



Louisiana

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: 01/01/2023

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 policy 00417.

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 Are Considered Investigational

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

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**.*

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Based on review of available data, the Company considers 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.

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).

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Paired Somatic-Germline Testing

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

Paired genetic testing is different than concurrent somatic-germline testing. In concurrent testing, the germline results are not used to filter the somatic results. Rather, the laboratories perform large, separate panels of germline and somatic variants. The goal is to identify options for genome-informed treatment and to identify hereditary cancer risk. 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.

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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

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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.

Background/Overview

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 (eg, 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,

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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. 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.

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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.

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 (eg, Sanger sequencing) are needed.

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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 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.

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

Treatment	Indication in Ovarian Cancer	Companion Diagnostic	Biomarkers
<i>Targeted Treatment for Ovarian Cancer</i>			
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	Myriad myChoice CDx (Myriad Genetic Laboratories, Inc.)	BRCA1 and BRCA2 genes and/or positive Genomic Instability Score

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	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 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		
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	BRCAAnalysis 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

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	complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status defined by either: <ul style="list-style-type: none"> • 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.)	<i>BRCA1</i> and <i>BRCA2</i> mutations
		FoundationFocus CDxBRCA Assay (Foundation Medicine, Inc.)	<i>BRCA1</i> and <i>BRCA2</i> alterations
		FoundationOne CDx (Foundation Medicine, Inc.)	<i>BRCA1</i> and <i>BRCA2</i> alterations
		FoundationOne Liquid CDx (Foundation Medicine, Inc.)	<i>BRCA1</i> and <i>BRCA2</i> alterations
Immunotherapy for Solid Tumors			
Pembrolizumab (Keytruda [®]) [‡]	Adult and pediatric patients with unresectable or metastatic microsatellite instability-high	FoundationOne CDx (Foundation Medicine, Inc.)	Microsatellite instability-High (MSI-H)

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	(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		
	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); 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.

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

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practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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 epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive *BRCA1/2* variant testing, homologous recombination deficiency (HRD) testing, or 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 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.

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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. 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).

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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. 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.

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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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12/01/2022 Medical Policy Committee review

12/14/2022 Medical Policy Implementation Committee approval. New policy. Senate bill review.

Next Scheduled Review Date: 12/2023

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Code Type	Code
CPT	0037U, 0172U, 0239U, 81162, 81479
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

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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.

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