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MODERN METHODS FOR DETERMINING HOMOLOGOUS RECOMBINATION DEFICIENCY IN OVARIAN CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *As scientists continue to explore and deepen their understanding of cancer genomics, they are increasingly able to identify broader molecular "fingerprints" characteristic of various forms of cancer. One such marker is homologous recombination deficiency (HRD), which is gaining importance in understanding the biology of different cancer types.*

The study aimed to *review the available methods used in clinical practice to assess homologous recombination deficiency status in ovarian cancer.*

Methods: *This review utilized various literature sources, including scientific articles and reviews. Literature search was conducted in databases such as PubMed, Cochrane Library, Scopus, and Web of Science using keywords like "ovarian cancer," "homologous recombination deficiency", and "homologous recombination repair". Articles were included in the review based on their content and relevance to the research topic. The search covered a period of 5 years (2020-2025).*

Results: *Each method presented in the review has specific advantages and disadvantages. It is important to compare the available tests with the gold standard (BRCA1/2, GIS) in clinical trials to better characterize their prognostic value and integrate them into treatment regimens. The combination of multiple tests may provide higher prognostic value. It is crucial to consider the technical heterogeneity that characterizes internal HRD tests. Variations in certain technical characteristics (e.g., reference range, analyzed genomic markers, panel expansion) highlight the importance of harmonizing analytical procedures before implementing internal HRD tests.*

Conclusion: *HRD status analysis is essential in treating ovarian cancer. However, several pre-analytical and analytical factors can influence its clinical testing in surgical pathology laboratories. In recent years, numerous HRD tests have appeared on the market, but their clinical implementation is still far from routine practice. Multicenter efforts should determine the best approaches to ensure adequate HRD testing for all patients with HGSOC.*

Keywords: *ovarian cancer, homologous recombination deficiency (HRD), biomarker, mutation.*

Introduction: As scientists continue to explore and delve deeper into the fundamentals of cancer genomics, they are increasingly able to identify broader molecular "fingerprints" characteristic of various forms of malignancies. One such hallmark is homologous recombination deficiency (HRD), which is gaining importance in the context of understanding the biology of different cancer types – including ovarian, breast, and pancreatic tumors, as well as cancers of the uterus, genitourinary system, colorectal tract, gastrointestinal tract, hepatocellular carcinoma, biliary tract cancer, sarcoma, and malignant neoplasms of the prostate. HRD is a complex genomic feature that arises when cells lose the ability to repair DNA double-strand breaks through the homologous recombination repair (HRR) pathway. Cells must efficiently resolve DNA damage to maintain genomic stability and proper cellular function [1]. This repair system ensures the integrity of chromosomal DNA and maintains cellular viability.

The study aimed to review the available methods used in clinical practice to assess homologous recombination deficiency status in ovarian cancer.

Materials and Methods: This literature search identified approximately 200 different sources, including scientific articles and reviews, of which 51 were selected for analysis. The search was conducted in databases such as PubMed, Cochrane Library, Scopus, and Web of Science using the keywords "ovarian cancer," "homologous recombination deficiency," and "homologous recombination repair." Articles were included in the review based on their content and relevance to the research topic. The search covered a period of 5 years (2020-2025).

Results: Numerous genes are involved in the homologous recombination process, among which BRCA1 and BRCA2 play a key role [3 - 7] (Table 1). When the HRR pathway is disrupted, damaged DNA regions are not properly repaired, and the cell resorts to a less accurate mechanism, known as non-homologous end joining. This may lead to genomic instability, manifested as characteristic "scars" in the genome, which contributes to the development of malignant tumors [8].

Genomic markers associated with HRD are also known as "genomic scars" (Table 2).

Table 1 – Most significant genes involved in the homologous recombination repair pathway [1]

ARID1A	EMSY	MSH2
ATM	FANCA	NBN
ATR	FANCC	PALB2
BRCA1/2	FANCE	PTEN
BARD1	FANCF	RAD50
BAP1	FANCD2	RAD51
BRIP1	FANCG	RAD51B
BLM	FANCI	RAD51C
CDK12	FANCL	RAD51D
CHEK1	H2AX	RAD54L
CHEK2	MRE11	TP53

Table 2 – Types of "genomic scars" included in the genomic instability score [9 - 11]

Name	Characteristics
Loss of heterozygosity	One of the two alleles of a given gene is lost, resulting in the cell becoming homozygous for that gene. If the second allele also be-comes nonfunctional, this may promote malignant transformation.
Telomeric allelic imbalance	Occurs when the allele ratio at the telomeric region of a chromosome is disrupted, meaning one chromosome in the pair contains more alleles than the other.
Large-scale transitions	Represent regions of chromosomal breaks that disrupt the normal structure and concordance of paired chromosomes.

HRD status can be determined either by analyzing mutations in key genes involved in homologous recombination (such as BRCA1, BRCA2, and other HRR genes) or by assessing the presence of characteristic genomic scars. Today, several diagnostic tests are available to determine HRD status, each using its criteria [12]. Some existing tests focus solely on evaluating loss of heterozygosity (LOH). However, recent studies indicate that more accurate identification of HRD-positive tumors is achieved through a comprehensive analysis that combines multiple genomic indicators - LOH, telomeric allelic imbalance (TAI), and large-scale transitions (LST) [13, 14]. This approach provides a sensitive and reliable characterization of HRD and other oncology-related genomic alterations present in the sample.

