2.04.156	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)		
Original Policy Date:	November 1, 2022	**Effective Date:**	December 1, 2022
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Policy Statement

I. Germline and somatic *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 therapies.

II. 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 are considered **investigational**.

III. 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 therapies.

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

V. Microsatellite instability (MSI) and/or mismatch repair (MMR) testing of tumor tissue may be considered **medically necessary** for individuals with unresectable or metastatic ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved therapies (e.g. pembrolizumab/Keytruda).

VI. Other uses of MSI/MMR testing of ovarian, fallopian tube, or primary peritoneal tumor tissue to guide targeted therapy or immunotherapy are considered **investigational**.

VII. Circulating tumor DNA testing (liquid biopsy) to guide treatment in individuals with ovarian, fallopian tube, or primary peritoneal cancer is considered **investigational**.

VIII. 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).

Note: 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

HRD TESTING VS. HRR: Homologous recombination deficiency (HRD) is a tumor characteristic that is defined by the inability to accurately repair double-strand breaks (DSBs) in DNA via homologous recombination. HRD can be assessed via 2 different types of biomarkers. In ovarian cancers, these include individual mutations in BRCA1 or BRCA2 and the assessment of genomic instability (Loss of Heterozygosity or LOH, Large-scale State Transitions or LST and Telomeric Allelic Imbalance or TAI). Genomic instability, or large-scale structural rearrangements to chromosomes, results in specific measurable genomic aberrations and serves as the "collateral damage" that can occur to the genome as a result of HRD. Tumor samples that have individual BRCA1/2 mutations or markers of genomic instability are characterized as HRD positive. HRD testing is done routinely for ovarian cancer.

HRR gene mutations (beyond BRCA) are not interchangeable with genomic instability **but are otherwise similar to HRD**. **There are about 14 HRR genes**. The HRR pathway is sometimes referred to as the PARP pathway. HRR mutations are an indication for PARP inhibitor (e.g., Olaparib/ Lynparza) treatment.

MSI/dMMR: Microsatellites are small repeat sequences in non-coding DNA, usually 2-7 nucleotides. A simple PCR test can identify them. MMR genes (e.g., MSH2, MSH6, PMS2, and MH1) function to repair these insertions and deletions (indels). When MMR genes are deficient (dMMR), the microsatellites become more frequent or unstable (MSI-H). dMMR can be checked using IHC (ImmunoHisto Chemistry) that looks for absence of the normal proteins produced by the MMR genes, or by looking for mutations in the genes. dMMR usually leads to MSI-H.

This policy does not address NTRK testing.

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

For expanded panel testing, see Blue Shield of California Medical Policy: Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

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.

Repeat Genomic Testing

There may be utility in repeated testing of gene variants for determining targeted therapy or immunotherapy in individuals with ovarian cancer, as a resistance mechanism to platinum-based chemotherapies and poly adenosine diphosphate-ribose polymerase (PARP) inhibitors in BRCA-mutant cancers is the acquisition of *BRCA* reversion mutations that restore protein function (Lin et. al. 2019; PMID 30425037). ASCO currently suggests repeat genomic testing for patients on targeted therapy with suspected acquired resistance, especially if choice of next-line therapy would be guided. The ASCO guidance is not tumor specific, and cautions to consider clinical utility (Chakravarty et. al. 2022; PMID 35175857).

Paired Somatic-Germline Testing

Testing for genetic changes in tumor tissue assesses somatic changes. Some somatic testing involves a paired blood analysis in order to distinguish whether findings in tumor tissue are acquired somatic changes or germline changes. Some laboratories offer paired tumor sequencing and germline sequencing which is done at the same time and in the same laboratory. The goal of this paired testing is to identify truly somatic changes to guide treatment. However, paired testing can also identify potential germline changes that might indicate an inherited cancer syndrome. These results would need to be confirmed through germline testing if personal and family cancer history is consistent with an inherited cancer syndrome (see policies related to inherited cancer syndromes, Blue Shield of California Medical Policies: 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.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" - to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease

Variant Classification	Definition
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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.

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.

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 and Immunotherapy in Breast Cancer
- Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
- Germline Genetic Testing for Ovarian Cancer Risk (BRIP1, RAD51C, RAD51D, NBN)
- Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the 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 mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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 27, 2022. 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.

The table does not include NTRK testing.

