2.04.156	Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, NTRK)		
Original Policy Date:	November 1, 2022	**Effective Date:**	October 1, 2025
Section:	2.0 Medicine	**Page:**	Page 1 of 19

Policy Statement

I. 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.

II. 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.

III. 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**.

IV. 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.

V. All other uses of HRD testing of tumor tissue to guide targeted therapy for ovarian, fallopian tube, or primary peritoneal cancer are considered **investigational**.

VI. *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.

VII. 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**.

VIII. *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.

IX. 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**.

X. 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).

Testing for other variants may become available between policy updates.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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

Testing for other variants may become available between policy updates.

Testing for individual genes (not gene panels) associated with 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 Blue Shield of California Medical Policy: Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

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

FDA approves tests in between policy review cycles. As such, newly approved tests might need to be considered per local Plan discretion. For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)(https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools) for an updated list of FDA-approved tumor markers and consult the most current version of NCCN management algorithms.

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

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 Blue Shield of California Medical Policies related to inherited cancer syndromes: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2 and Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes).

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 Blue Shield of California Medical Policy: Genetic Cancer Susceptibility Panels Using Next Generation Sequencing for germline panel, and see Blue Shield of California Medical Policy: Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies for somatic panel.

Concurrent Somatic Liquid-based and Tissue-based Genomic Testing

Liquid biopsy testing uses blood samples and assesses cancer DNA and non-cancer DNA in the same blood sample. The goal is to identify options for genome-informed treatment. Some providers will order a liquid biopsy test and a tissue biopsy test at the same time, not for filtering or for comparison as in the paired genetic testing section above, but to hasten time to treatment. If the intent of concurrent testing is to follow 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.

Coding

See the Codes table for details.

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.

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 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 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 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.

Additional Information
Not applicable.

Related Policies

- Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
- Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer (BRCA1, BRCA2, PIK3CA, Ki-67, RET, BRAF, ESR1, NTRK)
- Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

SB 535
Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California

Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

SB 496

SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

FDA-Approved Targeted Treatments and Companion Diagnostic Tests

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 August 1, 2024. 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.[5,6,7,] 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	Indication in Ovarian Cancer	Companion Diagnostics	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
Vitrakvi (larotrectinib)	Recurrence treatment for platinum-sensitive disease in epithelial ovarian, fallopian tube, and primary peritoneal cancers who have NTRK gene fusions.	FoundationOne CDx (Foundation Medicine, 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.3.2024)[9,]
Rozlytrek (entrectinib)	Recurrence treatment for platinum-sensitive disease in epithelial ovarian, fallopian tube, and primary peritoneal cancers who have NTRK gene fusions.	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.3.2024)[9,]

Treatment	Indication in Ovarian Cancer	Companion Diagnostics	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
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. Maintenance treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-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	Not applicable	First-line maintenance treatment: PRIMA (NCT02655016)[11,12,] Maintenance treatment of recurrent germline *BRCA*-mutated ovarian cancer: NOVA (NCT01847274)[13,]	2A Ovarian Cancer (V.3.2024)[9,]
Olaparib (Lynparza)	Maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-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. In combination with bevacizumab for the maintenance	BRACAnalysis CDx® (Myriad Genetic Laboratories, Inc.)	*BRCA1* and *BRCA2* mutations	First-line maintenance *BRCA*-mutated advanced ovarian cancer: SOLO-1 (NCT01844986)[14,15,]	2A Ovarian Cancer (V.3.2024)[9,]
	FoundationOne CDx (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations		First-line maintenance treatment in combination with bevacizumab, HRD-positive advanced ovarian cancer: PAOLA-1 (NCT02477644)[16,]	
	Myriad myChoice CDx (Myriad Genetic Laboratories, Inc)	*BRCA1* and *BRCA2* mutations and/or positive Genomic Instability Score		Maintenance treatment of recurrent ovarian cancer: SOLO-2 (NCT01874353)[17,18,] Study 19 (NCT00753545[19,]	

