OneCell Diagnostics
OncoHRD™
Synthetic Lethality Meets Precision

OncoHRD®- A Next Generation-Assistive Homologous Recombination Deficiency Assay

What is Homologous recombination deficiency (HRD)?

Tumors are highly responsive to platinum-based chemotherapy and poly (ADP-ribose) polymerase inhibitor (PARPi) therapy. Various PARPi inhibitors have been FDA approved to treat breast, ovarian, pancreatic and prostate cancers while growing evidence also suggest its relevance in gastric, endometrial, colon, bladder, lung, as well as other solid tumors. HRD testing is currently performed using diagnostic laboratory tests which is usually performed using Next Generation sequencing (NGS) method.

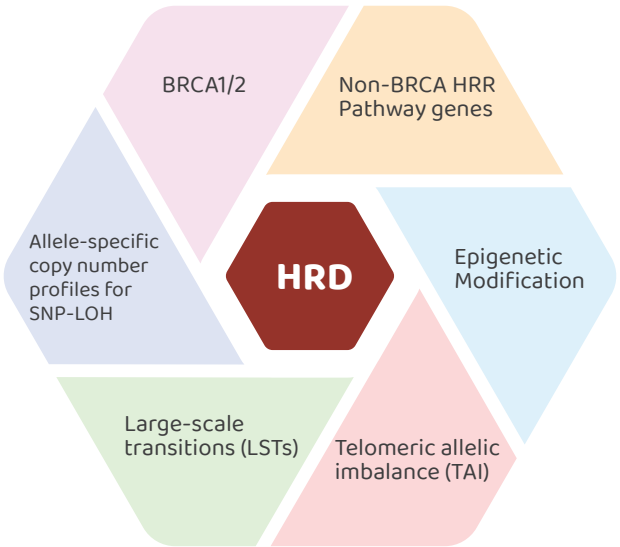
Significance of Homologous recombination deficiency (HRD) for PARPi therapy

Homologous Recombination Deficiency (HRD) typically arises when genes involved in the homologous recombination repair (HRR) pathway are altered or disrupted, leading to an inability of cells to perform effective DNA repair. Thus, if the HRR pathway is impaired in tumor cells, PARP inhibitors can be used to inhibit action of PARP enzymes which mediate DNA repair of tumor cells thereby making HRD an important biomarker to identify patients who may benefit from PARPi therapy.

Importance of identifying Homologous recombination deficiency (HRD) tumor patients?

Traditionally, HRD status has been mainly linked to mutations in BRCA1 and BRCA2 genes. Several studies have now established other key biomarkers in determining HRD status such as Allele-specific copy number profiles for SNP–LOH, Large-scale transitions (LSTs), Telomeric allelic imbalance (TAI), Epigenetic modification, Non-BRCA HRR Pathway genes (Figure 1).

Figure 1: Relevant Biomarkers for HRD status identification and PARPi treatment eligibility



BRCA1 and BRCA2 alterations in Homologous recombination deficiency (HRD)

Germline BRCA1 and BRCA2 alterations are key members of the HRR pathway and majority of HRD tumors occur in these cases, however, somatic BRCA1 and BRCA2 mutations as well as other mutations in the HR pathway can also be indicative of HRD. Genomic Instability HRD also gives rise to specific patterns of mutations, Indels, Copy number variations and structural rearrangements. The larger genomic alterations give rise to Genomic Instability and comprises Loss of heterozygosity, Telomeric allelic imbalance and large scale state transitions all of which are also predictive of HRD.

Loss of Heterozygosity as a factor of Homologous recombination deficiency (HRD)

Loss of Heterozygosity (LOH) is the loss of one of the two alleles at a heterozygous locus. HRD impairs normal DNA damage repair which results in loss or duplication of chromosomal regions and causes genomic loss of heterozygosity (LOH). Therefore, LOH is a relevant biomarker of HRD. Telomeric allelic imbalance Telomeric allelic imbalance, another known predictor of HRD, is caused by unequal contribution of paternal and maternal allele sequences regardless of whether the copy number has changed and is defined as the number of allelic imbalance regions which extend to the telomere but do not cross the centromere. They are significantly present in tumors with BRCA1 and BRCA2 deficiency as well as tumors which are sensitive to platinum chemotherapy.

