Prima Cancer Genetics

MEDGENOME

Homologous Recombination Repair (HRR) Gene Testing

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Homologous Recombination Repair (HRR) Gene Testing

Homologous recombination repair genes are involved in repair of damaged DNA. Mutations in these genes can lead to deficiency in repair of damaged DNA. It has been established that tumors that are deficient in DNA repair mechanism, particularly the Homologous Recombination mechanism are sensitive to PARP inhibitor therapy in certain cancer types such as breast and ovarian cancers, while the clinical trials are ongoing in other cancer types such as pancreatic, prostate, endometrial and other cancers.

Clinical Application:

Prognostic and Predictive biomarker for platinum-based chemotherapy and PARP inhibitor therapy

Test Utility

1) Targeted Therapy (deciding the best drug treatment of choice)
2) Disease prognostication (impact on overall survival rate of breast and ovarian cancer patients)
3) Tumor profiling has the advantage of detecting both germline and somatic mutations together in a single assay for any given patient.
   Reflex testing on blood sample is recommended to confirm the germline predisposition
4) Hereditary risk assessment (presence of personal or family history)

Majority of the homologous recombination defect observed in ovarian cancers are attributed to germline BRCA1/BRCA2 variants.[1]

Platinum based chemotherapy has been shown to be more effective in Ovarian Cancer patients with HRR mutations (Germline/somatic) [2]

Mutation in HRR genes (HRR defective tumors) in Triple Negative Breast Cancer in predictive of complete Pathological Response in these tumors [3]

The cancer genome atlas study shows that 17% of high grade serous ovarian cancer had germline BRCA1/2 mutations, while 28% had somatic mutations in the broader category i.e., HRR genes that includes BRCA1/2 as well as other genes such as *CDK12*, *RAD51C*, *PPP2R2A*, *CHEK1*, *RAD51B*, *RAD51D*, *CHEK2*, *RAD51L*, *BARD1*, *BRIP1*, *ATM*, *FANCL*, *PALB2* [1]

In relapsed / recurrent setting of ovarian cancers: Niraparib and Rucaparib have shown significant improvement in PFS and more likely to show clinical benefit as maintenance therapy. This recommendation was based on the outcome from the ENGOT-OV16/NOVA trial (553 platinum-sensitive relapsed epithelial ovarian carcinoma patients), where Niraparib had shown PFS benefits (12.9 months vs. 3.8 months) in the non-gBRCA cohort of patients who were HRD positive [4]

ARIEL-3 phase III studies on 564 patients with high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma, patients with a homologous recombination deficient carcinoma, Rucaparib, had shown PFS benefits (13·6 months versus 5·4 months (P<0·0001), in BRCA mutated as well as HR-deficient subgroups, thus demonstrating comparable efficacy of these drugs in HRR-deficient patients [5-8]

Who should be tested?

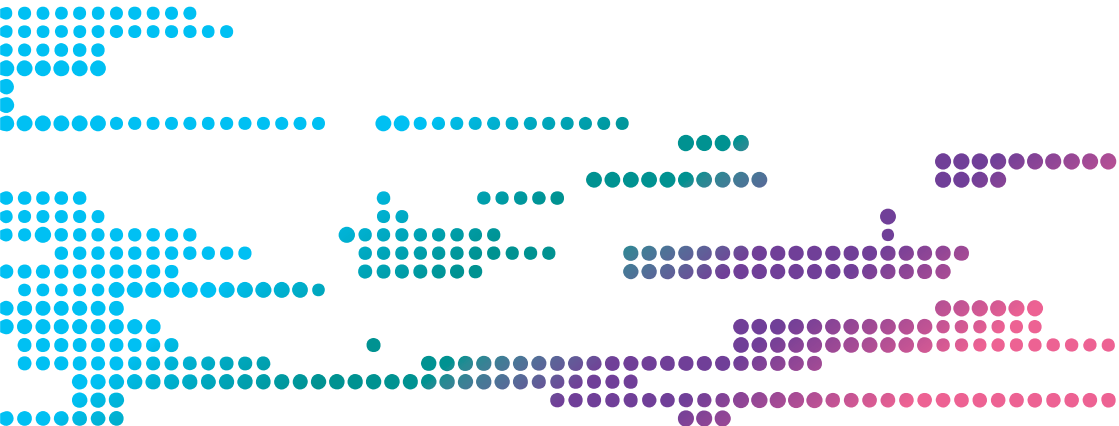
1. Individual diagnosed with Breast cancer and suspected to have gBRCA1/2 mutation
2. Any woman diagnosed with epithelial ovarian, fallopian tube, and peritoneal cancers can undergo genetic testing as per SGO recommendation.
3. Women with ovarian cancer who may benefit from PARPi maintenance therapy
4. Women with ovarian cancer resistant to platinum therapy
5. Men with castration resistant prostate cancer who have progressed in prior treatment
6. Patients with pancreatic cancer who may have suspected BRCA 1/2 mutations

Sensitivity and Specificity NGS based HRR testing:

100%

Limit of Detection

5% for SNVs and **10%** for Short indels (<10bp)



Test requirements

MedGenome offers	Test Code	Test Sample Requirements	TAT
HRR gene panel	**MGM1623**	 FFPE Blocks	**16** working days

Genes Covered:

CDK12	*BRCA1*	*PPP2R2A*	*RAD51B*
CHEK2	*RAD54L*	*ATM*	*PALB2*
RAD51C	*BRCA2*	*CHEK1*	*RAD51D*
BARD1	*BRIP1*	*FANCL*	

Notes:

- Tumor biopsies with good formalin fixation; Absence of fat, mucin, bony component, crushing artifacts, necrosis, autolysis and other tissue processing artefacts have good diagnostic value and would be ideal for NGS based testing for HRR gene mutations.
- Large deletions of more than 10 base pairs long or copy number variations / rearrangements cannot be assessed using this test assay
- Due to poor quality of FFPE DNA, possibility of assay failure/compromised results that include low HRR gene coverage and low depth, cannot be ruled out.
- Intronic variants are not assessed using this test.
- Treatment decisions based on these mutations may be taken in correlation with other
- Clinical and pathological information.

