FEP Medical Policy Manual

FEP 2.04.155 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations)

Annual Effective Policy Date: January 1, 2024

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
2.04.157 - Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy (BRAF, MSI/MMR, PD-L1, TMB)
2.04.33 - Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
2.04.45 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB)
2.04.53 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, and HER2)
2.04.77 - Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy (BRAF)
2.04.88 - Genetic Testing for PTEN Hamartoma Tumor Syndrome
2.04.93 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
5.01.122 - Vitrakvi (larotrectinib)
5.21.134- Rozlytrek (entrectiinib)

Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations)

Description

Biomarker-targeted therapy has shown a clear survival benefit in individuals with metastatic prostate cancer. Typically, the evaluation of biomarker status requires tissue biopsy. Circulating tumor DNA (ctDNA) (also known as liquid biopsy) is proposed as a non-invasive alternative.

OBJECTIVE

The objective of this evidence review is to summarize the evidence and guidelines on biomarker testing to select targeted treatment for 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 may be considered **medically necessary**.

All other uses of germline *BRCA1/2* variant analysis to guide prostate cancer targeted therapy 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 may be considered **medically necessary**.

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

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

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

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

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

Testing for other variants may become available between policy updates.

Testing for individual genes (not gene panels) associated with Food and Drug Administration (FDA)-approved therapeutics for therapies with NCCN recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

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.

For expanded panel testing, see evidence review 2.04.115.

For somatic biomarker testing related to use of immune checkpoint inhibitor therapy (*BRAF,* microsatellite instability/mismatch repair [MSI/MMR], PD-L1, tumor mutational burden [TMB]), see evidence review 2.04.157.

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

FDA approves tests in between policy review cycles. As such, newly approved tests might need to be considered per local Plan discretion. For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (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.

Note: Extensive evidence review is not included for somatic tests of individual genes (not gene panels) associated with FDA-approved therapies with NCCN recommendations of 2A or higher. The pivotal evidence is included in Table 1 for informational purposes. Additionally, no evidence review is provided for somatic tests of individual genes that do not have associated FDA-approved therapies regardless of NCCN recommendations, as these off-label therapies are deemed investigational per the Blue Cross and Blue Shield Association Medical Policy Program Policies and Procedures.

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 evidence reviews 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.

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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.

Some Plans may have contract or benefit exclusions for genetic testing or have state mandates for biomarker testing coverage.

FDA REGULATORY STATUS

Table 1 summarizes the targeted treatments approved by the FDA for individuals with prostate cancer, along with the approved companion diagnostic tests. The information in Table 1 was current as of August 21, 2023. An up-to-date list of FDA cleared or approved companion diagnostics is available at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

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

Treatment	Indications in Prostate Cancer	Companion Diagnostics Date	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
Niraparib + abiraterone acetate (AKEEGA)	With prednisone, for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated metastatic castration-resistant prostate cancer.	FoundationOne CDx (Foundation Medicine, Inc.) 2023	*BRCA1 and BRCA2 alterations*	MAGNITUDE NCT03748641 Chi et al (2023)[4],	None
Olaparib (Lynparza)	In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated mCRPC.	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.) 2020	*BRCA1* and *BRCA2* alterations	PROfound NCT02987543 Hussain et al (2020)[5],	2A/ Prostate Cancer[3],
		FoundationOne Liquid CDx (Foundation Medicine, Inc.) 2020	*BRCA1*, *BRCA2*, and *ATM* alterations	PROpel NCT03732820 Clarke et al (2022)[6],	
	Adults with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone.	FoundationOne CDx (Foundation Medicine, Inc.) 2020	Homologous recombination repair (HRR) genes: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*,*CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*,*RAD51D,* and *RAD54L* alterations	PROfound NCT02987543 Hussain et al (2020)[5],	2A/ Prostate Cancer[3],
Rucaparib (Rubraca)	Adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.	FoundationOne Liquid CDx (Foundation Medicine, Inc.) 2020	*BRCA1* and *BRCA2* alterations	TRITON2 NCT02952534 Abida et al (2020)[7], TRITON 3 NCT02975934	2A/ Prostate Cancer[3],

				Fizazi et al (2023)[8,]	
Talazoparib (Talzenna)	In combination with enzalutamide for the treatment of adult patients with HRR gene-mutated metastatic castration-resistant prostate cancer.	No FDA companion diagnostic for this indication	HRR genes	TALAPRO-2 NCT03395197 Agarwal et al (2023)[9,]	2A/ Prostate Cancer[3,]

NCCN: National Comprehensive Cancer Network.

