WHAT CAN THE LABORATORY DO TO ENSURE THE REQUESTING PHYSICIAN UNDERSTANDS AND CAN ACT UPON THE RESULTS?

CHECKLIST ITEM[1,3]	✓
Initial logistics and communication with treating physician	• Clearly title or name the report stating the test is a tumour *BRCA* test • Return results in a quick and efficient manner that is compliant with regulations • Ensure the physician is aware of how the results will be returned (e.g., web portal, fax, email) • Return results as soon as possible and within turnaround times (TAT) guidelines
Results Report	• The reported results should be presented in a brief and unambiguous way to aid easy interpretation • The report should highlight the clinical significance of any variants found, i.e., if the patient has a pathogenic or likely pathogenic *BRCA* variant or not, and should include possible treatment options • The report should indicate suitability of the sample, and whether these are acceptable for the specific testing method, and if not, what is the follow-up procedure • Indicate any follow-up process if tests fail • The report may indicate follow-up germline testing or counselling for *BRCA* positive patients and why
Information for follow-up, post-test results	• Contact details should be provided in case the physician has any questions regarding the test • Ensure the gene NM reference sequence accession ID is included and Human Genome Variation Society (HGVS) nomenclature is used • Provide information on any test limitations, such as if no large genomic rearrangement testing is performed on tumours and the implications, and any required follow-up; test limit of detection

REFERENCES:
1. Capoluongo, E. *et al.* Guidance Statement On BRCA1/2 Tumor Testing in Ovarian Cancer Patients. *Semin. Oncol.* 44, 187–197 (2017).
2. Hennessy, B. T. J. *et al.* Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP Ribose) polymerase inhibitors in ovarian cancer. *J. Clin. Pathol.* 28, 3570–3576 (2010).
3. Cree, I. A. *et al.* Guidance for laboratories performing molecular pathology for cancer patients. *J. Clin. Pathol.* 67, 923–931 (2014).

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SUCCESSFUL TUMOUR *BRCA* TESTING FOR OVARIAN CANCER

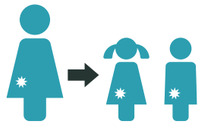
A GUIDE FOR TESTING LABORATORIES

This guide is for laboratories involved in *BRCA* testing to support effective and efficient communication with ordering physicians.

Why are physicians requesting tumour *BRCA* testing?

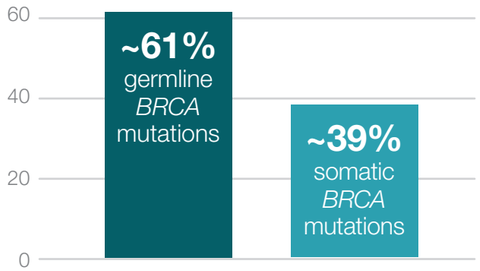
Treating physicians request a **tumour** *BRCA* test to determine the eligibility of their patients for different treatment options. By testing a sample of the tumour, they are able to determine if the patient has a *BRCA* pathogenic or likely pathogenic variant, which may be either a germline or somatic *BRCA* mutation.[1]

SOMATIC VERSUS GERMLINE



Germline *BRCA* mutations present in every cell of the body and account for approximately two-thirds of *BRCA*-mutated ovarian cancer patients. These inherited germline mutations can be found in tumour or blood samples from ovarian cancer patients.[1]

In a sample of unselected OC tumours, up to ~39% of positive *BRCA* mutations were somatic.[1,2]



Somatic *BRCA* mutations are <u>not</u> inherited and are found only in the tumour sample, and account for around one-third of *BRCA* mutations in ovarian cancer patients.[1,2]

Performing an initial tumour *BRCA* test (followed by subsequent confirmatory germline testing via blood-based samples if a significant variant is identified) will potentially reduce the overall volume of testing required compared to undertaking germline testing first.[1] This is because germline testing will not identify those with a somatic mutation thereby missing approximately one-third of ovarian cancer patients with *BRCA* mutations.[1,2]

Identifying all women with ovarian cancer and a *BRCA* mutation, whether germline or somatic, will require fewer patients to undergo two rounds of *BRCA* testing if the initial test is conducted on a tumour sample (a greater number of women with ovarian cancer will test negative on germline testing than will test positive on tumour testing).

If you conduct a blood test first and the result is negative, a subsequent tumour test would be required for all negative patients to establish whether the individual has a somatic *BRCA* mutation.

If you conduct a tumour test first and the result is positive, a subsequent blood test would only be needed for positive patients to determine whether there are implications for the patient and their relatives.

WHAT CAN THE LABORATORY DO TO ENSURE QUICK AND EFFICIENT *BRCA* TESTING?

The laboratory plays an important role in the management of ovarian cancer patients as the information provided may increase the treatment options for a patient and also alert her to further cancer risks to her family.[1]

To ensure the process is optimized, the laboratory should inform the physician of what is required for testing (sample and information requirements):

CHECKLIST ITEM	
Sample	• Sample requirements, including how much sample and in what format (fresh/frozen) • Sample ID information, such as archival block ID or Patient ID number • Other relevant information that may affect testing (e.g., age of the sample)
Paperwork	• Test requisition forms or other documentation requirements • How to obtain the correct forms (including signed consent documents) • How and where to send forms
Ordering Physician Details	• Contact information in case of damaged/inadequate sample • Details of who to contact in case of a delay to results
Patient Information	• List of what patient information is required to perform testing (e.g., patients' diagnosis, relevant cancer family history, familial *BRCA* mutations, prior treatment)
Logistics	• How to package and send the sample (e.g., specific collection kits, storage temperature and conditions) • Lab contact details of where to send the samples and paperwork • Provide information on fast-track options, if any
Return of Results	• How results will be returned to them (e.g., fax, web portal, email) • Who to send the results to (name, institution, email, fax) • Expected timeframe for results