Homologous recombination deficiency (HRD) in ovarian cancer (OC). HRD is an emerging biomarker with both predictive and prognostic value in high-grade serous ovarian carcinoma (HGSOC). According to data from The Cancer Genome Atlas (TCGA), approximately 50% of patients with HGSOC exhibit signs of HRD. The underlying mechanisms can be diverse, and many of them remain incompletely understood. Most commonly, HRD is caused by inactivating mutations or epigenetic alterations in the BRCA1/2 genes, as well as in several other key players in the HRR pathway such as ATM, BARD1, BRIP1, H2AX, MRE11, PALB2, RAD51, RAD51C/D, RPA, and Fanconi anemia-associated genes [1, 15, 16] (see Table 1). These molecular alterations are considered significant contributors to HRD development in HGSOC.

Poly(ADP-ribose) polymerase (PARP) inhibitors were developed based on the concept of synthetic lethality, implying their selective efficacy against tumor cells with HRD. The enzyme PARP1 (poly(ADP-ribose) polymerase 1) plays a crucial role in the repair of single-strand DNA breaks, particularly via base excision repair mechanisms [16, 18]. When damage occurs, PARP inhibitors block PARP1 activity, preventing the repair of single-strand breaks [19]. As a result, such lesions can evolve into more severe double-strand breaks (DSBs), particularly during replication. Cells harboring mutations in BRCA1/2 or other components of the HRD pathway are unable to efficiently repair DSBs, leading to the accumulation of genomic damage and eventual cell death. These mechanisms form the basis for using HRD as a potential predictive biomarker for PARP inhibitor therapy in HGSOC, as well as in breast, pancreatic, and prostate cancers [19-23].

BRCA gene mutation testing can be performed on both tumor tissue and peripheral blood samples, allowing detection of both somatic and germline (inherited) variants. According to current guidelines, all patients with low-grade or unspecified OC should undergo testing for somatic BRCA mutations at the time of diagnosis. If a tumor sample tests positive, subsequent genetic testing on a blood sample is required to differentiate between germline and somatic mutations. Germline alterations necessitate genetic counseling and may warrant testing of close relatives [1, 24-26].

It is important to note that HRD can be observed not only in the presence of germline or somatic BRCA1/2 mutations, but also in cases of epigenetic suppression of BRCA1 expression or dysfunction of other key DNA repair genes such as ATM, ATR, BARD1, BRIP1, EMSY, PALB2, RAD51, as well as Fanconi anemia-related genes [1, 27 - 32]. Patients with such molecular alterations exhibit the so-called "BRCAness" phenotype, which resembles the clinical picture of BRCA1/2 mutation carriers. It is characterized by a serous histological subtype, high sensitivity to plati-

num-based chemotherapy, prolonged recurrence-free intervals, and a more favorable overall survival prognosis [33-36].

Identifying the BRCAness phenotype enables stratification of a subgroup of patients with sporadic OC who have a better prognosis [19] and demonstrate high sensitivity to platinum agents and PARP inhibitors [37]. Currently, PARP inhibitors are approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for the treatment of high-grade serous carcinoma (HGSC) in various clinical settings:

1. As first-line maintenance therapy for patients who achieved a complete or partial response to platinum-based chemotherapy.

2. As maintenance therapy following platinum-sensitive recurrence, regardless of BRCA mutation or HRD status.

3. As monotherapy in HGSC with confirmed BRCA mutations (Olaparib or Rucaparib), or with a positive HRD status (Niraparib), after two lines of chemotherapy [1, 38].

The publication of the SOLO-1 trial results in 2018 marked a turning point, after which the EMA and FDA approved Olaparib as first-line maintenance therapy for patients with BRCA1/2 mutations. This decision laid the foundation for a new treatment standard. In 2019, data from three major Phase III randomized trials–PRIMA, PAOLA-1, and VELIA–were presented, evaluating the efficacy of PARP inhibitors in first-line therapy for both BRCA-mutated tumors and in combination therapeutic regimens. These studies formed the basis for expanded indications: Niraparib was approved as maintenance therapy regardless of biomarker status, and the combination of Olaparib with Bevacizumab was approved for advanced OC with a positive HRD status [39].

Homologous Recombination Deficiency (HRD) Testing in Clinical Practice. Clinical tests aimed at determining HRD status are based on the analysis of specific genomic alterations that reflect HRD. HRD determination plays a key role in selecting patients who may benefit from PARP inhibitor therapy or other agents that act by inducing DNA damage, especially in the treatment of ovarian cancer. However, for correct interpretation of results and optimal use of these tests in clinical practice, a clear understanding of both their methodological foundations and existing limitations is required [40] (see Table 3).

