

# Biomarkers in Diagnosis and Treatment



## RISK FACTORS FOR OVARIAN CANCER

- Family history of cancer (e.g., ovarian, breast)
- Genetic predisposition (e.g., mutated *BRCA1/2* or Lynch syndrome)
- Personal history of breast cancer at a younger age
- Increasing age
- Use of hormone replacement therapy
- Endometriosis
- Obesity
- Smoking
- Nulliparous or fertility issues
- Early menstruation or late menopause

Historically, germline *BRCA1/2* mutations were thought to be the cause of most cases of hereditary epithelial ovarian cancer (EOC). However, ovarian cancer research has identified a number of other genetic mutations associated with hereditary EOC that are thought to target specific cell signaling pathways (e.g., *TP53*, *BRAF*, *KRAS*).

Another example is Lynch syndrome, in which germline mutations in *MLH1*, *MSH2/EPCAM*, *MSH6* and *PMS2* genes have been found.

Biomarker testing can be used to identify these mutations and others to determine if the tumor can be treated with targeted therapy.



**Women with germline *BRCA1/2* mutations have a 30- to 40-fold increased risk of ovarian cancer.**

# Biomarkers in Diagnosis and Treatment

## BIOMARKER TESTING

NCCN Guidelines® recommend that all patients undergo genetic risk evaluation, which includes germline and somatic testing to identify molecular alterations that can inform treatment planning. Germline and somatic testing are described below.

### Germline Testing

- **Germline mutations** (or germline variants) are changes in a person's DNA that are present in every cell of the body, including egg and sperm
- **Germline testing** is a type of DNA testing that looks for inherited mutations that have been present since birth
- Germline testing can be done with saliva or blood samples
- Also called genetic testing



### Somatic Testing

- **Somatic mutations** are changes in a person's DNA that occur after birth and are present only in the cells of the tumor tissue
  - Unique to each individual and specific to the cancer tissue that is being analyzed
- **Somatic testing** looks for acquired or spontaneous mutations in a confined set of cells or tissue
- Also known as tumor testing, tumor analysis or tumor sequencing



## NCCN Guidelines for Tumor Analysis

NCCN Guidelines recommend tumor analysis in 2 settings:

1

**In the upfront setting:**

To identify molecular alterations (i.e., genetic mutations) that can inform use of interventions that have demonstrated benefit in this setting, such as poly (ADP-ribose) polymerase (PARP) inhibitors

2

**In the recurrent setting:**

Guides treatment decisions by identifying specific tumor characteristics, such as therapy resistance, which may improve outcomes and QoL

Details on selected molecular alterations in each setting are provided in the table on the next page.

# Biomarkers in Diagnosis and Treatment

## SELECTED MOLECULAR ALTERATIONS INCLUDED IN NCCN GUIDELINES FOR MOLECULAR TESTING

Molecular Alteration	Description
<b>Upfront Setting</b>	
<i>BRCA1/2</i>	<ul style="list-style-type: none"> <li>Tumor-suppressor genes that play a role in regulating cell growth</li> <li>Involved in repairing double-stranded DNA breaks via the homologous recombination repair (HRR) pathway</li> </ul>
Homologous recombination deficiency (HRD) status <sup>a</sup>	HRD is a genetic alteration that causes cells to lose the ability to effectively repair double-stranded DNA breaks via the HRR pathway
<b>Recurrent Setting<sup>b</sup></b>	
HER2 status (by IHC)	<ul style="list-style-type: none"> <li>The HER2 protein helps control normal cell growth</li> <li>HER2-positive tumors may grow more quickly and are more likely to metastasize in comparison to tumors without this alteration</li> </ul>
Microsatellite instability (MSI)/MSI-H (high)	<ul style="list-style-type: none"> <li>Cancer cells that have a high number of mutations within microsatellites, which are short, repeated sequences of DNA; more common in endometrial cancer than ovarian cancer</li> <li>MSI-H tumors may respond to immunotherapy</li> </ul>
Tumor mutational burden (TMB)	<ul style="list-style-type: none"> <li>Total number of mutations found in a cancer cell's DNA</li> <li>Tumors that have a high number of mutations may be more likely to respond to certain types of immunotherapy</li> </ul>
BRAF	A kinase enzyme that helps to control cell growth and signaling; kinases help to regulate cellular activity by phosphorylating proteins, acting as molecular on/off switches for various cell functions
FR $\alpha$	<ul style="list-style-type: none"> <li>FR<math>\alpha</math> is a membrane protein that binds to and transports folate into cells; may be overexpressed in HGSOE</li> <li>FR<math>\alpha</math>-positive, platinum-resistant tumors may respond to treatment with the antibody-drug conjugate (ADC) mirvetuximab soravtansine-gynx</li> </ul>

IHC, immunohistochemistry testing

<sup>a</sup>In the absence of a germline *BRCA* mutation. <sup>b</sup>*BRCA1/2* and HRD status are also analyzed in the recurrent setting.

