
Medical Policy



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***Current Policy Effective Date: 3/1/26**
(See policy history boxes for previous effective dates)

Title: Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, NTRK)

Description

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

Medical Policy Statement

Germline *BRCA1/2* variant analysis using tissue biopsy or circulating tumor DNA testing (liquid biopsy) for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies is **established** when criteria are met.

Somatic *BRCA1/2* variant analysis using tumor tissue for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies is **established** when criteria are met.

Homologous recombination deficiency (HRD) of tumor tissue for analysis of tumor tissue or circulating tumor DNA testing (liquid biopsy) for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies is **established** when criteria are met.

BRCA1/2 variant analysis using circulating tumor DNA (liquid biopsy) 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 is **established** when criteria are met.

NTRK1, NTRK2, and NTRK3 gene fusion analysis of tumor tissue for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies is **established** when criteria are met.

Inclusionary and Exclusionary Guidelines

Inclusions (for all FDA-approved therapies, please check the FDA site):

-Germline and somatic biomarker testing using tumor tissue or circulating tumor DNA (Liquid Biopsy) for targeted treatment in ovarian cancer (*BRCA1*, *BRCA2*, Homologous Recombination Deficiency) have been established when **ANY** of the following criteria are met.

- Germline *BRCA1/2* variant analysis 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 for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies.
- Homologous recombination deficiency (HRD) analysis of tumor tissue or circulating tumor DNA testing (liquid biopsy) for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies.
- *BRCA1/2* variant analysis using circulating tumor DNA (liquid biopsy) 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.
- Somatic testing of NTRK1, NTRK2, and NTRK3 gene fusion analysis using tumor tissue or circulating tumor DNA testing (liquid biopsy) for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies. The following medications (Repotrectinib, Larotrectinib and Entrectinib) are FDA approved when NTRK mutation is identified.

-Repeat testing for gene variants using tissue biopsy or circulating tumor DNA (liquid biopsy) for individuals with ovarian cancer when both of the following are met:

- For determining targeted therapy or immunotherapy
- With suspected acquired resistance at time of cancer progression.

-Paired somatic-germline testing in order to distinguish whether findings in tumor tissue are acquired somatic changes or germline changes. The goal of this paired testing is to identify truly somatic changes to guide treatment.

-Concurrent somatic liquid-based and tissue-based genomic testing. 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.

Exclusions:

- 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**.
- All other uses of HRD testing of tumor tissue to guide targeted therapy for ovarian, fallopian tube, or primary peritoneal cancer are considered **investigational**.
- All other uses of circulating tumor DNA testing tissue biopsy or circulating tumor (liquid biopsy) to guide targeted therapy in individuals with ovarian, fallopian tube, or primary peritoneal cancer are considered **investigational**. 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**.
- All other uses of NTRK1, NTRK2, and NTRK2 gene fusion analysis of tumor tissue to guide targeted therapy for ovarian, fallopian tube, or primary peritoneal cancer are considered **investigational**.

Circulating Tumor DNA (liquid biopsy)

The clinical utility of circulating tumor DNA and circulating tumor cells for germline and somatic biomarker testing for targeted treatment in ovarian cancer is established when there is clinical documentation that tissue-based testing cannot be performed (e.g., insufficient sample, inaccessible tumor or where there may be a delay in obtaining tumor sample) OR tissue-based testing is not required when there is an FDA-approved companion diagnostic device that is a circulating tumor test (liquid biopsy).

Note: Blue Cross Blue Shield of Michigan and Blue Care Network follow National Comprehensive Cancer Network (NCCN) 2A and above recommendations. Due to frequent NCCN updates, please refer to the appropriate guideline for the most recent standards and intended coverage.

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
81191	81192	81193	81194	81212	81215
81216	81217	81301	81408	81432	81479*
0037U	0172U	0239U			

* Policy criteria must be met. This code is subject to individual review.

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.

Background

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.(1,2) 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.(3) 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%.(4)

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.

Neurotrophic Receptor Tyrosine Kinase (NTRK) Gene Fusion Testing

The presence of NTRK gene fusion can be detected by multiple methods including next-generation sequencing, reverse transcription-polymerase chain reaction, fluorescence in situ hybridization and immunohistochemistry.(4) Next-generation sequencing provides the most comprehensive view of a large number of genes and may identify NTRK gene fusions as well

as other actionable alterations, with minimal tissue needed. The fluorescence in situ hybridization using break-apart probes can detect gene rearrangements in DNA that may generate a fusion transcript. The immunohistochemistry techniques have generally been used in the research setting. Reverse transcription-polymerase chain reaction is designed to identify only known translocation partners and breakpoints and cannot identify novel breakpoints or novel fusion partners.

