Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 7/1/24**
(See policy history boxes for previous effective dates)

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

Description/Background

Targeted Treatment in Metastatic Castrate Resistant Prostate Cancer

DNA damage happens daily, and most are repaired to allow normal cell functioning. Double strand breaks (DSB) in the DNA are particularly damaging. Repair of DSB utilizes the homologous recombination repair (HRR) pathway. Many types of cancer, however, are unable to repair DNA damage. This leads to the accumulation of genetic errors, such as loss of DNA, rearrangements in the DNA, and loss of entire genes. The consequence of these errors is genomic instability. The loss of the HRR and associated genomic instability is called homologous recombination deficiency (HRD). HRD is associated with several types of cancer including prostate cancer, where estimates as high as 30% of metastatic castrate-resistant prostate cancer (mCRPC) tumors have genetic changes that result in the loss of DNA repair capacity.[1,]

Friends of Cancer Research convened a consortium addressing the lack of consistency in the way HRD is defined and measurement methods.[2,] They proposed the following definition: “HRD is a phenotype that is characterized by the inability of a cell to effectively repair DNA double-strand breaks using the HRR pathway.” Additionally, they encourage the use of “HRD” and “HRP” to reflect homologous recombination deficiency and homologous recombination proficiency. While the consortium did not explicitly define how to measure homologous recombination repair status, they acknowledge that it might involve gene variant testing as well as genomic instability measurement and call for transparency and standardization.

Specific to prostate cancer, the National Comprehensive Cancer Network (NCCN) prostate cancer guideline gives examples genes (BR*CA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D,* and *RAD54L).*Germline and somatic alterations in these genes may be predictive of the clinical benefit of PARP inhibitors in mCRPC.[3] Olaparib (Lynparza) and rucaparib (Rubraca) were the first PARP inhibitors to receive FDA approval for the treatment of mCRPC. In 2023, niraparib in combination with abiraterone acetate (marketed as Akeega) and talazoparib (Talzenna) were also approved for use in mCRPC (see Table 1).

Circulating Tumor DNA (Liquid Biopsy)

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA. Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or circulating tumor cells. Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA (ctDNA) can be used for genomic characterization of the tumor.

Repeat Genomic Testing

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

Paired genetic testing is different than concurrent somatic-germline testing. In concurrent testing, the germline results are not used to filter the somatic results. Rather, the laboratories perform large, separate panels of germline and somatic variants. The goal is to identify options for genome-informed treatment and to identify hereditary cancer risk.

Concurrent Somatic Liquid-based and Tissue-based Genomic Testing

Liquid biopsy testing uses blood samples and assesses cancer DNA and non-cancer DNA in the same blood sample. The goal is to identify options for genome-informed treatment. Some providers will order a liquid biopsy test and a tissue biopsy test at the same time, not for filtering or for comparison as in the paired genetic testing section above, but to hasten time to treatment. If the intent of concurrent testing is to follow an individual over time for resistance mutations/response to therapy, then consideration could be given to doing liquid biopsy at diagnosis with the tissue biopsy to make sure that whatever mutations are going to be followed longitudinally can be detected by the liquid biopsy. For example, monitoring of *BRCA* mutation evolution (reversion mutations) in individuals with prostate cancer during poly adenosine diphosphate-ribose polymerase (PARP) inhibitor therapy may be achieved with serial circulating tumor DNA (ctDNA) sampling, and allow for earlier detection of resistance and selection of alternative therapies to reduce the risk of resistance (Goodall et al, 2017; 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.

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 devices in vitro and imaging tools website**.**

https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

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

Treatment	Indications in Prostate Cancer	Companion Diagnostics Date	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
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 Fizazi et al (2023)[8]	2A/ Prostate Cancer[3]
Talazoparib (Talzenna)	In combination with enzalutamide for the treatment of adult patients with HRR gene-mutated metastatic castration-resistant prostate cancer	No FDA companion diagnostic for this indication	HRR genes	TALAPRO-2 NCT03395197 Agarwal et al (2023)[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.

Medical Policy Statement

Germline *BRCA1/2* variant analysis for individuals with metastatic castrate-resistant prostate cancer (mCRPC) to select treatment with FDA-approved targeted therapies is 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 or circulating tumor DNA testing (liquid biopsy) for homologous recombination repair (HRR) gene alterations (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D,* and *RAD54L*) to select treatment for mCRPC with FDA-approved targeted therapies is considered **medically necessary**.

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

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

Inclusionary and Exclusionary Guidelines

Inclusions:

The clinical utility of Germline and Somatic Biomarker Testing using tumor tissue or circulating tumor DNA (Liquid Biopsy) for Targeted Treatment in Prostate Cancer (*BRCA1/2,* Homologous Recombination Repair Gene Alterations) has been established when any of the following criteria are met.

