BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 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)

Effective Policy Date: January 1, 2023

Original Policy Date: December 2022

Related Policies:

2.04.02 - Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
2.04.08 - Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
2.04.101 - Genetic Testing for Li-Fraumeni Syndrome
2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
2.04.141 - Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
2.04.149 - Molecular Testing for Germline Variants Associated with Ovarian Cancer (BRIP1, RAD51C, RAD51D, NBN)
2.04.151 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer
2.04.45 - Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer
2.04.53 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, MMR/MSI, HER2, and TMB)
2.04.77 - Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy or Immunotherapy
2.04.88 - Genetic Testing for PTEN Hamartoma Tumor Syndrome

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)

Description

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.

OBJECTIVE

The objective of this evidence review is to determine whether using biomarker testing to select targeted treatment and immunotherapy improves the net health outcome in individuals with ovarian cancer.

POLICY STATEMENT

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.

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**.

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.

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**.

Microsatellite instability/mismatch repair (MSI/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.

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

Tumor mutational burden testing to predict response to immunotherapy in individuals with ovarian, fallopian tube, or primary peritoneal cancer is considered **investigational**.

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

Simultaneous testing using liquid and tumor biopsies (outside of paired or concurrent somatic-germline testing) to guide treatment in individuals with ovarian, fallopian tube, or primary peritoneal cancer is considered **investigational** (see Policy Guidelines).

Testing for other variants may become available between policy updates.

POLICY GUIDELINES

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

For expanded panel testing, see evidence review 2.04.115.

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, 2.04.02, 2.04.08, 2.04.88, 2.04.101).

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 evidence review 2.04.93 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing for germline panel, and see evidence review 2.04.115 - 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
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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient"s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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.

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	Myriad myChoice CDx (Myriad	*BRCA1* and *BRCA2*

	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	Genetic Laboratories, Inc.)	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 and whose cancer is associated with HRD-positive status defined by either: • a deleterious or suspected deleterious BRCA mutation, and/or • genomic instability	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	*BRCA1* and *BRCA2* mutations
		FoundationOne CDx (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations
		Myriad myChoice CDx (Myriad Genetic Laboboratories, Inc)	*BRCA1* and *BRCA2* mutations and/or positive Genomic Instability Score
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

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 overall survival (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 tumor mutational burden (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.

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16. National Comprehensive Cancer Network. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed August 29, 2022.

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2022	New policy - Add to Genetics section	Policy created with literature review through August 15, 2022. Biomarker testing for BRCA1/2 variants, homologous recombination deficiency, and microsatellite instability/mismatch repair may be considered medically necessary for individuals with ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved therapies. Tumor mutational burden testing and circulating tumor DNA testing (liquid biopsy) to guide treatment with targeted therapy or immunotherapy in individuals with ovarian, fallopian tube, or primary peritoneal cancer is considered investigational.