Several companion diagnostic tests for rucaparib in ovarian cancer have been FDA approved. However, as of June 2022, BRCA testing is no longer required for this indication.[4,]

Table 1. Targeted Treatments for Ovarian Cancer and FDA-Approved Companion Diagnostic Tests

Treatment	Indication in Ovarian Cancer	Companion Diagnostic	Biomarkers
Targeted Treatment for Ovarian Cancer			
Niraparib (Zejula)	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. Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Treatment of advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous reproductive recombination deficiency (HRD) positive status defined by either: a deleterious or suspected deleterious BRCA mutation, or • genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy	Myriad myChoice CDx (Myriad Genetic Laboratories, Inc.)	*BRCA1* and *BRCA2* genes and/or positive Genomic Instability Score
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. 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	BRACAnalysis CDx® (Myriad Genetic Laboratories, Inc.)	*BRCA1* and *BRCA2* mutations
		FoundationOne CDx (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations
		Myriad myChoice CDx (Myriad Genetic Laboratories, Inc)	*BRCA1* and *BRCA2* mutations and/or positive Genomic Instability Score

Treatment	Indication in Ovarian Cancer	Companion Diagnostic	Biomarkers
	and whose cancer is associated with HRD-positive status defined by either: • a deleterious or suspected deleterious BRCA mutation, and/or • genomic instability		
Rucaparib (Rubraca®)[1]	Maintenance treatment of adult patients with 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.)	*BRCA1* and *BRCA2* mutations
		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
Immunotherapy for Solid Tumors			
Pembrolizumab (Keytruda®)	Adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options	FoundationOne CDx (Foundation Medicine, Inc.)	Microsatellite instability-High (MSI-H)
	Adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (≥10 mutations/megabase) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options	FoundationOne CDx (Foundation Medicine, Inc.)	TMB ≥ 10 mutations per megabase

[1] As of June 2022, *BRCA* testing is not required for rucaparib treatment in ovarian cancer.
Sources: Food and Drug Administration (2022)[5]; Drugs@FDA[6]

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

BRCA1 and *BRCA2* Variants

The prevalence of *BRCA* variants is approximately 0.1% to 0.2% in the general population. The prevalence may be much higher for particular ethnic groups with characterized founder mutations (e.g., 2.5% [1/40] in the Ashkenazi Jewish population). Family history of breast and ovarian cancer is

an important risk factor for the *BRCA* variant; additionally, age and ethnicity could be independent risk factors.

Several genetic syndromes with an autosomal dominant pattern of inheritance that features breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC) and some cases of hereditary site-specific breast cancer have in common causative variants in *BRCA* (breast cancer susceptibility) genes. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early-onset breast cancer with or without male cases, but without ovarian cancer. For this evidence review, BCBSA refers collectively to both as *hereditary breast and/or ovarian cancer*.

Germline variants in the *BRCA1* and *BRCA2* genes are responsible for the cancer susceptibility in most HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific cancer, BRCA variants are responsible only for a proportion of affected families. *BRCA* gene variants are inherited in an autosomal dominant fashion through maternal or paternal lineage. It is possible to test for abnormalities in *BRCA1* and *BRCA2* genes to identify the specific variant in cancer cases and to identify family members at increased cancer risk. Family members without existing cancer who are found to have *BRCA* variants can consider preventive interventions for reducing risk and mortality.

Homologous Recombination Deficiency

Homologous recombination repair describes a process in a cell in which a group of proteins work together to repair DNA damage.[1,] 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.[2,]

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.[3,]

Detecting 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.

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total ctDNA. Therefore, more sensitive methods than the standard sequencing approaches (e.g., Sanger sequencing) are needed.

Literature Review

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.

Biomarker Testing Using Tissue Biopsy to Select Targeted Treatment and Immunotherapy (*BRCA1, BRCA2*, Homologous Repair Deficiency, and Microsatellite Instability/Mismatch Repair)

Clinical Context and Test Purpose

Ovarian cancer treatment selection is informed by tumor type, grade, stage, patient performance status and preference, prior treatments, and the molecular characteristics of the tumor such as the presence of driver mutations. One purpose of biomarker testing of patients who have advanced cancer is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment).

The question addressed in this evidence review is: Does germline testing for *BRCA1/2* variants; and, *BRCA1/2*, HRD, and microsatellite instability/mismatch repair (MSI/MMR) testing using tissue biopsy improve the net health outcome in individuals with ovarian, fallopian tube, or primary peritoneal cancer? Note that this policy does not review *NTRK* gene fusions.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with ovarian, fallopian tube, or primary peritoneal cancer for whom the selection of targeted treatment depends on the molecular characterization of the tumor.

