

## Cancer Trials Ireland opens study to enable upfront and streamlined germline and somatic BRCA1/2 mutation testing in women with ovarian cancer

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The t-BRCA trial (CTRIAL- IE 18-01) will assess the feasibility of a novel oncology provider-led pathway that involves routinely testing the tumours of women with high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer (HGSEC) for mutations in the BRCA1 and BRCA2 genes.

In Ireland, ovarian cancer is the 6th commonest cancer diagnosed in women, yet it is the 4th commonest cause of female cancer deaths in Ireland (National Cancer Registry). HGSEC is by far the most common, aggressive and lethal form of ovarian cancer, accounting for about 70% of cases. Anatomical location and a poorly understood latent phase of disease means ovarian cancer presents at a late stage (stage III and IV), when outcomes are poor despite aggressive surgery and chemotherapy, with cure achievable in up to 30% of cases.

Women with HGSEC who are newly diagnosed or in the first relapse of their disease are eligible to participate in the study. It aims to recruit 200 women over 18 months in up to six cancer trials units in hospitals in Ireland. The study is sponsored by Cancer Trials Ireland, and funded by Astra Zeneca, the Emer Casey Foundation and Ovacare.

Recent therapeutic developments are significantly benefiting some women with ovarian cancer: polyadenoribose polymerase (PARP) inhibitors are a novel class of biological agents that target BRCA1/2-mutated ovarian cancers. PARP inhibitors, given as a daily continuous oral therapy, significantly improve progression-free survival in BRCA1/2-mutated ovarian cancer, when given as maintenance treatment after platinum-based chemotherapy in patients with newly diagnosed disease, or with ovarian cancer recurring later than 6 months after completing primary platinum-based chemotherapy. In 2017, the PARP inhibitor olaparib was approved for use in Ireland in the maintenance setting following platinum-based chemotherapy in patients with platinum sensitive relapsed disease. Approval for olaparib in the first line maintenance setting is under review at the European Medicines Agency.

BRCA1/2 mutations are observed in up to 25% of cases of HGSEC. In approximately 2/3 of these cases, the mutation is inherited, or germline. Germline BRCA1/2 mutations confer up to 40-80% and 40-60% lifetime risks of breast and ovarian cancers, respectively. There are thus implications in terms of breast cancer prevention for the patient, as well as cancer prevention for male and female relatives who may also carry this mutation. Somatic BRCA1/2 mutations are observed in 5-7% of ovarian cancers, are found solely in the patient's tumour tissue and thus aren't inherited (Figure 1). Recent studies show that patients with somatic BRCA1/2 mutations derive similar clinical benefits from PARP inhibitors as those with germline mutations.

Up to recently, pathways for the identification of BRCA1/2 mutations amongst patients with ovarian cancer in Ireland involved a clinical risk assessment usually done in the oncology

clinic, based on a patient's age, cancer diagnoses, and pattern of family history of cancer, to select patients who should be referred to a clinical geneticist for full genetic counselling prior to germline BRCA1/2 mutation testing using a blood sample. The current waiting list for a patient referred for suspected hereditary breast and ovarian cancer syndrome, the majority of which are due to germline BRCA1/2 mutations, ranges from 6-18 months in Ireland. Given the prevalence and therapeutic implications of germline BRCA1/2-mutated ovarian cancer, international guidelines now recommend testing all patients with non-mucinous ovarian cancer for germline BRCA1/2 mutations, thereby significantly increasing referrals to the clinical genetics service. Together with the approval of olaparib, germline BRCA1/2 mutation testing performed in the oncology setting is available through the National Cancer Control Programme for patients meeting this indication. This pathway, however, excludes patients with HGSC who do not meet the indication for olaparib. Finally, none of the current testing pathways test for somatic BRCA1/2 mutations.

The t-BRCA study aims to evaluate the feasibility of a routine upfront systematic ovarian cancer tumour tissue BRCA1/2 mutation testing pathway initiated in the oncology clinic for women with ovarian cancer in Ireland, regardless of their personal or family history of breast/ovarian cancer. Brief genetic counselling by a trained medical/surgical oncologist will be done ahead of BRCA1/2 mutation testing. Tumour tissue will be tested, followed by reflex germline testing using a blood sample, should a tumour mutation be identified. An integrated somatic and germline BRCA1/2 mutation report will be then be issued to the requesting clinician. Only patients with a germline mutation will be referred to the clinical genetics service for full genetic counselling, thereby streamlining genetic counsellors' time to patients who need it most.

In addition to routinely testing the tumours, this study will evaluate the feasibility of this novel oncology provider-led pathway by using questionnaires to assess patients' and clinician's experience and satisfaction, and to evaluate the impact on patient management. A health economic analysis will also be performed. The study will also examine the patterns of germline and somatic BRCA1/2 mutations and the clinical characteristics of BRCA1/2-mutated HGSEC in Ireland.

**Further information on this and all other cancer studies and trials open in Ireland is available at [cancertrials.ie](http://cancertrials.ie).**

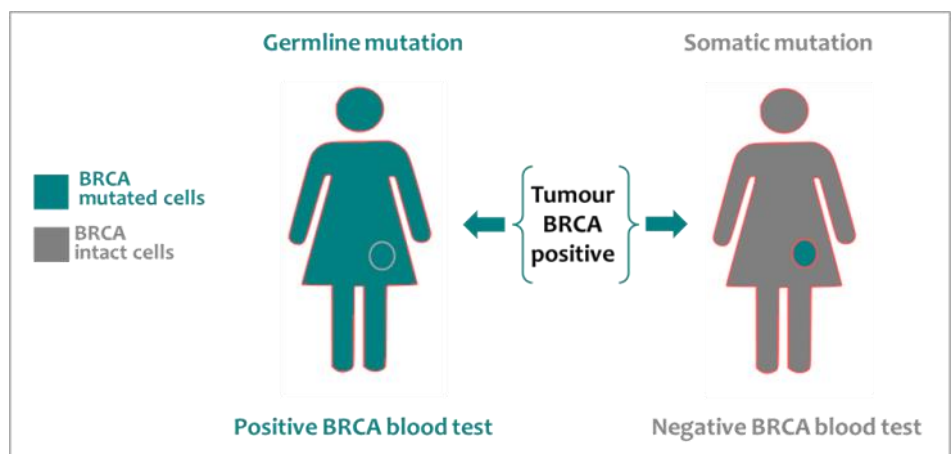


Figure 1. Tumour and blood test results for germline and somatic BRCA1/2 mutations