References

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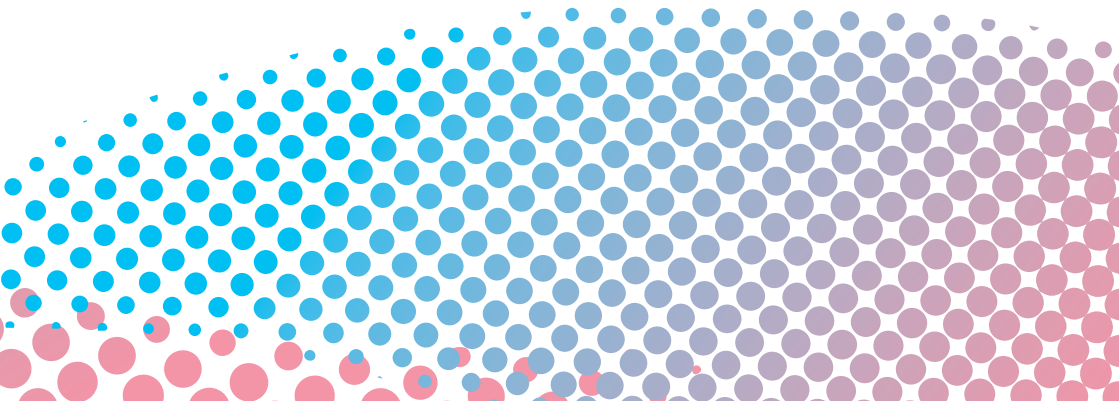
4. Coleman, Robert L., et al. "Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial." The Lancet 390.10106 (2017): 1949-1961

5. Konstantinopoulos, Panagiotis A., and Ursula A. Matulonis. "PARP inhibitors in ovarian cancer: a trailblazing and transformative journey." Clinical Cancer Research 24.17 (2018): 4062-4065.

6. Freed, D., et al., The Sentieon Genomics Tools—a fast and accurate solution to variant calling from next-generation sequence data. . bioRxiv 2017.

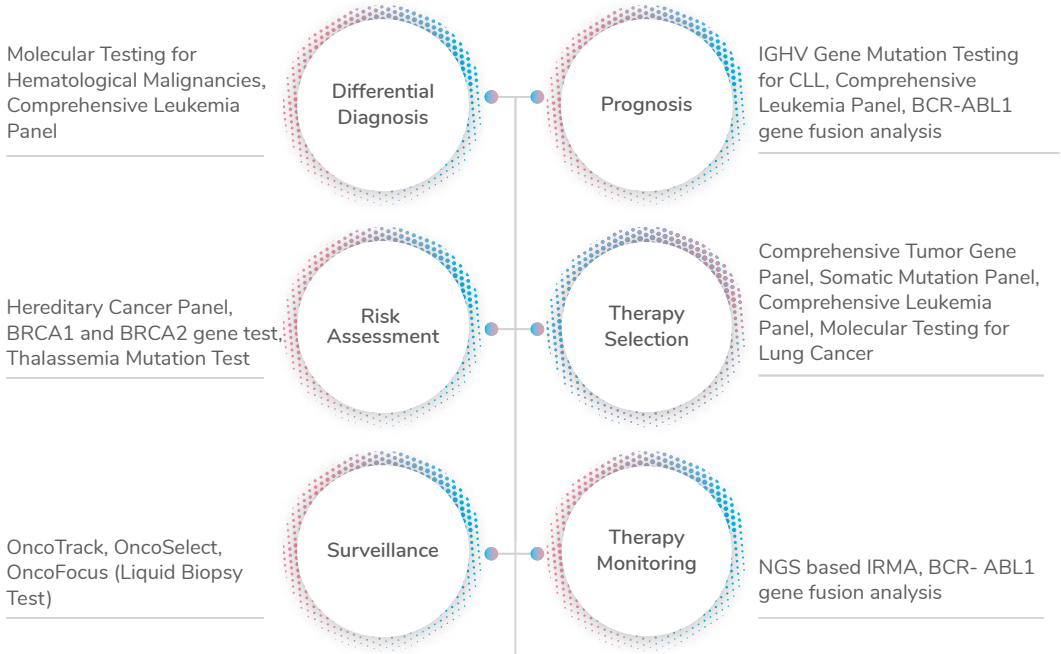
7. National Centre for Biotechnology Information. Assembly GRCh37.p13. 2013; Available from: https://www.ncbi.nlm.nih.gov/assembly/GCF_000001405.25/.

8. Wilm A. et al. LoFreq: A sequence-quality aware, ultra-sensitive variant caller for uncovering cell-population heterogeneity from high-throughput sequencing datasets. Nucleic Acids Res., 2012. 40(22): 11189-11201.



MEDGENOME

Prima by MedGenome offers a wide range of Oncology and Haematology genetic tests, these include:



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