Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: Keystone First	**Submission Date**: 7/1/224
Policy Number: ccp.1485	**Effective Date:** 6/2021 **Revision Date:** June 1, 2024
Policy Name: Molecular analysis for targeted therapy for ovarian cancer	

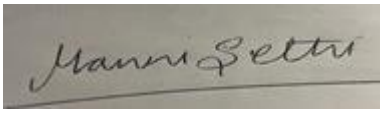
Type of Submission – Check all that apply:

- **New Policy**
- x **Revised Policy***
- **Annual Review – No Revisions**
- **Statewide PDL**

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

See tracked changes below.

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Keystone First
Family of Health Plans

Molecular analysis for targeted therapy for ovarian cancer

Clinical Policy ID: CCP.1485

Recent review date: 6/2024

Next review date: 10/2025

Policy contains: BRCA; homologous recombination deficiency; molecular testing; Myriad myChoice; PARP inhibitors; ovarian cancer; targeted therapy.

Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First, on a case by case basis, when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First's clinical policies are not guarantees of payment.

Coverage policy

As the landscape of targeted therapies is rapidly evolving molecular analysis for targeted therapy for ovarian cancer is clinically proven and, therefore, may be medically necessary for indications specified in National Comprehensive Cancer Network (2024) clinical practice guidelines and U.S. Food and Drug Administration-approved package labeling for indication and usage. Validated molecular testing should be performed in a Clinical Laboratory Improvement Amendments-approved laboratory or by a U.S. Food and Drug Administration-approved companion diagnostic test (see Appendix) for the following biomarkers in the detection of:

- Deleterious or suspected deleterious germline BRCA variant to assess candidacy for niraparib (U.S. Food and Drug Administration, 2022b).
- Homologous recombination deficiency (deleterious or suspected deleterious BRCA variant or genomic instability) to assess candidacy for olaparib (U.S. Food and Drug Administration, 2020a).
- Deleterious germline or somatic BRCA variant to assess candidacy for rucaparib (U.S. Food and Drug Administration, 2020c).
- Mismatch repair (encoded by genes MLH1, MSH2, MSH6, and PMS2), microsatellite instability testing, or tumor mutational burden to assess candidacy for pembrolizumab (U.S. Food and Drug Administration, 2023b).
- Tyrosine receptor kinase gene fusion (rearrangements of genes NTRK1, NTRK2, and NTRK3) to assess candidacy for larotrectinib or entrectinib (U.S. Food and Drug Administration, 2019, 2022b).
- Folate receptor alpha 1 (FOLR1) protein expression to assess candidacy for mirvetuximab soravtansine-gynx (U.S. Food and Drug Administration, 2022a).

- BRAF V600E expression to assess candidacy for dabrafenib (off-label use; National Comprehensive Cancer Network, 2024).
- RET gene fusion expression to assess candidacy for selpercatinib (off-label use; National Comprehensive Cancer Network, 2024).
- BRAF V600E expression or V600K expression to assess candidacy for trametinib and binimetinib (off-label use; National Comprehensive Cancer Network, 2024).
- Mismatch repair deficient recurrent or advanced solid tumors to assess candidacy for dostarlimab-gxly (U.S. Food and Drug Administration, 2024b).

Molecular analyses may be performed on circulating tumor deoxyribonucleic acid (DNA) when tissue-based analysis is not clinically feasible (National Comprehensive Cancer Network, 2024).

For determinations of medical necessity relating to medication type, refer to the applicable state-approved pharmacy policy.

Limitations

Variant molecular testing other than the ones listed in the Coverage section (above) are investigational/not clinically proven and, therefore, not medically necessary for targeted therapy provision in members with ovarian cancer.

Molecular tumor profiling tests not listed in the Appendix (e.g., Caris Molecular Intelligence® Tumor Profiling, Caris Life Sciences, Irving, Texas), are investigational/not clinically proven and, therefore, not medically necessary, as these have not been validated and approved by the U.S. Food and Drug Administration for predicting response to the targeted therapies in members with recurrent, progressive, or metastatic ovarian cancer.

Molecular testing for the purpose of clinical trial eligibility determination is not medically necessary.

Alternative covered services

Standard of care for management of ovarian cancer.
Other individualized molecular testing reviewed on a case by case basis.

