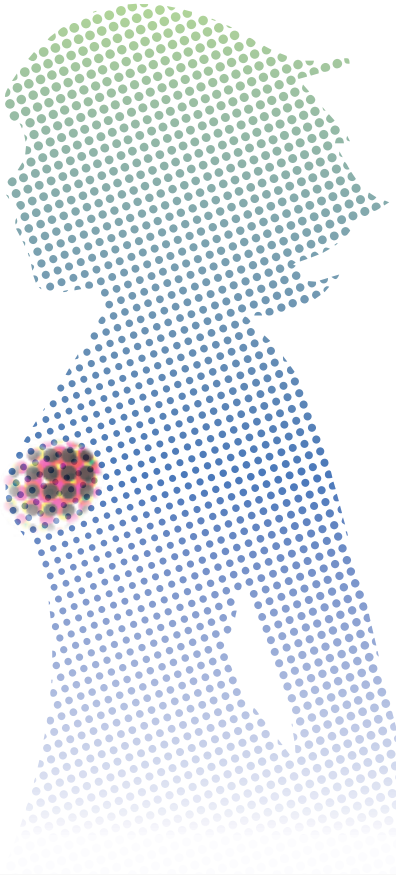
MEDGENOME

Prima Cancer Genetics

Therapeutic Decision Making in **Breast** and **Ovarian Cancer** based on **BRCA1** and **BRCA2** Mutation



Background of BRCA1 and BRCA2 testing in Breast and Ovarian Cancer

- With an annual incidence of approximately 1.4 lakh new cases of breast cancers in India, it has now become the most common female cancer in urban India (ICMR).
- It is projected that cancer incidence in Indian women to increase from 110 cases per lakh to 190-200 cases per lakh by 2025 (ICMR).
- Mortality to incidence ratio is worst in India for breast and ovarian cancers with one in every 28 women likely to develop it during her lifetime and one in every two women diagnosed with it succumbs[1].
- It has been estimated that, by 20 years after a first breast cancer diagnosis, about 40% of women who carry a harmful BRCA1 mutation and about 26% of women who carry a harmful BRCA2 mutation will develop cancer in their other breast[2].

BRCA1 and BRCA2 testing for treatment decisions

- BRCA1 and BRCA2 mutations that include single nucleotide variations (SNVs) that change the protein sequence and function or mutations that result in truncation of protein which finally leads to inactivation are most commonly known variations
- Technically, genetic variants include non-sense, frameshift, splice site, mis-sense, and large deletions, duplications and rearrangements in the coding region of BRCA1 and BRCA2
- Breast cancers associated with BRCA1 and BRCA2 mutations have poorer prognosis, poorly differentiated, high grade and highly proliferative lesions[3].
- BRCA1 mutations are associated with a higher risk for triple negative breast cancer[4].
- PARP inhibitors are indicated in adult patients with Platinum sensitive relapsed BRCA1 and BRCA2 mutated high grade serous carcinoma of ovary as maintenance therapy[5].

Rationale for BRCA1 and BRCA2 Tumor Testing

- By doing a tumor tissue DNA based BRCA1 and BRCA2 testing, one can identify the pool of both germline and somatic BRCA mutations (however, it cannot distinguish between germline and somatic origin. To further confirm this distinction, germline test on peripheral blood may be suggested as per requirement)
- One single test is able to identify deleterious mutations in BRCA1 and BRCA2 genes for any given individual who could benefit from PARP inhibitor treatment

MedGenome BRCA1 and BRCA2 Gene Test

- It is based on Next Generation Sequencing for tumor genomic DNA analysis to identify pathogenic mutations. It's a target capture based method
- Mutations Covered- Single Nucleotide Variations (SNVs) and short insertions and deletions (InDels).
- Sensitivity and Specificity- The BRCA1 and BRCA2 genes are covered 100%. Sensitivity- 95%, specificity- 100%, LOD- 5%
- Reporting- Somatic Mutations are reported based on 3 tier classification as per ASCO, AMP and CAP guidelines

Salient Features of MedGenome BRCA1 and BRCA2 Somatic Test:

1. Cost Effective
2. Short Turn Around Time
3. Genetic Counselling, if required, will be offered free of cost
4. In-house developed bioinformatics pipeline

Test Code	Test Name	TAT	Sample Requirements
MGM537	BRCA1 & BRCA2 somatic mutation testing	28 working days	FFPE (Minimum of 10% neoplastic cell content as assessed by in-house pathologist. non-necrotic fixation artifacts- 100-150 tumor cells per high power field)

- Clinical interpretation explains therapeutic consequence of a given mutation as per the mutation class and possibility of response to PARP inhibitor therapy or wild type.
- NGS QC pass criteria:
  >90% gene coverage
  >500x depth for somatic variants
  >80 - 100x depth for germline variants

References

1. http://cancerindia.org.in/cancer-statistics/
2. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. 1998 Sep 4 [Updated 2016 Dec 15]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993- 2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1247/
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