# Biomarkers in Diagnosis and Treatment

## BIOMARKERS IN EARLY- AND LATE-STAGE TREATMENT PLANNING

### Biomarkers in the Upfront Setting

#### **BRCA1/2**

Informs selection of maintenance therapy following completion of platinum-based first-line chemotherapy

#### **HRD Status**

May provide information on the magnitude of benefit of PARP inhibitor maintenance therapy for tumors without a *BRCA1/2* mutation

## BIOMARKERS IN THE RECURRENT SETTING

Biomarkers may include, but are not limited to:	Therapeutic Class	Key Points
<i>BRAF</i> V600E–positive tumors	<i>BRAF</i> inhibitor + MEK1/2 inhibitor	<ul style="list-style-type: none"> <li>• <i>BRAF</i> inhibitors: dabrafenib, vemurafenib, encorafenib</li> <li>• MEK inhibitors: trametinib, binimetinib</li> <li>• These products are used in combination for tumors with <i>BRAF</i> V600E mutations</li> </ul>
<i>NTRK</i> gene fusion–positive tumors	TRK inhibitors	<ul style="list-style-type: none"> <li>• TRK inhibitors: larotrectinib, entrectinib</li> <li>• Block TRK fusion proteins that act as oncogenic drivers, promoting cell proliferation and survival in tumor cell lines</li> </ul>
<i>RET</i> gene fusion–positive tumors	<i>RET</i> kinase inhibitor	<ul style="list-style-type: none"> <li>• <i>RET</i> kinase inhibitors: pralsetinib, selpercatinib</li> <li>• <i>RET</i> mutations can trigger uncontrolled cell growth</li> </ul>
FR $\alpha$ -expressing tumors	FR $\alpha$ -targeting ADC	<ul style="list-style-type: none"> <li>• FR<math>\alpha</math>-targeting ADC: mirvetuximab soravtansine-gynx</li> <li>• <math>\approx</math>35% of advanced EOC tumors test positive for FR<math>\alpha</math> expression</li> </ul>
dMMR/MSI-H recurrent or advanced solid tumors	Immune checkpoint inhibitors (ICIs)	<ul style="list-style-type: none"> <li>• PD-1 inhibitors are a type of ICI: dostarlimab-gxly, pembrolizumab, others</li> <li>• ICIs target PD-1/PD-L1 on T cells to prevent their binding and supplement the body’s immune response</li> </ul>
TMB-H tumors $\geq$ 10 mutations/megabase		
HER2-positive tumors	HER2-directed ADC	<ul style="list-style-type: none"> <li>• HER2-directed ADCs: fam-trastuzumab-deruxtecan-nxki, others</li> <li>• Block HER2 receptors from receiving growth signals to slow or stop the growth of cancer cells</li> </ul>

More information on the use of biomarkers in the recurrent setting and platinum-resistant ovarian cancer will be provided in Micromoment 04.

## REFERENCES

American Cancer Society. [.org/cancer/types/ovarian-cancer/causes-risks-prevention.html](https://www.cancer.org/cancer/types/ovarian-cancer/causes-risks-prevention.html) Ovarian Cancer Causes, Risk Factors, and Prevention. Accessed August 5, 2025. [https://www.cancer](https://www.cancer.org/cancer/types/ovarian-cancer/causes-risks-prevention.html)

Berek JS, Renz M, Kehoe S, et al. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. *Int J Gynaecol Obstet.* 2021;155 Suppl 1(Suppl 1):61-85.

Carter D. MD Anderson Cancer Center: Ret Inhibitors: A treatment for any RET-altered cancer. Accessed July 24, 2025. <https://www.mdanderson.org/cancerwise/ret-inhibitors--a-treatment-for-any-ret-altered-cancer.h00-159544479.html>

Gouda MA, Subbiah V. Expanding the Benefit: Dabrafenib/Trametinib as Tissue-Agnostic Therapy for BRAF V600E-Positive Adult and Pediatric Solid Tumors. *Am Soc Clin Oncol Educ Book.* 2023;43:e404770.

Han SY. TRK Inhibitors: Tissue-Agnostic Anti-Cancer Drugs. *Pharmaceuticals.* 2021;29;14(7):632.

Matulonis UA, Lorusso D, Oaknin A et al, Safety of mirvetuximab soravtansine in patients with platinum-resistant ovarian cancer with high folate receptor alpha expression: results from the SORAYA Study. *J Clin Oncol.* 2023;41(13):2436-2445.

National Comprehensive Cancer Network. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 3.2025 — May 23, 2025. Accessed August 5, 2025. <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1453>

National Cancer Institute. Dictionary of cancer terms. Accessed August 5, 2025. <https://www.cancer.gov/publications/dictionaries/cancer-terms>

National Cancer Institute. What's at the root of ovarian cancer? New study may have found part of the answer. Accessed June 5, 2025. <https://www.cancer.gov/news-events/cancer-currents-blog/2025/ovarian-cancer-stic-high-risk-mscs>

Ovarian Cancer Research Alliance. Somatic vs Germline. Accessed July 7, 2025. <https://ocrahope.org/news/germline-vs-somatic-testing-genomic-vs-genetic-testing/#:~:text=What%20is%20germline%20testing?,genes%20inherited%20from%20a%20parent>

Pietragalla A, Arciere M, Marchetti C et al. Ovarian cancer predisposition beyond BRCA1 and BRCA2 genes. *Int J Gynecol Cancer.* 2020;30:1803–1810.

Radu MR, Prădatu A, Duică F, et al. Ovarian cancer: Biomarkers and targeted therapy. *Biomedicines.* 2021;18;9(6):693.

Rassy E, Rached L, Pistilli B. Antibody drug conjugates targeting HER2: Clinical development in metastatic breast cancer. *Breast.* 2022;66:217-226.

Vitrakvi (larotrectinib) [prescribing information]. Stamford, CT: Loxi Oncology Inc. 2018.