and F1 LDT CTA ATM/BRCA1/BRCA2 positive population, which were comparable with the observed radiological PFS hazard ratio and the corresponding 95% confidence intervals of 0.34 [0.25, 0.47] for the F1 LDT CTA *ATM/BRCA1/BRCA2* positive population.

Rucaparib

FoundationOne Liquid is an FDA-approved companion diagnostic to identify with patients BRCA1/2 alterations eligible for rucaparib treatment in prostate cancer. [15,]There are no FDA-approved tissue-based companion diagnostic alternatives for this indication. Approval was based on results of the TRITON2 clinical trial (NCT02952534). The ORR in the primary efficacy population was 46.3% (95% CI, 30.7% to 62.6%) in *BRCA*-positive patients determined by FoundationOne Liquid CDx, which was comparable to the ORR of 43.5% (31.0% to 56.7%) in patients identified by the clinical trial assay (central plasma, central tissue, or local testing). Loehr et al (2020) reported confirmed ORR by enrollment assay in 62 evaluable participants with measurable disease and found overlapping confidence intervals for all 3 estimates.[16,] Those enrolled by central tissue testing had an ORR of 55.0% (95% CI, 31.5% to 76.9%; 11/20), compared with 31.3% (95% CI, 11.0% to 58.7%; 5/16) in patients enrolled by central plasma test and 42.3% (95% CI, 23.4 to 63.1; 11/26) in patients enrolled by local test.

Section Summary: Biomarker Testing with Circulating Tumor DNA (Liquid Biopsy) to Guide Treatment in Prostate Cancer

Clinical trials have evaluated the effectiveness of PARP inhibitor drugs in individuals with prostate cancer confirmed to have *BRCA1, BRCA2, or ATM* alterations as determined by FoundationOne Liquid.

Summary of Evidence

For individuals with prostate cancer who receive *BRCA1/2* variant testing, HRR gene alteration testing (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L), or microsatellite instability testing using tumor tissue to guide targeted treatment or immunotherapy, the evidence includes nonrandomized clinical trials. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Clinical trials have demonstrated clinical benefit when testing was used to identify individuals for treatment with FDA-approved therapies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.
For individuals with prostate cancer who receive TMB testing to select treatment with immunotherapy, the evidence includes a prespecified retrospective subgroup analysis of a nonrandomized phase 2 trial. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Objective responses were observed in 35% of participants who had both TMB-high status and PD-L1-positive tumors and in 21% of participants who had TMB-high status and PD-L1-negative tumors. High TMB status was associated with improved response irrespective of PD-L1 status. Median OS and PFS were not significantly different between TMB groups. Because no patients with prostate cancer were included in these analyses, it is not possible to draw conclusions about the clinical validity and utility of TMB in this group of patients. Well-designed prospective studies enrolling patients in the population of interest are required. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with prostate cancer who receive ctDNA testing (liquid biopsy) to guide treatment, the evidence includes nonrandomized studies. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Given the breadth of methodologies available to assess circulating tumor DNA and circulating tumor cells, the clinical validity of each commercially available test must be established independently. Clinical trials have evaluated the effectiveness of PARP inhibitor drugs in individuals with prostate cancer confirmed to have a *BRCA1, BRCA2, or ATM* alterations as determined by FoundationOne Liquid. 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 Society of Clinical Oncology

In 2022, the American Society of Clinical Oncology (ASCO) published a provisional clinical opinion on the appropriate use of tumor genomic testing in patients with metastatic or advanced solid tumors.[17,] The opinion notes the following:

PCO 1.1. Genomic testing should be performed for patients with metastatic or advanced solid tumors with adequate performance status in the following 2 clinical scenarios:

- When there are genomic biomarker–linked therapies approved by regulatory agencies for their cancer.
- When considering a treatment for which there are specific genomic biomarker-based contraindications or exclusions (strength of recommendation: strong).

PCO 1.2.1. For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker–linked therapy that a regulatory agency has approved (strength of recommendation: moderate).
PCO 1.2.2. Multigene panel–based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency–approved therapy (strength of recommendation: strong).
PCO 2.1. Mismatch repair deficiency status (dMMR) should be evaluated on patients with metastatic or advanced solid tumors who are candidates for immunotherapy. There are multiple approaches, including using large multigene panel-based testing to assess microsatellite instability (MSI). Consider the prevalence of dMMR and/or MSI-H status in individual tumor types when making this decision (strength of recommendation: strong).

PCO 2.2. When tumor mutational burden (TMB) may influence the decision to use immunotherapy, testing should be performed with either large multigene panels with validated TMB testing or whole-exome analysis (strength of recommendation: strong).

PCO 4.1. Genomic testing should be considered to determine candidacy for tumor-agnostic therapies in patients with metastatic or advanced solid tumors without approved genomic biomarker–linked therapies (strength of recommendation: moderate).

National Comprehensive Cancer Network

Germline Testing

The current National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer are version 4.2022.[3]. Guidelines are updated frequently; refer to the source for the most current recommendations.

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: intermediate-risk prostate cancer with intraductal/cribriform histology

Somatic Testing

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

Tumor testing for microsatellite instability-high (MSI-H) or dMMR is recommended in patients with metastatic castration-resistant prostate cancer and may be considered in patients with regional or castration-naïve metastatic prostate cancer. TMB testing may be considered in patients with metastatic castration-resistant prostate cancer.

Tumor Specimen and Assay Considerations

The panel strongly recommends a metastatic biopsy for histologic and molecular evaluation. When unsafe or unfeasible, plasma ctDNA assay is an option, preferably collected during biochemical (PSA) and/or radiographic progression in order to maximize diagnostic yield. Caution is needed when interpreting ctDNA-only evaluation due to potential interference from clonal hematopoiesis of indeterminate potential (CHIP), which can result in a false-positive biomarker signal.

DNA analysis for MSI and immunohistochemistry (IHC) for MMR are different assays measuring different biological effects caused by dMMR function. If MSI is used, testing using a next-generation sequencing (NGS) assay validated for prostate cancer is preferred.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 (e.g., *BRCA1*, *BRCA2*, *ATM* germline, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*). Post-test genetic counseling to assess for the possibility of Lynch syndrome is recommended if MSI-H or dMMR is found.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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			
NCT02975934[a]	TRITON3: A Multicenter, Randomized, Open Label Phase 3 Study of Rucaparib Versus Physician's Choice of Therapy for Patients With Metastatic Castration Resistant Prostate Cancer Associated With Homologous Recombination Deficiency	405	Mar 2023
NCT04019964	Nivolumab as a Non-Castrating Therapy for MMR-deficient and CDK12- Altered Prostate Cancer With PSA Recurrence After Local Therapy	15	Jan 2025

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

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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

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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 (ie, detection of large gene rearrangements)
	81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
	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)
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.

Definitions of Decision Determinations

Medically Necessary: 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, are: (a) consistent with Blue Shield 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 patient; 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/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

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.

We are 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.

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

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. 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 contract language,

including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
New Policy **Policy Statement:** N/A	**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) 2.04.155** **Policy Statement:** I. Germline *BRCA1/2* variant analysis for individuals with metastatic castrate-resistant prostate cancer (mCRPC; See Policy Guidelines) to select treatment with FDA-approved targeted therapies or immunotherapy may be considered **medically necessary**. II. All other uses of germline *BRCA1/2* variant analysis to guide prostate cancer targeted therapy or immunotherapy 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 or immunotherapy may be considered **medically necessary**. (Note: Testing for HRR gene mutations is not the same as HRD-Homologous Recombination Deficiency- associated with ovarian cancer) See Policy Guidelines. IV. All other uses of somatic testing for HRR gene alterations to guide prostate cancer targeted therapy or immunotherapy are considered **investigational**. V. Tumor testing for microsatellite instability(MSI) or deficient mismatch repair (dMMR; MSH 2, MSH 6, PMS 2 and MLH 1)) to select treatment for unresectable or metastatic prostate cancer with FDA-approved targeted therapies or immunotherapy (e.g., pembrolizumab/Keytruda). may be considered **medically necessary**. See Policy Guidelines. VI. All other uses of tumor testing for MSI or dMMR to guide prostate cancer targeted therapy or immunotherapy are considered **investigational**.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
	VII. *BRCA1/2* and *ATM* variant analysis using ctDNA (liquid biopsy) for individuals with mCRPC to select treatment with FDA-approved targeted therapies may be considered **medically necessary**. (Note: most liquid biopsies are larger panels and individual gene testing is not available, so a panel including these 3 genes can be approved for this purpose). VIII. All other uses of biomarker testing with ctDNA (liquid biopsy) to guide prostate cancer targeted therapy or immunotherapy is considered **investigational** (see Policy Guidelines). Testing for other variants may become available between policy updates.