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.

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 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.

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. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Summary of Evidence

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. 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. 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. 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 *NTRK* gene fusion testing using tumor tissue to guide treatment with a TRK inhibitor, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A. 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 *NTRK* gene fusion testing using tumor tissue to guide treatment with a tropomyosin receptor kinase (TRK) 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.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms. The following is a summary of the key literature to date.

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.

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

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

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

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 NCCN recommendations of 2A. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

Somatic *BRCA1/2* Variant Testing Using Tissue Biopsy to Select Targeted Treatment in Ovarian Cancer

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. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

Homologous Recombination Deficiency Testing to Select Targeted Treatment in Ovarian Cancer

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 PAR inhibitor, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

Somatic *BRCA1/2* Variant Testing Using Liquid Biopsy to Select Targeted Treatment in Ovarian Cancer

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. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

NTRK Gene Fusion Testing to Select Targeted Treatment in Ovarian Cancer

For individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive NTRK gene fusion testing using tumor tissue to guide treatment with a tropomyosin receptor kinase (TRK) inhibitor, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A. The evidence includes the pivotal studies leading to the FDA and 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 Society of Clinical Oncology

In 2022, the American Society of Clinical Oncology published updated recommendations on poly adenosine diphosphate-ribose polymerase (PARP) inhibitors in the management of ovarian cancer.⁽⁵⁾ The recommendations included the following:

Newly Diagnosed Ovarian Cancer

"Recommendation 2.1. Patients with newly diagnosed stage III-IV EOC [epithelial ovarian cancer] who are incomplete or partial response to first-line platinum-based chemotherapy should be offered PARP inhibitor maintenance therapy in high-grade serous or endometrioid ovarian cancer. For those with germline or somatic pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* genes, options should include olaparib (300 mg orally every 12 hours for 2 years), niraparib (200-300 mg orally daily for 3 years) or rucaparib (600 mg twice a day for 2 years). Longer duration could be considered in selected individuals after discussion of risks. For those who are HRD [homologous recombination deficiency] positive, determined using FDA-approved companion diagnostic tests, rucaparib and niraparib are options. Niraparib or rucaparib may be offered for non-*BRCA* mutated/HRD negative patients. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.)"

Recurrent Ovarian Cancer: Second-Line or Greater Maintenance and Treatment

"Recommendation 3.0. PARP inhibitor monotherapy maintenance (second-line or more) may be offered to patients with EOC who have not already received a PARP inhibitor and who have responded to platinum-based therapy regardless of *BRCA* mutation status; treatment is continued until progression of disease or toxicity despite dose reductions and best supportive care. Options include olaparib 300 mg every 12 hours, rucaparib 600 mg every 12 hours or

niraparib 200-300 mg once daily. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.) Maintenance treatment with niraparib for patients without germline or somatic *BRCA* mutation should weigh potential PFS benefit against possible OS decrement. (Type: Evidence-based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Moderate.)"

"Recommendations 3.1/3.2. PARP inhibitor monotherapy should not be routinely offered to patients for the treatment of recurrent platinum sensitive EOC. (Type: Evidence-based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate.) *Evidence on PARP inhibitor use in this setting is evolving and data are continuing to emerge. Any decision to proceed with PARP inhibitor treatment in select populations (BRCA mutation, No prior PARP inhibitor use, Platinum Sensitive, Advanced Lines of Treatment) should be based on individualized patient and provider assessment of risks, benefits, and preferences.*"

"Recommendation 3.3. PARP inhibitor monotherapy is not recommended for treatment for patients with either *BRCA* wild-type or platinum-resistant recurrent EOC. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.)"

National Comprehensive Cancer Network

The current NCCN guidelines for ovarian cancer (including fallopian tube cancer and primary peritoneal cancer) are version 3.2025.(9) Guidelines are updated frequently; refer to the source for most current recommendations.