Background

Ovarian cancer (epithelial carcinoma of the ovary) encompasses ovarian epithelial, fallopian tube, and primary peritoneal cancers, all of which are histologically similar that arise from epithelial tissue and are treated in the same way. Ovarian cancer is one of the most common and deadly gynecologic malignancies, and is the sixth most frequent cause of cancer death in women. It is rare under the age of 40 and most frequently diagnosed among women ages 55 – 64; with 50% of all cases occurring in women older than 65 years. The hallmark of these cancers is their early peritoneal spread of metastases, as evidenced by the high prevalence of regional or distant spread at diagnosis (National Cancer Institute, 2024).

A family history of ovarian cancer in a first-degree relative is the most important risk factor, and the majority of these cancers are linked to inherited changes in the BRCA1/2 genes. Other risk factors include advancing age, hereditary conditions such as hereditary nonpolyposis colorectal cancer (also called Lynch syndrome), endometriosis, and postmenopausal hormone therapy (National Cancer Institute, 2024).

An estimated 41% to 50% of ovarian cancers exhibit deficiency in the homologous recombination DNA repair pathway. This pathway plays an important role in repairing damaged DNA, which, if left unrepaired, can result in accumulated variants, unregulated cell division, and cancer susceptibility. Genetic variants involving homologous repair can occur in germline cells or somatic cells. The most well-known are germline BRCA 1/2 gene variants

for their prognostic and predictive value, but other germline variants, somatic variants, and variants of other genes involved in the pathway have been implicated (da Cunha Colombo Bonadio, 2018). These other variants include ATM, BRIP1, PALB2, RAD51C, RAD51D, and NBN (National Comprehensive Cancer Network, 2024).

Ovarian cancers with homologous recombination deficiency exhibit an increased responsiveness to cytotoxic chemotherapy, especially platinum agents. Treatment options for patients with all stages of ovarian cancer generally consist of cytoreductive surgery, followed by platinum-based chemotherapy — with or without consolidation therapy. For platinum-sensitive tumors, bevacizumab, hormone therapy, poly-ADP-ribose polymerase inhibitors, and other targeted therapies may be administered as maintenance therapy or to patients with advanced or recurrent disease that expresses certain genetic variants (National Cancer Institute, 2024).

Molecular testing options include next-generation sequencing for germline or somatic BRCA 1/2 variants, polymerase chain reaction for microsatellite instability, and immunohistochemistry for detecting DNA mismatch repair protein (National Comprehensive Cancer Network, 2024). Testing options for detection of neurotrophic tyrosine receptor kinase gene fusion are next-generation sequencing, immunohistochemistry, DNA fluorescence in situ hybridization, and polymerase chain reaction. Targeted gene panel sequencing is most often used to determine tumor mutational burden status.

For homologous recombination deficiency, the three main testing strategies are (da Cunha Colombo Bonadio, 2018):

- Germline mutation screening of genes related to homologous recombination repair using next generation sequencing DNA from blood.
- Somatic (tumor) mutation screening of DNA related to homologous recombination repair, which can inform treatment strategies. However, when somatic screening identifies a variant, germline analysis of normal cells is still necessary to determine whether the variant is germline or somatic.
- Genomic instability secondary to homologous recombination deficiency, which is calculated based on the loss of heterozygosity, telomeric allelic imbalance, and large-scale transitions. A high loss of heterozygosity (defined as ≥ 14% to 16% with next-generation sequencing) suggests the presence of homologous recombination deficiency. The Myriad myChoice® HRD test (Myriad Genetics Inc., Salt Lake City, Utah) is a proprietary composite homologous recombination deficiency score comprised of loss of heterozygosity, telomeric allelic imbalance, and large-scale transitions. The efficiency of the HRD test score may overcome the limitations of next-generation sequencing, which captures many variants of unknown significance.

The U.S. Food and Drug Administration (2024a) has approved several companion diagnostic tests for determining candidacy for targeted ovarian cancer therapies, including the myChoice HRD test for genomic instability (Appendix). These companion diagnostic tests have been validated as providing essential information for the safe and effective use of a corresponding therapeutic product.

