NEO GENOMICS

PRECISION ONCOLOGY

WHITE PAPER

Homologous Recombination Deficiency (HRD) and Folate Receptor Alpha (FOLR1) in Ovarian Cancer

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Ovarian cancer continues to have the highest mortality rate of all gynecologic malignancies, largely due to late-stage diagnosis and high recurrence rates, resulting in a 5-year overall survival of less than 50% in advanced disease subtypes.[1] Despite advances in surgery and chemotherapy, conventional platinum-based regimens fail to cure most patients, highlighting the need for biomarker-driven targeted therapies to personalize therapy.[1-4] Homologous recombination deficiency (HRD) and folate receptor alpha (FOLR1) are two clinically actionable biomarkers that play a central role in guiding targeted treatment in ovarian cancer. Incorporating these biomarkers into routine testing and treatment planning is increasingly important in community oncology settings.

Key insight

Understanding HRD status helps clinicians optimize personalized treatment selection as well as assess eligibility and magnitude of benefit from PARP inhibitors, in the absence of a BRCA mutation.

Homologous recombination deficiency in ovarian cancer

HRD arises from germline or somatic mutations in *BRCA1/2* or other homologous recombination repair (HRR) genes, as well as from epigenetic alterations that impair DNA repair pathways.[2,3] Homologous recombination status is often measured by *BRCA1/2* mutation status and markers of genomic instability or "scarring", including loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST).[2] Approximately 20–25% of high-grade serous ovarian carcinoma (HGSOC) tumors harbor *BRCA* mutations, while up to 50% display HRD, highlighting the clinical significance of this biomarker.[4]

Clinical trials have validated HRD as a predictive biomarker for PARP inhibitor therapy. The SOLO-1 trial demonstrated that olaparib maintenance in newly diagnosed *BRCA*-mutated advanced ovarian cancer significantly prolonged progression-free survival (PFS) compared with placebo.[5] The PRIMA trial further established the benefit of niraparib in HRD-positive tumors, including those without *BRCA* mutations.[6] The PAOLA-1 trial reported that combining olaparib with bevacizumab improved outcomes in HRD-positive patients compared with bevacizumab alone.[7] These findings support HRD testing as standard-of-care for guiding frontline and recurrent therapy decisions for ovarian cancer patients.

In practice, HRD testing provides clinical information informing eligibility for PARP inhibitors and predicting response to platinum chemotherapy, expanding patient eligibility for targeted therapies beyond *BRCA* alone. Clinical guidelines recommend molecular tumor profiling, including HRD or homologous recombination status, in patients with persistent or recurrent ovarian cancer, if not previously performed.

NeoGenomics testing platform for HRD

NeoGenomics utilizes NGS for HRD assessment through the PanTracer™ Tissue + HRD assay:

- PanTracer Tissue + HRD detects single-nucleotide variants (SNVs), insertions/deletions (Indels), copy number variations (CNVs), tumor including amplifications, tumor mutational burden (TMB), microsatellite instability (MSI), RNA fusions, and splice variants, enabling comprehensive genomic profiling across 517 genes.
- For the evaluation of HRD in primary epithelial ovarian cancers, PanTracer Tissue + HRD assesses *BCRA 1/2* somatic mutation status and loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transitions (LST), which are combined to generate a genomic instability score (GIS). HRD status is reported as positive when GIS scores are ≥42 and/or *BRCA1/BRCA2* pathogenic mutations are detected.

Folate Receptor Alpha (FOLR1) in ovarian cancer

Folate Receptor Alpha (FRα, or FOLR1) is a cell-surface glycoprotein responsible for folate transport and cell proliferation. It is overexpressed in several cancers, including ovarian and endometrial, while being minimally expressed in normal tissues, making it an ideal therapeutic target.[8,9] High FOLR1 expression has been associated with platinum resistance and poor prognosis in select patient subsets.[10] With the development of FOLR1 inhibitors, measuring FOLR1 expression has become a key biomarker for identifying patients who may benefit from FOLR1-directed therapy.

Mirvetuximab soravtansine-gynx (MIRV), an antibody-drug conjugate (ADC) targeting FOLR1, has demonstrated significant activity in platinum-resistant ovarian cancer. The SORAYA trial reported an overall response rate of 32% in FRα-high patients with acceptable safety.[11] In the MIRASOL Phase III trial, mirvetuximab soravtansine significantly improved progression-free and overall survival compared to standard chemotherapy in FRα-high tumors.[12] These results highlight the clinical importance of identifying FOLR1 expression for patient selection of targeted therapies.

NeoGenomics testing platforms for FOLR1

FOLR1 expression is determined using immunohistochemistry (IHC), categorizing tumors as FRα-high or FRα-low. Standardized scoring ensures accurate selection for FRα -directed targeted therapy.[8,9]

NeoGenomics utilizes IHC for FOLR1 assessment via the VENTANA FOLR1 RxDx Assay, an FDA-approved companion diagnostic. This assay quantifies FOLR1 expression on tumor cells to select patients for FRα-targeted therapy, with high expression (typically ≥75% of tumor cells with moderate-to-strong staining) indicating eligibility for mirvetuximab soravtansine.

A real-world analysis of 6,695 tumor samples tested for FRα at NeoGenomics showed an overall FRα prevalence of 41%.[13] Ovarian cancers accounted for most cases, with a 39% FRα-positive rate, consistent with MIRV clinical trial data (35%). Of 1,678 samples with known histological subtype, FRα positive expression was observed in samples from serous (43.5% [646/1486]), mixed (37% [14/38]), and endometrioid (10% [5/48]) histology, whereas FRα positive expression was absent across all clear cell (0/91) and mucinous subtypes (0/15). FRα expression was detectable in samples less than one year to over five years old, supporting the use of archival tissue when recent samples are unavailable.

Summary

HRD and FOLR1 are pivotal biomarkers in ovarian cancer that guide targeted therapy and influence patient outcomes. HRD testing via NGS informs PARP inhibitor therapy, while FOLR1 testing via IHC informs FOLR1-directed therapy. Routine and accurate biomarker testing is essential to ensure patients receive the most effective targeted therapy options while minimizing unnecessary toxicity. As testing and therapeutic strategies continue to evolve, biomarker-driven care will continue to transform ovarian cancer management and improve patient outcomes.

Assay	Biomarker	Detection Method	Clinical Threshold	Therapy Implication
PanTracer Tissue + HRD	HRD	NGS *includes somatic BRCA1/2 and genomic stability score (LOH, TAI, and LST)*	HRD-positive and/or *BRCA1/2* mutation detected	PARP inhibitor therapy, predicts platinum sensitivity
FOLR1 IHC	FOLR1	IHC	FRα-high	Eligible for mirvetuximab soravtansine (ADC)

Table 1: HRD and FOLR1 Testing at NeoGenomics

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CORP-MRKT-0394 04.26