The guidelines include the following relevant recommendations on biomarker testing to guide targeted therapy in ovarian cancer:

- "In the up-front setting, choice of somatic testing should, at a minimum, optimize identification of molecular alterations that can inform use of interventions that have demonstrated benefit in this setting, including HER2 status (by IHC), *BRCA1/2*, loss of heterozygosity (LOH), or homologous recombination deficiency (HRD) status in the absence of a germline *BRCA* mutation.
- In the recurrence setting, tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, *BRCA1/2*, HRD status, MSI, MMR, TMB, *FRa*, *RET*, *BRAF*, and NTRK if prior testing did not include these markers.
- Molecular analyses may be performed on circulating tumor DNA (ctDNA or liquid biopsy) when tissue-based analysis is not clinically feasible.
- Validated molecular testing should be performed in a CLIA-approved facility."

Recommendations on the use of PARP inhibitors for ovarian cancer include the following:

Maintenance Therapy After Recurrence

- "PARP inhibitor options include niraparib, olaparib, or rucaparib.
- Niraparib is limited to those with a deleterious or suspected deleterious germline *BRCA* mutation.
- Olaparib and Rucaparib are limited to those with a deleterious or suspected deleterious *BRCA* mutation.
- Caution should be used when using maintenance PARP inhibitor for longer than 24 months.
- There are limited data on the use of a maintenance PARP inhibitor in patients who previously received a PARP inhibitor.
- Combination bevacizumab/PARP inhibitor is not recommended at this time for maintenance after recurrence therapy."

First-Line Maintenance Therapy

"After first-line therapy with bevacizumab, data are limited on maintenance therapy with a single-agent PARP inhibitor (olaparib or niraparib) for patients with a *BRCA*1/2 mutation. However, based on the magnitude of benefit of PARP inhibitor maintenance therapy for other subgroups, single-agent PARP inhibitors can be considered."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Regulatory Status

Table 1 summarizes the targeted treatments approved by the FDA for individuals with ovarian cancer, along with the approved companion diagnostic tests. The information in Table 1 was current as of 2025. 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>

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.(6,7,8) 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 FDA-Approved Companion Diagnostic Tests

Treatment	Indication in Ovarian Cancer	Companion Diagnostics Date	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
Vitrakvi (larotrectinib)	Treatment of adult and pediatric patients with solid tumors that: • have a <i>NTRK</i> gene fusion without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and • have no satisfactory alternative treatments or have progressed following treatment.	FoundationOne CDx (Foundation Medicine, Inc.) TruSight Oncology Comprehensive (Illumina, Inc.)	NTRK1, NTRK2 and NTRK3 fusions	Recurrence therapy for platinum-sensitive disease: LOXO-TRK, SCOUT, NAVIGATE (NCT02122913, NCT02637687 , and NCT02576431) 8,	2A Ovarian Cancer (V.3.2025)9,
Rozlytrek (entrectinib)	Treatment of adult and pediatric patients older than 1 month of age with solid tumors that: • have a <i>NTRK</i> gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and • have progressed following treatment or have no satisfactory alternative therapy.	FoundationOne CDx (Foundation Medicine, Inc.) FoundationOne Liquid CDx (Foundation Medicine, Inc.)	NTRK1, NTRK2 and NTRK3 fusions	Recurrence therapy for platinum-sensitive disease: STARTRK-1 and STARTRK-2 (NCT02097810 and NCT02568267) 10,	2A Ovarian Cancer (V.3.2025)9,

Niraparib (zejula)	Maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either: - a deleterious or suspected deleterious <i>BRCA</i> mutation, and/or - genomic instability Maintenance treatment of adult patients with deleterious or suspected deleterious germline <i>BRCA</i>-mutated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum- based chemotherapy. Select patients for therapy based on an FDA- approved companion diagnostic for Zejula.	None for this indication	<i>BRCA1</i> and <i>BRCA2</i> variants and/or positive Genomic Instability Score (HRD variants)Not applicable	First-line maintenance treatment: PRIMA (NCT02655016) ^{11, 12} Maintenance treatment of recurrent germline <i>BRCA</i> -mutated ovarian cancer: NOVA (NCT01847274) ¹³ .	2A Ovarian Cancer (V.3.2025) ⁹ .
Olaparib (lynparza)	Maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic <i>BRCA</i> -mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.	BRACAnalysis CDx® (Whole Blood) ^a (Myriad Genetic Laboratories, Inc.)	<i>BRCA1</i> and <i>BRCA2</i> variants	First-line maintenance <i>BRCA</i> - mutated advanced ovarian cancer: SOLO-1 (NCT01844986) ^{14,15} First-line maintenance treatment in combination with bevacizumab, HRD-positive advanced ovarian cancer: PAOLA-1 (NCT02477644) ¹⁶ .	2A Ovarian Cancer (V.3.2025) ⁹ .
	In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with	FoundationOne CDx (Foundation Medicine, Inc.)	<i>BRCA1</i> and <i>BRCA2</i> variants	Maintenance treatment of recurrent ovarian cancer: SOLO-2 (NCT01874353) ^{17,18} , Study 19 (NCT00753545) ¹⁹ .	

