REVIEW PAPER

JMS Journal of Medical Science

Indications and timing for genetic testing in ovarian cancer

Cezary Miedziarek
Division of Gynaecological Oncology, Department of Gynaecology, Poznan University of Medical Sciences, Poland
https://orcid.org/0000-0002-1933-7530
Corresponding author: cezary.miedziarek@gmail.com

Maksymilian Markwitz
Department of Dermatology, Poznan University of Medical Sciences, Poland
https://orcid.org/0009-0003-5417-1075

Michał Potograbski
Division of Gynaecological Oncology, Department of Gynaecology, Poznan University of Medical Sciences, Poland
–

Mikołaj Piotr Zaborowski
Division of Gynaecological Oncology, Department of Gynaecology, Poznan University of Medical Sciences, Poland
Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznań, Poland
https://orcid.org/0000-0002-4400-6688

https://doi.org/10.20883/medical.e1274

Keywords: ovarian cancer, BRCA, HRD

Received 2025-04-03
Accepted 2025-04-23
Published 2025-06-30

How to Cite: Miedziarek C, Markwitz M, Potograbski M, Zaborowski M. Indications and timing for genetic testing in ovarian cancer. Journal of Medical Science. 2025 June;94(2);e1274. doi:10.20883/medical.e1274

ABSTRACT

Modern management of ovarian cancer (OC) relies on molecular diagnostics, with genetic testing playing a central role in therapeutic decisions. High-grade serous ovarian cancer (HGSOC) is frequently associated with mutations in the BRCA1 and BRCA2 genes, as well as other alterations within the homologous recombination repair (HRR) pathway. The identification of pathogenic variants is critical for selecting patients eligible for treatment with poly (ADP-ribose) polymerase inhibitors (PARPi), which significantly improve progression-free survival, especially in individuals with BRCA mutations and homologous recombination deficiency (HRD).

Current guidelines recommend BRCA testing at diagnosis for all patients with HGSOC, followed by HRD testing. Various techniques are used to assess genetic alterations and HRD status. Commercial tests assess mutations in genes in HRR pathways, genomic instability, or HRR functional status to quantify HRD.

Despite the availability of these assays, challenges remain regarding test standardisation, predictive accuracy, and cost-effectiveness. Moreover, emerging research highlights the potential for artificial intelligence (AI) to enhance molecular profiling, utilising whole-slide imaging (WSI) and deep learning to predict homologous recombination deficiency (HRD) and other tumour characteristics.

The integration of molecular subtypes, as defined by The Cancer Genome Atlas (TCGA), into routine clinical practice holds promise for tailoring therapy beyond BRCA or homologous recombination deficiency (HRD) status. As the field advances, comprehensive genetic testing combined with AI-driven analytics may become the cornerstone of precision oncology in ovarian cancer.

Introduction

The aetiology of ovarian cancer (OC) involves a combination of genetic, reproductive, hormonal, and environmental factors. Genetic predispositions, particularly mutations in the *BRCA1* and *BRCA2* genes, play a significant role in its development [1]. High-grade serous epithelial ovarian

cancer (HGSOC) is the most common and aggressive subtype. Characteristic molecular abnormalities in HGSOC include germline and somatic mutations in the *BRCA1* or *BRCA2* genes, *BRCA1* promoter methylation, and alterations in other genes involved in DNA repair through homologous recombination (HR) [2,3]. *TP53* gene mutations are found in up to 96% of HGSOC cases [4]. Among many identified genes whose alterations are related to OC pathogenesis are *NF1*, *CDK12*, *RB1*, *CHEK2*, *RAD51*, *BRIP1*, *PALB2*, and *CCNE1* [5–11]. Alterations in *BRCA* and other genes associated with homologous recombination play a crucial role in determining appropriate adjuvant therapy [12] and genetic counselling for affected individuals' families [13].

Modern OC treatment is not possible without genetic diagnostics. Recent targeted therapies, such as PARP inhibitors (PARPi), exploit genetic disorders associated with *BRCA* mutations and other genes involved in DNA repair through homologous recombination [14,15]. This underscores the importance of research on molecular disorders in OC and the ongoing efforts to integrate these findings into clinical practice. This study aims to summarise the genetic diagnostics used in managing OC.

Relevance of molecular testing in treatment planning

The management of OC depends on the stage of the disease. Primary debulking surgery is performed for operable tumours, followed by adjuvant chemotherapy, potentially combined with an antiangiogenic agent – bevacizumab. If complete cytoreduction is not possible, treatment begins with neoadjuvant chemotherapy, followed by interval debulking surgery [16,17]. Patients with

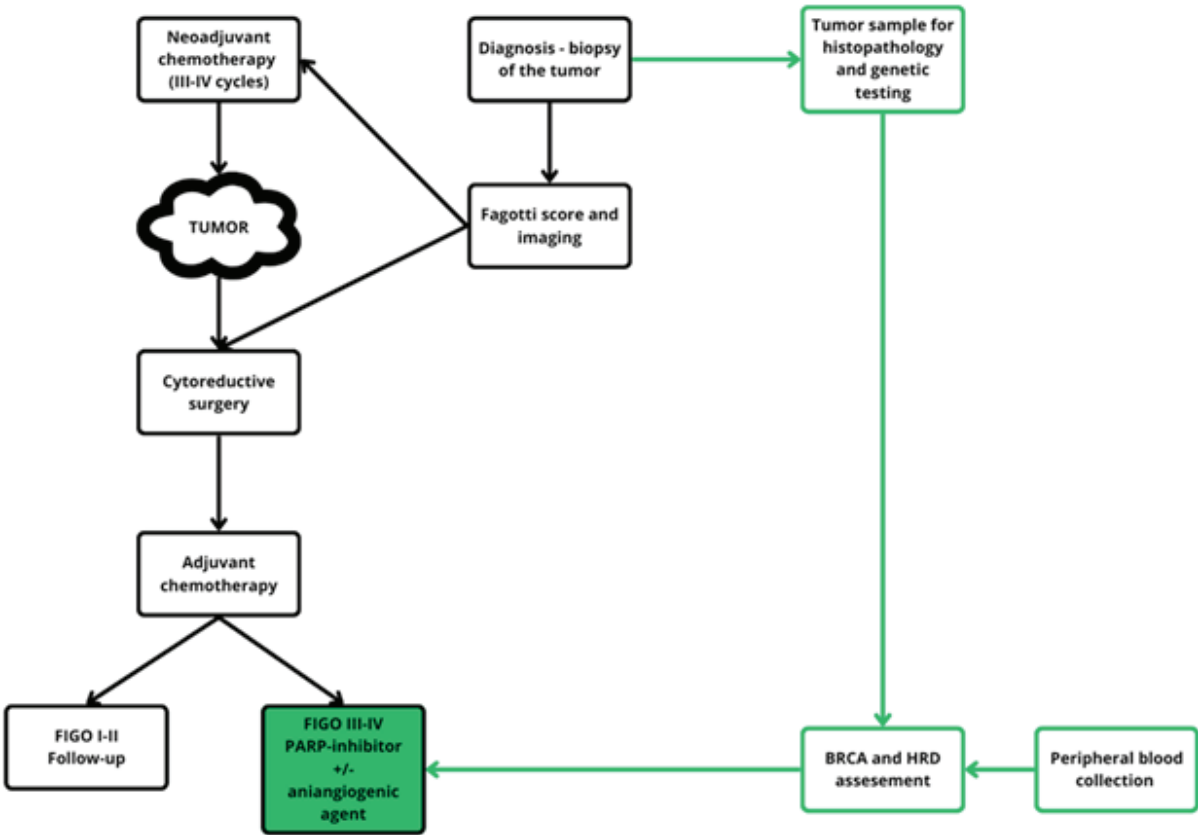

Figure 1. Ovarian cancer treatment algorithm including molecular diagnostics. Treatment of ovarian cancer must be preceded by histopathological confirmation. Molecular diagnostics should be performed on the initial biopsy, which should contain a sufficient amount of tumour tissue—at least 30% tumour cells—to ensure material for analysis. This enables the assessment of eligibility for PARP inhibitor therapy. The result should ideally be available by the third cycle of chemotherapy, as this is when the decision is made regarding the use of the PAOLA-1 treatment regimen. Peripheral blood analysis is used to determine whether the detected mutations are of somatic or germline origin.

advanced disease (FIGO III, IV) who have responded to platinum-based chemotherapy are eligible for maintenance therapy with poly (ADP-ribose) polymerase (PARP) inhibitors [14,15]. Patients with BRCA1/2 mutation or another HR deficiency benefit more from PARPi than from maintenance therapy with bevacizumab. Therefore, genetic testing results are necessary for the treatment decision process. For this reason, every patient diagnosed with OC should be tested for *BRCA1/2* gene variants. The assessment should determine whether the abnormality is somatic or germline in origin. In the case of a typical BRCA1/2 sequence, a homologous recombination deficit (HRD) status evaluation is required [18].

BRCA1 and *BRCA2* genes

The *BRCA* genes belong to the class of tumour suppressor genes. Germline mutations in these genes significantly increase the familial risk of developing breast and OC, known as hereditary breast and ovarian cancer syndrome (HBOC) [19]. A mutation in the *BRCA1* gene increases the lifetime risk of developing OC to 39–58%, while a *BRCA2* mutation raises this risk to 13–29% [20]. *BRCA1/2* gene mutations are present in approximately one-quarter of patients with OC [21]. Approximately three-quarters of these mutations are germline, while the remaining one-quarter are somatic [22].