Findings

The National Comprehensive Cancer Network recommends tumor molecular analysis both in the upfront setting and upon recurrence. At a minimum, testing for germline or somatic BRCA1/2 and microsatellite instability or mismatch repair deficiency status should be performed if not previously done, as the results of these tests can affect eligibility for maintenance therapy for platinum-sensitive disease. Evaluation of loss of heterozygosity can be considered. In the absence of a germline BRCA/1/2 variant, tumor homologous recombination deficiency status may inform the magnitude of benefit of poly-ADP-ribose polymerase inhibitor therapy. Individual patient evaluation and provider preference will determine the breadth and timing of molecular germline and somatic testing (National Comprehensive Cancer Network, 2024).

In the setting of refractory or recurrent disease, additional somatic tumor testing may be considered to identify genetic alterations for which U.S. Food and Drug Administration-approved tumor-specific or tumor-agnostic targeted therapies exist. Testing can include HER2 status by immunohistochemistry, BRCA1/2, hormone receptor status, microsatellite instability, mismatch repair, tumor mutational burden, BRAF, FOLR1, and NTRK, if prior testing did not include these markers. More comprehensive tumor analysis may be important for less common histologies with limited approved treatment options. Molecular analyses may be performed on circulating tumor DNA ("liquid biopsy") when tissue-based analysis is not clinically feasible (National Comprehensive Cancer Network, 2024).

The National Comprehensive Cancer Network (2024) recommends the following targeted therapies for ovarian cancer in some circumstances, although ovarian cancer represents an off-label use. Molecular testing for these targeted therapies should be performed in a Clinical Laboratory Improvement Amendments-approved facility using the most recent available tumor tissue:

- Pazopanib (multi- tyrosine kinase inhibitor but no molecular biomarker identified) (U.S. Food and Drug Administration, 2009).
- Dabrafenib (kinase inhibitor for BRAF V600E-positive tumors) (U.S. Food and Drug Administration, 2013b).
- Trametinib (for BRAF V600E-positive tumors or V600K mutations as detected by an approved test) (U.S. Food and Drug Administration, 2013a).
- Selpercatinib (for RET gene fusion-positive tumors) (U.S. Food and Drug Administration, 2020b).
- Binimetinib (for BRAF V600E V600K-positive tumors) (U.S. Food and Drug Administration, 2018).

Validated molecular testing is required to detect these variants and inform targeted therapy provision. Validated molecular testing should be performed in a Clinical Laboratory Improvement Amendments-approved laboratory using the most recent available tumor tissue or an approved companion diagnostic test. The Appendix lists eligible targeted therapies for ovarian cancer and corresponding companion diagnostic tests required for candidacy, where available.

In 2023, we made changes to the policy coverage based on National Comprehensive Cancer Network guideline recommendations and U.S. Food and Drug Administration-approved package labeling for indication and usage.

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In 2024, we updated the references and the list of companion diagnostic tests and indications in the appendix. We added one new targeted therapy indication for molecular testing to coverage: Dostarlimab-gxly for mismatch repair deficient recurrent or advanced solid tumors using the Ventana MMR RxDx Panel (Ventana Medical Systems, Inc.) (U.S. Food and Drug Administration, 2024a, 2024b).

References

On May 2, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "ovarian neoplasm" (MeSH), "molecular therapy" (MeSH), and "genetic testing" (MeSH). We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

da Cunha Colombo Bonadio RR, Fogace RN, Miranda VC, Diz M. Homologous recombination deficiency in ovarian cancer: A review of its epidemiology and management. *Clinics (Sao Paulo).* 2018;73(suppl 1):e450s. Doi: 10.6061/clinics/2018/e450s.

National Cancer Institute. Ovarian epithelial, fallopian tube, and primary peritoneal cancer treatment (PDQ®)–health professional version. https://www.cancer.gov/types/ovarian/hp/ovarian-epithelial-treatment-pdq. Updated April 16, 2024.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Ovarian cancer including fallopian tube cancer and primary peritoneal cancer. Version 1.2024. www.nccn.org. Published January 17, 2024.

