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Article

Homologous Recombination Deficiency (HRD) assessment for clinical management using the OncoDEEP® Kit

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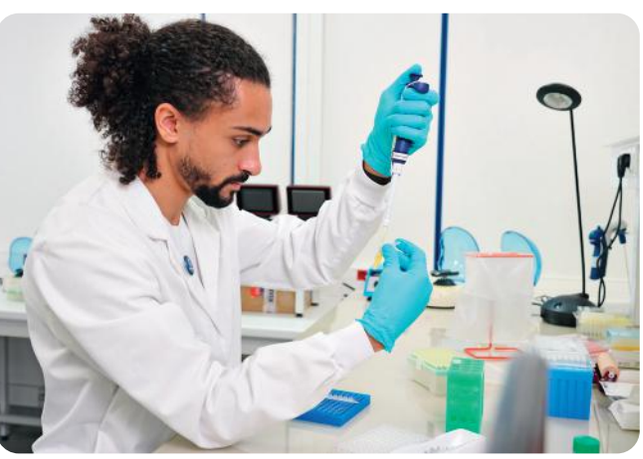

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The Homologous Recombination Repair (HRR) pathway repairs DNA double-strand breaks (DSB). HRR deficiency leads to the accumulation of genomic aberrations and genomic instability which can promote malignant transformation. This phenotype of loss of the HRR capability and the associated genomic instability is called Homologous Recombination Deficiency (HRD). This phenotype has been associated with several cancer types. The determination of HRD status can provide crucial information, which can be used to personalize the treatment of patients with ovarian cancer. Indeed, recently targeted treatments have been approved by the FDA and EMA for treating patients with ovarian cancer depending on their HRD status. Hence, with the knowledge of the HRD status, oncologists can be further aided in their clinical decision-making and to determine the best course of treatment for their patients.

In this perspective, OncoDNA has developed a comprehensive genomic profiling assay that screens for a very wide range of cancer biomarkers and genomic signatures such as HRD status which can reduce the costs of testing and deliver faster results in the selection of appropriate cancer treatment options.

Homologous Recombination Repair (HRR) Pathway and repair of DNA damage

Homologous Recombination Repair (HRR) is an essential and conserved mechanism to repair double-stranded DNA breaks (DSBs), caused by a variety of endogenous and exogenous factors such as ultraviolet (UV) light, reactive oxygen species and errors from DNA replication[1].

HRR is a process by which DSBs are repaired in an error-free way, using the second copy of the gene as a DNA template to repair the break and restore genome integrity[2]. HRR works by two mechanisms: DSB repair and fork protection (Figure 1)[3].