Interventions
The technologies being considered are germline testing for *BRCA1/2* variants; and, *BRCA1/2*, HRD, and microsatellite instability/mismatch repair (MSI/MMR) testing using tissue biopsy.

Comparators
Decisions about treatment in ovarian cancer are based on clinical characteristics. The comparator would be no variant testing to guide treatment.

Outcomes
The general outcomes of interest in oncology are overall survival (OS), disease-specific survival, quality of life (QOL), treatment-related mortality and morbidity.

Beneficial outcomes resulting from a true-positive test result are prolonged survival, reduced toxicity, and improved QOL associated with receiving a more effective targeted therapy. Beneficial outcomes from a true negative result are prolonged survival associated with receiving chemotherapy in those without driver mutations.

Harmful outcomes resulting from a false-negative test result include shorter survival from receiving less effective and more cytotoxic chemotherapy in those with driver mutations; possible harmful outcomes resulting from a false-positive test result are a shorter survival from receiving potentially ineffective targeted treatment and delay in initiation of chemotherapy in those without driver mutations.

The overall response rate (ORR) may be used as a surrogate endpoint reasonably likely to predict clinical benefit in patients with refractory solid tumors. ORR can be measured by the proportion of patients with best overall confirmed response of complete response or partial response by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1),[7,] or Response Assessment in Neuro-Oncology criteria,[8,] as appropriate by a blinded and independent adjudication committee.

There are clearly defined quantitative thresholds for the follow-up of patients in oncology trials. A general rule is a continuation of treatment until disease progression or unacceptable toxicity. Long-term follow-up outside of a study setting is conducted to determine survival status. The duration of follow-up for the outcomes of interest is 6 months and 1 year.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for randomized controlled trials (RCTs);
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

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.

Clinically Valid and Clinically Useful

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Review of Evidence

Clinical trials have evaluated the effectiveness of poly adenosine diphosphate-ribose polymerase (PARP) inhibitor drugs in individuals with ovarian cancer confirmed to have a *BRCA1*/2 mutation. Summarized below are the pivotal trials that supported the *BRCA* variant-related FDA-approved indications in ovarian cancer.

Niraparib

FDA approval for niraparib for treatment of ovarian cancer was based on the QUADRA phase 2 clinical trial.[9,] QUADRA evaluated the safety and activity of niraparib in adult patients with relapsed, high-grade serous (grade 2 or 3) epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more previous chemotherapy regimens. The primary objective was the proportion of patients achieving an investigator-assessed confirmed overall response in patients with HRD-positive tumors (including patients with *BRCA* and without *BRCA* pathogenic variants) sensitive to their last platinum-based therapy who had received 3 or 4 previous anticancer therapy regimens (primary efficacy population). Thirteen of 47 patients (28%) in the primary efficacy population achieved an overall response according to RECIST (95% CI, 15.6% to 42.6%; p=.00053).

Olaparib

The effectiveness of olaparib as maintenance therapy in newly diagnosed advanced ovarian cancer was demonstrated in the phase 3 SOLO-1 RCT comparing olaparib to placebo in 391 individuals with newly diagnosed, advanced, high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer with a *BRCA* mutation.[10,] After a median follow-up of 41 months, the risk of disease progression or death was 70% lower with olaparib than with placebo (Kaplan-Meier estimate of the rate of freedom from disease progression and from death at 3 years, 60% vs. 27%; hazard ratio for disease progression or death, 0.30; 95% CI, 0.23 to 0.41; p<.001).

Rucaparib

Several companion diagnostic tests have been FDA-approved to select individuals with *BRCA1*/2 variants for treatment with rucaparib for ovarian cancer. Subsequently, however, the indication for rucaparib was changed to no longer require *BRCA* testing for this indication.[4,] The indication change was based on results from the ATHENA trial (NCT03522246) which showed improvement in progression-free survival (PFS) regardless of *BRCA* variant status.[11,]

Pembrolizumab

FDA approval of pembrolizumab was supported by the phase 2 KEYNOTE-158 study. The trial included a total of 233 previously treated participants with MSI-H/dMMR solid tumors, 15 of whom had ovarian cancer. In the full cohort, the overall response rate was 34.3% (95% CI, 28.3% to 40.8%). Median PFS was 4.1 months (95% CI, 2.4 to 4.9 months) and median OS was 23.5 months (95% CI, 13.5 months to not reached). Treatment-related adverse events occurred in 151 patients (64.8%).[12,]

Section Summary: Biomarker Testing Using Tissue Biopsy to Select Targeted Treatment and Immunotherapy (*BRCA1*, *BRCA2*, Homologous Repair Deficiency, and Microsatellite Instability/Mismatch Repair)

Clinical trials have demonstrated clinical benefit when testing was used to identify individuals for treatment with FDA-approved therapies.

