Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Ovarian Cancer

Policy # 00810
Original Effective Date: 01/01/2023
Current Effective Date: 01/01/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Germline Genetic Testing for Hereditary Breast and or Ovarian Cancer is addressed separately in medical policy 00047.

Note: Genetic Testing for Lynch Syndrome and Other Inherited Colon is addressed separately in medical policy 00190.

Note: Genetic Testing for Li-Fraumeni Syndrome is addressed separately in medical policy 00424.

Note: Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies is addressed separately in medical policy 00423.

Note: Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) is addressed separately in medical policy 00497.

Note: Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer is addressed separately in medical policy 00731.

Note: Molecular Analysis Including Liquid Biopsy for Targeted Therapy or Immunotherapy of Non-Small Cell Lung Cancer is addressed separately in medical policy 00452.

Note: Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer is addressed separately in medical policy 00233.

Note: Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Melanoma or Glioma is addressed separately in medical policy 00320.

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Note: Genetic Testing for PTEN Hamartoma Tumor Syndrome is addressed separately in medical policy00417.

Note: Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing is addressed separately in medical policy 00382.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider germline *BRCA1/2* variant analysis and somatic *BRCA1/2* variant analysis in the absence of a previously identified germline *BRCA1/2* pathogenic or likely pathogenic variant for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved therapies to be **eligible for coverage.****

Based on review of available data, the Company may consider homologous recombination deficiency (HRD) analysis (e.g., myChoice CDx) of tumor tissue for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer in the absence of a previously identified germline or somatic *BRCA1/2* pathogenic or likely pathogenic variant to select treatment with FDA-approved therapies (e.g., niraparib [Zejula], Olaparib [Lynparza]) to be **eligible for coverage.****

Based on review of available data, the Company may consider tumor tissue testing for microsatellite instability/mismatch repair (*MSI/MMR*), *BRCA1/2*, *BRAF*, *NTRK*, and tumor mutational burden (TMB), using FDA-approved companion diagnostic test (e.g., FoundationOne CDx) if prior testing did not include these markers for individuals with persistent or recurrent unresectable or metastatic ovarian, fallopian tube, or primary peritoneal cancer that has proven to be refractory or at time of relapse, to select treatment with FDA-approved therapies to be **eligible for coverage.****

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Note:
It is recommended that tumor molecular analysis is performed on the most recent available tumor tissue using validated molecular testing and performed in a CLIA-approved facility.

Panel testing performed on the same specimen and date of services needs to be reported with a single most appropriate procedure code rather than billing numerous procedure codes.

Per the AMA, when a PLA code is available to report a given proprietary laboratory service, the service should not be reported with any other CPT code(s).

Testing for other variants may become available between policy updates.

When Services May Be Eligible for Coverage

Based on review of available data, the Company may consider *BRCA1/2* variant analysis using circulating tumor DNA testing (liquid biopsy) in individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select FDA-approved targeted therapies when all criteria are met to be **eligible for coverage** .**

- Tissue-based analysis is not clinically feasible (i.e., tumor tissue quantity is not sufficient for standard molecular testing using formalin-fixed paraffin-embedded tissue or invasive biopsy is medically contraindicated); **AND**
- Prior somatic tumor testing (if done) did not include testing of the same biomarkers; **AND**
- Liquid biopsy test must have a U.S. Food and Drug Administration (FDA) approved or cleared indication as an in vitro companion diagnostic for use in ovarian cancer (i.e., FoundationOne®‡ Liquid CDx, see Policy Guidelines); **AND**
- The requested test was not used before; **AND**
- Treatment is considered with genomic biomarker-linked therapies approved by regulatory agencies for individual's cancer.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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Based on review of available data, the Company considers all other uses of germline and somatic *BRCA1/2* variant analysis to guide targeted therapy or immunotherapy for ovarian, fallopian tube, or primary peritoneal cancer, including but not limited to repeat testing, to be **investigational.***

Based on review of available data, the Company considers all other uses of HRD testing (e.g., myChoice CDx) of tumor tissue to guide targeted therapy or immunotherapy for ovarian, fallopian tube, or primary peritoneal cancer, including but not limited to repeat testing or use in patients with known germline or somatic *BRCA1 or 2* pathogenic or likely pathogenic variant, to be **investigational.***

Based on review of available data, the Company considers all other uses of *MSI/MMR, BRAF, NTRK* and TMB testing of ovarian, fallopian tube, or primary peritoneal tumor tissue to guide targeted therapy or immunotherapy, including but not limited to use in initial diagnosis or for repeat testing, to be **investigational.***

Based on review of available data, the Company considers all other uses of circulating tumor DNA testing (liquid biopsy) to guide treatment in individuals with ovarian, fallopian tube, or primary peritoneal cancer, including but not limited to simultaneous testing using liquid and tumor biopsies, to be **investigational.***

Policy Guidelines

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

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) 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 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 National Comprehensive Cancer Network (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. 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.

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.

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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 Genetic Cancer Susceptibility Panels Using Next Generation Sequencing for germline panel, and 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 patients 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.

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Background/Overview

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.

Homologous Recombination Deficiency
Homologous recombination repair describes a process in a cell in which a group of proteins work together to repair DNA damage. Changes in the homologous recombination repair pathway that result in the inability to repair DNA are called homologous recombination deficiency (HRD) and may lead to diseases such as cancer. Drugs that affect this pathway are being studied in the prevention and treatment of cancer and other diseases.

There are a number of genes associated with homologous recombination repair, and a number of tests for HRD. 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 treatment with niraparib. 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.