In clinical practice, detecting a pathogenic *BRCA* gene variant enables the implementation of PARP inhibitor therapy [4,14]. Based on the results of the SOLO-1 trial, olaparib is indicated as a first-line maintenance treatment in women with somatic or germline *BRCA*-mutated advanced OC after first-line platinum-based chemotherapy [23]. The SOLO-2 trial demonstrated the benefits of olaparib for second-line maintenance treatment in patients with germline *BRCA* mutations who had responded to platinum-based chemotherapy [24]. The PRIMA trial showed the benefit of niraparib across all patient populations, including those with HR proficiency, though the effect was moderate in this group [25].

It is worth noting that mutations in other genes that interact with the *BRCA* genes may also be associated with an increased risk of ovarian cancer. *BRIP1*, also referred to as *BACH1* (*BRCA1*-Associated C-Terminal Helicase), was identified during investigations of *BRCA1* gene functions. The BRCT domain of *BRIP1* is essential for its interaction with *BRCA1*, forming a protein complex that facilitates the repair of double-stranded DNA breaks through, among others, HR pathways. Mutations affecting the BRCT domains disrupt this interaction, thereby impairing DNA repair processes [26,27]. *BRIP1* pathogenic variants have been related to hereditary breast and ovarian cancers that are independent of *BRCA1/2* mutations. Individuals carrying heterozygous deleterious variants in *BRIP1* have an elevated risk of developing ovarian cancer [26]. The carriers have an estimated 5–15% lifetime risk, significantly higher than the approximate 2% risk observed in the general population [28]. The PALB2 protein (Partner And Localizer of *BRCA2*) plays a crucial role in HR. Its primary function is to act as a molecular bridge linking the *BRCA* complex, comprising *BRCA1*, *PALB2*, *BRCA2*, and *RAD51*, and to support the activity of RAD51, a key protein involved in strand invasion during HR [29]. Women harbouring *PALB2* mutations face a lifetime ovarian cancer risk of approximately 5% [30]. Given shared mechanisms, carriers of *BRIP1* and *PALB2* pathogenic variants should be included in *BRCA1/2*-based therapies and trials as they can potentially benefit from them [31,32].

BRCA variants testing

The diagnosis of pathogenic variants in the *BRCA* genes can be performed using various techniques. Classical methods, such as Sanger sequencing or quantitative polymerase chain reaction (qPCR), are used as a first step in population-based screening or for confirming variants identified through next-generation sequencing (NGS) [33–36]. A key limitation of these techniques is their ability to detect only selected pathogenic variants, typically those most common in a given population, including so-called founder mutations [36]. Hence, some less common but pathogenic variants remain undetected. A negative result from those methods should prompt further diagnostic evaluation using NGS. This approach allows the comprehensive analysis of the entire coding sequence of the *BRCA* genes. This is particularly important given their

large size. Moreover, clinically significant variants can be distributed throughout the whole coding region [36–38]. Another advantage of NGS is the possibility of analysing other genes associated with OC pathogenesis in panel sequencing that, in addition to *BRCA1/2*, may include *RAD51C/D*, *BRIP*, and *PALB2* [39,40]. Multiplex ligation-dependent probe amplification (MLPA) is typically employed to detect large chromosomal rearrangements in *BRCA* genes [41].

The clinical relevance of specific *BRCA* gene variants is classified. These include pathogenic or likely pathogenic variants (*BRCAmut*) and the absence of such variants, referred to as wild type (*BRCAwt*) [26]. Further diagnostic steps determine whether the mutation is somatic (*sBRCAmut*) or germline (*gBRCAmut*) [27]. Tumour-only testing (*tBRCAmut*) [28] cannot determine the somatic or germline nature of the mutation. Molecular testing of the host genome, typically from peripheral blood, is required to identify the germline nature of the variant. According to The American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guidelines, variants are classified using a five-tier scale as benign (B, class 1), likely benign (LB, class 2), variant of unknown significance (VUS, class 3), likely pathogenic (LP, class 4), and pathogenic (P, class 5) [29]. Pathogenic variants (PVs) in the *BRCA1* and *BRCA2* genes are detected in 10–15% of unselected epithelial OC cases [42]. Patients with likely pathogenic and pathogenic variants are eligible for treatment with PARP inhibitors [30]. It should be noted, however, that specific variants of unknown significance may be considered pathogenic in the future as the number of patients with such a variant grows. Therefore, those patients and their families may require increased monitoring, especially if other cases appear to suggest a hereditary syndrome.

Homologous recombination deficit

From a practical perspective, detecting HRD allows qualifying patients for PARPi therapy [14,15]. Based on the results of the PRIMA trial, niraparib can be used as maintenance therapy for all patients, including those with HRD and HRP tumours [25]. The PAOLA-1 trial demonstrated the efficacy of olaparib in combination with bevacizumab compared to bevacizumab monotherapy. Based on the results of this study, the drug combination has been approved for HRD-positive patients who respond to first-line platinum-based chemotherapy [43].

The detection of recombination defects remains a significant challenge. Identification of patients, beyond carriers of *BRCA1/2* gene mutations, who may benefit from maintenance therapy remains ineffective [44]. HRD test results are often inconclusive due to differences between available tests and the lack of standardised criteria for defining HRD [18]. Studies involving niraparib, olaparib, and veliparib utilised the *myChoice* test developed by Myriad Genetic Laboratories [45–47]. This test detects mutations in the BRCA1/2 genes. It determines the Genomic Instability Score (GIS), which is based on the extent of loss of heterozygosity, the number of subchromosomal regions with allele imbalance extending to the telomere, and the number of large-scale genomic rearrangements. [44]. Different clinical trials have applied varying threshold values for the GIS determined by the *myChoice* test to define the presence of homologous recombination deficiency (42 in the PAOLA-1 trial and 33 in the VELIA trial), highlighting the lack of clarity in patient stratification based on this metric [45,47]. Another test, *FoundationFocus CDxBRCA* by Foundation Medicine, is based on the assessment of subchromosomal loss of heterozygosity and the detection of *BRCA1/2* mutations in tumour tissue [44] and was utilised in the clinical trial evaluating the efficacy of rucaparib [48]. In contrast, the PRIME clinical trial of niraparib employed the *BGI Genomics* test [49]. There are substantial differences among these assays, and their negative predictive value remains low [44]. Consequently, accurately identifying patients who will not respond to treatment remains challenging.

The currently used methods rely on so-called genomic "scars" (indicators of genomic instability), which are static and may not accurately reflect the current status of DNA repair in the tumour. These genetic features may change throughout the disease and in response to applied treatments [50]. Tests may yield false-positive or false-negative results (estimated in 10–15% of cases). Moreover, the heterogeneity within tumour cells

can lead to different classifications of the same tumour depending on the biopsy site [51].

HRD testing should be performed as early as possible following the diagnosis of OC, ideally at the time of primary diagnosis. A stepwise diagnostic approach is also acceptable if molecular testing of the *BRCA* genes is conducted first. If the tumour is *BRCA* wild type (*BRCAwt*), HRD testing is subsequently performed. Economic considerations primarily justify this approach. However, current reports on cost-effectiveness are inconsistent [52–54].

HRD testing methods

The currently used tests for HRD status assessment can be categorised into three main groups – assessing mutations in genes in HRR pathways, genomic instability, or HRR functional status by nuclear RAD51 tests [18,55–57].

The first group is based on the detection of typical causes of HRD. They assess the loss of function of germline and somatic mutations in the HRR pathway genes, including *BRCA1/2* [18] and *BRCA1* promoter methylation [57]. However, it is worth noting that the lack of mutations in those genes should not be considered equivalent to HRP status.

The second group determines the HRD by calculating the genomic instability (GI) score [58]. It is calculated as the sum of events collectively referred to as "genomic scars". These are loss of heterozygosity (LOH), large-scale state transition (LST), and telomere allele imbalance (TAI) [18,55,58]. These disorders reflect the abnormalities occurring in HRD cells.

LOH is a frequent genetic condition in cancer cells [59]. It occurs when a heterozygous genetic locus loses one of its parental alleles, resulting in homozygosity. The remaining allele's dysfunction can lead to a neoplastic transformation. LOH can be categorised into two primary types: LOH with copy number loss (CNL-LOH) and copy number neutral LOH (CNN-LOH). During cancer progression, tumour cells may experience the loss of an allele due to partial chromosomal deletion, which characterises CNL-LOH. Subsequently, CNL-LOH may undergo recombination, utilising the homologous chromosome as a template for repair, leading to copy number neutral LOH (CNN-LOH) [18,59,60].

Large-scale transitions (LST) refer to significant chromosomal modifications, including translocations, inversions, and deletions resulting from chromosomal breakage events. These alterations involve chromosomal gains or losses of at least 10 megabases (Mb) in size [61,62].

In cells with proficient DNA repair mechanisms, double-strand breaks are accurately repaired through homologous recombination, using the identical sister chromatid as a template, thereby preventing telomeric allelic imbalance (TAI). However, error-prone pathways are utilised when DNA repair is impaired in HRD, resulting in chromosomal rearrangements and abnormal radial chromosome formations. After mitotic division, this defective repair leads to TAI, characterised by an unequal contribution of parental telomeric chromosome segments in the daughter cells [63].