- Germline BRCA1/2 variant analysis for individuals with advanced for metastatic castrate-resistant prostate cancer (mCRPC) with FDA-approved targeted therapies.
- Somatic BRCA1/2 variant analysis using tumor tissue for individuals with advanced for metastatic castrate-resistant prostate cancer (mCRPC) with FDA-approved targeted therapies.
- Somatic testing using tissue biopsy or circulating tumor DNA testing (liquid biopsy) for homologous recombination repair (HRR) gene alterations (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51*

B, *RAD51C*, *RAD51D,* and *RAD54L*) to select treatment for metastatic castrate-resistant prostate cancer (mCRPC) with FDA-approved targeted therapies.
- Somatic testing using circulating tumor DNA testing (liquid biopsy) for *BRCA1*, *BRCA2*, and *ATM* alterations to select treatment for mCRPC with FDA-approved targeted therapies.

Exclusions:

- All other uses of germline *BRCA1/2* variant analysis to guide prostate cancer targeted therapy are considered investigational.
- All other uses of somatic testing using tissue biopsy for HRR gene alterations to guide prostate cancer targeted therapy are considered investigational.
- 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.

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

Established codes:

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

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

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

0129U

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

Rationale

Testing for individual genes (not gene panels) associated with Food and Drug Administration (FDA)-approved therapeutics for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. The pivotal evidence is included in Table 1 for informational purposes. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

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

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

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

For individuals with mCRPC who receive somatic testing for homologous recombination repair (HRR) gene alterations
(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.

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

For individuals with mCRPC who receive somatic testing for *BRCA1*, *BRCA2*, and *ATM* alterations using ctDNA (liquid biopsy) to guide treatment with a PARP inhibitor, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated.

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

For individuals with mCRPC who receive somatic testing for *BRCA1*, *BRCA2*, and *ATM* alterations using ctDNA (liquid biopsy) to guide treatment with a PARP inhibitor, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated.

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 ctDNA (liquid biopsy) to guide treatment with a PARP inhibitor, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and National Comprehensive Cancer Network (NCCN) recommendations.

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

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Urological Association/Society of Urologic Oncology
In 2023, the American Urological Association and the Society of Urologic Oncology published amended guidelines on advanced prostate cancer.[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 4.2023.[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*, *RAD51 B*, *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 and who have not yet had treatment in the setting of CRPC."

- "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

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

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

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

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

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:

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

b. The diagnostic laboratory test using NGS must have:

-Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
-an FDA-approved or -cleared indication for use in that patient's cancer; and,
-results provided to the treating physician for management of the patient using a report template to specify treatment options."[13],

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04550494	Measuring the Effects of Talazoparib in Patients With Advanced Cancer and DNA Repair Variations	36	Dec 2023
NCT04038502	Carboplatin or Olaparib for BRcA Deficient Prostate Cancer (COBRA)	100	Aug 2025
NCT04497844[a]	A Study of Niraparib in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for the Treatment of Participants With Deleterious Germline or Somatic Homologous Recombination	692	May 2027

	Repair (HRR) Gene-Mutated Metastatic Castration-Sensitive Prostate Cancer (mCSPC) (AMPLITUDE)		
NCT05689021	CJNJ-67652000 and Prednisone for Treatment of Metastatic Castration-Resistant Prostate Cancer and SPOP Gene Mutations	30	Sept 2025

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

Government Regulations
National:

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

Indications and Limitations of Coverage

B. Nationally Covered Indications
1. Somatic (Acquired) Cancer
Effective for services performed on or after March 16, 2018, the Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:
a. Patient has:

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

b. The diagnostic laboratory test using NGS must have:
i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
ii. an FDA-approved or -cleared indication for use in that patient's cancer; and,
iii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

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

i. ovarian or breast cancer; and,
ii. a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer; and,
iii. a risk factor for germline (inherited) breast or ovarian cancer; and

iv. not been previously tested with the same germline test using NGS for the same germline genetic content.

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

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

C. Nationally Non-Covered Indications

1. Somatic (Acquired) Cancer

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

D. Other

1. Somatic (Acquired) Cancer

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

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

2. Germline (Inherited) Cancer

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

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

Local:

NA

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

Related Policies

- Germline and Somatic Biomarker Testing (Including Liquid Biopsy) For Targeted Treatment in Ovarian Cancer (BRCA 1, BRCA2, Homologous Recombination Deficiency)

- Circulating Tumor DNA and Circulating Tumor Cells for Selecting targeted therapy for advanced solid Cancers (Liquid Biopsy)
- Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy (BRAF, MSI/MMR, PD-L1, TMB)
- Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)
- Genetic Testing – BRAF Mutation in Selecting Melanoma Patients for Targeted Therapy
- Genetic Testing – Molecular Analysis for Targeted Therapy of Non-Small-Cell-Lung Cancer
- Somatic Biomarker Testing (Including liquid biopsy) for targeted treatment and immunotherapy in metastatic colorectal cancer (KRAS, NRAS, BRAF, MMR/MSI, and HER2)
- Genetic Testing – NGS (NEXT-GENERATION SEQUENCING) Testing of Multiple Genes (Panel) for Solid and Hematolymphoid Malignant Conditions

References

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 11/1/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

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

Next Review Date: 4th Qtr, 2024

Pre-Consolidation Medical Policy History

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

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

I. Coverage Determination:

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

II. Administrative Guidelines:

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