MEDICAL POLICY

POLICY TITLE	**GERMLINE AND SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT IN OVARIAN CANCER (BRCA1, BRCA2, HOMOLOGOUS RECOMBINATION DEFICIENCY, NTRK)**
POLICY NUMBER	**MP 2.395**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**RETIRED 7/1/2026**

I. POLICY

Germline *BRCA1/2* variant analysis may be considered **medically necessary** for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies.

Somatic *BRCA1/2* variant analysis using tumor tissue may be considered **medically necessary** for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies.

All other uses of germline and somatic *BRCA1/2* variant analysis to guide targeted therapy for ovarian, fallopian tube, or primary peritoneal cancer are considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Homologous recombination deficiency (HRD) analysis of tumor tissue may be considered **medically necessary** for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies.

All other uses of HRD testing of tumor tissue to guide targeted therapy for ovarian, fallopian tube, or primary peritoneal cancer are considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

BRCA1/2 variant analysis using circulating tumor DNA (liquid biopsy) may be considered **medically necessary** for individuals with advanced epithelial ovarian, fallopian tube,

or primary peritoneal cancer to select treatment with FDA-approved targeted therapies when tissue-based analysis is not clinically feasible.

All other uses of circulating tumor DNA testing (liquid biopsy) to guide targeted therapy in individuals with ovarian, fallopian tube, or primary peritoneal cancer are considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

NTRK1, *NTRK2,* and *NTRK3* gene fusion analysis of tumor tissue may be considered **medically necessary** for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies.

All other uses of *NTRK1*, *NTRK2,* and *NTRK3* gene fusion analysis of tumor tissue to guide targeted therapy for ovarian, fallopian tube, or primary peritoneal cancer are considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Simultaneous testing using liquid and tumor biopsies (outside of paired or concurrent somatic-germline testing) to guide treatment in individuals with ovarian, fallopian tube, or primary peritoneal cancer is considered **investigational** (see Policy Guidelines). There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Testing for other variants may become available between policy updates.

Policy Guidelines

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics 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 expanded panel testing, see **MP 2.259**.

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 **MP 2.388**.

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.

MEDICAL POLICY

POLICY TITLE	GERMLINE AND SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT IN OVARIAN CANCER (BRCA1, BRCA2, HOMOLOGOUS RECOMBINATION DEFICIENCY, NTRK)
POLICY NUMBER	MP 2.395

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.

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

Repeat Genomic Testing

There may be utility in repeated testing of gene variants for determining targeted therapy or immunotherapy in individuals with ovarian cancer, as a resistance mechanism to platinum-based chemotherapies and poly adenosine diphosphate-ribose polymerase (PARP) inhibitors in BRCA-mutant cancers is the acquisition of *BRCA* reversion mutations that restore protein function (Lin et al 2019; PMID 30425037). ASCO currently suggests repeat genomic testing for patients 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 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, **MP 2.211, MP 5.013, MP 2.255, MP 2.274**).

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 **MP 2.325 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing** for germline panel, and see **MP 2.259 – Molecular Panel Testing of Cancers to Identify Targeted 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 a patient 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 *BRCA* mutation evolution (reversion mutations) in individuals with ovarian cancer during PARP inhibitor therapy may be achieved with serial ctDNA sampling and allow for earlier detection of resistance and selection of alternative therapies to reduce the risk of resistance. This testing strategy has not been fully studied and is not yet discussed in the NCCN guidelines for ovarian 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.

Cross-References:

MP 2.211 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers
MP 2.255 Genetic Testing for PTEN Hamartoma Tumor Syndrome
MP 2.259 Molecular Panel Testing of Cancers to Identify Targeted Therapies
MP 2.274 Genetic Testing for Li-Fraumeni Syndrome
MP 2.325 Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

POLICY TITLE	GERMLINE AND SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT IN OVARIAN CANCER (BRCA1, BRCA2, HOMOLOGOUS RECOMBINATION DEFICIENCY, NTRK)
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MP 2.388 Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy
MP 2.392 Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes
MP 2.393 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer
MP 2.394 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Prostate Cancer
MP 5.013 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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Biomarker Testing and Targeted Treatment in Ovarian 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 ovarian cancer. Poly adenosine diphosphate-ribose polymerase (PARP) inhibitors are used to target tumor cells with alterations in the HRR genes *BRCA1* and *BRCA2*. Currently, 3 PARP inhibitors are FDA-approved for use in ovarian cancer (Table 1).