Sources: Food and Drug Administration (2023);[10,] Drugs@FDA (2023)[11,]

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 metastatic castrate-resistant prostate cancer (mCRPC) who receive germline *BRCA1/2* variant testing to guide treatment with a poly adenosine diphosphate-ribose polymerase (PARP) inhibitor, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and National Comprehensive Cancer Network (NCCN) recommendations.

For individuals with mCRPC who receive somatic testing for homologous recombination repair (HRR) gene alterations (B*RCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D,* and *RAD54L*) using tissue biopsy to guide treatment with a PARP inhibitor, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with mCRPC who receive somatic testing for *BRCA1*, *BRCA2*, and *ATM* alterations using circulating tumor DNA (ctDNA; liquid biopsy) to guide treatment with a PARP inhibitor, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

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 Urological Assocation/Society of Urologic Oncology

In 2023, the American Urological Assocation and the Society of Urologic Oncology published amended guidelines on advanced prostate cancer.[12,] The guidelines included the following relevant recommendation (level of evidence) on the treatment of mCRPC:

- In patients with mCRPC, clinicians should offer germline (if not already performed) and somatic genetic testing to identify DNA repair deficiency, microsatellite instability (MSI) status, tumor mutational burden, and other potential mutations that may inform prognosis and familial cancer risk, as well as direct potential targeted therapies.(Clinical Principle)

National Comprehensive Cancer Network

The current National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer are version 3.2023.[3,] Guidelines are updated frequently; refer to the source for the most current recommendations.

The guidelines include the following relevant recommendations:

Targeted Therapy

- "Consider inclusion of olaparib in patients who have an HRR mutation and whose cancer has progressed on prior treatment with androgen receptor-directed therapy regardless of prior docetaxel therapy. Olaparib is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*) who have been treated previously with androgen receptor-directed therapy."
- "Consider inclusion of rucaparib for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. If the patient is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given."
- "Olaparib with abiraterone is an option for patients with a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet received a novel hormone therapy or docetaxel."
- "Talazoparib plus enzalutamide is a treatment option for patients with metastatic CRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (*BRCA1*, *BRCA2*, *ATM*, *ATR*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, or *RAD51C*) who have not yet had treatment in the setting of CRPC."

Germline Testing

The Principles of Genetics section (PROS-B) provides appropriate scenarios for germline genetic testing in individuals with a personal history of prostate cancer.

Germline testing is recommended in patients with a personal history of prostate cancer in the following scenarios related to the tumor: metastatic, regional (node-positive), very-high risk localized, high-risk localized prostate cancer.

Germline testing may be considered in patients with a personal history of prostate cancer in the following scenarios related to the tumor: intermediate-risk prostate cancer with intraductal/cribriform histology; or a prior personal history any of the following cancers: of exocrine pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, and small intestinal.

Somatic Testing

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

Tumor Specimen and Assay Considerations

The panel strongly recommends a metastatic biopsy for histologic and molecular evaluation. When unsafe or unfeasible, plasma ctDNA assay is an option, preferably collected during biochemical (PSA) and/or radiographic progression in order to maximize diagnostic yield.

Caution is needed when interpreting ctDNA-only evaluation due to potential interference from clonal hematopoiesis of indeterminate potential (CHIP), which can result in a false-positive biomarker signal.

The preferred method of selecting patients for rucaparib treatment is somatic analysis of *BRCA1* and *BRCA2* using a ctDNA sample.

Post-Test Considerations

Post-test genetic counseling is recommended if pathogenic/likely pathogenic variant (mutation) identified in any gene that has clinical implications if also identified in germline (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*).

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (CMS) National Coverage Determination on Next Generation Sequencing (90.2) states:

"Effective for services performed on or after March 16, 2018, [CMS] has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

a. Patient has:

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

b. The diagnostic laboratory test using NGS must have:

i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,

ii. an FDA-approved or -cleared indication for use in that patient's cancer; and,

iii. results provided to the treating physician for management of the patient using a report template to specify treatment options."[13,]

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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.
December 202023	Replace policy	Policy updated with literature search through August 1, 2023. Evidence opinion extensively pruned. Pivotal studies added to Table 1. Indications related to immunotherapy and tumor mutational burden testing removed and added to policy 2.04.157. Title changed accordingly. Medically necessary policy statements revised for clarity and to align with PICOs; intent unchanged.