Table 3 – Advantages and limitations of homologous recombination deficiency (HRD) testing methods [40]

Type of test	Principle	Advantages	Limitations
Genetic testing (BRCA and HRR genes)	Analysis of germline and/or somatic mutations in BRCA1/2 and other HRR genes	Allows identification of hereditary and acquired mutations; an accessible method	Does not always reflect functional HRR status; it does not account for other HRD mechanisms.
Genomic scar analysis (LOH, TAI, LST)	Evaluation of structural genome alterations using SNP arrays or NGS	Widely used in clinical practice	Reflects "historical" instability rather than the current HRR function
Composite genomic instability score	Integration of LOH, TAI, and LST to calculate the overall HRD score	Validated in randomized trials	Requires standardization; limited use in other cancer types
Mutational signatures (WGS/WES)	Whole-genome or exome sequencing to identify specific mutation patterns	Potentially more accurate prediction of HRD and therapy sensitivity	Requires fresh-frozen samples; expensive; not widely implemented
Functional tests (RAD51)	Measurement of RAD51 protein activity involved in HRR	Reflects current functional HRR status; applicable to FFPE samples	Requires standardization; limited availability of laboratories

Note: FFPE – formalin-fixed, paraffin-embedded tissue; LOH – loss of heterozygosity; LST – large-scale chromosomal transitions; TAI – telomeric allelic imbalance; WGS – whole-genome sequencing; WES – whole-exome sequencing, covering only coding genomic regions (exons); RAD51 – protein involved in the homologous recombination DNA repair process.

Although HRD testing is currently FDA-approved only for ovarian cancer, it also has potential significance in the treatment of prostate, pancreatic, and breast cancers. Therefore, in such cases, testing is recommended on an individual basis. The primary objective remains the development of tests capable of accurately identifying the HRD phenotype of a tumor and predicting sensitivity to PARP inhibitors, allowing for more precise patient selection and maximizing therapeutic benefit [41].

There are three main approaches to HRD testing:

1. Analysis of germline and somatic mutations in HRR pathway genes;

2. Detection of "genomic scars" or mutational profiles indicating genomic instability;

3. Assessment of the functional status of the HRR system (Figure 1) [42].

Mutations in HRR Genes. The BRCA1 and BRCA2 genes play a key role in the HRR mechanism. Disruption of their function is one of the main factors contributing to the development of HRD in tumors [12]. All patients with newly diagnosed epithelial OC are recommended to undergo both germline and somatic BRCA testing. BRCA1/2 mutations are the most common cause of hereditary OC and are detected in approximately 20% of cases [44].

The BRCA genes function independently, ensuring genomic stability through the homologous recombination mechanism [45]. Testing helps identify patients who are potentially sensitive to PARP inhibitor therapy. Even with negative results for germline mutations, somatic testing may reveal additional mutation cases (an additional 6-7%) [28].

