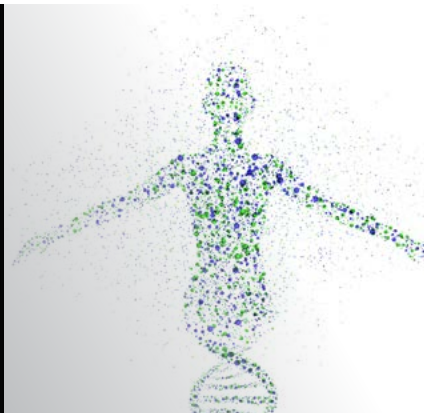
GTLDNA
GENETIC TESTING LABORATORIES
Call: 1300 482 165

targeting your health together

PERSONALISED MOLECULAR DIAGNOSTICS > FOR SOMATIC DISEASE > FOR YOU

Genetic Testing for Ovarian Cancer



BRCA1 and BRCA2 are two human genes (tumour suppressor genes) that are involved in repair of damaged DNA.

Mutations in *BRCA1* and *BRCA2* increase the risk of developing female breast and ovarian cancers as well as other cancers including pancreatic cancer and endometrial cancer. BRCA1 and BRCA2 mutations account for about 5 to 10 percent of all breast cancers and 20 to 25 percent of hereditary breast cancers. Mutations in BRCA1 and BRCA2 also account for about 15 percent of ovarian cancers. Patients with BRCA1 and BRCA2 mutations tend to develop breast cancers at a younger age than patients with sporadic breast cancers.

The vast majority of ovarian carcinomas associated with BRCA mutations reported in the literature are high-grade and advanced-stage serous carcinomas [1]. In an analysis of 28 ovarian cancers with BRCA1/2 mutations, ~40% were deemed to be somatic mutations , occurring in the tumour and not in other cells [2].

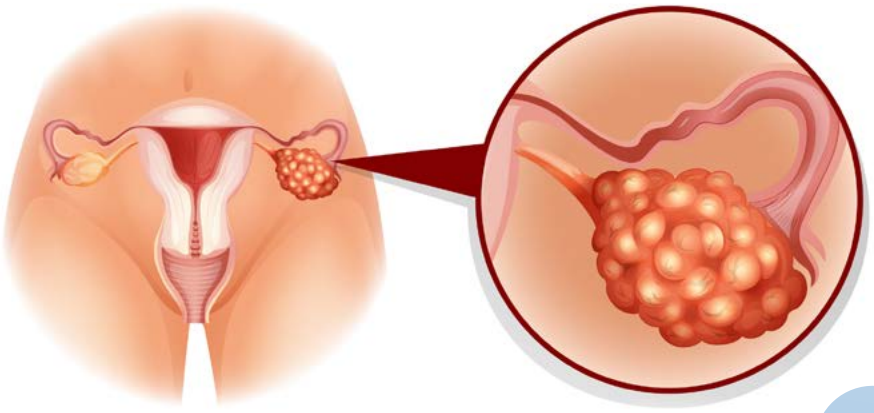
Ovarian carcinomas with either germline or somatic mutations are more aggressive than sporadic ovarian carcinomas, however, the tumours show a higher susceptibility to platinum-salts and other DNA-damaging agents [1]. Platinum-salts interfere with DNA cross-links creating double-strand breaks in the DNA helix, which cannot be repaired in BRCA deficient tumours due to homologous recombination deficiency. Comparison of patients who were positive for a somatic versus germline BRCA mutation showed no significant difference in progression-free survival (PFS) (p=0.69) [2].

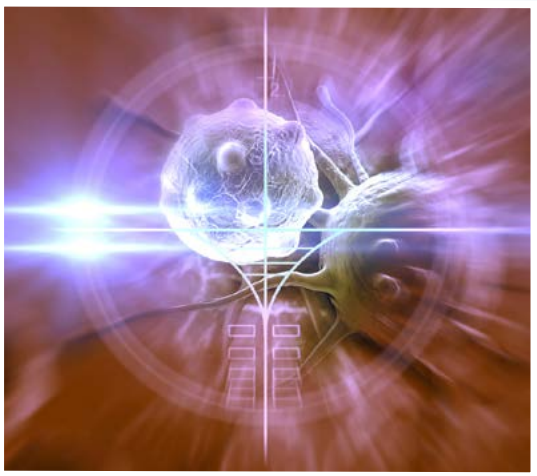
Poly (adenosine diphosphate [ADP]) ribose polymerase (PARP) inhibitors (PARPi) have been developed over the last few years and have shown encouraging results in the BRCA1/2 mutation-related cancers. PARPi selectively target BRCA-deficient cancer cells while sparing

Genetic Testing

Genetic testing is available for BRCA1 and BRCA2. There are different tests available.