U.S. Food and Drug Administration. List of cleared or approved companion diagnostic devices (in vitro and imaging tools). https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Content current as of May 1, 2024.(a)

U.S. Food and Drug Administration. Product label. ELAHERE™ (mirvetuximab soravtansine-gynx). https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761310s000lbl.pdf. Approved 2022. (a)

U.S. Food and Drug Administration. Product label. JEMPERLI (dostarlimab-gxly) https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s010lbl.pdf. Approved 2021. Last updated March 2024.(b)

U.S. Food and Drug Administration. Product label. KEYTRUDA® (pembrolizumab) injection. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125514s128lbl.pdf. Approved 2014. Updated January 2023. (b)

U.S. Food and Drug Administration. Product label. LYNPARZA® (olaparib) tablets. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s016lbl.pdf. Approved 2014. Updated December 2020. (a)

U.S. Food and Drug Administration. Product label. MEKINIST®. Trametinib. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204114s000lbl.pdf. Approved 2013. (a)

U.S. Food and Drug Administration. Product label. MEKTOVI®. Binimetinib. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210498lbl.pdf. Approved 2018.

U.S. Food and Drug Administration. Product label. RETEVMOTM®. Selpercatinib. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213246s000lbl.pdf. Approved 2020. (b)

U.S. Food and Drug Administration. Product label. ROZLYTREK (entrectinib) capsules. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212725s000lbl.pdf. Approved 2019.

U.S. Food and Drug Administration. Product label. RUBRACA® (rucaparib) tablets. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s008lbl.pdf. Approved 2016. Updated October 2020. (c)

U.S. Food and Drug Administration. Product label. TAFINLAR®. Dabrafenib. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202806s000lbl.pdf. Approved 2013. (b)

U.S. Food and Drug Administration. Product label. VITRAKVI® (larotrectinib) oral solution. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/210861s008lbl.pdf. Approved November 2018. Updated November 2022. (b)

U.S. Food and Drug Administration. Product label. VOTRIENT®. Pazopanib. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022465lbl.pdf. Approved 2009.

U.S. Food and Drug Administration. Product label. ZEJULA® (niraparib) capsules. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208447s025lbl.pdf. Approved 2017. Updated December 2022. (b)

Policy updates

5/2021: initial review date and clinical policy effective date: 6/2021

5/2023: Policy references updated. Coverage modified.

6/2024: Policy references updated. Coverage modified.

Appendix

List of cleared or approved companion diagnostic tests

The companion diagnostic tests, including nucleic acid-based companion diagnostic tests, listed below have been validated as tests that provide essential information for the safe and effective use of a corresponding therapeutic product. The use of a companion diagnostic device is stipulated in the instructions for use in the labeling of both the diagnostic device and the therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product.

Diagnostic test name/ manufacturer	**Drug trade name (generic) — NDA/BLA**
BRACAnalysis CDx® Myriad Genetic Laboratories, Inc. (whole blood nucleic acid-based test)	Lynparza (olaparib) — NDA 208558 Rubraca (rucaparib) — NDA 20911
FoundationOne® CDx Foundation Medicine, Inc.	Lynparza (olaparib) — NDA 208558 Solid tumors (tumor mutational burden ≥ 10 mutations per megabase) and microsatellite instability-high (MSI-H) • Keytruda (pembrolizumab) — BLA 125514 Solid tumors (neurotrophic tyrosine receptor kinase 1/2/3 fusions) • Vitrakvi (larotrectinib) — NDA 210861, 211710 • Rozlytrek (entrectinib) — NDA 212725 Solid tumors (RET fusions) • RETEVMO (selpercatinib) — NDA214246
FoundationOne® Liquid CDx Foundation Medicine, Inc. (liquid biopsy)	Rubraca (rucaparib) — NDA 209115 (plasma)
FoundationFocus™ CDxBRCA Assay Foundation Medicine, Inc. (nucleic acid-based test)	Rubraca (rucaparib) — NDA 209115
Myriad myChoice CDx	Lynparza (olaparib) — NDA 208558

Diagnostic test name/ manufacturer	Drug trade name (generic) — NDA/BLA
Myriad Genetic Laboratories, Inc.	
Ventana FOLR1 (FOLR-2.1) RxDx Assay (Ventana Medical Systems, Inc.)	Elahere (mirvetuximab soravtansine-gynx) — BLA 761310
Ventana MMR RxDx Panel (Ventana Medical Systems, Inc.)	Deficient mismatch repair proteins • Keytruda (pembrolizumab) — BLA 125514 • Jemperli (dostarlimag-gxly) — NDA 761174

Source: U.S. Food and Drug Administration (2024a).