Tumor Mutational Burden Testing to Guide Treatment for Ovarian Cancer

Clinical Context and Test Purpose

The purpose of tumor mutational burden (TMB) testing in patients who have ovarian cancer is to inform a decision on whether patients should receive immunotherapy versus another systemic therapy. The goal of immunotherapy is to preferentially kill malignant cells without significant damage to normal cells so that there is improved therapeutic efficacy along with decreased toxicity.

The question addressed in this evidence review is: In individuals with ovarian cancer, does the use of tumor mutational burden testing improve the net health outcome?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with ovarian cancer.

Interventions

Tumor mutational burden, a measure of gene mutations within cancer cells, is proposed as a biomarker for response to immunotherapy.

Comparators

The comparator is treatment as usual without TMB testing.

Outcomes

The general outcomes of interest in oncology are OS, disease-specific survival, QOL, treatment-related mortality and morbidity. Beneficial outcomes resulting from a true-positive test result are prolonged survival, reduced toxicity, and improved QOL associated with receiving a more effective targeted therapy. Beneficial outcomes from a true negative result are prolonged survival associated with receiving chemotherapy in those without driver mutations. Harmful outcomes resulting from a false-negative test result include shorter survival from receiving less effective and more cytotoxic chemotherapy in those with driver mutations; possible harmful outcomes resulting from a false-positive test result are a shorter survival from receiving potentially ineffective targeted treatment and delay in initiation of chemotherapy in those without driver mutations.

The ORR may be used as a surrogate endpoint reasonably likely to predict clinical benefit in patients with refractory solid tumors. ORR can be measured by the proportion of patients with best overall confirmed response of complete response or partial response by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1),[7,] or Response Assessment in Neuro-Oncology criteria,[8,] as appropriate by a blinded and independent adjudication committee.

There are clearly defined quantitative thresholds for the follow-up of patients in oncology trials. A general rule is a continuation of treatment until disease progression or unacceptable toxicity. Long-term follow-up outside of a study setting is conducted to determine survival status. The duration of follow-up for the outcomes of interest is 6 months and 1 year.

Study Selection Criteria

For the evaluation of clinical validity, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology;
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
FDA-Approved Companion Diagnostic Test
FoundationOne CDx is FDA-approved as a companion diagnostic for use with pembrolizumab in patients with TMB-high (≥ 10 mutations per megabase) solid tumors. Approval was based on results of the KEYNOTE-158 study that enrolled patients with solid tumors, but none of the patients evaluated had ovarian cancer.

Clinical Validity
Nonrandomized Trial
Marabelle et al (2020) reported the association of high TMB to response to pembrolizumab in patients with solid tumors enrolled in a prespecified exploratory analysis of the KEYNOTE-158 study.[12,] High TMB was defined as >10 mutations per megabase according to the FoundationOne CDx panel. The proportion of patients with an objective response in the TMB-high group was 29%. At a median follow-up of approximately 3 years, the median duration of response was not reached in the TMB-high group and was 33.1 months in the non-TMB-high group. Notably, TMB-high status was associated with improved response irrespective of programmed death-ligand 1 (PD-L1). Median PFS and OS did not differ between the high and non-high TMB groups. Objective responses were observed in 24 (35%; 95% CI, 24% to 48%) of 68 participants who had both TMB-high status and PD-L1-positive tumors (i.e., PD-L1 combined positive score of ≥1) and in 6 (21%; 95% CI, 8% to 40%) of 29 participants who had TMB-high status and PD-L1-negative tumors. Study eligible cancers were limited to anal, biliary, cervical, endometrial, mesothelioma, neuroendocrine, salivary, small-cell lung, thyroid, and vulvar. Because no patients with ovarian cancer were included in these analyses, it is not possible to draw conclusions about the clinical validity and utility of TMB in this group of patients.