The third group of tests assesses the HRR status by nuclear RAD51 functional tests [55,18]. The RAD51 family comprises five paralogous proteins (RAD51B, RAD51C, RAD51D, XRCC2, and XRCC3) that mediate DNA damage signalling to facilitate break repair. RAD51 is the key protein in homologous recombination, playing a crucial role in cellular damage sensing and checkpoint signalling pathways [64,65]. Consequently, cell phenotypes resembling those of *BRCA*-mutated cells can also result from other, less common alterations, such as mutations in *PALB2*, *RAD51C*, and *RAD51D* or the epigenetic silencing of HR genes [66]. When homologous recombination repair functions correctly, RAD51 assembles into nuclear foci, indicating HRR proficiency (HRP). Conversely, the absence of nuclear foci signifies HRR deficiency [64].

Numerous commercial tests are available to assess HRD in OC patients. *MyChoice® CDx Plus* and *FoundationOne® CDx* were the first tests approved by the FDA for this purpose. *MyChoice® CDx Plus* is based on sequencing 15 HRR genes and a genome-wide single-nucleotide polymorphism-based assay (GW-SNP). HRD is determined based on a *BRCAmut* result or a genome instability score (GIS) ≥ 42. GIS is evaluated as a combined score of LOH, TAI, and LST [67]. *FoundationOne® CDx* analyses 324 genes using next-generation sequencing (NGS) and a genome-wide single-nucleotide polymorphism-based assay (GW-SNP). HRD is defined by the presence of a *BRCAmut*

variant or a genome-wide loss of heterozygosity (gLOH) score of ≥ 16% [67,68].

Several other commercially available tests are designed to assess homologous recombination deficiency (HRD). *OncoDEEP®* utilises next-generation sequencing (NGS) to assess 638 genes and an RNA-based 20-gene panel for detecting gene fusions and splicing events. The test evaluates *BRCA* status and determines the genome instability score (GIS) based on a developed algorithm [67,69]. *SeqONE HRD* utilises NGS and shallow whole genome sequencing (sWGS) to assess *BRCA* and HRD status, which is based on a composite score of LOH and LGA (large genomic alterations) and genes *CCNE1* and *RAD51B* amplification at two specific locations [67,70]. *SOPHiA DDM™ Dx HRD CE-IVD* performs next-generation sequencing (NGS) analysis of 324 selected genes and shallow whole-genome sequencing (sWGS). HRD assessment is conducted based on a proprietary algorithm [67,71]. *HRD Focus* utilises next-generation sequencing (NGS) to detect *BRCA* gene mutations and assess genomic instability using a genome-wide single-nucleotide polymorphism-based assay (GW-SNP). HRD is defined by the presence of *BRCAmut* or a genome scar score (GSS) ≥ 50 [67,72]. *Caris HRD Status* determines the presence of *BRCA* mutations and assesses a GSS based on gLOH and LST [67]. *The AmoyDx® HRD Complete Panel* detects genetic alterations in 20 HRR genes and determines overall HRD status. Its proprietary GIS algorithm, based on machine learning, evaluates genomic instability by analysing multiple types of copy number variations across the genome [73]. In addition to the tests described above, several established assays are currently used for academic purposes. These include the *Geneva HRD Test*, *NOGGO GIS Assay*, *GIScar*, *Leuven HRD test*, *Shallow HRDv2*, and *BRCA-Like Classifier* [67].

Molecular subtypes of ovarian cancer according to TCGA analysis – potential expansion of genetic diagnostics

The TCGA (The Cancer Genome Atlas) database and its analysis have significantly benefited gynecologic oncology by identifying molecular subtypes of endometrial cancer, which now directly influence clinical decision-making [74,75]. Given these advancements, it is no surprise that gynecologic oncologists are increasingly interested in further utilising the resources of this database. Based on the analysis of data from TCGA, four molecular subtypes of OC have been identified: mesenchymal, proliferative, immunoreactive, and differentiated [4]. The mesenchymal subtype is characterised by high expression of *HOX* genes (a group of genes responsible for the morphological development of specific body parts during early embryonic stages) and markers suggesting increased stromal components (such as *FAP*, *ANGPTL2*, and *ANGPTL1* genes). The proliferative

Table 1 – Summary of commercial and academic tests for assessing HRD based on "Homologous recombination deficiency in ovarian cancer: Global expert consensus on testing and a comparison of companion diagnostics" [67].

Tests for assessing HRD			
Approved Commercial Tests	**HRD definition**	**Academic Tests**	**HRD definition**
MyChoice® CDx Plus	BRCAm and/or GIS ≥42	Geneva HRD Test	GIS ≥15
OncoDEEP®	GIS >39	NOGGO GIS Assay	NOGGO GIS ≥83
SeqONE HRD	BRCAm and/or HRD status (probability ≥50%; based on composite score and gene amplification at two locations)	GIScar	GIScar score ≥0.48
SOPHiA DDM™ Dx HRD CE-IVD	GII >0	Leuven HRD test	BRCAm and/or GIS ≥56
FoundationOne® CDx	BRCAm and/or gLOH score ≥16%	Shallow HRDv2	>20 LGAs
HRD Focus	BRCAm and/or a GSS ≥50	BRCA-Like Classifier	Posterior probability >0.5
Caris HRD Status	BRCAm or high GSS		

BRCAm, BRCA mutation; CDx, companion diagnostic; GI, genome instability; GII, genome instability index; GIS, genome instability score; gLOH, genomic loss of heterozygosity; GSS, genome scar score; HRD, homologous recombination deficiency; HRR, homologous recombination repair; indel, insertion or deletion; LGA, large genomic alterations

subtype exhibits high expression of transcription factors such as HMGA2 and SOX11 and proliferation markers like MCM2 and PCNA. However, it shows low expression of OC markers, including MUC1 and MUC16.

Additionally, this subtype is associated with a reduced frequency of *MYC* amplification and *RB1* deletion. The presence of T-cell ligands CXCL11 and CXCL10, along with their receptor CXCR3, defines the immunoreactive subtype. Moreover, 3q26.2 amplification (MECOM) occurs more frequently in this subtype. The differentiated subtype is characterised by higher differentiation features, including increased expression of MUC1, MUC16, and the secretory fallopian tube marker SLPI [4].

The current standard of care does not use information on molecular subtypes of OC defined in the TCGA project. It has been demonstrated that patients with mesenchymal and proliferative subtypes derive more significant benefits from bevacizumab treatment [76–78]. Furthermore, the mesenchymal subtype is more responsive to dose-dense taxane chemotherapy, which suggests that the preferred treatment regimen should be dose-dense paclitaxel with carboplatin (ddTC) [79,80]. The possibility of routine molecular subtype profiling could be helpful in clinical decision-making. The main obstacles include costs and technical challenges, particularly those related to standardising the methodology [79,81]. Conducting specialised tests, such as using microarrays solely for this purpose, may be challenging [82]. Attempts have been made to histopathologically profile ovarian tumours based on their molecular subtypes, which could facilitate access to knowledge about specific tumour biology [80].

Artificial intelligence in molecular profiling of ovarian cancer

Artificial intelligence (AI), particularly machine learning, is increasingly utilised in medicine to support diagnostics and treatment planning. Learning algorithms can identify patterns that may be imperceptible to human experts. These techniques are applied in areas such as radiological image analysis, disease progression prediction, and personalised therapy [83,84]. Several studies have integrated genomics, epigenomics, transcriptomics, and clinical or pathological data to enhance the diagnosis, prognosis, and prediction of treatment response in OC. Approaches using machine learning and deep learning demonstrated that multiomics models outperform single-omics models in tasks such as survival prediction, subtype classification, and response to therapy [85,86]. AI techniques have the potential to effectively surpass classical methods of identifying patients with HRD.

An example of this is DeepHRD, a platform trained to predict HRD from hematoxylin and eosin (H&E)–stained histopathological slides. Compared to four standard molecular tests, this model identified more tumours exhibiting HRD-related features [87]. AI utilises the analysis of histopathological images obtained through Whole Slide Imaging (WSI), which involves scanning and digitising entire histology slides [88–90]. Algorithms identify morphological patterns associated with HRD, such as hemorrhagic necrosis at tumour margins, lymphocytic infiltration, fibrosis, and high tumour cell density [89]. There are also ongoing efforts to apply machine learning and neural networks for classifying ovarian cancers into distinct subgroups and for analysing data derived from single-cell image analysis [91–93]. It is essential to emphasise the critical role of building large-scale databases that include macroscopic and microscopic images and omics data, such as TCGA.

Conclusions

Molecular diagnostics are now essential for planning the treatment of patients diagnosed with OC. Molecular profiling is crucial for implementing maintenance therapy as part of first-line treatment. *BRCA* and HRD testing are fundamental in guiding treatment decisions, particularly in selecting patients for PARP inhibitor therapy. *BRCA1* and *BRCA2* mutations and homologous recombination deficiency (HRD) are key predictive biomarkers that determine responsiveness to targeted therapies.

