# Oxford Molecular Genetics Laboratory

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## Hereditary Breast and Ovarian Cancer – OMIM 113705 (*BRCA1*), 600185 (*BRCA2*)

### INTRODUCTION

Germline pathogenic variants in *BRCA1* and *BRCA2* are strongly associated with a predisposition to breast and ovarian cancer; penetrance is variable. Together *BRCA1* and *BRCA2* pathogenic variants account for approximately 20%- 25% of all hereditary breast cancers, 5-10% of all breast cancers and for approximately 15% of all hereditary ovarian cancers [1,2,3]. *BRCA1*/*BRCA2* germline variants are also associated with a predisposition to prostate cancer, pancreatic cancer and melanoma [4]. The likelihood of there being a hereditary predisposition to breast cancer in a patient is increased by a patient having early-onset breast cancer, bilateral breast cancer, or the fact that they have Ashkenazi Jewish ancestry.

[1] Easton, 1999, Breast Cancer Research, 1(1):14-17. [2] Campeau et al, 2008, Human Genetics, 124(1):31-42. [3] Pal et al, 2005, Cancer, 104(12):2807-16. [4] Levy-Lahas and Friedman, 2007, Br J Cancer, 96(1):11-5.

### REFERRALS

Referrals are accepted via Clinical Genetics or approved mainstreaming referrers (such as Consultant Oncologists, Consultant Gynaeoncologists, Consultant Breast Surgeons). For NHSE referrals please refer to eligibility criteria: https://www.england.nhs.uk/wp-content/uploads/2018/08/rare-and-inherited-disease-eligibility-criteria-march-19.pdf (R207/R208)

### TESTING STRATEGY

- Diagnostic screen: Sequence and dosage analysis of all coding regions of *BRCA1* and *BRCA2* is undertaken in patients who meet clinical criteria set out in guidelines produced by NICE [Familial Breast Cancer, May 2004, updated June 2013, Clinical Guidance 164] and the eligibility criteria listed by NHSE for the Genomic Medicine service: https://www.england.nhs.uk/wp-content/uploads/2018/08/rare-and-inherited-disease-eligibility-criteria-march-19.pdf R207 & R208
- Ashkenazi Jewish population testing: clinically appropriate patients can be screened for the 3 pathogenic founder variants in this population. These variants are: *BRCA1* c.68_69delAG, *BRCA1* c.5266dupC, and *BRCA2* c.5946delT. Individuals referred for family testing who have one of the Ashkenazi Jewish founder variants previously identified in their family are tested for all three variants.
- Polish population testing: clinically appropriate patients can be screened for the 3 pathogenic founder variants in this population. These variants are: *BRCA1* c.181T>G, *BRCA1* c.4035delA, *BRCA1* c.5266dupC
- Family tests (predictive or diagnostic confirmations): testing for known pathogenic/likely pathogenic *BRCA1*/*BRCA2* variant previously identified in an individual's family. If a family has not been previously analysed in-house, the familial test should ideally be discussed with the laboratory in advance so a control can be obtained if possible.

### TECHNICAL INFORMATION

- Sequence and dosage analysis of *BRCA1* and *BRCA2* genes is undertaken by Next Generation Sequencing using the Custom Hereditary Cancer Solution (HCS) by Sophia Genetics along with the Sophia DDM analytical platform. Data is generated for 38 cancer susceptibility genes; however, analysis is restricted to *BRCA1* and *BRCA2* only. Data reveal and analysis of additional clinically relevant genes is available, if required.
- Regions of interest (ROI) are minimally defined as coding exons +/- 20bp and are guaranteed to be covered to 100% at >50x reads. Analytical sensitivity for single nucleotide substitutions is estimated to be >99%; analytical sensitivity for small insertions/deletions may be slightly lower.
- Putative pathogenic variants detected by NGS are confirmed by Sanger sequencing or Multiplex Ligation-dependent Probe Amplification (MLPA), as appropriate.
- Targeted testing (e.g. Ashkenazi Jewish population testing or family testing) is undertaken by Sanger sequencing of the relevant exon or MLPA, as appropriate.

### TARGET REPORTING TIMES (National Target)

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| Diagnostic screen: | 42 calendar days |
| Urgent diagnostic screen: | 21 calendar days |
| Predictive testing for known familial variant: | 14 calendar days |
| Diagnostic testing for known familial variant: | 42 calendar days |

**N.B. Details are correct for the date of printing only – last updated 02/07/2019**