Clinical Utility
Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. There is no direct evidence of clinical utility of TMB testing to guide ovarian cancer treatment.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. Because the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Tumor Mutational Burden Testing to Guide Treatment for Ovarian Cancer
In a prespecified exploratory analysis of a nonrandomized trial of pembrolizumab in patients with various solid tumors, objective responses were observed in 35% of participants who had both TMB-high status and PD-L1-positive tumors and in 21% of participants who had TMB-high status and PD-L1-negative tumors. A TMB-high status was associated with improved response irrespective of PD-L1 status. Median OS and PFS survival were not significantly different between TMB groups. Because no patients with ovarian, fallopian tube, or primary peritoneal cancer were included in these analyses, it is not possible to draw conclusions about the clinical validity and utility of TMB in this group of patients. These results need to be confirmed in well-designed prospective studies enrolling patients in the relevant population.

Circulating Tumor DNA Testing (Liquid Biopsy) to Guide Treatment for Ovarian Cancer

Clinical Context and Test Purpose

One purpose of liquid biopsy testing of patients who have ovarian cancer is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment).

The question addressed in this evidence review is: Does use of circulating tumor DNA (ctDNA) testing to select treatment in patients with ovarian cancer improve the net health outcome?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with ovarian cancer being considered for targeted therapy or immunotherapy.

Interventions

The test being considered is liquid biopsy using ctDNA.

Comparators

In patients who are able to undergo a biopsy, molecular characterization of the tumor is performed using standard tissue biopsy samples. Patients unable to undergo a biopsy generally receive standard therapy.

Outcomes

True-positive liquid biopsy test results lead to the initiation of appropriate treatment (e.g., targeted therapy) without a tissue biopsy. False-positive liquid biopsy test results lead to the initiation of inappropriate therapy, which could shorten PFS.

In patients able to undergo a tissue biopsy, negative liquid biopsies reflex to tissue testing. In patients unable to undergo a tissue biopsy, a negative liquid biopsy result would not change empirical treatment. Therefore, health outcomes related to negative test results do not differ between liquid biopsy and tissue biopsy.

The time frame for outcomes measures varies from several months to several years.

Study Selection Criteria

For the evaluation of clinical validity, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology;
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Review of Evidence

FDA-Approved Companion Diagnostic Test

In October 2020, FoundationOne Liquid was FDA-approved as a companion diagnostic to identify individuals with *BRCA*-mutated ovarian cancer to select patients for treatment with rucaparib.[13,] Approval was based on analysis of pre-treatment plasma samples from the phase 2 ARIEL2 study. Subsequently, in June 2022 the indication for rucaparib was changed to no longer require *BRCA* testing.

There are no other FDA -cleared or -approved liquid biopsy companion diagnostic tests for use in selecting targeted treatment or immunotherapy in individuals with ovarian cancer.

Clinical Validity

In 2018, the American Society of Clinical Oncology and College of American Pathologists jointly convened an expert panel to review the current evidence on the use of ctDNA assays.[14,] The literature review included a search for publications on the use of ctDNA assays for solid tumors in March 2017 and covers several different indications for the use of liquid biopsy. The search identified 1338 references to which an additional 31 references were supplied by the expert panel. Seventy-seven articles were selected for inclusion. Much of the literature on the use of ctDNA to guide treatment selection was for non-small-cell lung cancer, metastatic colorectal cancer, and breast cancer, The literature review did not specifically address ovarian cancer. The authors concluded that "There is little evidence of clinical validity and clinical utility to support the widespread use of ctDNA assays in most patients with advanced cancer, with the exception of those with demonstrated clinical utility or those with regulatory approval."

Clinical Utility

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. There is no direct evidence of clinical utility of ctDNA testing to guide ovarian cancer treatment.

The clinical utility of FoundationOne liquid was evaluated using plasma samples from participants in the ARIEL2 trial. However, *BRCA* testing is no longer indicated prior to rucaparib treatment in ovarian cancer and so the relevance of this evidence is uncertain.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. Because the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Circulating Tumor DNA Testing (Liquid Biopsy) to Guide Treatment for Ovarian Cancer

The clinical utility of FoundationOne liquid was evaluated using plasma samples from participants in the ARIEL2 trial. However, *BRCA* testing is no longer indicated prior to rucaparib treatment in ovarian cancer and so the relevance of this evidence is uncertain. Clinical validity has not been demonstrated in multiple well-designed and conducted studies; therefore, a chain of indirect evidence to show clinical utility cannot be established.

