BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.156 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency)

Annual Effective Policy Date: January 1, 2024

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
2.04.157 - Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy (BRAF, MSI/MMR, PD-L1, TMB)
2.04.45 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB)
2.04.53 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, and HER2)
2.04.77 - Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy (BRAF)
2.04.88 - Genetic Testing for PTEN Hamartoma Tumor Syndrome
2.04.93 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency)

Description

Description

Biomarker-targeted therapy has shown a clear survival benefit in patients with ovarian cancer. Typically, the evaluation of biomarker status requires tissue biopsy. Circulating tumor DNA testing (also known as a liquid biopsy) is proposed as a non-invasive alternative.

OBJECTIVE

The objective of this evidence review is to summarize the evidence and guidelines on biomarker testing to select targeted treatment for individuals with ovarian cancer.

POLICY STATEMENT

Germline *BRCA1/2* variant analysis may be considered **medically necessary** for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies.

Somatic *BRCA1/2* variant analysis using tumor tissue may be considered **medically necessary** for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies.

All other uses of germline and somatic *BRCA1/2* variant analysis to guide targeted therapy for ovarian, fallopian tube, or primary peritoneal cancer are considered **investigational**.

Homologous recombination deficiency (HRD) analysis of tumor tissue may be considered **medically necessary** for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies.

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

BRCA1/2 variant analysis using circulating tumor DNA (liquid biopsy) may be considered **medically necessary** for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies when tissue-based analysis is not clinically feasible.

All other uses of circulating tumor DNA testing (liquid biopsy) to guide targeted therapy in individuals with ovarian, fallopian tube, or primary peritoneal cancer are considered **investigational**.

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

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

Testing for other variants may become available between policy updates.

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

For expanded panel testing, see evidence review 2.04.115.

For somatic biomarker testing related to use of immune checkpoint inhibitor therapy (BRAF, microsatellite instability/mismatch repair [MSI/MMR], PD-L1, tumor mutational burden [TMB]), see evidence review 2.04.157.

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

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

Note: Extensive evidence review is not included for somatic tests of individual genes (not gene panels) associated with FDA-approved therapies with NCCN recommendations of 2A or higher. The pivotal evidence is included in Table 1 for informational purposes. Additionally, no evidence review is

provided for somatic tests of individual genes that do not have associated FDA-approved therapies regardless of NCCN recommendations, as these off-label therapies are deemed investigational per the Blue Cross and Blue Shield Association Medical Policy Program Policies and Procedures.

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

Repeat Genomic Testing

There may be utility in repeated testing of gene variants for determining targeted therapy or immunotherapy in individuals with ovarian cancer, as a resistance mechanism to platinum-based chemotherapies and poly adenosine diphosphate-ribose polymerase (PARP) inhibitors in BRCA-mutant cancers is the acquisition of *BRCA* reversion mutations that restore protein function (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 evidence reviews 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.

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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.

Some Plans may have contract or benefit exclusions for genetic testing or have state mandates for biomarker testing coverage.

FDA REGULATORY STATUS

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

Voluntarily Withdrawn Indications for Maintenance Therapy

In 2022, the manufacturers of all 3 PARP inhibitors used to treat ovarian cancer voluntarily withdrew indications for third-line or greater treatment in ovarian cancer.[5,6,7,] The withdrawals were based on updated survival results from the ARIEL4 (NCT02855944), SOLO3 (NCT02282020), and QUADRA (NCT02354586) trials. The withdrawals did not affect other indications in ovarian cancer.

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

Treatment	Indication in Ovarian Cancer	Companion DiagnosticsDate	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
Niraparib (Zejula)	Maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy. Maintenance treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Zejula.	None for this indication	Not applicable	First-line maintenance treatment: PRIMA (NCT02655016)[8,9,] Maintenance treatment of recurrent germline *BRCA*-mutated ovarian cancer: NOVA (NCT01847274)[10,]	2A Ovarian Cancer (V.2.2023)[11,]
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	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	*BRCA1* and *BRCA2* mutations	First-line maintenance *BRCA*-mutated advanced ovarian cancer: SOLO-1 (NCT01844986)[12,13,]	2A Ovarian Cancer (V.2.2023)[11,]

	complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status defined by either: • a deleterious or suspected deleterious *BRCA* mutation, and/or • genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.			First-line maintenance treatment in combination with bevacizumab, HRD-positive advanced ovarian cancer: PAOLA-1 (NCT02477644)[14,] Maintenance treatment of recurrent ovarian cancer: SOLO-2 (NCT01874353)[15,16,] Study 19 (NCT00753545[17,]	
		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 a deleterious *BRCA*mutation (germline and/or somatic)-associated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	*BRCA1* and *BRCA2* mutations	ARIEL3 (NCT01968213)[18,]	2A Ovarian Cancer (V.2.2023)[11,]
		FoundationFocus CDxBRCA Assay (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations		
		FoundationOne CDx (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations		
		FoundationOne Liquid CDx (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations		

Sources: Food and Drug Administration (2023)[19,]; Drugs@FDA[20,]

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 advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive germline *BRCA1/2* variant testing to guide treatment with a poly adenosine diphosphate-ribose polymerase (PARP) inhibitor, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive somatic *BRCA1/2* variant testing using tissue biopsy to guide treatment with a PARP inhibitor, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive homologous recombination deficiency (HRD) testing using tumor tissue to guide treatment with a PARP inhibitor, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive somatic *BRCA1/2* variant testing using circulating tumor DNA testing (liquid biopsy) to guide treatment with a PARP inhibitor, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology

In 2022, the American Society of Clinical Oncology published updated recommendations on poly adenosine diphosphate-ribose polymerase (PARP) inhibitors in the management of ovarian cancer.[4,] The recommendations included the following:

Newly Diagnosed Ovarian Cancer

"Recommendation 2.1. Patients with newly diagnosed stage III-IV EOC [epithelial ovarian cancer] who are in complete or partial response to first-line platinum-based chemotherapy should be offered PARP inhibitor maintenance therapy in high-grade serous or endometrioid ovarian cancer. For those with germline or somatic pathogenic or likely pathogenic variants in *BRCA*1 or *BRCA*2 genes, options should include olaparib (300 mg orally every 12 hours for 2 years), niraparib (200-300 mg orally daily for 3 years) or rucaparib (600 mg twice a day for 2 years). Longer duration could be considered in selected individuals after discussion of risks. For those who are HRD [homologous recombination deficiency] positive, determined using FDA-approved companion diagnostic tests, rucaparib and niraparib are options. Niraparib or rucaparib may be offered for non-*BRCA* mutated/HRD negative patients. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.)"

Recurrent Ovarian Cancer: Second-Line or Greater Maintenance and Treatment

"Recommendation 3.0. PARP inhibitor monotherapy maintenance (second-line or more) may be offered to patients with EOC who have not already received a PARP inhibitor and who have responded to platinum-based therapy regardless of *BRCA* mutation status; treatment is continued until progression of disease or toxicity despite dose reductions and best supportive care. Options include olaparib 300 mg every 12 hours, rucaparib 600 mg every 12 hours or niraparib 200-300 mg once daily. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.) Maintenance treatment with niraparib for patients without germline or somatic *BRCA* mutation should weigh potential PFS benefit against possible OS decrement. (Type: Evidence-based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Moderate.)"

"Recommendations 3.1/3.2. PARP inhibitor monotherapy should not be routinely offered to patients for the treatment of recurrent platinum sensitive EOC. (Type: Evidence-based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate.) *Evidence on PARP inhibitor use in this setting is evolving and data are continuing to emerge. Any decision to proceed with PARP inhibitor treatment in select populations* (*BRCA mutation, No prior PARP inhibitor use, Platinum Sensitive, Advanced Lines of Treatment) should be based on individualized patient and provider assessment of risks, benefits, and preferences*."

"Recommendation 3.3. PARP inhibitor monotherapy is not recommended for treatment for patients with either *BRCA* wild-type or platinum-resistant recurrent EOC. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.)"

National Comprehensive Cancer Network

The current NCCN guidelines for ovarian cancer (including fallopian tube cancer and primary peritoneal cancer) are version 2.2023.[11,] Guidelines are updated frequently; refer to the source for most current recommendations.

The guidelines include the following relevant recommendations on biomarker testing to guide targeted therapy in ovarian cancer:

- "In the up-front setting, choice of somatic testing should, at a minimum, optimize identification of molecular alterations that can inform use of interventions that have demonstrated benefit in this setting, including BRCA1/2, loss of heterozygosity (LOH), or homologous recombination deficiency (HRD) status in the absence of a germline BRCA mutation.
- In the recurrence setting, tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, *BRCA1/2*, HRD status, MSI, MMR, TMB, *FRa, RET,BRAF*, and NTRK if prior testing did not include these markers.
- Molecular analyses may be performed on circulating tumor DNA (ctDNA or liquid biopsy) when tissue-based analysis is not clinically feasible.
- Validated molecular testing should be performed in a CLIA-approved facility."

Recommendations on the use of PARP inhibitors for ovarian cancer include the following:

Maintenance Therapy After Recurrence

- "PARP inhibitor options include niraparib, olaparib, or rucaparib.
- For patients with platinum-sensitive disease who have completed two or more lines of platinum based therapy. Olaparib may be used regardless of *BRCA* status (preferred for those with a *BRCA* mutation).
- Niraparib is limited to those with a deleterious or suspected deleterious germline *BRCA* mutation.
- Rucaparib is limited to those with a deleterious or suspected deleterious *BRCA* mutation.
- Caution should be used when using maintenance PARP inhibitor for longer than 24 months.
- There are limited data on the use of a maintenance PARP inhibitor in patients who previously received a PARP inhibitor or after recurrence therapy with bevacizumab.
- Combination bevacizumab/PARP inhibitor is not recommended at this time for maintenance after recurrence therapy."

First-Line Maintenance Therapy

- "After first-line therapy with bevacizumab, data are limited on maintenance therapy with a single-agent PARP inhibitor (olaparib, niraparib, or rucaparib) for patients with a germline or somatic *BRCA*1/2 mutation. However, based on the magnitude of benefit of PARP inhibitor maintenance therapy for other subgroups, single-agent PARP inhibitors can be considered."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (CMS) National Coverage Determination on Next Generation Sequencing (90.2) states:

"Effective for services performed on or after March 16, 2018, [CMS] has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

a. Patient has:

1. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
2. not been previously tested with the same test using NGS for the same cancer genetic content, and
3. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

b. The diagnostic laboratory test using NGS must have:

1. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
2. an FDA-approved or -cleared indication for use in that patient's cancer; and,
3. results provided to the treating physician for management of the patient using a report template to specify treatment options." [21,]

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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.
December 2023	Replace policy	Policy updated with literature search through August 1, 2023. Evidence opinion extensively pruned. Pivotal studies added to Table 1. Indications related to immunotherapy and tumor mutational burden testing removed and added to policy 2.04.157. Title changed accordingly. New medically necessary statement added for BRCA1/2 testing using circulating tumor DNA (liquid biopsy) to select treatment with FDA-approved targeted therapies. Other policy statements revised for clarity and to align with indications; intent unchanged.