Microsatellite Instability/Mismatch Repair
High levels of microsatellite instability (MSI-H) and mismatch repair deficiency (dMMR) describe cells that have alterations in certain genes involved in correcting errors made when DNA is replicated. dMMR tumors are characterized by a high tumor mutational load and potential responsiveness to anti-PD-L1-immunotherapy. Mismatch repair deficiency is most common in colorectal cancer, other types of gastrointestinal cancer, and endometrial cancer, but it may also be found in other cancers. Microsatellite instability testing is generally performed using polymerase chain reaction (PCR) for 5 biomarkers, although other biomarker panels and next generation sequencing are sometimes performed. High microsatellite instability is defined as 2 or more of the

5 biomarkers showing instability or more than 30% of the tested biomarkers showing instability depending on what panel is used. Microsatellite instability testing is generally paired with immunohistochemistry (IHC) assessing lack of protein expression from 4 DNA MMR genes thereby reflecting dMMR.

Tumor Mutational Burden
Tumor mutational burden (TMB), a measure of gene mutations within cancer cells, is an emerging biomarker of outcomes with immunotherapy in multiple tumor types. Initially, assessments of TMB involved whole exome sequencing (WES). More recently, targeted next generation sequencing (NGS) panels are being adapted to estimate TMB. Currently FoundationOne®‡ CDx is the only FDA-approved panel for estimating TMB, but others are in development.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Table 1 summarizes the targeted treatments approved by the FDA for patients with ovarian cancer, along with the approved companion diagnostic tests. The information in Table 1 was current as of August 30, 2023. An up-to-date list of FDA cleared or approved companion diagnostics is available at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

Several companion diagnostic tests for rucaparib in ovarian cancer have been FDA approved. However, as of August 2023, BRCA testing is no longer required for this indication.

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 FDA-Approved Companion Diagnostic Tests

Treatment	Indication in Ovarian Cancer	Companion DiagnosticsDate	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	None for this indication	Not applicable	First-line maintenance treatment: PRIMA (NCT02655016) Maintenance treatment of recurrent germline *BRCA*-mutated ovarian cancer: NOVA (NCT01847274)	2A Ovarian Cancer (V.2.2023)

	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.				
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	BRACAnalysis CDx®‡ (Myriad Genetic Laboratories, Inc.)	*BRCA1* and *BRCA 2* mutations	First-line maintenance *BRCA*-mutated advanced ovarian cancer: SOLO-1 (NCT01844986) First-line maintenance treatment in	2A Ovarian Cancer (V.2.2023)
		FoundationOne CDx (Foundation Medicine, Inc.)	*BRCA1* and *BRCA 2* alterations		

	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 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	Myriad myChoice CDx (Myriad Genetic Laboboratories, Inc)	*BRCA1* and *BRCA 2* mutations and/or positive Genomic Instability Score	combination with bevacizumab, HRD-positive advanced ovarian cancer: PAOLA-1 (NCT02477644) Maintenance treatment of recurrent ovarian cancer: SOLO-2 (NCT01874353) Study 19 (NCT00753545	

	cancer is associated with HRD-positive status defined by either: • a deleterious or suspected deleterious *BRCA* 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.				
Rucaparib (Rubraca)	Maintenance treatment of adult patients with a deleterious *BRCA*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 Genˢ®‡ Genetic Laboratories, Inc.)	*BRCA1* and *BRCA2* mutations	ARIEL3 (NCT01968213)	2A Ovarian Cancer (V.2.2023)
		FoundationFocus CDxBRCA Assay (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations		
		FoundationOne CDx (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations		
		FoundationOne Liquid CDx (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations		

Sources: Food and Drug Administration (2023); Drugs@FDA

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.

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Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Description

Biomarker-targeted therapy has shown a clear survival benefit in patients with ovarian cancer. More recently, testing for microsatellite instability/mismatch repair (MSI/MMR) and tumor mutational burden (TMB) status to select patients for immunotherapy has been proposed. 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, somatic *BRCA1/2* variant testing or homologous recombination deficiency (HRD) testing using tumor tissue biopsy, or somatic *BRCA1/2* variant testing using circulating tumor DNA testing (liquid biopsy), 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 epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive MSI/MMR or TMB testing using tumor tissue to guide targeted treatment or immunotherapy, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated.

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.

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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 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 2.2023. 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, *BRCA1/2*, HRD status, MSI, MMR, TMB, *FR*a, *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.
- For patients with platinum-sensitive disease who have completed two or more lines of platinum-based therapy. Olaparib may be used regardless of BRCA status (preferred for those with a BRCA mutation).
- Niraparib is limited to those with a deleterious or suspected deleterious germline BRCA mutation.
- Rucaparib is 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 or after recurrence therapy with bevacizumab.
- 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, niraparib, or rucaparib) for patients with a germline or somatic *BRCA1/2* 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.

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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."

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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Policy History

Original Effective Date: 01/01/2023
Current Effective Date: 01/01/2024

12/01/2022	Medical Policy Committee review
12/14/2022	Medical Policy Implementation Committee approval. New policy. Senate bill review.
01/13/2023	Coding update
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Policy updated with literature search through August 1, 2023. Evidence opinion extensively pruned, NCCN 2023 guidelines incorporated. Pivotal studies added to Table 1. New codes effective 01/01/2024 added to policy.

Next Scheduled Review Date: 12/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of

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descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0037U, 0172U, 0242U, 0239U, 0326U, 81162, 81479 Add codes effective 01/01/2024: 81457, 81458, 81459, 81462, 81463, 81464
HCPCS	No codes
ICD-10 Diagnosis	C481-C482, C561-C569, C5700-C5702, D3910-D3912

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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 that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.