Hereditary Breast and Ovarian Cancer Syndrome: \textit{BRCA1}/\textit{BRCA2} Gene Sequencing and Deletion/Duplication Panel

\textbf{Test Code:} MM070  
\textbf{Turnaround time:} 3 weeks  
\textbf{CPT Codes:} 81162 x1

\section*{Condition Description}

Mutations in the genes \textit{BRCA1} and \textit{BRCA2} cause hereditary breast and ovarian cancer syndrome (HBOC), an autosomal dominant cancer predisposition syndrome. Mutations in these genes are rare and account for only a small percentage of cancers; about 5-10\% of all breast cancers and 10-15\% of ovarian cancers are due to mutations in the \textit{BRCA1} or \textit{BRCA2} genes. Individuals with mutations in these genes, however, are at a significantly increased risk for developing breast, ovarian, and other cancers than those in the general population.

In families with HBOC syndrome, there is typically a pattern of early onset breast cancer (before the age of 50 or premenopausal). Additionally, the family history may show more than one primary breast cancer in an individual, breast cancer in two or more generations, breast cancer in a male relative, and ovarian cancer, with or without a breast cancer diagnosis. Females with a \textit{BRCA1} mutation have a 50-85\% risk of developing breast cancer and up to a 44\% risk of developing ovarian cancer. Females with a \textit{BRCA2} mutation have a 40-70\% risk of developing breast cancer and up to a 27\% risk of developing ovarian cancer. Males with a \textit{BRCA1} or \textit{BRCA2} mutation can have up to a 5-10\% lifetime risk for male breast cancer and an elevated risk of prostate cancer. Additionally, both males and females with \textit{BRCA1} or \textit{BRCA2} mutations may be at elevated risks for other cancers. Individuals with a mutation in the \textit{BRCA1} or \textit{BRCA2} gene have a 50\% risk of passing on the mutation to their children.

According to the National Comprehensive Cancer Network (NCCN) recommendations, \textit{BRCA1} and \textit{BRCA2} testing is suggested for individuals with a personal or family history of any of the following:

- Early-onset breast cancer (before the age of 50 or premenopausal).
- Two primary breast cancers or a diagnosis of both breast and ovarian cancer in one individual.
- Personal or family history of male breast cancer.
- Ovarian cancer at any age.
- Ethnicity with a higher mutation frequency (e.g., Ashkenazi Jewish).

EGL offers the following for \textit{BRCA1} and \textit{BRCA2} testing:

- \textit{BRCA1}/\textit{BRCA2} Full Gene Sequencing and Deletion/Duplication Panel
- \textit{BRCA1}/\textit{BRCA2} Full Gene Sequencing Panel
- \textit{BRCA1}/\textit{BRCA2} Deletion/Duplication Panel

This test is for the \textit{BRCA1}/\textit{BRCA2} Full Gene Sequencing and Deletion/Duplication Panel.


\section*{References}


\section*{Genes}

\textit{BRCA1}, \textit{BRCA2}

\section*{Indications}

This test is indicated for:

- Confirmation of a clinical diagnosis of HBOC.
- Carrier testing in adults with a family history of HBOC.

\section*{Methodology}

\textbf{Next Generation Sequencing:} In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

\textbf{For Deletion/Duplication Analysis:} DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-
target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

**Next Generation Sequencing:** Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions/duplications will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient’s clinical/biochemical phenotype.

Analytical Sensitivity: ~99%.

**Deletion/Duplication**

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient’s clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:

* Infants (2 years): 3-5 ml
* Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Related Tests**

- **BRCA1/BRCA2 Full Gene Sequencing**
- **BRCA1/BRCA2 Deletion/Duplication Panel**
- Sequencing and deletion/duplication analysis is also available for other breast/ovarian cancer syndromes, including: **TP53, PTEN, STK11, MLH1, PMS2, MSH6, and MSH2**.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.