Genetic testing is typically a blood test using DNA, the genetic material which contains all the genes, extracted from blood cells. Testing can also be performed on fixed tumour tissue.





Call: 1300 482 165 Fax: 02 9475 4330 Email: info@gtldna.com.au Web: www.gtldna.com.au

Genetic Testing for Breast and Ovarian Cancer

normal tissues, which retain a normal copy of the BRCA gene [3, 4]. PARPi have shown a benefit in BRCA-mutated ovarian carcinoma [3, 4].

In a multi-centre, international, randomised, double-blind, placebo-controlled Phase 2 clinical trial (NCT00753545) conducted in unselected women with ovarian cancer patients were randomised, within eight weeks after completion of their last dose of platinum-based chemotherapy, to receive either olaparib maintenance therapy (400 mg b.d., capsule formulation) or placebo [5, 6]. The median progression-free survival (PFS) in the olaparib group was 8.4 months from the time of randomisation (on completion of platinum-based chemotherapy), versus to 4.8 months in the comparator group. This equated to a hazard ratio of 0.35 (95% confidence interval [CI] 0.25 to 0.49, p<0.001) [5, 6].

Results of a retrospective subgroup analysis demonstrated that olaparib maintenance therapy was associated with a statistically significant and clinically meaningful PFS benefits in patients who were BRCA mutation positive. In the subgroup of patients with a germline BRCA mutation (determined from a blood sample, N=166), there was a 7.1 month improvement in median PFS for patients treated with olaparib compared with placebo (median 11.2 versus 4.1, p<0.001). A similar PFS benefit was observed when patients with BRCA mutations determined from tumour DNA were included in the analysis (N=196 with a median PFS of 11.2 months versus 4.3 months, p<0.0001) [5].

Massively parallel sequencing (MPS) (Next generation sequencing) is performed routinely on a number of tumour types for multigene panels. MPS has been performed on 68 ovarian and 30 breast FFPE samples for BRCA1/2 and was sensitive enough to detect low level mutations using a short amplicon design [7]. The result were confirmed by repeat MPS and validated by Sanger sequencing. 87/98 of samples (89%) (not including replicates) had a coverage of >90% at a minimum depth of 100x. The mean depth of coverage was >5000x for samples with the recommended input of DNA and the majority of samples gave a mean depth of coverage of >1000x for the regions covered by the assay. In this study BRCA mutations were detected if present in >10% of the sample DNA [7].

The Thermo Fisher Ampliseq MPS BRCA1/2 panel performs on FFPE material and uses minimal amounts of DNA which is ideal for FFPE samples.

REFERENCES:

1. Girolimetti, G., et al., *BRCA-associated ovarian cancer: from molecular genetics to risk management.* Biomed Res Int, 2014. **2014**: p. 787143.
2. Hennessy, B.T., 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 Oncol, 2010. **28**(22): p. 3570-6.
3. Benafif, S. and M. Hall, *An update on PARP inhibitors for the treatment of cancer.* Onco Targets Ther, 2015. **8**: p. 519-28.
4. Lee, J.M., J.A. Ledermann, and E.C. Kohn, *PARP Inhibitors for BRCA1/2 mutation-associated and BRCA-like malignancies.* Ann Oncol, 2014. **25**(1): p. 32-40.
5. Ledermann, J., et al., *Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial.* Lancet Oncol, 2014. **15**(8): p. 852-61.
6. Ledermann, J., et al., *Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer.* N Engl J Med, 2012. **366**(15): p. 1382-92.
7. Ellison, G., et al., *A reliable method for the detection of BRCA1 and BRCA2 mutations in fixed tumour tissue utilising multiplex PCR-based targeted next generation sequencing.* BMC Clin Pathol, 2015. **15**: p. 5.