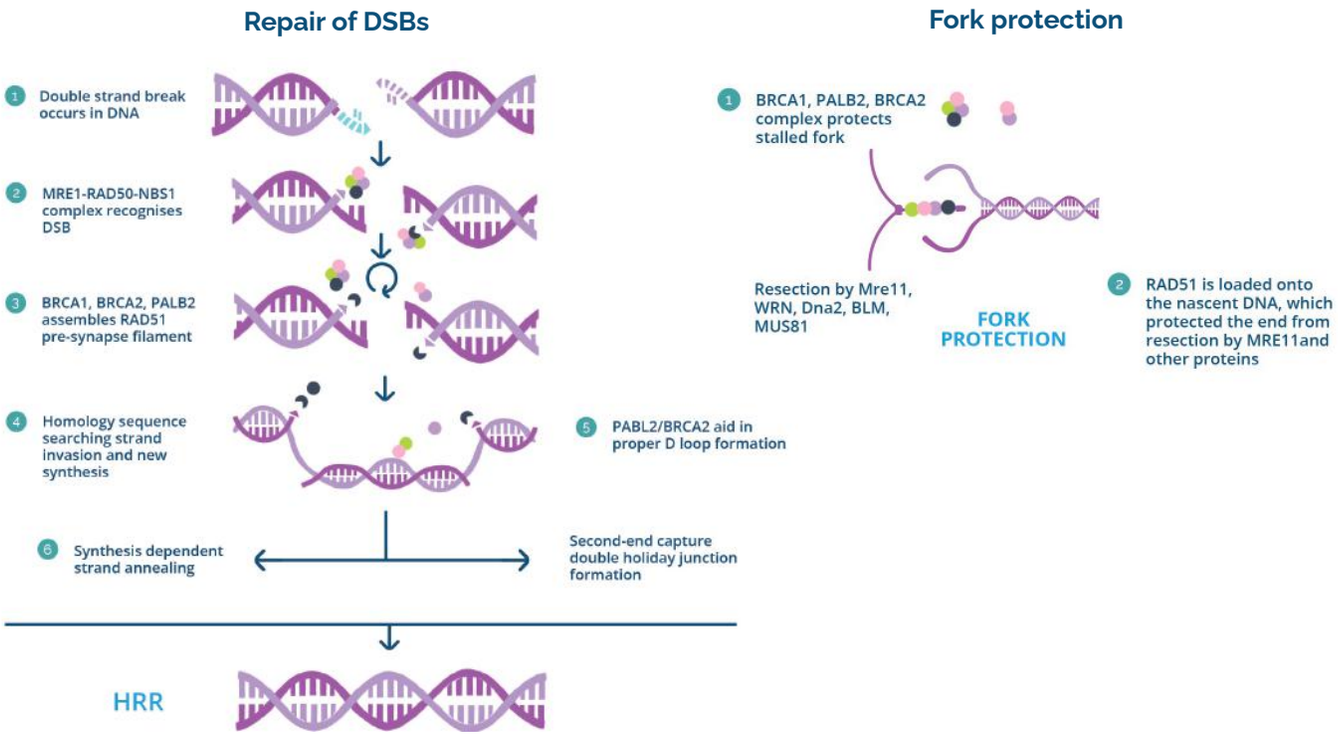

Figure 1: Overview of HRR[2,3]

Cells with mal-functioning HRR rely on error-prone pathways such as Non-Homologous End-Joining to repair DSBs, leading to the accumulation of genetic aberrations and genomic instability. Such aberrations can be loss or rearrangement of sections of DNA, including entire genes. This phenotype of loss of HRR capability and the associated genomic instability is called Homologous Recombination Deficiency, or HRD[4,5] (Figure 2).

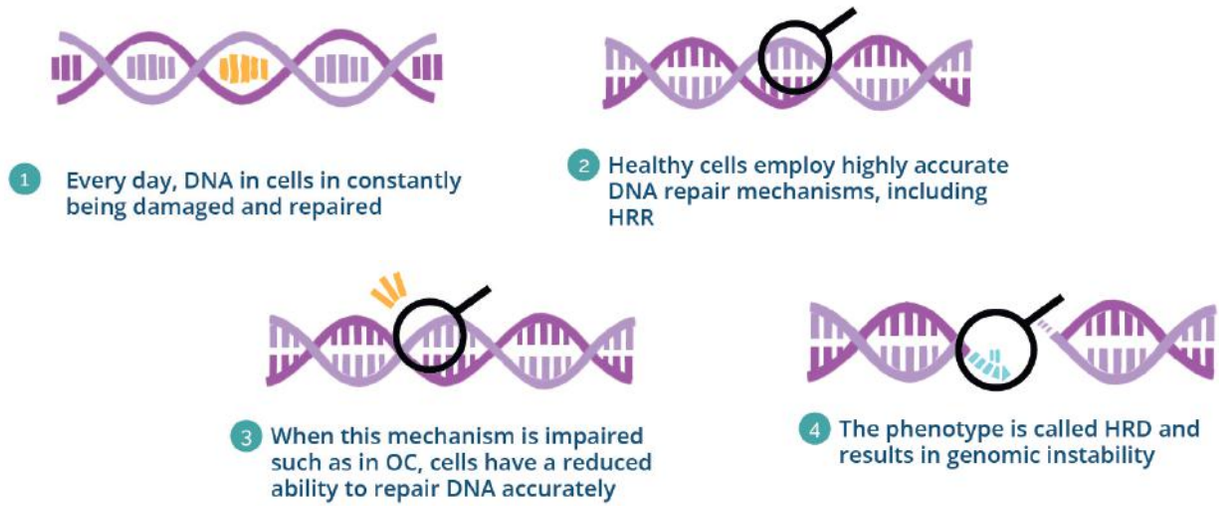

Figure 2 : HRD biology[1,4,5]

When HRR is compromised, it results in genomic instability characterized by somatic copy number aberration structural variation in the number of gene copies. However, in cells with proficient HRR, DSBs can be repaired by the HRR pathway, restoring the stability of the genome (Figure 3).