Focusing on alternative molecular pathways is equally essential as targeting *BRCA* mutations and HRD-related alterations in OC. This is particularly relevant for patients who are resistant to PARP inhibitors or do not meet the criteria for this treatment. Additionally, research into

OC subtypes other than HGSOC is crucial, as BRCA mutations and HRD are less prevalent in these tumours. Targeted therapies tailored to the unique molecular characteristics of non-HGSOC remain underdeveloped, highlighting the need for further studies. AI models play an increasingly important role in the diagnosis, prognosis, and personalisation of OC treatment, particularly by integrating omics, imaging, and clinical data.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

References

1. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, Gaudet MM, Jemal A, Siegel RL. Ovarian cancer statistics, 2018. CA A Cancer J Clinicians 2018;68:284–96. https://doi.org/10.3322/caac.21456.
2. Takamatsu S, Brown JB, Yamaguchi K, Hamanishi J, Yamanoi K, Takaya H, Kaneyasu T, Mori S, Mandai M, Matsumura N. Utility of Homologous Recombination Deficiency Biomarkers Across Cancer Types. JCO Precision Oncology 2022:e2200085. https://doi.org/10.1200/PO.22.00085.
3. Yamulla RJ, Nalubola S, Flesken-Nikitin A, Nikitin AY, Schimenti JC. Most Commonly Mutated Genes in High-Grade Serous Ovarian Carcinoma Are Nonessential for Ovarian Surface Epithelial Stem Cell Transformation. Cell Reports 2020;32:108086. https://doi.org/10.1016/j.celrep.2020.108086.
4. The Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609–15. https://doi.org/10.1038/nature10166.
5. Bukłaho PA, Kiśluk J, Wasilewska N, Nikliński J. Molecular features as promising biomarkers in ovarian cancer. Adv Clin Exp Med 2023;32:1029–40. https://doi.org/10.17219/acem/159799.
6. Moyer CL, Ivanovich J, Gillespie JL, Doberstein R, Radke MR, Richardson ME, Kaufmann SH, Swisher EM, Goodfellow PJ. Rare BRIP1 Missense Alleles Confer Risk for Ovarian and Breast Cancer. Cancer Research 2020;80:857–67. https://doi.org/10.1158/0008-5472.CAN-19-1991.
7. Yang X, Leslie G, Doroszuk A, Schneider S, Allen J, Decker B, Dunning AM, Redman J, Scarth J, Plaskocinska I, Luccarini C, Shah M, Pooley K, Dorling L, Lee A, Adank MA, Adlard J, Aittomäki K, Andrulis IL, Ang P, Barwell J, Bernstein JL, Bobolis K, Borg Å, Blomqvist C, Claes KBM, Concannon P, Cuggia A, Culver JO, Damiola F, De Pauw A, Diez O, Dolinsky JS, Domchek SM, Engel C, Evans DG, Fostira F, Garber J, Golmard L, Goode EL, Gruber SB, Hahnen E, Hake C, Heikkinen T, Hurley JE, Janavicius R, Kleibl Z, Kleiblova P, Konstantopoulou I, Kvist A, Laduca H, Lee ASG, Lesueur F, Maher ER, Mannermaa A, Manoukian S, McFarland R, McKinnon W, Meindl A, Metcalfe K, Mohd Taib NA, Moilanen J, Nathanson KL, Neuhausen S, Ng PS, Nguyen-Dumont T, Nielsen SM, Obermair F, Offit K, Olopade OI, Ottini L, Penkert J, Pylkäs K, Radice P, Ramus SJ, Rudaitis V, Side L, Silva-Smith R, Silvestri V, Skytte A-B, Slavin T, Soukupova J, Tondini C, Trainer AH, Unzeitig G, Usha L, Van Overeem Hansen T, Whitworth J, Wood M, Yip CH, Yoon S-Y, Yussuf A, Zogopoulos G, Goldgar D, Hopper JL, Chenevix-Trench G, Pharoah P, George SHL, Balmaña J, Houdayer C, James P, El-Haffaf Z, Ehrencrona H, Janatova M, Peterlongo P, Nevanlinna H, Schmutzler R, Teo S-H, Robson M, Pal T, Couch F, Weitzel JN, Elliott A, Southey M, Winqvist R, Easton DF, Foulkes WD, Antoniou AC, Tischkowitz M. Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families. JCO 2020;38:674–85. https://doi.org/10.1200/JCO.19.01907.
8. Guo T, Dong X, Xie S, Zhang L, Zeng P, Zhang L. Cellular Mechanism of Gene Mutations and Potential Therapeutic Targets in Ovarian Cancer. CMAR 2021;Volume 13:3081–100. https://doi.org/10.2147/CMAR.S292992.
9. Gorski JW, Ueland FR, Kolesar JM. CCNE1 Amplification as a Predictive Biomarker of Chemotherapy Resistance in Epithelial Ovarian Cancer. Diagnostics 2020;10:279. https://doi.org/10.3390/diagnostics10050279.
10. Feng Y, Wang D, Xiong L, Zhen G, Tan J. Predictive value of RAD51 on the survival and drug responsiveness of ovarian cancer. Cancer Cell Int 2021;21:249. https://doi.org/10.1186/s12935-021-01953-5.
11. Lawrenson K, Iversen ES, Tyrer J, Weber RP, Concannon P, Hazelett DJ, Li Q, Marks JR, Berchuck A, Lee JM, Aben KKH, Anton-Culver H, Antonenkova N, Australian Cancer Study (Ovarian Cancer), Australian Ovarian Cancer Study Group, Bandera EV, Bean Y, Beckmann MW, Bisogna M, Bjorge L, Bogdanova N, Brinton LA, Brooks-Wilson A, Bruinsma F, Butzow R, Campbell IG, Carty K, Chang-Claude J, Chenevix-Trench G, Chen A, Chen Z, Cook LS, Cramer DW, Cunningham JM, Cybulski C, Plisiecka-Halasa J, Dennis J, Dicks E, Doherty JA, Dörk T, Du Bois A, Eccles D, Easton DT, Edwards RP, Eilber U, Ekici AB, Fasching PA, Fridley BL, Gao Y-T, Gentry-Maharaj A, Giles GG, Glasspool R, Goode EL, Goodman MT, Gronwald J, Harter P, Hasmad HN, Hein A, Heitz F, Hildebrandt MAT, Hillemanns P, Hogdall E, Hogdall C, Hosono S, Jakubowska A, Paul J, Jensen A, Karlan BY, Kjaer SK, Kelemen LE, Kellar M, Kelley JL, Kiemeney LA, Krakstad C, Lambrechts D, Lambrechts S, Le ND, Lee AW, Cannioto R, Leminen A, Lester J, Levine DA, Liang D, Lissowska J, Lu K, Lubinski J, Lundvall L, Massuger LFAG, Matsuo K, McGuire V, McLaughlin JR, Nevanlinna H, McNeish I, Menon U, Modugno F, Moysich KB, Narod SA, Nedergaard L, Ness RB, Noor Azmi MA, Odunsi K, Olson SH, Orlow I, Orsulic S, Pearce CL, Pejovic T, Pelttari LM, Permuth-Wey J, Phelan CM, Pike MC, Poole EM, Ramus SJ, Risch HA, Rosen

B, Rossing MA, Rothstein JH, Rudolph A, Runnebaum IB, Rzepecka IK, Salvesen HB, Budzilowska A, Sellers TA, Shu X-O, Shvetsov YB, Siddiqui N, Sieh W, Song H, Southey MC, Sucheston L, Tangen IL, Teo S-H, Terry KL, Thompson PJ, Timorek A, Tworoger SS, Nieuwenhuysen EV, Vergote I, Vierkant RA, Wang-Gohrke S, Walsh C, Wentzensen N, Whittemore AS, Wicklund KG, Wilkens LR, Woo Y-L, Wu X, Wu AH, Yang H, Zheng W, Ziogas A, Coetzee GA, Freedman ML, Monteiro ANA, Moes-Sosnowska J, Kupryjanczyk J, Pharoah PD, Gayther SA, Schildkraut JM. Common variants at the CHEK2 gene locus and risk of epithelial ovarian cancer. CARCIN 2015;36:1341–53. https://doi.org/10.1093/carcin/bgv138.