Summary of Evidence

For individuals with epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive *BRCA1/2* variant testing, homologous recombination deficiency (HRD) testing, or microsatellite instability/mismatch repair (MSI/MMR) testing using tumor tissue to guide targeted treatment or immunotherapy, the evidence includes nonrandomized clinical trials. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Clinical trials have demonstrated clinical benefit when testing was used to identify individuals for treatment with FDA-approved therapies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with unresectable or metastatic ovarian, fallopian tube, or primary peritoneal cancer who receive TMB testing to select treatment with immunotherapy, the evidence includes a prespecified retrospective subgroup analysis of a nonrandomized phase 2 trial. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Objective responses were observed in 35% of participants who had both TMB-high status and PD-L1-positive tumors and in 21% of participants who had TMB-high status and PD-L1-negative tumors. High TMB status was associated with improved response irrespective of PD-L1 status. Median OS and progression free survival were not significantly different between TMB groups. Because no patients with ovarian cancer were included in these analyses, it is not possible to draw conclusions about the clinical validity and utility of TMB in this group of patients.

Well-designed prospective studies enrolling patients in the population of interest are required. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with ovarian, fallopian tube, or primary peritoneal cancer who receive circulating tumor DNA testing (liquid biopsy) to guide treatment, the evidence includes nonrandomized studies. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Given the breadth of methodologies available to assess circulating tumor DNA, the clinical validity of each commercially available test must be established independently. The clinical utility of FoundationOne liquid was evaluated using plasma samples from participants in the ARIEL2 trial. However, *BRCA* testing is no longer indicated prior to rucaparib treatment in ovarian cancer. Clinical validity has not been demonstrated in multiple well-designed and conducted studies; therefore, a chain of indirect evidence to show clinical utility cannot be established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

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 a provisional clinical opinion on the appropriate use of tumor genomic testing in patients with metastatic or advanced solid tumors.[15,] The opinion notes the following:

PCO 1.1. Genomic testing should be performed for patients with metastatic or advanced solid tumors with adequate performance status in the following 2 clinical scenarios:

- When there are genomic biomarker–linked therapies approved by regulatory agencies for their cancer.
- When considering a treatment for which there are specific genomic biomarker–based contraindications or exclusions (strength of recommendation: strong).

PCO 1.2.1. For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker–linked therapy that a regulatory agency has approved (strength of recommendation: moderate).

PCO 1.2.2. Multigene panel–based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency–approved therapy (strength of recommendation: strong).

PCO 2.1. Mismatch repair deficiency status (dMMR) should be evaluated in patients with metastatic or advanced solid tumors who are candidates for immunotherapy. There are multiple approaches, including using large multigene panel–based testing to assess microsatellite instability (MSI). Consider the prevalence of dMMR and/or MSI-H status in individual tumor types when making this decision (strength of recommendation: strong).

PCO 2.2. When TMB may influence the decision to use immunotherapy, testing should be performed with either large multigene panels with validated TMB testing or whole-exome analysis (strength of recommendation: strong).

PCO 4.1. Genomic testing should be considered to determine candidacy for tumor-agnostic therapies in patients with metastatic or advanced solid tumors without approved genomic biomarker–linked therapies (strength of recommendation: moderate).

National Comprehensive Cancer Network

The current NCCN guidelines for ovarian cancer (including fallopian tube cancer and primary peritoneal cancer) are version 4.2022.[16,] Guidelines are updated frequently; refer to the source for most current recommendations.

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 (HR) 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*, HR status, MSI, MMR, TMB, BRAF, and NTRK if prior testing did not include these markers.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in August 2022 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

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

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
	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)
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.

Definitions of Decision Determinations

Medically Necessary: 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, are: (a) consistent with Blue Shield 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 patient; 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/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

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.

We are 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.

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

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. 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 contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER**
New Policy **Policy Statement:** N/A	**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) 2.04.156** **Policy Statement:** I. Germline and somatic *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 therapies. II. 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 are considered **investigational**. III. 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 therapies. IV. All other uses of HRD testing of tumor tissue to guide targeted therapy or immunotherapy for ovarian, fallopian tube, or primary peritoneal cancer are considered **investigational**. V. Microsatellite instability (MSI) and/or mismatch repair (MMR) testing of tumor tissue may be considered **medically necessary** for individuals with unresectable or metastatic ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved therapies (e.g. pembrolizumab/Keytruda). VI. Other uses of MSI/MMR testing of ovarian, fallopian tube, or primary peritoneal tumor tissue to guide targeted therapy or immunotherapy are considered **investigational**.

POLICY STATEMENT	
BEFORE	**AFTER**
	VII. Circulating tumor DNA testing (liquid biopsy) to guide treatment in individuals with ovarian, fallopian tube, or primary peritoneal cancer is considered **investigational**. VIII. 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). **Note:** Testing for other variants may become available between policy updates.