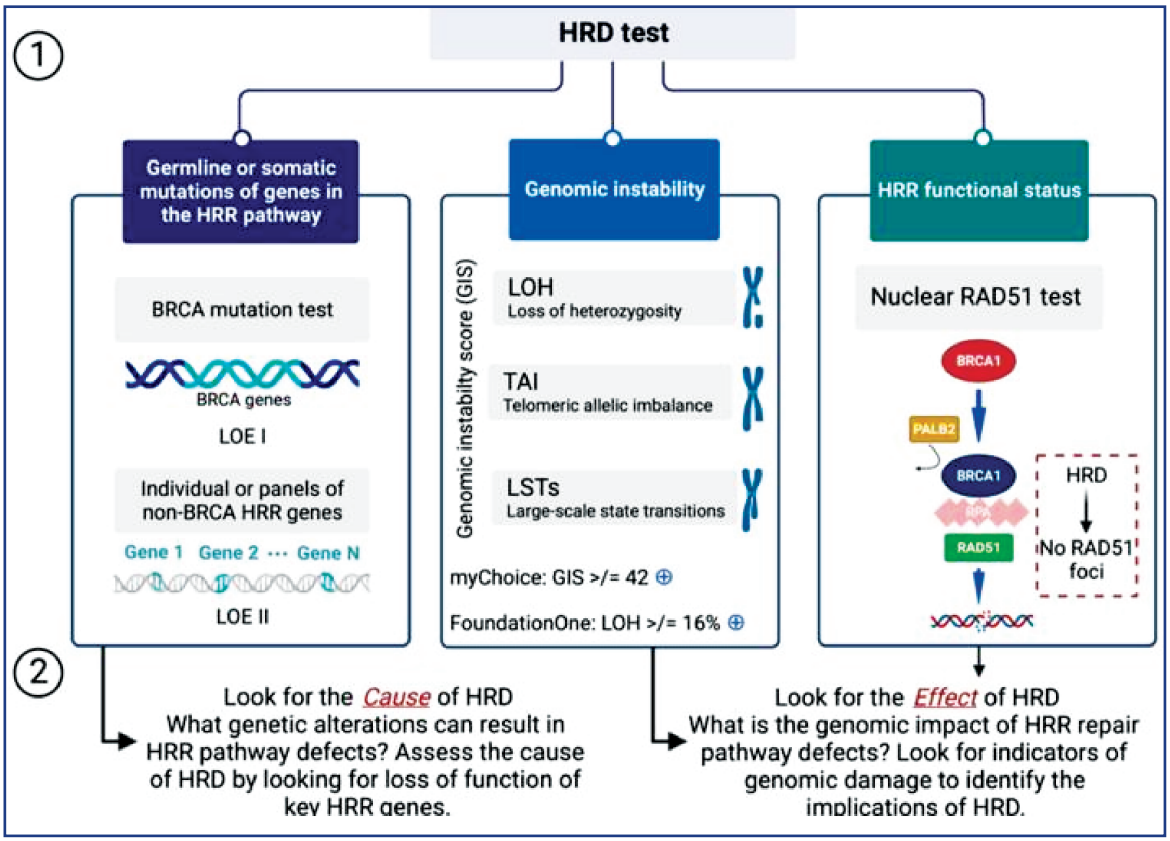

Figure 1 – Main approaches to HRD testing [adapted from: 1]

According to TCGA data, approximately 30% of patients with HGSOC exhibit alterations in HRR genes [28]. Mutations in RAD51C, RAD51D, BRIP1, and other pathway components, including ATM, CHEK1, CHEK2, and CDK12, also increase sensitivity to DNA repair inhibitors [34, 44, 45]. Amplification of the EMSY gene (a BRCA2 inhibitor) is associated with HRD, while CCNE1 amplification correlates with intact homologous recombination and poor prognosis [48].

Clinical data show that somatic mutations in HRR genes (beyond BRCA) may also provide comparable survival outcomes and sensitivity to platinum-based therapy. However, due to the rarity of these mutations, their impact is assessed collectively [38].

Genomic Scars and Mutational Markers of Genomic Instability. Modern HRD tests often use SNP microarrays to analyze somatic copy number variations (CNV). Several studies have used CNV analysis to assess BRCA status, measuring parameters such as LST [101], LOH [9], and TAI [10]. Combining these indicators increases the accuracy of distinguishing tumors with intact versus deficient HRR function [13].

Among commercial tests, FoundationOne (Foundation Medicine, USA) uses LOH analysis, while myChoice HRD (Myriad Genetics, USA) calculates a genomic instability score by integrating LOH, TAI, and LST (Figure 2).

The genomic instability index (GIS) assessment method is the only one validated in randomized clinical trials [38]. Although mutation-based tests using whole-genome sequencing potentially offer greater accuracy, they require fresh-frozen samples, while in clinical practice, formalin-fixed and paraffin-embedded (FFPE) blocks are more commonly available. Moreover, there is currently insufficient data to confirm the effectiveness of such tests in predicting response to PARP inhibitors in HGSOC.

Functional Tests for Homologous Recombination Deficiency. All available HRD tests are based on DNA analysis, reflecting mutations accumulated in the tumor. However, therapeutic pressure may induce resistance, particularly in metastatic tumors, which reduces the accuracy of such tests.

A functional alternative is the assessment of nuclear RAD51 protein levels, which is involved in homologous recombination. RAD51 forms foci in the nucleus upon DNA damage, and this process depends on the BRCA1-PALB2-BRCA2 complex. In model systems, reduced RAD51 activity is associated with BRCA deficiency and sensitivity to PARP inhibitors [48].

The RAD51 test has demonstrated reliability in FFPE tissues, particularly in selecting patients with ovarian and breast cancer who respond to PARP inhibitors [49, 50].

Homologous Recombination Deficiency Testing in Laboratory Practice. HRD testing methods vary and include cause-based and effect-based analyses, sequencing, and SNP-based techniques to evaluate genomic instability. Various HRD tests are available on the market, intended for laboratories equipped with high-throughput NGS plat-

forms. European academic centers are developing their tests, aiming to replicate the results of Myriad MyChoice CDx – for example, the Leuven test, developed within the ENGOT European initiative.

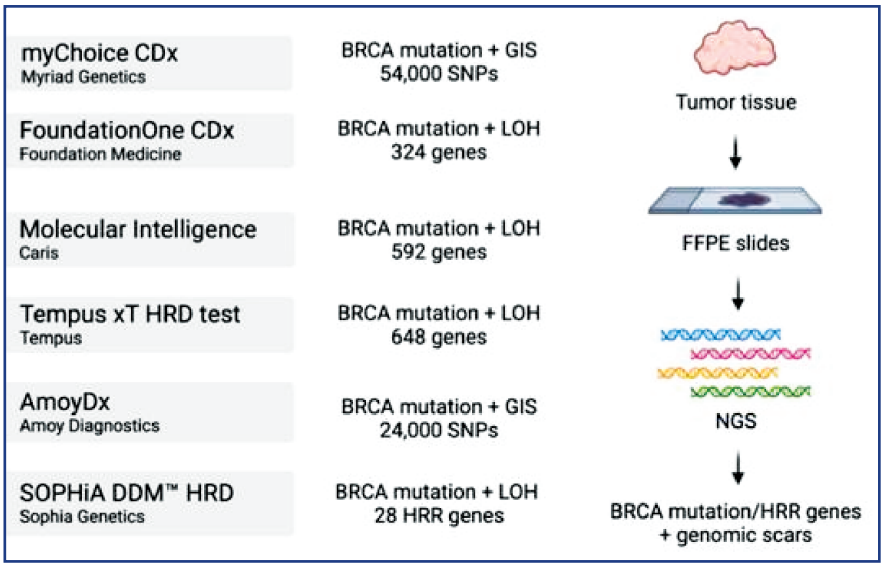

Figure 2 – Methods to assess HRD status in commercial tests [adapted from: 41]

