## Condition Description

Most cases of breast cancer are sporadic with no family history of the cancer; but, 5-10% of cases are understood to be due to a hereditary predisposition. Nearly 1 in 8 women (12%) will develop breast cancer in their lifetime (SEER). The clinical features suggestive of a hereditary cancer predisposition include: diagnosis at a young age (< 50); multiple primary cancers in a single individual; diagnosis of a cancer type that is not common in the general population; and several relatives affected with related cancers over multiple generations.

Like breast cancer, most cases of ovarian cancer are sporadic with no family history of the cancer; but, 5-10% of cases are understood to be due to a hereditary predisposition. The population risk of ovarian cancer is 1 in 71 (SEER).

The EGL Breast and Ovarian Cancer Panel includes genes involved in hereditary cancer predisposition syndromes that have an increased risk for breast and/or ovarian cancer. They include hereditary breast and ovarian cancer syndrome (BRCA1 and BRCA2), hereditary diffuse gastric cancer syndrome (CDH1), Li-Fraumeni syndrome (TP53), Cowden syndrome (PTEN), Peutz-Jeghers syndrome (STK11), ataxia telangiectasia (ATM), Lynch syndrome (MLH1, MSH2, MSH6, PMS2, and EPCAM), and MUTYH-associated polyposis syndrome (MUTYH).

It is estimated that 20-25% of familial breast cancer risk can be ascribed to mutations in the BRCA1 or BRCA2 genes (van der Groep 2011). The contribution of mutations in the CDH1, PTEN, STK11, and TP53 genes to familial breast cancer risk is considerably lower than the contribution of BRCA1 and BRCA2 mutations.

Reports have shown that the lifetime risk to develop ovarian cancer is between 24-54% for BRCA1 mutation carriers and 11-27% for BRCA2 mutation carriers. Women with BRCA1 or BRCA2 mutations have a ~41-84% lifetime risk to develop breast cancer and an up to 50% risk for contralateral breast cancer. Additionally, other cancers associated with mutations in BRCA1 and BRCA2 in women include fallopian tube carcinoma, and uterine serous carcinoma. The lifetime risk for breast cancer in males with a known or expected to be pathogenic variant carriers is estimated to be 4% for BRCA1 and 7% for BRCA2 mutation.

Women with Lynch syndrome have an ~13% lifetime risk of developing ovarian cancer.

### References:

## Genes

ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MRE11, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMARCA4, STK11, TPD3, XRCC2

## Indications

The test is indicated for:
- Individuals with a clinical or suspected diagnosis of breast or ovarian cancers.

## Methodology

**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. Please note that EPCAM is not included in the sequencing analysis.

**Deletion/Duplication Analysis:** DNA isolated from peripheral blood is hybridized to a gene-targeted CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes that cover the entire genomic region. Please note that PMS2 and SMARCA4 are not included in the deletion/duplication analysis. 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 Analysis:** 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

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Ship sample at room temperature with overnight delivery.

**Type: Isolated DNA**

Specimen Requirements:

In microtainer: 60 ug

Isolation using the Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping: Refrigerate until time of shipment in 100 ng/ul of TE buffer. Ship sample at room temperature with overnight delivery.

**Special Instructions**

This test is for germline mutation analysis. DNA isolated from FFPE tumor samples is not suitable for this test.

**Related Tests**

- Hereditary Cancer Syndrome: Sequencing Panel