## Hereditary Breast/Ovarian Cancer (R208) – OMIM 604370, 612555

### Background

Breast and ovarian cancers are among the most common cancers worldwide affecting around 10% of women in their lifetime. 5-10% of all breast cancers and ovarian cancers are hereditary and are mostly linked to pathogenic variants in *BRCA1* (OMIM 113705) or *BRCA2* (OMIM 600185) genes. However, pathogenic variants in other genes can also be responsible and the routine screen for patients with a suitable family history now also includes the genes *PALB2* (OMIM 610355), RAD51C (OMIM 613399), RAD51D (OMIM 614291), ATM (OMIM 114480) and CHEK2 (OMIM 114480). If a pathogenic variant is found in one of these genes then other family members can be tested. The pattern of inheritance in the context of cancer susceptibility, is autosomal dominant, therefore there is a 50% chance of an affected adult passing the disease allele onto his/her child (although breast cancer is rare in men, males with a pathogenic variant are at increased risk of some cancers and can pass the pathogenic variant on to their children).

### Recommended Clinical Referral Criteria

- Family history of breast and/or ovarian cancer: Requests for testing for this reason are only accepted from the clinical genetics service. The guidelines for referral to clinical genetics are available here: https://medicalgenomicswales.co.uk/index.php/health-professional-information/are-you-referring-a-patient
  Genetic testing will only be offered by the genetics clinical team where appropriate.

- Personal history of high grade serous ovarian cancer at any age: mainly referred from gynaecological oncologists. *BRCA1* and *BRCA2* tested. When a pathogenic variant is found, treatment with PARP-inhibitors may be appropriate. Both blood and tumour samples can be tested and tumour testing may also include genomic instability testing (referred to as HRD (homologous recombination deficiency) testing when combined with a BRCA test). These tests can be performed concurrently. The form for this testing is available here: https://medicalgenomicswales.co.uk/index.php/download-services?start=50 - see 'Ovarian cancer (tumour testing)' and 'Ovarian cancer (blood testing)'.

- Breast oncologists, or clinical genetics, may request testing of BRCA1, BRCA2, PALB2, RAD51C, RAD51D, ATM and CHEK2 in the context of:
  - Triple negative breast cancer diagnosed at age <60
  - Breast cancer under 40
  - Male breast cancer (any age)

Breast oncologists may also request this testing in the context of **Olaparib eligibility**. The form for this testing is available here https://medicalgenomicswales.co.uk/index.php/download-services - see 'Breast cancer (oncology)'

## Molecular Analysis

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| **Variant screen on blood samples:** Next generation sequence (NGS) and dosage analysis of *BRCA1*,*BRCA2 and, as appropriate, PALB2* (any gaps will be filled by Sanger sequencing) and *RAD51C, RAD51D, ATM and CHEK2* (gaps not filled, percentage coverage stated on report, only truncating variants investigated). Dosage results of the 5 non-BRCA genes will only be reported when NGS dosage analysis is successful. |
| **Variant screen on FFPE tissue**: NGS analysis of *BRCA1* and *BRCA2* (gaps not filled, percentage coverage stated on report and no dosage analysis). |
| **Common variant analysis:** Testing for three common Ashkenazi Jewish pathogenic variants: c.68_69delAG and c.5266dupC in *BRCA1* and c.5946delT in *BRCA2.* |
| **Familial follow-up:** Testing for known familial pathogenic variants in *BRCA1*, *BRCA2*, *PALB2, RAD51C, RAD51D, CHEK2* and *ATM* genes. |

## Turnaround Times (TAT)

Prices available on request, please contact the laboratory using details below.

| Test | TAT (calendar days) |
|---|---|
| Tumour testing for treatment options | 21 |
| Test for known familial mutations in genes listed above | 28 |
| Test for three common Ashkenazi Jewish mutations in *BRCA1* and *BRCA2* | 28 |
| Next generation sequencing and dosage analysis (of *BRCA1* and *BRCA2 or all 7 genes*) | 42 |

| Contact Details | Sample Requirements |
|---|---|
| All Wales Genomics Laboratory,<br>Institute of Medical Genetics,<br>University Hospital of Wales,<br>Heath Park,<br>Cardiff CF14 4XW<br>Tel: 029 2184 2641<br>Fax: 029 2184 4043<br>lab.genetics@wales.nhs.uk | Blood – 5ml in EDTA<br>Please label samples with three identifiers and date of collection.<br>FFPE – 10 x 5 micron air-dried sections mounted on slides, 1 x 5 micron H&E stained slide with tumour area highlighted, copy of histopathology report.<br>Please contact laboratory prior to sending a prenatal sample.<br>**All samples must be accompanied by request form** |

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| medicalgenomicswales.co.uk<br>Accredited to ISO 15189:2012 (8988) | Consent for testing & DNA storage is assumed when request for test received |

**Links**

Orphanet: http://www.orpha.net/
OMIM: http://www.omim.org/
Genetic Test Registry: http://www.ncbi.nlm.nih.gov/gtr/

**Support**

http://www.macmillan.org.uk/information-and-support/diagnosing/causes-and-risk-factors/genetic-testing-and-counselling/inherited-cancers-breast-ovarian.html