The PAOLA-1/ENGOT-ov25 study, which analyzed 468 ovarian cancer samples, demonstrated a strong correlation between the Leuven HRD test and Myriad myChoice PLUS results. Modern tests such as AmoyDX HRD Focus, Oncomine Comprehensive Assay Plus, SOPHiA DDM HRD Solution, and Illumina TruSight Oncology 500 HRD offer different thresholds to determine HRD status. To more precisely characterize their prognostic value, these tests need to be compared with the gold standard (BRCA1/2, GIS) [1] in clinical studies, which will help determine their role in therapy selection. Moreover, the combined use of several such tests may enhance prognostic significance and requires further investigation, as results must be aligned with the treatment initiation timeline.

Currently, several HRD tests are commercially available. However, implementation of this testing strategy in routine clinical practice remains an open question. The study by Fumagalli et al. evaluated the technical feasibility of the HRD Focus Assay (Amoy Diagnostics, China), which can detect pathogenic BRCA1/2 alterations and calculate HRD scores [51]. In a retrospective series of 95 HGSOC patients who underwent external testing using the myChoiceCDx solution (Myriad Genetics, USA), the success rate of the internal testing strategy was 84.2%. Furthermore, a statistically significant degree of concordance (97.3%) was observed between the molecular BRCA1/2 assessments obtained using these two methodological approaches. The internal testing approach demonstrated outstanding negative predictive value (100.0%) and encouraging positive predictive value (83.3%) compared to the external solution.

One of the key advantages of performing internal tests is the ability to control sample quality and quantity, as well as select the most appropriate material. However, the technical heterogeneity inherent in internal HRD testing must be taken into account. Differences in parameters such as reference ranges, analyzed genomic indicators [1], and the composition of extended panels emphasize the need for standardization of analytical processes before the broad implementation of internal HRD testing.

Limitations of Homologous Recombination Deficiency (HRD) Analysis.

1. FFPE Material. The selection of appropriate tumor material for HRR gene analysis is a critical step. In cases of disease recurrence, preference is given to formalin-fixed paraffin-embedded (FFPE) material, as the tumor's HRD profile may change between the initial diagnosis and disease relapse. However, in some cases, the quantity and quality of FFPE tissue may be insufficient, rendering the sample unsuitable for analysis. In such situations, it is preferable to use the material obtained at the time of the primary diagnosis. Nevertheless, this is not always feasible, especially when treatment has been administered across different medical institutions at various stages of the disease. In such cases, and if the laboratory's technical capabilities allow, germline BRCA mutation analysis should be considered (Figure 3).

Moreover, FFPE samples frequently present alterations that are not true mutations but rather artifacts, such as base deamination or severe DNA fragmentation. These artifacts are often difficult to interpret accurately. Incorrect fixation – whether due to delayed initiation or excessively prolonged fixation – significantly affects sample quality and the reliability of molecular genetic analysis.