Clinical Significance of HRD

Studies have shown that HRD as a biomarker predicts sensitivity to PARP inhibitor therapies. Tumors that have deficient DNA repair pathways become dependent on other pathways; for example, a tumor with deficient HRR pathway is more dependent on the base-excision repair (BER) pathway. As PARP is part of the BER pathway, HRD cells treated with PARP inhibitors are left with multiple impaired DNA repair pathways, leading them to be preferentially killed by platinum-based chemotherapy over normal cells. Thus, HRD is an important predictive marker in identifying patients who will benefit from PARPi and platinum-based chemotherapy. Consequently, several therapies have received FDA approval for indications characterized by HRD status, such as advanced HRD-positive endometrial cancers.

Conclusion

Homologous recombination deficiency is a status that encompasses mutations and loss of function in the homologous recombination repair pathway, by examining BRCA1 and BRCA2 alterations, loss of heterozygosity, telomeric allelic imbalances, and large-scale transitions. Increasingly, HRD has become an important biomarker for a few solid-tumor cancers, while investigations continue in other cancer types. Tumor HRD status can help predict patient response to PARP inhibitors and platinum-based chemotherapy, identifying those who will benefit most from such treatments. As a result, HRD testing can help physicians make more effective treatment decisions for their patients.

References:

1. Li, L., Gu, Y., Zhang, M., Shi, X., Li, Z., Xu, X., Sun, T., Dong, Y., Xue, C., Zhu, X. and Lv, R., 2023. HRD effects on first-line adjuvant chemotherapy and PARPi maintenance therapy in Chinese ovarian cancer patients. NPJ Precision Oncology, 7(1), p.51.
2. Stewart, M.D., Merino Vega, D., Arend, R.C., Baden, J.F., Barbash, O., Beaubier, N., Collins, G., French, T., Ghahramani, N., Hinson, P. and Jelinic, P., 2022. Homologous recombination deficiency: concepts, definitions, and assays. The Oncologist, 27(3), pp.167-174.
3. Christinat, Y., Ho, L., Clément, S., Genestie, C., Sehouli, J., Cinieri, S., Gonzalez Martin, A., Denison, U., Fujiwara, K., Vergote, I. and Tognon, G., 2023. Normalized LST is an efficient biomarker for homologous recombination deficiency and olaparib response in ovarian carcinoma. JCO Precision Oncology, 7, p.e2200555.
4. Ngoi, N.Y.L. and Tan, D.S.P., 2021. The role of homologous recombination deficiency testing in ovarian cancer and its clinical implications: do we need it?. Esmo Open, 6(3), p.100144.
5. Kaundal, B., McGrail, D.J., Li, Y., Smith, R.S., Feng, B., Dai, H., Hu, L., Dennehey, B., Awasthi, S., Mendillo, M.L. and Sood, A.K., 2024. Widespread BRCA1/2-independent homologous recombination defects are caused by alterations in RNA binding proteins. Cancer Research, 84(6_Supplement), pp.3344-3344.
6. Siedel, J.H., Ring, K.L., Hu, W., Dood, R.L., Wang, Y., Baggerly, K., Darcy, K.M., Conrads, T.P., Gallagher, S., Tshiaba, P. and Neff, C., 2021. Clinical significance of homologous recombination deficiency score testing in endometrial Cancer. Gynecologic oncology, 160(3), pp.777-785.

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About the Company

OneCell Diagnostics is on a mission to democratize precision cancer monitoring and testing to make cancer testing an Actionable, Accessible, and Affordable solution. We bring the power of Genomics data and Artificial Intelligence (AI) to healthcare. We intend to impact millions of cancer patients' lives by providing high-quality precision therapy options to all needful patients worldwide.

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