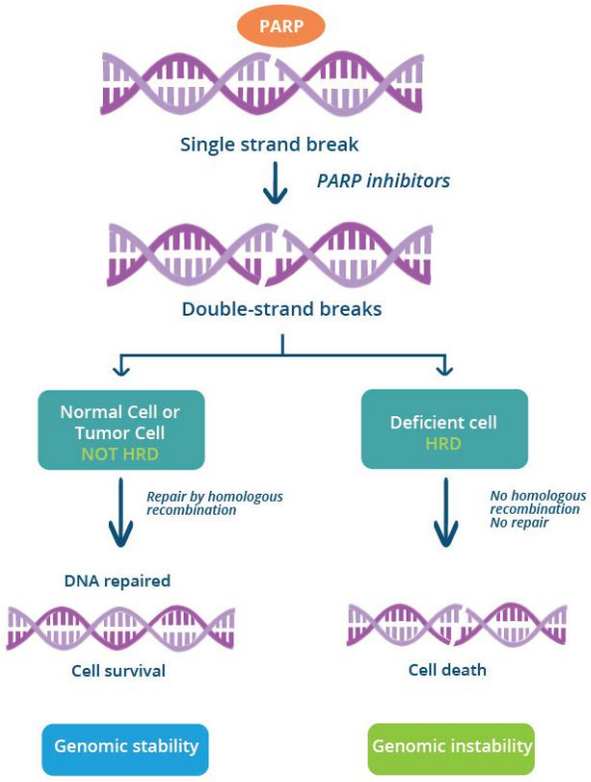

Figure 3 : HRR pathway and genomic instability

Genes involved in HRR include *ATM*, *ATR*, *BRCA1/2*, *BRIP1*, *CK12*, *CHEK1/2*, *NBN*, *PALB2* which are often mutated or epigenetically modified in High-Grade Serous Ovarian Cancer (HGSOC).

Approaches for assessing HRD status

HRD is a complex genomic signature that encompasses many issues that can be triggered by a defect in one of the steps of the HRR pathway. In recent years, organizations have made significant efforts in the attempt to harmonize HR definition, diagnosis and reporting[7].

There are two main approaches to detect tumors with defects in HRR capability and the associated HRD phenotype:

1. The current practice is to sequence HRR genes to look for pathogenic, or deleterious, mutations that disrupt function of genes involved in HR repair, such as *BRCA1* and *BRCA2*. This is called an HRR gene panel test.

2. The other approach is to detect and quantify the genomic alterations that result from loss of HRR capability and are characteristic of HRD phenotype. This is called HRD genomic instability (GI) assay, also known as scar test. GI biomarkers are loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST).

Notably, there is an increasing interest to develop alternative to NGS-based HRD tests, one of which is the functional assays (such as RAD51 foci assay) that can directly measure the ability of cells to carry out HR repair by quantifying the formation of RAD51 foci at sites of DSBs.

HRD Limitations

To date, no uniformly accepted gold standard for HRD assessment exists[8,9]. The ideal method for detecting HRD would measure HRR capacity directly, however functional tests are some way off routine clinical use[8].

Current tests for HRD have solely focused on detecting response to PARPi treatment, therefore may not be appropriate for novel therapies targeting DNA repair[8].

Common HRD tests detect all historical mutations and are unable to detect HRD reversion which results in resistance to PARPis and platinum-based chemotherapy[8]. Real-time detection of HRD is required, with methods such as liquid biopsies under investigation[8].

HRD Status and Clinical Utility in Cancer Treatment

HRD has been reported in numerous cancer types, including ovarian, breast, pancreatic and prostate cancer. In recent years, HRD status analysis has emerged as a promising tool for identifying patients who may benefit from targeted cancer therapies.

The utility of HRD in cancer treatment lies in its ability to predict response to specific types of therapy. Tumors with HRD are often more sensitive to DNA-damaging agents, such as platinum-based chemotherapy and PARP inhibitors[9]. By identifying HRD-positive tumors, oncologists can tailor treatment plans to improve patient outcomes and reduce side effects. Therefore, a positive or negative HRD status is used as a biomarker in cancer profiling which can help clinicians determine the best treatment option for their patients.

"We test for HRD status as there is a benefit for the patient. It is a common feature of high-grade serious ovarian, breast, prostate, and pancreatic cancer. HRD patient status can help identify potential therapeutic options,"

Jessie Hong, Senior Scientist Support at OncoDNA

HRD tests that incorporate scores of allelic imbalances (GIS or LOH) have been shown to identify a subgroup of BRCA wild-type, platinum-sensitive cancers that derive a greater magnitude of benefit from PARPi therapy in some settings[7]. Moreover, higher HRD scores have been associated with improved PFS in newly diagnosed advanced ovarian cancer [10].

How can we detect this complex genomic signature?

As mentioned earlier, the assessment of Homologous Recombination Deficiency (HRD) can be carried out in labs using various biomarkers, including individual mutations and genomic instability markers such as LOH, LST and TAI. Alternatively, ready-made solutions such as the OncoDEEP® Kit can be used to report the HRD signature and get the most accurate results.

Designed by oncology experts, the OncoDEEP® panel contains the most relevant and complete cancer gene panel. This panel is optimized to include all clinically-relevant oncology targets. It is composed of 638 genes, reporting genomic alterations (SNV, insertion, deletion, CNV) and complex genomic signature (HRD, MSI and TMB).

OncoDEEP® Kit, recommended in Germany for HRD scoring

By successfully completing the External Proficiency Testing (EPT) issued by the German QuIP (Qualitätssicherungs-Initiative Pathologie) and supported by AstraZeneca, OncoDEEP KIT already established itself as a game-changer for HRD clinical assessment. The exceptional quality of OncoDEEP KIT's HRD scoring has been demonstrated through the German QuIP Proficiency testing.

See the **ring trial details** and **results.**

Interested by our
OncoDEEP® Kit? Get in touch with our **Sales team**

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