PAN-TUMOR

Homologous Recombination Deficiency (HRD) Overview

FOUNDATION MEDICINE®

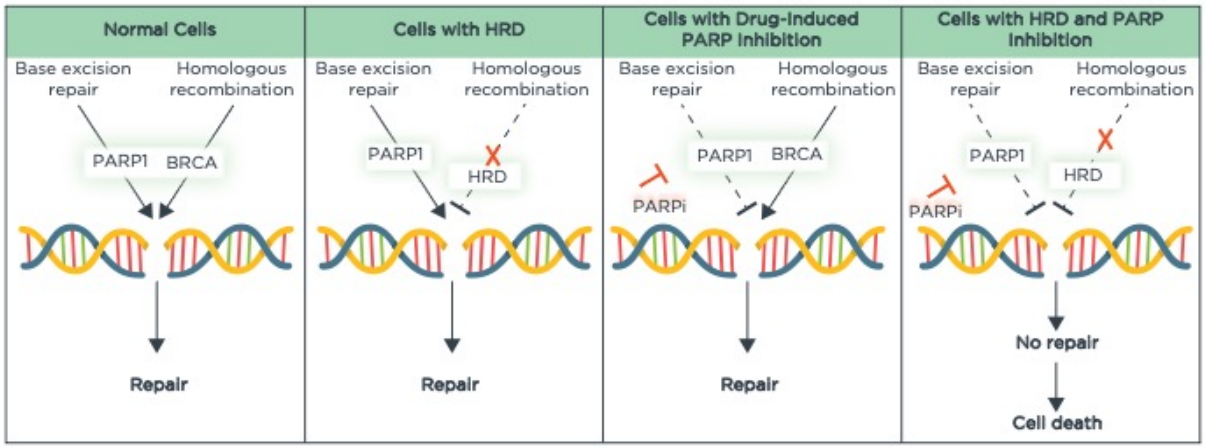
This document introduces the concept of HRD and its therapeutic relevance, including difficulties associated with detection.

Homologous Recombination Deficiency (HRD) Overview[1,2]

Cancer cells with HRD are unable to repair DNA through the process of homologous recombination.[1,2]

- These tumors are sensitive to PARP inhibitors (PARPi) and platinum-based chemotherapy.
- HRD-deficient tumors display genomic scarring due to their defective DNA repair.

Overview of HRD and PARPi Synthetic Lethality



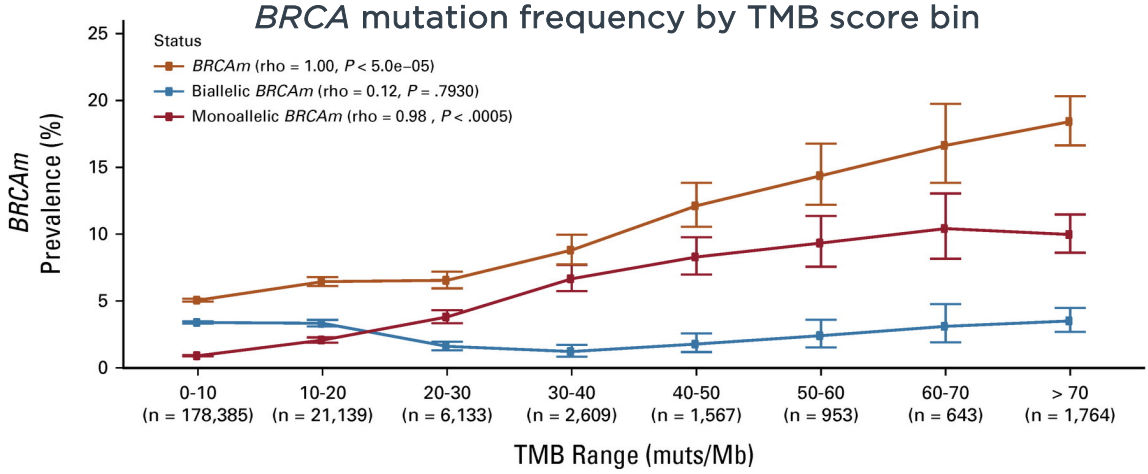
Adapted from Iglehart JD, Silver DP. *N Engl J Med.* 2009;361(2):189-91

Many PARP inhibitor labels use *BRCA* or other homologous recombination repair (HRR) gene status to determine therapy eligibility, but this strategy has limitations.[2,3]

- **Sensitivity:** HRD may be caused by non-genomic mechanisms like methylation, which is not detected by next-generation sequencing.
- **Specificity:** Not all genomic alterations in HRR genes lead to HRD.

Monoallelic BRCA Alterations Increase With TMB[2]

- *BRCA1/2* are large genes. In a pan-tumor analysis of Foundation Medicine's database, the frequency of monoallelic *BRCA* alterations increased as tumor mutational burden (TMB) increased. However, the frequency of biallelic *BRCA* alterations did not increase with TMB.



The Need for a Pan-Tumor HRD Biomarker[1-3]

- HRD arises from various cellular mechanisms detailed in the table below. Previous research has referred to "BRCAness" to describe tumors with similar phenotype to a *BRCA*-altered tumor.

Alteration leading to HRD	Limitations
BRCA genomic alteration	Passenger *BRCA* alterations are not likely to cause HRD
BRCA/other HRR gene methylation	Methylation is not detected by next-generation sequencing
Other HRR gene alteration	High rate of false positives as not all genes in the pathway contribute equally to HRD, and passenger alterations may also be frequent
Unknown mechanism	Difficult to identify unless measuring HRD through functional readout or genomic scarring

Foundation Medicine has developed a tissue-based, pan-tumor HRD signature (HRDsig) biomarker to identify a population that may have potential benefit from PARP inhibitors and/or platinum chemotherapy.

- *HRDsig is reported on FoundationOne®CDx as a laboratory professional service that has not been reviewed or approved by the FDA.*
- By measuring the scarring associated with HRD, HRDsig can identify HRD from the genomic and non-genomic causes listed above.
- HRD biomarker research has been focused primarily on the cancers in which PARP inhibitors are approved (ovarian, prostate, breast, and pancreatic), but HRD occurs across solid tumor types.

Please see our HRDsig resources to learn about Foundation Medicine's pan-tumor biomarker. Have questions? Contact Medical Affairs at med.info@foundationmedicine.com.

References

1. Iglehart JD, Silver DP. *N Engl J Med.* 2009 Jul 9;361(2):189-91. 2. Sokol ES, et al. *JCO Precis Oncol*. 2022;6:e2100531 3. Moore JA, et al. *JCO Precis Oncol*. 2023;7:e2300093. doi:10.1200/PO.23.00093.

HRDsig is reported as a laboratory professional service that has not been reviewed or approved by the FDA.
FoundationOne®CDx is a qualitative next-generation sequencing based *in vitro* diagnostic test for advanced cancer patients with solid tumors and is for prescription use only. The test analyzes 324 genes as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) and is a companion diagnostic to identify patients who may benefit from treatment with specific therapies in accordance with the approved therapeutic product labeling. Additional genomic findings may be reported and are not prescriptive or conclusive for labeled use of any specific therapeutic product. Use of the test does not guarantee a patient will be matched to a treatment. A negative result does not rule out the presence of an alteration. Some patients may require a biopsy. For the complete label, including companion diagnostic indications and important risk information, please visit www.F1CDxLabel.com.

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