	HRD-positive status defined by either: - a deleterious or suspected deleterious <i>BRCA</i> mutation, and/or - genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either: - a deleterious or suspected deleterious <i>BRCA</i> mutation, and/or - genomic instability	Myriad myChoice CDx (Myriad Genetic Laboratories, Inc)	<i>BRCA1</i> and <i>BRCA2</i> variants and/or positive Genomic Instability Score (HRD variants)		
Rucaparib (rubraca) ¹	Maintenance treatment of adult patients with a deleterious <i>BRCA</i> mutation (germline and/or somatic)-associated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum- based chemotherapy.	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	<i>BRCA1</i> and <i>BRCA2</i> variants	ARIEL3 (NCT01968213) ²⁰ .	2A Ovarian Cancer (V.3.2025) ⁹ .
		FoundationFocus CDx BRCA Assay (Foundation Medicine, Inc.)	<i>BRCA1</i> and <i>BRCA2</i> variants		
		FoundationOne Liquid CDx (Foundation Medicine, Inc.)	<i>BRCA1</i> and <i>BRCA2</i> variants		

Sources: Food and Drug Administration (2024)(19); Drugs@FDA (22).

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.

Government Regulations

National:

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."(21)

Local:

N/A

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov did not identify any trials that would likely influence this review.

(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 Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, NTRK Gene Fusion)
- GT-Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy (BRAF, MSI/MMR, PD-L1, TMB)
- Circulating Tumor DNA and Circulating Tumor Cells for Selecting Targeted Therapy for Advanced Solid Cancers (Liquid Biopsy)
- Genetic Testing – NGS of Multiple Genes (Panel) for Solid and Hematolymphoid Malignant Conditions

- Somatic Biomarker Testing (including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, MMR/MSI, HER2, and TMB)
- Genetic Testing - 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)
- Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)
- Genetic Testing—BRAF Mutation in Selecting Melanoma Patients for Targeted Therapy Including Liquid Biopsy

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November, 2025 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	1/5/24		Joint policy established Vendor: N/A (ky) Post JUMP changes/comments: Added 81408 to the policy under EST to cover ATM. Added (FoundationFocus CDx BRCA) to CPT 81162. (ky)
3/1/25	12/17/24		• Routine Maintenance • Title changed to Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, NTRK). • Jump policy aligns with BCBSA except for the use of ctDNA/liquid biopsy (when criteria are met). BCBSA still finds liquid biopsy investigational. • Added NTRK1, NTRK2, and NTRK3 gene fusion analysis of tumor tissue for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies is considered established to medical policy statement and Inclusion section. • Edits to the Title, MPS, rationale, inclusions, exclusions and summary of evidence. • Added codes 81191-81194 NTRK translocation analysis code range under EST.

			- Removed the reference to BRACAnalysis CDx on the billing code 81479. - Code 81432 nomenclature revised EFD 1/1/25. - Code 81433 added under EST. - Vendor: N/A Post JUMP changes: - Updates made to MPS and Inclusions based on Jump committee input. - Code 81433 was not added to policy as this code will be deleted effective 1/1/25. (ky)
3/1/26	12/16/25		- Routine Maintenance (jf) - Minor Edits - Vendor managed: NA - Edits to the inclusions and exclusions - Formatting edits 0211U reviewed. It is inappropriate for this policy; it is covered on other JUMP policies. Added in the inclusions: - Edits to inclusions, formatting edits and Added Repeat testing for gene variants using tissue biopsy or circulating tumor DNA (liquid biopsy) for individuals with ovarian cancer when both of the following are met: - For determining targeted therapy or immunotherapy - With suspected acquired resistance at time of cancer progression. - Concurrent somatic liquid-based and tissue-based genomic testing. 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.
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Next Review Date: 4th Qtr, 2026

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 OVARIAN CANCER (BRCA1, BRCA2, HOMOLOGOUS RECOMBINATION DEFICIENCY, NTRK)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
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.