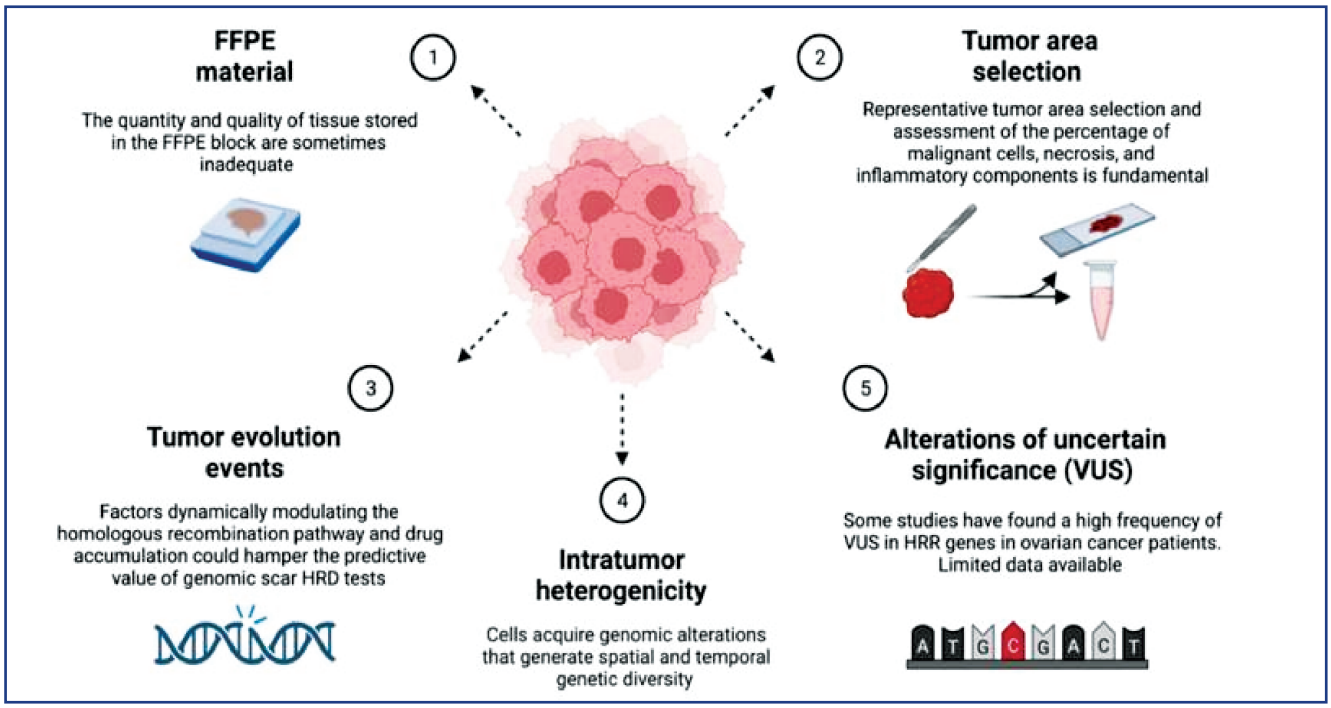

Figure 3 – Limitations of Homologous Recombination Deficiency Analysis

Therefore, it is recommended that molecular laboratories and pathology departments adhere to recognized national and international standards, such as ISO 15189. This is essential to ensure high quality at both the pre-analytical and analytical stages.

2. Selection of a Representative Tumor Area. Choosing the correct tumor area for investigation and assessing parameters such as the percentage of malignant cells, necrosis, and inflammatory infiltration play a key role in the molecular assessment of HRD. To allow for the reliable detection of genetic alterations, the tumor cell content in the tested sample should be at least 30%, and at least 40% for certain tests. This condition can be challenging to meet in tumors with marked inflammatory cell infiltration, which is frequently observed in HRD-associated cancers.

3. Tumor Evolution Events. The clinical relevance of HRD testing in OC is currently assessed primarily in the context of predicting PARP inhibitor efficacy, rather than as a direct indicator of HRD biological status. Beyond BRCA1/2 mutations, a major unresolved issue is whether genomic scars can serve as prognostic biomarkers that predict tumor sensitivity to platinum salts or PARP inhibitors. One of the key limitations of current genomic scar tests is their inability to detect tumor evolution events, such as the restoration of homologous recombination activity in response to therapy. These factors, which dynamically modulate the homologous recombination pathway and drug accumulation, may significantly reduce the predictive value of HRD "genomic scar" tests.

Furthermore, there are currently no documented cases where secondary mutations or BRCA1/2 reversions restore homologous recombination ability. Although a BRCA mutation may initially cause a genomic scar indicative of HRD, the tumor may regain homologous recombination proficiency even if the scar remains visible. This is especially relevant in OC, where approximately half of all BRCA-mutated tumors resistant to platinum-based therapy eventually restore BRCA function after platinum treatment. Additionally, many mechanisms of resistance to PARP inhibitors unrelated to BRCA1 mutations cannot be detected using HRD "genomic scar" tests.

For example, membrane transporters may play a key role in both innate and acquired resistance. In this regard, tests that enable the functional assessment of homologous recombination activity in tumor material may become a valuable tool in clinical practice, offering significant advantages. For a more precise approach within personalized medicine, the ideal strategy would be to integrate data on platinum sensitivity, "genomic scars", mutational markers, and functional tests - providing a comprehensive view of the presence of HRD and the tumor's DNA repair capability throughout treatment.

4. Intratumoral Heterogeneity. One of the major challenges to effective diagnosis and therapy is intratumoral heterogeneity, which refers to genetic differences between the primary tumor, biopsy site, and metastatic areas. Within a single tumor, multiple subclones of cells with distinct mutational profiles may coexist. Studies investigating the mutational spectrum in various segments of tumor tissue have shown significant variation in genetic alterations depending on the location of the sampled tissue [15]. These data confirm the presence of spatial genomic heterogeneity, which can significantly

impact the reliability of results when analyzing biomarkers such as "genomic scars". Such discrepancies may arise even when analyzing individual biopsy samples [16], which complicates data interpretation and underscores the need for a careful approach in selecting material for molecular analysis.

Thus, the same tumor may be classified as either HRD-positive or HRD-negative depending on the biopsy site, which is explained by potential sampling bias. This phenomenon includes both biological differences observed between separate biopsies and technical artifacts inherent to the method, including even minor variations in tissue composition between samples. It is also important to consider the genetic diversity that may exist within different parts of the same tumor specimen.