In ovarian cancer targeted therapies, HRD-positive status is generally defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability. Myriad MyChoice® is an FDA-approved companion diagnostic for the assessment of tumor genomic instability score (GIS) and the detection and classification of variants in the *BRCA1* and *BRCA2* genes, for the selection of patients who are eligible for targeted treatment. A patient's Myriad HRD status is determined by detecting single nucleotide variants (SNVs), variants in

homopolymer stretches, insertions and deletions (indels), and large rearrangements (LRs) in the *BRCA1* and *BRCA2* genes and determining a genomic instability score (GIS) using DNA obtained from ovarian tumor tissue. A positive Myriad HRD Status result is due to either the presence of a pathogenic variant in *BRCA1* and/or *BRCA2* and/or a GIS above a defined threshold. Approximately 41% to 50% of epithelial ovarian cancers are estimated to exhibit HRD. Germline alterations in *BRCA1* and *BRCA2* genes have been identified in up to 17% of individuals diagnosed with epithelial ovarian cancer, and somatic mutations are found in an additional 7%.

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 can be used for genomic characterization of the tumor.

Regulatory Status

Table 1 summarizes the targeted treatments approved by the FDA for individuals with ovarian cancer, along with the approved companion diagnostic tests. 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.

Voluntarily Withdrawn Indications for Maintenance Therapy

In 2022, the manufacturers of all 3 PARP inhibitors used to treat ovarian cancer voluntarily withdrew indications for third-line or greater treatment in ovarian cancer. The withdrawals were based on updated survival results from the ARIEL4 (NCT02855944), SOLO3 (NCT02282020), and QUADRA (NCT02354586) trials. The withdrawals did not affect other indications in ovarian cancer.

Table 1. Targeted Treatments for Ovarian Cancer and NTRK fusions with FDA-approved companion diagnostic tests

Treatment	Companion Diagnostics
Vitrakvi (larotrectinib)	FoundationOne CDx (Foundation Medicine, Inc.)
Rozlytrek (entrectinib)	FoundationOne CDx (Foundation Medicine, Inc.) FoundationOne Liquid CDx (Foundation Medicine, Inc.)

Niraparib (Zejula)	None for this indication
Olaparib (Lynparza)	BRACAnalysis CDx® (Myriad Genetic Laboratories, Inc.) FoundationOne CDx (Foundation Medicine, Inc.) Myriad myChoice CDx (Myriad Genetic Laboratories, Inc)
Rucaparib (Rubraca)	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.) FoundationFocus CDxBRCA Assay (Foundation Medicine, Inc.) FoundationOne Liquid CDx (Foundation Medicine, Inc.)

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.

IV. RATIONALE

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For individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer 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 NCCN recommendations.

For individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive somatic *BRCA1/2* variant testing 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 advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive homologous recombination deficiency (HRD) testing using tumor tissue to guide treatment with a PARP inhibitor, the evidence includes FDA-approved therapeutics with NCCN

recommendations of 2A or higher and were not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive somatic *BRCA1/2* variant testing using circulating tumor DNA testing (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.

V. DEFINITIONS/BACKGROUND

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NA

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement. The codes need to be in numerical order.

Investigational; therefore, not covered:

Procedure Codes							
81432	0129U						

Covered when medically necessary:

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Procedure Codes							
81162	81163	81164	81165	81166	81167	81191	81192
81193	81194	81212	81215	81216	81217	0037U	0172U
0239U							

ICD-10-CM Diagnosis Code	Description
C48.1-C48.2	Malignant neoplasm of peritoneum code range
C56.1-C56.9	Malignant neoplasm of ovary code range
C57.00-C57.02	Malignant neoplasm of fallopian tube code range
D07.39	Carcinoma in situ of other female genital organs
D39.10- D39.12	Neoplasm of uncertain behavior of ovary code range

VIII. REFERENCES

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IX. POLICY HISTORY

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MP 2.395	**01/20/2025 Major Review.** New Policy Adoption
	06/24/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	03/03/2026 Retirement Review. Service will be managed by the vendor Evicore.

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