Treatment	Indication in Ovarian Cancer	Companion Diagnostics	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
	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 HRD-positive status defined by either: • a deleterious or suspected deleterious *BRCA* mut ation, 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.				
Rucaparib (Rubraca)	Maintenance treatment of adult patients with a deleterious *BRCA*muta tion (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.	BRACAnalysi s CDx (Myriad Genetic Laboratories , Inc.)	*BRCA1* and *B RCA2* mutatio ns	Maintenance treatment of recurrent ovarian cancer: ARIEL3 (NCT01968213)[20,]	2A Ovarian Cancer (V.3.2024)[9,]
		FoundationF ocus CDxBRCA Assay (Foundation Medicine, Inc.)	*BRCA1* and *B RCA2* alterati ons		
		FoundationO ne Liquid CDx (Foundation Medicine, Inc.)	*BRCA1* and *B RCA2* alterati ons		

Sources: Food and Drug Administration (2023)[21,]; 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.

Rationale

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.

Literature Review

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 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 or higher and was not extensively evaluated. 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 or higher and was not extensively evaluated. 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 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.

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 or higher and was not extensively evaluated. 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 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.

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 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 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 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.

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.[4,]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 in complete 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 *BRCA*1 or *BRCA*2 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 3.2024.[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 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, HER2 status (by IHC), *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.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (CMS) National Coverage Determination on Next Generation Sequencing (90.2) states:
"Effective for services performed on or after March 16, 2018, [CMS] has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:
a. Patient has:
- i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
- ii. not been previously tested with the same test using NGS for the same cancer genetic content, and
- iii. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

b. The diagnostic laboratory test using NGS must have:
- i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
- ii. an FDA-approved or -cleared indication for use in that patient's cancer; and,
- iii. results provided to the treating physician for management of the patient using a report template to specify treatment options." [23,]

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in August 2023 did not identify any trials that would likely influence this review.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
- Clinical findings (i.e., pertinent symptoms and duration)
- Comorbidities
- Activity and functional limitations
- Family history, if applicable

- Reason for procedure/test/device, when applicable
- Pertinent past procedural and surgical history
- Pertinent past and present diagnostic testing and results
- Prior pertinent treatments, duration, and response
- Treatment plan (i.e., surgical or medication intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, US)

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)
- New medications prescribed

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
	0129U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
	0172U	Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score
	0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
	81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis

Type	Code	Description
	81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (e.g., solid tumors) translocation analysis
	81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (e.g., solid tumors) translocation analysis
	81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (e.g., solid tumors) translocation analysis
	81194	NTRK (neurotrophic receptor tyrosine kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis
	81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
	81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
	81408	Molecular pathology procedure, Level 9
	81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/01/2022	New policy.
06/01/2023	Annual review. Policy statement, guidelines and literature updated. Policy title changed from Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, Tumor Mutational Burden, Microsatellite Instability/Mismatch Repair) to current one. Coding update.
11/01/2023	Policy statement and Policy guidelines updated.
10/01/2025	Policy reactivated. Previously archived from 07/01/2024 to 09/30/2025.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the member's illness, injury, or disease.
Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into

consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	AFTER Blue font: Verbiage Changes/Additions
Reactivated Policy **Policy Statement:** N/A	**Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, NTRK) 2.04.156** **Policy Statement:** I. 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. II. 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. III. 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**. IV. 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. V. All other uses of HRD testing of tumor tissue to guide targeted therapy for ovarian, fallopian tube, or primary peritoneal cancer are considered **investigational**. VI. *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

POLICY STATEMENT	
BEFORE	AFTER Blue font: Verbiage Changes/Additions
	cancer to select treatment with FDA-approved targeted therapies when tissue-based analysis is not clinically feasible. VII. 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**. VIII. *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. IX. 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**. X. 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). Testing for other variants may become available between policy updates.