12. Arcieri M, Tius V, Andreetta C, Restaino S, Biasioli A, Poletto E, Damante G, Ercoli A, Driul L, Fagotti A, Lorusso D, Scambia G, Vizzielli G. How BRCA and homologous recombination deficiency change therapeutic strategies in ovarian cancer: a review of literature. Front Oncol 2024;14:1335196. https://doi.org/10.3389/fonc.2024.1335196.
13. Kowalik A, Chudecka-Głaz A, Kufel-Grabowska J, Skoneczna I, Kubiatowski T. Diagnostics and treatment of BRCA-associated cancers with olaparib — expert position statement. Oncol Clin Pract 2024;20:229–44. https://doi.org/10.5603/ocp.99216.
14. Baradács I, Teutsch B, Váradi A, Bilá A, Vincze Á, Hegyi P, Fazekas T, Komoróczy B, Nyirády P, Ács N, Bánhidy F, Lintner B. PARP inhibitor era in ovarian cancer treatment: a systematic review and meta-analysis of randomized controlled trials. J Ovarian Res 2024;17:53. https://doi.org/10.1186/s13048-024-01362-y.
15. Giannini A, Di Dio C, Di Donato V, D'oria O, Salerno MG, Capalbo G, Cuccu I, Perniola G, Muzii L, Bogani G. PARP Inhibitors in Newly Diagnosed and Recurrent Ovarian Cancer. American Journal of Clinical Oncology 2023;46:414–9. https://doi.org/10.1097/COC.0000000000001024.
16. Lliberos C, Richardson G, Papa A. Oncogenic Pathways and Targeted Therapies in Ovarian Cancer. Biomolecules 2024;14:585. https://doi.org/10.3390/biom14050585.
17. Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A. Interval debulking surgery for advanced epithelial ovarian cancer. Cochrane Database of Systematic Reviews 2016;2016. https://doi.org/10.1002/14651858.CD006014.pub7.
18. Mangogna A, Munari G, Pepe F, Maffii E, Giampaolino P, Ricci G, Fassan M, Malapelle U, Biffi S. Homologous Recombination Deficiency in Ovarian Cancer: from the Biological Rationale to Current Diagnostic Approaches. JPM 2023;13:284. https://doi.org/10.3390/jpm13020284.
19. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews®, Seattle (WA): University of Washington, Seattle; 1993.
20. Daly MB, Pal T, Maxwell KN, Churpek J, Kohlmann W, AlHilli Z, Arun B, Buys SS, Cheng H, Domchek SM, Friedman S, Giri V, Goggins M, Hagemann A, Hendrix A, Hutton ML, Karlan BY, Kassem N, Khan S, Khoury K, Kurian AW, Laronga C, Mak JS, Mansour J, McDonnell K, Menendez CS, Merajver SD, Norquist BS, Offit K, Rash D, Reiser G, Senter-Jamieson L, Shannon KM, Visvanathan K, Welborn J, Wick MJ, Wood M, Yurgelun MB, Dwyer MA, Darlow SD. NCCN Guidelines® Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2024: Featured Updates to the NCCN Guidelines. Journal of the National Comprehensive Cancer Network 2023;21:1000–10. https://doi.org/10.6004/jnccn.2023.0051.
21. Manchana T, Phoolcharoen N, Tantbirojn P. BRCA mutation in high grade epithelial ovarian cancers. Gynecologic Oncology Reports 2019;29:102–5. https://doi.org/10.1016/j.gore.2019.07.007.
22. Moschetta M, George A, Kaye SB, Banerjee S. BRCA somatic mutations and epigenetic BRCA modifications in serous ovarian cancer. Annals of Oncology 2016;27:1449–55. https://doi.org/10.1093/annonc/mdw142.
23. Banerjee S, Moore KN, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, Lisyanskaya A, Floquet A, Leary A, Sonke GS, Gourley C, Oza A, González-Martín A, Aghajanian C, Bradley WH, Holmes E, Lowe ES, DiSilvestro P. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology 2021;22:1721–31. https://doi.org/10.1016/S1470-2045(21)00531-3.
24. Poveda A, Floquet A, Ledermann JA, Asher R, Penson RT, Oza AM, Korach J, Huzarski T, Pignata S, Friedlander M, Baldoni A, Park-Simon T-W, Tamura K, Sonke GS, Lisyanskaya A, Kim J-H, Filho EA, Milenkova T, Lowe ES, Rowe P, Vergote I, Pujade-Lauraine E, Korach J, Huzarski T, Byrski T, Pautier P, Friedlander M, Harter P, Colombo N, Pignata S, Scambia G, Nicoletto M, Nussey F, Clamp A, Penson R, Oza A, Poveda Velasco A, Rodrigues M, Lotz J-P, Selle F, Ray-Coquard I, Provencher D, Prat Aparicio A, Vidal Boixader L, Scott C, Tamura K, Yunokawa M, Lisyanskaya A, Medioni J, Pécuchet N, Dubot C, De La Motte Rouge T, Kaminsky M-C, Weber B, Lortholary A, Parkinson C, Ledermann J, Williams S, Banerjee S, Cosin J, Hoffman J, Penson R, Plante M, Covens A, Sonke G, Joly F, Floquet A, Banerjee S, Hirte H, Amit A, Park-Simon T-W, Matsumoto K, Tjulandin S, Hoon Kim J, Gladieff L, Sabbatini R, O'Malley D, Timmins P, Kredentser D, Laínez Milagro N, Barretina Ginesta MP, Tibau Martorell A, Gómez De Liaño Lista A, Ojeda González B, Mileshkin L, Mandai M, Boere I, Ottevanger P, Nam J-H, Filho E, Hamizi S, Cognetti F, Warshal D, Dickson-Michelson E, Kamelle S, McKenzie N, Rodriguez G, Armstrong D, Chalas E, Celano P, Behbakht K, Davidson S, Welch S, Helpman L, Fishman A, Bruchim I, Sikorska M, Słowińska A, Rogowski W, Bidziński M, Śpiewankiewicz B, Casado Herraez A, Mendiola Fernández C, Gropp-Meier M, Saito T, Takehara K, Enomoto T, Watari H, Choi CH, Kim B-G, Weon Kim J, Hegg R, Vergote I. Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovar-

ian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Oncology 2021;22:620–31. https://doi.org/10.1016/S1470-2045(21)00073-5.
25. González-Martín A, Pothuri B, Vergote I, Graybill W, Lorusso D, McCormick CC, Freyer G, Backes F, Heitz F, Redondo A, Moore RG, Vulsteke C, O'Cearbhaill RE, Malinowska IA, Shtessel L, Compton N, Mirza MR, Monk BJ. Progression-free survival and safety at 3.5 years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer. European Journal of Cancer 2023;189:112908. https://doi.org/10.1016/j.ejca.2023.04.024.
26. Milano L, Alenezi WM, Fierheller CT, Serruya C, Revil T, Oros KK, Bruce J, Spiegelman D, Pugh T, Masson A-MM-, Provencher D, Foulkes WD, Haffaf ZE, Rouleau G, Bouchard L, Greenwood CMT, Ragoussis J, Tonin PN, Masson J-Y. Genetic and molecular analyses of candidate germline BRIP1/FANCJ variants implicated in breast and ovarian cancer 2023. https://doi.org/10.1101/2023.07.03.23290133.
27. Morgan RD, Burghel GJ, Flaum N, Schlecht H, Clamp AR, Hasan J, Mitchell C, Salih Z, Moon S, Hogg M, Lord R, Forde C, Lalloo F, Woodward ER, Crosbie EJ, Taylor SS, Jayson GC, Evans DGR. Extended panel testing in ovarian cancer reveals BRIP1 as the third most important predisposition gene. Genetics in Medicine 2024;26:101230. https://doi.org/10.1016/j.gim.2024.101230.
28. Daly MB, Pal T, Maxwell KN, Churpek J, Kohlmann W, AlHilli Z, Arun B, Buys SS, Cheng H, Domchek SM, Friedman S, Giri V, Goggins M, Hagemann A, Hendrix A, Hutton ML, Karlan BY, Kassem N, Khan S, Khoury K, Kurian AW, Laronga C, Mak JS, Mansour J, McDonnell K, Menendez CS, Merajver SD, Norquist BS, Offit K, Rash D, Reiser G, Senter-Jamieson L, Shannon KM, Visvanathan K, Welborn J, Wick MJ, Wood M, Yurgelun MB, Dwyer MA, Darlow SD. NCCN Guidelines® Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2024: Featured Updates to the NCCN Guidelines. Journal of the National Comprehensive Cancer Network 2023;21:1000–10. https://doi.org/10.6004/jnccn.2023.0051.
29. Wu S, Zhou J, Zhang K, Chen H, Luo M, Lu Y, Sun Y, Chen Y. Molecular Mechanisms of PALB2 Function and Its Role in Breast Cancer Management. Front Oncol 2020;10:301. https://doi.org/10.3389/fonc.2020.00301.
30. Yang X, Leslie G, Doroszuk A, Schneider S, Allen J, Decker B, Dunning AM, Redman J, Scarth J, Plaskocinska I, Luccarini C, Shah M, Pooley K, Dorling L, Lee A, Adank MA, Adlard J, Aittomäki K, Andrulis IL, Ang P, Barwell J, Bernstein JL, Bobolis K, Borg Å, Blomqvist C, Claes KBM, Concannon P, Cuggia A, Culver JO, Damiola F, De Pauw A, Diez O, Dolinsky JS, Domchek SM, Engel C, Evans DG, Fostira F, Garber J, Golmard L, Goode EL, Gruber SB, Hahnen E, Hake C, Heikkinen T, Hurley JE, Janavicius R, Kleibl Z, Kleiblova P, Konstantopoulou I, Kvist A, Laduca H, Lee ASG, Lesueur F, Maher ER, Mannermaa A, Manoukian S, McFarland R, McKinnon W, Meindl A, Metcalfe K, Mohd Taib NA, Moilanen J, Nathanson KL, Neuhausen S, Ng PS, Nguyen-Dumont T, Nielsen SM, Obermair F, Offit K, Olopade OI, Ottini L, Penkert J, Pylkäs K, Radice P, Ramus SJ, Rudaitis V, Side L, Silva-Smith R, Silvestri V, Skytte A-B, Slavin T, Soukupova J, Tondini C, Trainer AH, Unzeitig G, Usha L, Van Overeem Hansen T, Whitworth J, Wood M, Yip CH, Yoon S-Y, Yussuf A, Zogopoulos G, Goldgar D, Hopper JL, Chenevix-Trench G, Pharoah P, George SHL, Balmaña J, Houdayer C, James P, El-Haffaf Z, Ehrencrona H, Janatova M, Peterlongo P, Nevanlinna H, Schmutzler R, Teo S-H, Robson M, Pal T, Couch F, Weitzel JN, Elliott A, Southey M, Winqvist R, Easton DF, Foulkes WD, Antoniou AC, Tischkowitz M. Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families. JCO 2020;38:674–85. https://doi.org/10.1200/JCO.19.01907.
31. Tischkowitz M, Balmaña J, Foulkes WD, James P, Ngeow J, Schmutzler R, Voian N, Wick MJ, Stewart DR, Pal T. Management of individuals with germline variants in PALB2: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine 2021;23:1416–23. https://doi.org/10.1038/s41436-021-01151-8.
32. Long G, Hu K, Zhang X, Zhou L, Li J. Spectrum of BRCA1 interacting helicase 1 aberrations and potential prognostic and therapeutic implication: a pan cancer analysis. Sci Rep 2023;13:4435. https://doi.org/10.1038/s41598-023-31109-6.
33. Mu W, Lu H-M, Chen J, Li S, Elliott AM. Sanger Confirmation Is Required to Achieve Optimal Sensitivity and Specificity in Next-Generation Sequencing Panel Testing. The Journal of Molecular Diagnostics 2016;18:923–32. https://doi.org/10.1016/j.jmoldx.2016.07.006.
34. Ozcelik H, Shi X, Chang MC, Tram E, Vlasschaert M, Di Nicola N, Kiselova A, Yee D, Goldman A, Dowar M, Sukhu B, Kandel R, Siminovitch K. Long-Range PCR and Next-Generation Sequencing of BRCA1 and BRCA2 in Breast Cancer. The Journal of Molecular Diagnostics 2012;14:467–75. https://doi.org/10.1016/j.jmoldx.2012.03.006.
35. Liu K, Hu L, Wang S, Chen X, Liu Y, Zhao S, Wang H, Li L, Li H. An efficient qPCR assay for the quantification of human cells in preclinical animal models by targeting human specific DNA in the intron of BRCA1. Mol Biol Rep 2023;50:9229–37. https://doi.org/10.1007/s11033-023-08853-z.
36. Lucky MH, Baig S, Hanif M, H Asghar A. Systematic Review: Comprehensive Methods for Detecting BRCA1 and BRCA2 Mutations in Breast and Ovarian Cancer. Asian Pac J Cancer Biol 2025;10:229–38. https://doi.org/10.31557/apjcb.2025.10.1.229-238.
37. Ahmadloo S, Nakaoka H, Hayano T, Hosomichi K, You H, Utsuno E, Sangai T, Nishimura M, Matsushita K, Hata A, Nomura F, Inoue I. Rapid and cost-effective high-throughput sequencing for identification of germline mutations of BRCA1 and BRCA2. J

Hum Genet 2017;62:561–7. https://doi.org/10.1038/jhg.2017.5.
38. Wallace AJ. New challenges for BRCA testing: a view from the diagnostic laboratory. Eur J Hum Genet 2016;24:S10–8. https://doi.org/10.1038/ejhg.2016.94.
39. Vogel A, Haupts A, Kloth M, Roth W, Hartmann N. A novel targeted NGS panel identifies numerous homologous recombination deficiency (HRD)-associated gene mutations in addition to known BRCA mutations. Diagn Pathol 2024;19:9. https://doi.org/10.1186/s13000-023-01431-8.
40. Witz A, Dardare J, Betz M, Michel C, Husson M, Gilson P, Merlin J-L, Harlé A. Homologous recombination deficiency (HRD) testing landscape: clinical applications and technical validation for routine diagnostics. Biomark Res 2025;13:31. https://doi.org/10.1186/s40364-025-00740-y.
41. Riahi A, Chabouni-Bouhamed H, Kharrat M. Prevalence of BRCA1 and BRCA2 large genomic rearrangements in Tunisian high risk breast/ovarian cancer families: Implications for genetic testing. Cancer Genetics 2017;210:22–7. https://doi.org/10.1016/j.cancergen.2016.11.002.
42. Fostira F, Papadimitriou M, Papadimitriou C. Current practices on genetic testing in ovarian cancer. Ann Transl Med 2020;8:1703–1703. https://doi.org/10.21037/atm-20-1422.
43. Ray-Coquard I, Leary A, Pignata S, Cropet C, González-Martín A, Marth C, Nagao S, Vergote I, Colombo N, Mäenpää J, Selle F, Sehouli J, Lorusso D, Guerra Alia EM, Bogner G, Yoshida H, Lefeuvre-Plesse C, Buderath P, Mosconi AM, Lortholary A, Burges A, Medioni J, El-Balat A, Rodrigues M, Park-Simon T-W, Dubot C, Denschlag D, You B, Pujade-Lauraine E, Harter P. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. Annals of Oncology 2023;34:681–92. https://doi.org/10.1016/j.annonc.2023.05.005.
44. Miller RE, Leary A, Scott CL, Serra V, Lord CJ, Bowtell D, Chang DK, Garsed DW, Jonkers J, Ledermann JA, Nik-Zainal S, Ray-Coquard I, Shah SP, Matias-Guiu X, Swisher EM, Yates LR. ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. Annals of Oncology 2020;31:1606–22. https://doi.org/10.1016/j.annonc.2020.08.2102.
45. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, Okamoto A, Moore KN, Efrat Ben-Baruch N, Werner TL, Cloven NG, Oaknin A, DiSilvestro PA, Morgan MA, Nam J-H, Leath CA, Nicum S, Hagemann AR, Littell RD, Cella D, Baron-Hay S, Garcia-Donas J, Mizuno M, Bell-McGuinn K, Sullivan DM, Bach BA, Bhattacharya S, Ratajczak CK, Ansell PJ, Dinh MH, Aghajanian C, Bookman MA. Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. N Engl J Med 2019;381:2403–15. https://doi.org/10.1056/NEJMoa1909707.
46. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, McCormick C, Lorusso D, Hoskins P, Freyer G, Baumann K, Jardon K, Redondo A, Moore RG, Vulsteke C, O'Cearbhaill RE, Lund B, Backes F, Barretina-Ginesta P, Haggerty AF, Rubio-Pérez MJ, Shahin MS, Mangili G, Bradley WH, Bruchim I, Sun K, Malinowska IA, Li Y, Gupta D, Monk BJ. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med 2019;381:2391–402. https://doi.org/10.1056/NEJMoa1910962.
47. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, Fujiwara K, Vergote I, Colombo N, Mäenpää J, Selle F, Sehouli J, Lorusso D, Guerra Alía EM, Reinthaller A, Nagao S, Lefeuvre-Plesse C, Canzler U, Scambia G, Lortholary A, Marmé F, Combe P, De Gregorio N, Rodrigues M, Buderath P, Dubot C, Burges A, You B, Pujade-Lauraine E, Harter P. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med 2019;381:2416–28. https://doi.org/10.1056/NEJMoa1911361.
48. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, Colombo N, Weberpals JI, Clamp A, Scambia G, Leary A, Holloway RW, Gancedo MA, Fong PC, Goh JC, O'Malley DM, Armstrong DK, Garcia-Donas J, Swisher EM, Floquet A, Konecny GE, McNeish IA, Scott CL, Cameron T, Maloney L, Isaacson J, Goble S, Grace C, Harding TC, Raponi M, Sun J, Lin KK, Giordano H, Ledermann JA, Buck M, Dean A, Friedlander ML, Goh JC, Harnett P, Kichenadasse G, Scott CL, Denys H, Dirix L, Vergote I, Elit L, Ghatage P, Oza AM, Plante M, Provencher D, Weberpals JI, Welch S, Floquet A, Gladieff L, Joly F, Leary A, Lortholary A, Lotz J, Medioni J, Tredan O, You B, El-Balat A, Hänle C, Krabisch P, Neunhöffer T, Pölcher M, Wimberger P, Amit A, Kovel S, Leviov M, Safra T, Shapira-Frommer R, Stemmer S, Bologna A, Colombo N, Lorusso D, Pignata S, Sabbatini RF, Scambia G, Tamberi S, Zamagni C, Fong PC, O'Donnell A, Gancedo MA, Herraez AC, Garcia-Donas J, Guerra EM, Oaknin A, Palacio I, Romero I, Sanchez A, Banerjee SN, Clamp A, Drew Y, Gabra HG, Jackson D, Ledermann JA, McNeish IA, Parkinson C, Powell M, Aghajanian C, Armstrong DK, Birrer MJ, Buss MK, Chambers SK, Chen L, Coleman RL, Holloway RW, Konecny GE, Ma L, Morgan MA, Morris RT, Mutch DG, O'Malley DM, Slomovitz BM, Swisher EM, Vanderkwaak T, Vulfovich M. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet 2017;390:1949–61. https://doi.org/10.1016/S0140-6736(17)32440-6.
49. Li N, Zhu J, Yin R, Wang J, Pan L, Kong B, Zheng H, Liu J, Wu X, Wang L, Huang Y, Wang K, Zou D, Zhao H, Wang C, Lu W, Lin A, Lou G, Li G, Qu P, Yang H, Zhen X, Hang W, Hou J, Wu L. Efficacy and safety of niraparib as maintenance treatment in patients with newly diagnosed advanced ovarian cancer using an individualized starting dose (PRIME Study): A randomized, double-blind, placebo-controlled, phase 3 trial (LBA 5). Gynecologic Oncology 2022;166:S50–1. https://doi.org/10.1016/S0090-8258(22)01298-7.
50. Pellegrino B, Capoluongo ED, Bagnoli M, Arenare L, Califano D, Scambia G, Cecere SC, Silini EM, Scaglione GL, Spina A, Tognon G, Campanini N, Pisano C,

Russo D, Pettinato A, Scollo P, Iemmolo R, De Cecco L, Musolino A, Marchini S, Beltrame L, Paracchini L, Perrone F, Mezzanzanica D, Pignata S. Unraveling the complexity of HRD assessment in ovarian cancer by combining genomic and functional approaches: translational analyses of MITO16-MaNGO-OV-2 trial. ESMO Open 2025;10:104091. https://doi.org/10.1016/j.esmoop.2024.104091.

51. Guffanti F, Mengoli I, Damia G. Current HRD assays in ovarian cancer: differences, pitfalls, limitations, and novel approaches. Front Oncol 2024;14:1405361. https://doi.org/10.3389/fonc.2024.1405361.
52. Daly GR, Naidoo S, Alabdulrahman M, McGrath J, Dowling GP, AlRawashdeh MM, Hill ADK, Varešlija D, Young L. Screening and Testing for Homologous Recombination Repair Deficiency (HRD) in Breast Cancer: an Overview of the Current Global Landscape. Curr Oncol Rep 2024;26:890–903. https://doi.org/10.1007/s11912-024-01560-3.
53. Rognoni C, Lorusso D, Costa F, Armeni P. Cost-Effectiveness Analysis of HRD Testing for Previously Treated Patients with Advanced Ovarian Cancer in Italy. Adv Ther 2024;41:1385–400. https://doi.org/10.1007/s12325-024-02791-3.
54. Ngoi NYL, Tan DSP. The role of homologous recombination deficiency testing in ovarian cancer and its clinical implications: do we need it? ESMO Open 2021;6:100144. https://doi.org/10.1016/j.esmoop.2021.100144.
55. Miller RE, Leary A, Scott CL, Serra V, Lord CJ, Bowtell D, Chang DK, Garsed DW, Jonkers J, Ledermann JA, Nik-Zainal S, Ray-Coquard I, Shah SP, Matias-Guiu X, Swisher EM, Yates LR. ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. Annals of Oncology 2020;31:1606–22. https://doi.org/10.1016/j.annonc.2020.08.2102.
56. Kekeeva T, Andreeva Y, Tanas A, Kalinkin A, Khokhlova S, Tikhomirova T, Tyulyandina A, Popov A, Kuzmenko M, Volkonsky M, Chernorubashkina N, Saevets V, Dmitriev V, Nechushkina V, Vedrova O, Andreev S, Kutsev S, Strelnikov V. HRD Testing of Ovarian Cancer in Routine Practice: What Are We Dealing With? IJMS 2023;24:10497. https://doi.org/10.3390/ijms241310497.
57. Quesada S, Penault-Llorca F, Matias-Guiu X, Banerjee S, Barberis M, Coleman RL, Colombo N, DeFazio A, McNeish IA, Nogueira-Rodrigues A, Oaknin A, Pignata S, Pujade-Lauraine É, Rouleau É, Ryška A, Van Der Merwe N, Van Gorp T, Vergote I, Weichert W, Wu X, Ray-Coquard I, Pujol P. Homologous recombination deficiency in ovarian cancer: Global expert consensus on testing and a comparison of companion diagnostics. European Journal of Cancer 2025;215:115169. https://doi.org/10.1016/j.ejca.2024.115169.
58. Feng J, Lan Y, Liu F, Yuan Y, Ge J, Wei S, Luo H, Li J, Luo T, Bian X. Combination of genomic instability score and TP53 status for prognosis prediction in lung adenocarcinoma. Npj Precis Onc 2023;7:110. https://doi.org/10.1038/s41698-023-00465-x.
59. Zhang X, Sjöblom T. Targeting Loss of Heterozygosity: A Novel Paradigm for Cancer Therapy. Pharmaceuticals 2021;14:57. https://doi.org/10.3390/ph14010057.
60. McMahon JN, Gaffney EF, Aliaga-Kelly WJ, Stephens JF, Jalali A, Curran B. P53 loss of heterozygosity (LOH) in formalin-fixed paraffin-embedded leiomyosarcoma (LMS): a novel report. Ir J Med Sci 2024;193:65–71. https://doi.org/10.1007/s11845-023-03370-1.
61. Stewart MD, Merino Vega D, Arend RC, Baden JF, Barbash O, Beaubier N, Collins G, French T, Ghahramani N, Hinson P, Jelinic P, Marton MJ, McGregor K, Parsons J, Ramamurthy L, Sausen M, Sokol ES, Stenzinger A, Stires H, Timms KM, Turco D, Wang I, Williams JA, Wong-Ho E, Allen J. Homologous Recombination Deficiency: Concepts, Definitions, and Assays. The Oncologist 2022;27:167–74. https://doi.org/10.1093/oncolo/oyab053.
62. Schonhoft JD, Zhao JL, Jendrisak A, Carbone EA, Barnett ES, Hullings MA, Gill A, Sutton R, Lee J, Dago AE, Landers M, Bakhoum SF, Wang Y, Gonen M, Dittamore R, Scher HI. Morphology-Predicted Large-Scale Transition Number in Circulating Tumor Cells Identifies a Chromosomal Instability Biomarker Associated with Poor Outcome in Castration-Resistant Prostate Cancer. Cancer Research 2020;80:4892–903. https://doi.org/10.1158/0008-5472.CAN-20-1216.
63. Birkbak NJ, Wang ZC, Kim J-Y, Eklund AC, Li Q, Tian R, Bowman-Colin C, Li Y, Greene-Colozzi A, Iglehart JD, Tung N, Ryan PD, Garber JE, Silver DP, Szallasi Z, Richardson AL. Telomeric Allelic Imbalance Indicates Defective DNA Repair and Sensitivity to DNA-Damaging Agents. Cancer Discovery 2012;2:366–75. https://doi.org/10.1158/2159-8290.CD-11-0206.
64. Llop-Guevara A, Loibl S, Villacampa G, Vladimirova V, Schneeweiss A, Karn T, Zahm D-M, Herencia-Ropero A, Jank P, Van Mackelenbergh M, Fasching PA, Marmé F, Stickeler E, Schem C, Dienstmann R, Florian S, Nekljudova V, Balmaña J, Hahnen E, Denkert C, Serra V. Association of RAD51 with homologous recombination deficiency (HRD) and clinical outcomes in untreated triple-negative breast cancer (TNBC): analysis of the GeparSixto randomized clinical trial. Annals of Oncology 2021;32:1590–6. https://doi.org/10.1016/j.annonc.2021.09.003.
65. Gómez-Flores-Ramos L, Álvarez-Gómez RM, Villarreal-Garza C, Wegman-Ostrosky T, Mohar A. Breast cancer genetics in young women: What do we know? Mutation Research/Reviews in Mutation Research 2017;774:33–45. https://doi.org/10.1016/j.mrrev.2017.08.001.
66. Casartelli C, Tommasi C, Lazzarin A, Corianò M, Tornali C, Serra O, Campanini N, Gutiérrez-Enríquez S, Sikokis A, Zanoni D, Minari R, Bortesi B, Michiara M, Boggiani D, Uliana V, Llop-Guevara A, Serra V, Musolino A, Pellegrino B. Functional HRD by RAD51 identifies BRCA1 VUS associated with loss of gene function and response to DNA-damaging agents. ESMO Open 2024;9:103629. https://doi.org/10.1016/j.esmoop.2024.103629.
67. Quesada S, Penault-Llorca F, Matias-Guiu X, Banerjee S, Barberis M, Coleman RL, Colombo N, DeFazio A, McNeish IA, Nogueira-Rodrigues A, Oaknin A, Pig-

nata S, Pujade-Lauraine É, Rouleau É, Ryška A, Van Der Merwe N, Van Gorp T, Vergote I, Weichert W, Wu X, Ray-Coquard I, Pujol P. Homologous recombination deficiency in ovarian cancer: Global expert consensus on testing and a comparison of companion diagnostics. European Journal of Cancer 2025;215:115169. https://doi.org/10.1016/j.ejca.2024.115169.

68. Milbury CA, Creeden J, Yip W-K, Smith DL, Pattani V, Maxwell K, Sawchyn B, Gjoerup O, Meng W, Skoletsky J, Concepcion AD, Tang Y, Bai X, Dewal N, Ma P, Bailey ST, Thornton J, Pavlick DC, Frampton GM, Lieber D, White J, Burns C, Vietz C. Clinical and analytical validation of FoundationOne®CDx, a comprehensive genomic profiling assay for solid tumors. PLoS ONE 2022;17:e0264138. https://doi.org/10.1371/journal.pone.0264138.
69. Trautmann M, Falkenberg K, Braun L, Puller A-C, Kirmse S, Heinst L, Berthold R, Isfort I, Abbas M, Wardelmann E, Hartmann W. 1253P Analytic validation and implementation of OncoDEEP: A pan-cancer comprehensive genomic profiling NGS assay for assessing homologous recombination deficiency (HRD). Annals of Oncology 2023;34:S728. https://doi.org/10.1016/j.annonc.2023.09.2342.
70. Boidot R, Blum MGB, Wissler M-P, Gottin C, Ruzicka J, Chevrier S, Delhomme TM, Audoux J, Jeanniard A, Just P-A, Harter P, Pignata S, González-Martin A, Marth C, Mäenpää J, Colombo N, Vergote I, Fujiwara K, Duforet-Frebourg N, Bertrand D, Philippe N, Ray-Coquard I, Pujade-Lauraine E. Clinical evaluation of a low-coverage whole-genome test for detecting homologous recombination deficiency in ovarian cancer. European Journal of Cancer 2024;202:113978. https://doi.org/10.1016/j.ejca.2024.113978.
71. Pozzorini C, Andre G, Coletta T, Buisson A, Bieler J, Ferrer L, Kempfer R, Saintigny P, Harlé A, Vacirca D, Barberis M, Gilson P, Roma C, Saitta A, Smith E, Consales Barras F, Ripol L, Fritzsche M, Marques AC, Alkodsi A, Marin R, Normanno N, Grimm C, Müllauer L, Harter P, Pignata S, Gonzalez-Martin A, Denison U, Fujiwara K, Vergote I, Colombo N, Willig A, Pujade-Lauraine E, Just P-A, Ray-Coquard I, Xu Z. GIInger predicts homologous recombination deficiency and patient response to PARPi treatment from shallow genomic profiles. Cell Reports Medicine 2023;4:101344. https://doi.org/10.1016/j.xcrm.2023.101344.
72. Fumagalli C, Betella I, Ranghiero A, Guerini-Rocco E, Bonaldo G, Rappa A, Vacirca D, Colombo N, Barberis M. In-house testing for homologous recombination repair deficiency (HRD) testing in ovarian carcinoma: a feasibility study comparing AmoyDx HRD Focus panel with Myriad myChoiceCDx assay. Pathologica 2022;114:288–94. https://doi.org/10.32074/1591-951X-791.
73. AmoyDx® HRD Complete Panel - [AmoyDx]. https://www.amoydiagnostics.com/products/amoydx-hrd-complete-panel (accessed April 3, 2025).
74. The Cancer Genome Atlas Research Network, Levine DA. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497:67–73. https://doi.org/10.1038/nature12113.
75. Espinosa I, D'Angelo E, Prat J. Endometrial carcinoma: 10 years of TCGA (the cancer genome atlas): A critical reappraisal with comments on FIGO 2023 staging. Gynecologic Oncology 2024;186:94–103. https://doi.org/10.1016/j.ygyno.2024.04.008.
76. Kommoss S, Heitz F, Winterhoff BJN, Wang C, Sehouli J, Aliferis C, Kimmig R, Wang J, Ma S, De Gregorio N, Mahner S, Du Bois A, Tourani R, Park-Simon T-W, Baumann K, Taran FA, Kommoss F, Schroeder W, Dowdy SC, Pfisterer J. Significant overall survival improvement in proliferative subtype ovarian cancer patients receiving bevacizumab. JCO 2018;36:5520–5520. https://doi.org/10.1200/JCO.2018.36.15_suppl.5520.
77. Winterhoff BJN, Kommoss S, Oberg AL, Wang C, Riska SM, Konecny GE, Fan J-B, Shridhar V, Goode EL, Kommoss F, Du Bois A, Hilpert F, Chien J, Embleton AC, Parmar M, Kaplan RS, Perren T, Hartmann LC, Pfisterer J, Dowdy SC. Bevacizumab and improvement of progression-free survival (PFS) for patients with the mesenchymal molecular subtype of ovarian cancer. JCO 2014;32:5509–5509. https://doi.org/10.1200/jco.2014.32.15_suppl.5509.
78. Kommoss S, Winterhoff B, Oberg AL, Konecny GE, Wang C, Riska SM, Fan J-B, Maurer MJ, April C, Shridhar V, Kommoss F, Du Bois A, Hilpert F, Mahner S, Baumann K, Schroeder W, Burges A, Canzler U, Chien J, Embleton AC, Parmar M, Kaplan R, Perren T, Hartmann LC, Goode EL, Dowdy SC, Pfisterer J. Bevacizumab May Differentially Improve Ovarian Cancer Outcome in Patients with Proliferative and Mesenchymal Molecular Subtypes. Clinical Cancer Research 2017;23:3794–801. https://doi.org/10.1158/1078-0432.CCR-16-2196.
79. Murakami R, Matsumura N, Michimae H, Tanabe H, Yunokawa M, Iwase H, Sasagawa M, Nakamura T, Tokuyama O, Takano M, Sugiyama T, Sawasaki T, Isonishi S, Takehara K, Nakai H, Okamoto A, Mandai M, Konishi I. The mesenchymal transition subtype more responsive to dose dense taxane chemotherapy combined with carboplatin than to conventional taxane and carboplatin chemotherapy in high grade serous ovarian carcinoma: A survey of Japanese Gynecologic Oncology Group study (JGOG3016A1). Gynecologic Oncology 2019;153:312–9. https://doi.org/10.1016/j.ygyno.2019.02.010.
80. Murakami R, Matsumura N, Mandai M, Yoshihara K, Tanabe H, Nakai H, Yamanoi K, Abiko K, Yoshioka Y, Hamanishi J, Yamaguchi K, Baba T, Koshiyama M, Enomoto T, Okamoto A, Murphy SK, Mori S, Mikami Y, Minamiguchi S, Konishi I. Establishment of a Novel Histopathological Classification of High-Grade Serous Ovarian Carcinoma Correlated with Prognostically Distinct Gene Expression Subtypes. The American Journal of Pathology 2016;186:1103–13. https://doi.org/10.1016/j.ajpath.2015.12.029.
81. Reese SE, Archer KJ, Therneau TM, Atkinson EJ, Vachon CM, De Andrade M, Kocher J-PA, Eckel-Passow JE. A new statistic for identifying batch effects in high-throughput genomic data that uses guided principal component analysis. Bioinformatics

2013;29:2877–83. https://doi.org/10.1093/bioinformatics/btt480.
82. Zhang S, Jing Y, Zhang M, Zhang Z, Ma P, Peng H, Shi K, Gao W-Q, Zhuang G. Stroma-associated master regulators of molecular subtypes predict patient prognosis in ovarian cancer. Sci Rep 2015;5:16066. https://doi.org/10.1038/srep16066.
83. Jiang F, Jiang Y, Zhi H, Dong Y, Li H, Ma S, Wang Y, Dong Q, Shen H, Wang Y. Artificial intelligence in healthcare: past, present and future. Stroke Vasc Neurol 2017;2:230–43. https://doi.org/10.1136/svn-2017-000101.
84. Esteva A, Robicquet A, Ramsundar B, Kuleshov V, DePristo M, Chou K, Cui C, Corrado G, Thrun S, Dean J. A guide to deep learning in healthcare. Nat Med 2019;25:24–9. https://doi.org/10.1038/s41591-018-0316-z.
85. Hatamikia S, Nougaret S, Panico C, Avesani G, Nero C, Boldrini L, Sala E, Woitek R. Ovarian cancer beyond imaging: integration of AI and multiomics biomarkers. Eur Radiol Exp 2023;7:50. https://doi.org/10.1186/s41747-023-00364-7.
86. Orr BC, Uihlein AH, Montgomery R, Radolec M, Edwards RP. Using artificial intelligence-powered evidence-based molecular decision-making for improved outcomes in ovarian cancer. JCO 2024;42:5555–5555. https://doi.org/10.1200/JCO.2024.42.16_suppl.5555.
87. Bergstrom EN, Abbasi A, Díaz-Gay M, Galland L, Ladoire S, Lippman SM, Alexandrov LB. Deep Learning Artificial Intelligence Predicts Homologous Recombination Deficiency and Platinum Response From Histologic Slides. JCO 2024;42:3550–60. https://doi.org/10.1200/JCO.23.02641.
88. Frenel J-S, Bossard C, Rynkiewicz J, Thomas F, Salhi Y, Salhi S, Chetritt J. Artificial intelligence to predict homologous recombination deficiency in ovarian cancer from whole-slide histopathological images. JCO 2024;42:5578–5578. https://doi.org/10.1200/JCO.2024.42.16_suppl.5578.
89. Loeffler CML, El Nahhas OSM, Muti HS, Carrero ZI, Seibel T, Van Treeck M, Cifci D, Gustav M, Bretz K, Gaisa NT, Lehmann K-V, Leary A, Selenica P, Reis-Filho JS, Ortiz-Bruechle N, Kather JN. Prediction of homologous recombination deficiency from routine histology with attention-based multiple instance learning in nine different tumor types. BMC Biol 2024;22:225. https://doi.org/10.1186/s12915-024-02022-9.
90. Zhang K, Qiu Y, Feng S, Yin H, Liu Q, Zhu Y, Cui H, Wei X, Wang G, Wang X, Shen Y. Development of model for identifying homologous recombination deficiency (HRD) status of ovarian cancer with deep learning on whole slide images. J Transl Med 2025;23:267. https://doi.org/10.1186/s12967-025-06234-7.
91. Ueda A, