BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 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)

Effective Policy Date: January 1, 2023

Original Policy Date: December 2022

Related Policies:

2.04.02 - Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
2.04.08 - Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
2.04.101 - Genetic Testing for Li-Fraumeni Syndrome
2.04.111 - Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management
2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
2.04.141 - Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
2.04.151 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer
2.04.33 - Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
2.04.45 - Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer
2.04.53 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, MMR/MSI, HER2, and TMB)
2.04.77 - Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy or Immunotherapy
2.04.88 - Genetic Testing for PTEN Hamartoma Tumor Syndrome
5.01.122- Vitrakvi (larotrectinib)
5.21.134- Rozlytrek (entrectinib)

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)

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.

OBJECTIVE

The objective of this evidence review is to determine whether using biomarker testing to select targeted treatment and immunotherapy improves the net health outcome in individuals with metastatic prostate cancer.

POLICY STATEMENT

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

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

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**.

All other uses of somatic testing for HRR gene alterations to guide prostate cancer targeted therapy or immunotherapy are considered **investigational**.

Tumor testing for microsatellite instability (MSI) or mismatch repair (MMR) to select treatment for unresectable or metastatic prostate cancer with FDA-approved targeted therapies or immunotherapy may be considered **medically necessary**.

All other uses of tumor testing for MSI or MMR to guide prostate cancer targeted therapy or immunotherapy are considered **investigational**.

Tumor mutational burden (TMB) testing to guide prostate cancer targeted therapy or immunotherapy is considered **investigational**.

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**.

All other uses of biomarker testing with ctDNA (liquid biopsy) to guide prostate cancer targeted therapy or immunotherapy is considered **investigational** (see Policy Guidelines).

Simultaneous testing using liquid and tumor biopsies (outside of paired or concurrent somatic-germline testing) to guide treatment in individuals with prostate cancer is considered **investigational** (see Policy Guidelines).

Testing for other variants may become available between policy updates.

POLICY GUIDELINES

This policy does not address germline testing for inherited risk of developing cancer.

For expanded panel testing, see evidence review 2.04.115.

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 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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient"s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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.

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 for Lynparza.	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
		FoundationOne Liquid CDx (Foundation Medicine, Inc.)	*BRCA1*, *BRCA2*, and *ATM* alterations
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	FoundationOne CDx (Foundation Medicine, Inc.)	Microsatellite instability-High (MSI-H)
	Adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (≥10 mutations/megabase) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options	FoundationOne CDx (Foundation Medicine, Inc.)	TMB ≥ 10 mutations per megabase

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

Laboratory-Developed Tests

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed under CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals with prostate cancer who receive *BRCA1/2* variant testing, homologous recombination repair (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 overall survival (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 U.S. Food and Drug Administration (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 tumor mutational burden (TMB) testing to select treatment with immunotherapy, the evidence includes a prespecified retrospective subgroup analysis of a nonrandomized phase 2 trial. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Objective responses were observed in 35% of participants who had both TMB-high status and programmed death ligand-1 (PD-L1)-positive tumors and in 21% of participants who had TMB-high status and PD-L1-negative tumors. High TMB status was associated with improved response irrespective of PD-L1 status. Median OS and progression-free survival (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 circulating tumor DNA (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 poly adenosine diphosphate-ribose polymerase (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

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-nave 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 germline (eg, *BRCA1*, *BRCA2*, *ATM*, *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.

REFERENCES

1. Mateo J, Boysen G, Barbieri CE, et al. DNA Repair in Prostate Cancer: Biology and Clinical Implications. Eur Urol. Mar 2017; 71(3): 417-425. PMID 27590317
2. Stewart MD, Merino Vega D, Arend RC, et al. Homologous Recombination Deficiency: Concepts, Definitions, and Assays. Oncologist. Mar 11 2022; 27(3): 167-174. PMID 35274707
3. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Prostate Cancer. Verson 4.2022. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed August 25, 2022.
4. Bonneville R, Krook MA, Chen HZ, et al. Detection of Microsatellite Instability Biomarkers via Next-Generation Sequencing. Methods Mol Biol. 2020; 2055: 119-132. PMID 31502149
5. Merino DM, McShane LM, Fabrizio D, et al. Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. J Immunother Cancer. Mar 2020; 8(1). PMID 32217756
6. Food and Drug Administration. 2022. List of Cleared or Approved Companion Diagnostic Devices ((n Vitro and Imaging Tools). https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools. Accessed August 29, 2022.
7. Food and Drug Administration. 2022. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed August 28, 2022.
8. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. Jan 2009; 45(2): 228-47. PMID 19097774
9. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. Apr 10 2010; 28(11): 1963-72. PMID 20231676
10. Hussain M, Mateo J, Fizazi K, et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. Dec 10 2020; 383(24): 2345-2357. PMID 32955174
11. Abida W, Patnaik A, Campbell D, et al. Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration. J Clin Oncol. Nov 10 2020; 38(32): 3763-3772. PMID 32795228
12. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. Jan 01 2020; 38(1): 1-10. PMID 31682550
13. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. Oct 2020; 21(10): 1353-1365. PMID 32919526
14. Food and Drug Administration. 2020. FoundationOne Liquid CDx. Summary of Safety and Effectiveness Data. PMA Number P200016. https://www.accessdata.fda.gov/cdrh_docs/pdf20/P200016B.pdf. Accessed August 26, 2022.
15. Food and Drug Administration. FoundationOne Liquid CDx. Summary of Safety and Effectiveness Data. 2020. PMA Number P190032. https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190032B.pdf. Accessed August 27, 2022.
16. Loehr A, Patnaik A, Campbell D, et al. Response to Rucaparib in BRCA-Mutant Metastatic Castration-Resistant Prostate Cancer Identified by Genomic Testing in the TRITON2 Study. Clin Cancer Res. Dec 15 2021; 27(24): 6677-6686. PMID 34598946
17. Chakravarty D, Johnson A, Sklar J, et al. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. J Clin Oncol. Apr 10 2022; 40(11): 1231-1258. PMID 35175857

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2022	New policy - Add to Genetics section	Policy created with literature review through August 15, 2022. Biomarker testing using tissue biopsy for BRCA1/2 variants, homologous recombination repair (HRR) gene alterations, and microsatellite instability may be considered medically necessary for individuals with prostate cancer to select treatment with FDA-approved therapies. Biomarker testing for BRCA1/2 and ATM variants using ctDNA (liquid biopsy) may be considered medically necessary for individuals with prostate cancer to select treatment with FDA-approved therapies. Tumor mutational burden testing to guide treatment with targeted therapy or immunotherapy in individuals with prostate cancer is considered investigational.