Variants of Uncertain Significance. The high frequency of variants of uncertain significance (VUS) in other HRR-related genes is most likely due to the limited data available for interpreting mutations outside BRCA1 and BRCA2. When analyzing HRR genes, various databases are often used, which may contain contradictory or ambiguous information, as the clinical significance of many such alterations remains undetermined. Some studies [1, 3] have reported a high frequency of VUS in HRR genes among patients with ovarian cancer. However, they also emphasize that two decades of research on BRCA1 and BRCA2 have led to a substantial reduction in the frequency of VUS in these genes, resulting in VUS rates that are lower than in most other genes.

Discussion: Based on the data obtained, several key points can be identified that confirm the importance of testing for homologous recombination deficiency (HRD) in the treatment of ovarian cancer, particularly when using PARP inhibitors and other DNA-damaging agents.

The Significance of HRD in Ovarian Cancer Therapy. Homologous recombination deficiency serves as an important prognostic indicator to identify patients who are most likely to benefit from therapies targeting DNA repair mechanisms, including PARP inhibitors. Various factors can cause HRD, the most extensively studied of which are mutations in the BRCA1/2 genes, as well as alterations in other components of the DNA repair system, such as ATM, RAD51, and PALB2, among others [17]. Such genetic and epigenetic alterations render tumor cells more vulnerable to certain types of therapy, which can significantly improve clinical outcomes.

The Importance of Accurate Testing. The methods used to detect HRD vary in sensitivity and specificity, underscoring the need for their standardization and unification. Differences in technical execution, such as the gene panels used, threshold values, or the types of genomic alterations analyzed, can significantly impact the reliability of the data obtained. Therefore, it is especially important to correlate the results of various methods with an established reference standard, such as the detection of mutations in the BRCA1/2 genes. This approach enables a more objective evaluation of the prognostic value of each test, thereby enhancing the clinical accuracy of diagnosis.

Genetic Heterogeneity of the Tumor and Spatial Genomic Heterogeneity. The presence of mutational diversity within a single tumor represents a major challenge for molecular diagnostics and disease prognosis. Genetic heterogeneity, resulting from differences between regions of the same tumor, may lead to discrepancies in HRD test results depending on the site of biopsy sampling. This is due to both the tumor's intrinsic biological characteristics and technical factors, including the biopsy site and analysis of different tissue regions, requiring a cautious approach to result interpretation.

The Issue of Variants of Uncertain Clinical Significance (VUS). The high frequency of variants of uncertain significance in genes responsible for DNA repair in patients with ovarian cancer complicates the accurate interpretation of molecular tests and the making of informed therapeutic decisions. However, with the accumulation of data and improvements in mutation classification, there is a trend toward a decreasing proportion of VUS—particularly in BRCA1/2 genes—which positively influences diagnostic accuracy and prognostic evaluation.

Collaboration Between Institutions and the Development of New Diagnostic Approaches. Despite the availability of various methods to determine HRD status, their routine implementation in clinical practice remains limited. To overcome this barrier, active collaboration between research and clinical institutions is needed to develop, validate, and standardize testing approaches. Reliable and reproducible diagnostic methods, including functional assays, should become an integral part of the treatment protocol for all patients with high-grade serous ovarian carcinoma (HGSOC).

Conclusion: Determination of HRD status plays a key role in the personalized treatment of ovarian cancer, particularly in the administration of PARP inhibitors. However, the effectiveness of this approach largely depends on the quality and accuracy of the tests used, as well as on the ability of the methods to adequately reflect the spectrum of genetic alterations present in the tumor. It is essential to consider not only laboratory parameters but also clinical factors, including the spatial heterogeneity of the neoplasm and the influence of biological features on test results.

Successful implementation of HRD testing in clinical practice requires addressing issues of method standardization and optimization, as well as conducting additional studies aimed at improving tests and deepening the understanding of the mechanisms underlying tumor resistance. Multi-institutional efforts to develop a unified

approach to HRD testing will contribute to more accurate identification of patients eligible for PARP inhibitor therapy and improve treatment outcomes.

Looking ahead, it is essential to develop a comprehensive strategy that integrates all available data, from mutational markers to functional HRD analyses, and can serve as a foundation for a more precise and effective approach to ovarian cancer therapy, thereby ensuring the best possible outcomes for each patient.

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АҢДАТПА

АНАЛЫҚ БЕЗІ ҚАТЕРЛІ ІСІГІНІҢ ГОМОЛОГИЯЛЫҚ РЕКОМБИНАЦИЯ ТАПШЫЛЫҒЫН АНЫҚТАУДЫҢ ЗАМАНАУИ ӘДІСТЕРІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Ғалымдар қатерлі ісік геномикасының негіздерін зерттеуді және тереңірек зерттеуді жалғастыра отырып, олар қатерлі ісіктің әртүрлі формаларына тән барған сайын кеңірек молекулалық саусақ іздерін табуда. Осындай белгілердің бірі әртүрлі қатерлі ісіктердің биологиясын түсінуде барған сайын маңызды болып келе жатқан гомологиялық рекомбинация тапшылығы (homologous recombination deficiency, HRD) болып табылады.*

Зерттеудің мақсаты *– аналық безі қатерлі ісігінде гомологтық рекомбинация тапшылығы статусын бағалау үшін нарықта және клиникалық тәжірибеде қолданылатын қолданыстағы әдістерге шолу жасау.*

Әдістері: *Бұл шолуда әртүрлі әдебиет көздері пайдаланылды, соның ішінде ғылыми мақалалар, шолулар. Әдебиеттерді іздеу PubMed, Cochrane library, Scopus және Web of Science дерекқорларында «жұмыртқа безінің рагы», "homologous recombination deficiency", "homologous recombination repair" деген кілт сөздермен жүргізілді. Мақалаларды шолу жұмысына қосу олардың мазмұны мен зерттеу тақырыбына сәйкес келуіне негізделді. Іздеу тереңдігі 5 жылды (2020-2025 ж.) қамтыды.*

Нәтижелері: *Шолуда ұсынылған әр әдістің өз артықшылықтары мен кемшіліктері бар, сондықтан қолдағы тесттерді клиникалық зерттеулерде алтын стандартпен (BRCA1/2, GIS) салыстыру өте маңызды, бұл олардың болжамдық мәнін жақсырақ сипаттауға және оларды емдеу схемасына енгізуге мүмкіндік береді. Бірнеше тесттің комбинациясы жоғары болжамдық мәнді қамтамасыз етуі мүмкін. HRD ішкі тестілерін сипаттайтын техникалық біртекті еместікті ескеру маңызды. Кейбір техникалық сипаттамалардағы вариациялар (мысалы, референттік ауқым, талданатын геномдық көрсеткіштер, панельді кеңейту) ішкі HRD тестілерін енгізбестен бұрын аналитикалық процедураларды үйлестірудің маңыздылығын көрсетеді.*

Қорытынды: *HRD статусын талдау аналық безі қатерлі ісігі бар науқастарды терапевтикалық емдеуде қажет. Алайда бірнеше преаналитикалық және аналитикалық факторлар оның хирургиялық патология зертханаларындағы клиникалық сынақтарына әсер етуі мүмкін. Соңғы жылдары нарықта көптеген HRD тестілері пайда болды, бірақ олардың клиникалық қолданылуы әлі күнге дейін күнделікті тәжірибе болып табылмайды. Көп салалы күш-жігер аналық бездердің жоғары дәрежелі серозды карциномасы бар барлық пациенттер үшін сәйкес HRD тестін қамтамасыз ететін ең жақсы тәсілдерді анықтауы керек.*

Түйінді сөздер: *аналық безі қатерлі ісігі, гомологиялық рекомбинация тапшылығы (HRD), биомаркер, мутация.*

АННОТАЦИЯ

СОВРЕМЕННЫЕ МЕТОДЫ ОПРЕДЕЛЕНИЯ ДЕФИЦИТА ГОМОЛОГИЧНОЙ РЕКОМБИНАЦИИ ПРИ РАКЕ ЯИЧНИКОВ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *По мере того, как учёные продолжают изучать и углубляться в основы раковой геномики, им удаётся выявлять всё более обширные молекулярные «отпечатки», характерные для разных форм онкологических заболеваний. Одним из таких признаков является дефицит гомологичной рекомбинации (homologous recombination deficiency, HRD), значение которого возрастает в контексте понимания биологии различных видов рака.*

Цель исследования *– обзор существующих на рынке и в клинической практике методов оценки статуса дефицита гомологичной рекомбинации при раке яичников.*

Методы: *В данном обзоре были использованы различные источники литературы, включая научные статьи, обзоры. Поиск литературы был осуществлен в базах PubMed, Cochrane Library, Scopus и Web of Science, используя ключевые слова «рак яичников»,*

«homologous recombination deficiency», «homologous recombination repair». Включение статей в обзор происходило на основе их содержания и релевантности для темы исследования. Глубина поиска составила 5 лет (2020-2025 г.).

***Результаты:** Каждый из рассмотренных методов обладает своими сильными и слабыми сторонами. Для более точной оценки прогностической значимости различных тестов необходимо проводить их сравнение с признанными эталонными методами, такими как BRCA1/2 и геномный индекс нестабильности, в рамках клинических исследований. Использование комбинации нескольких тестов может повысить точность прогноза. При этом важно учитывать технические различия, характерные для локально разрабатываемых HRD-тестов. Разнообразие в технических параметрах — таких как диапазон референсных значений, геномные показатели, входящие в анализ, и состав панелей — подчеркивает необходимость стандартизации лабораторных процедур до широкого клинического внедрения таких тестов.*

***Заключение:** Определение HRD-статуса играет важную роль в выборе терапии для пациентов с раком яичников, однако на результативность тестирования могут повлиять как преаналитические, так и аналитические факторы, особенно в условиях лабораторий хирургической патологии. Несмотря на появление множества коммерчески доступных HRD-тестов в последние годы, их использование в повседневной клинической практике остаётся ограниченным. Требуются совместные усилия различных учреждений для выработки оптимальных стратегий, которые обеспечат качественное и стандартизированное определение HRD у всех пациентов с серозной карциномой яичников высокой степени злокачественности.*

***Ключевые слова:** рак яичника (РЯ), дефицит гомологичной рекомбинации (HRD), биомаркер, мутация.*

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