Biomarker Summary:

BRCA1/2

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Biological role

BRCA mutations cause homologous recombination deficiency (HRD), meaning cells are less able to repair DNA strand breaks and are more likely to develop multiple genetic alterations that can lead to cancer.

Clinical insights

Marker for inherited cancer syndrome: mutations associated with an increased risk of developing breast, ovarian, pancreatic, prostate, and other cancers.

Tumors with HRD are more sensitive to some therapies, including platinum chemotherapy and PARP inhibitors.

Applicable tumor types

Ovarian, breast, pancreas, prostate.
Suspected inherited syndrome, possibly all solid tumors.

Current agent indications

Olaparib

- **HER2-negative MBC** with **deleterious germline *BRCA1/2* mutations** after chemotherapy (and endocrine therapy if hormone receptor positive)[1]
- **Recurrent ovarian, fallopian tube,** or **primary peritoneal cancer** as maintenance therapy for CR or PR to platinum-based chemotherapy[2]
- **Ovarian cancer** with **deleterious germline *BRCA1/2* mutations** after ≥ 3 lines of therapy[3]

Niraparib

- **Recurrent ovarian, fallopian tube,** or **primary peritoneal cancer** as maintenance therapy for CR or PR to platinum-based chemo[4]

Rucaparib

- **Recurrent ovarian, fallopian tube,** or **primary peritoneal cancer** as maintenance therapy for CR or PR to platinum-based chemo[5]
- **Ovarian cancer** with **deleterious germline or somatic *BRCA1/2*** mutations after ≥ 2 lines of therapy[6]

References

1. Robson M, et al. N Engl J Med. 2017;377:523-533. 2. Pujade-Lauraine E, et al. Lancet Oncol. 2017;18:1274-1284. 3. Matulonis UA, et al. Ann Oncol. 2016;27:1013-1019. 4. Mirza MR. et al. N Engl J Med. 2016;375:2154-2164. 5. Coleman RL, et al. Lancet. 2017;390:1949-1961. 6. Swisher EM, et al. Lancet Oncol. 2017;18:75-87.

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Genetic risk evaluation

Current screening guidelines for genetic risk assessment recommend screening patients to identify a family history that may be associated with an increased risk of potentially harmful mutations in *BRCA1/2* genes followed by genetic counseling and, often, genetic testing.

For patients with **ovarian cancer,** *BRCA1/2* germline testing should be done at the time of diagnosis and somatic testing should be done just before initiating therapy.

For patients with **breast cancer,** *BRCA1/2* testing should be considered if diagnosed at ≤ 45 years of age; ≤ 50 years of age with an additional primary breast cancer or a close blood relative with breast, pancreatic, or prostate cancer; ≤ 60 years of age with triple-negative disease; or at any age with ≥ 2 close blood relatives with breast, pancreatic, or prostate cancer, a close blood relative with ovarian cancer or breast cancer diagnosed at ≤ 50 years of age, a close blood male relative with breast cancer, or ethnicity associated with high mutation frequency (Ashkenazi Jewish ancestry).

For patients with **prostate cancer,** *BRCA1/2* testing should be considered for those with **metastatic** disease or **high-grade** prostate cancer and a close blood relative with ovarian cancer or breast cancer diagnosed at ≤ 50 years of age or ≥ 2 close blood relatives with breast, pancreatic, or prostate cancer.

For patients with **pancreatic cancer,** *BRCA1/2* testing should be considered for those with Ashkenazi Jewish ancestry or a close blood relative with ovarian cancer or breast cancer diagnosed at ≤ 50 years of age or ≥ 2 close blood relatives with breast, pancreatic, or prostate cancer.

BRCA1/2 testing should also be considered for those with a personal history of **male breast cancer** or with family member(s) with known deleterious *BRCA1/2* genetic mutation.

FDA-approved testing assays and platforms

Agent(s)	Assay	Details	Indications
Olaparib Niraparib	*BRACAnalysis CDx*	Detection/classification of variant protein coding regions and intron/exon boundaries of the *BRCA1* and *BRCA2* genes Genomic DNA obtained from whole blood specimens	**Ovarian cancer** with deleterious or suspected deleterious germline *BRCA* variants **Breast cancer (olaparib only)** with deleterious or suspected deleterious germline *BRCA* variants
Rucaparib	*FoundationOne CDx*	Next-generation sequencing for qualitative detection of *BRCA1* and *BRCA2* alterations Formalin-fixed paraffin-embedded ovarian tumor tissue	**Ovarian cancer** *BRCA1/2* alterations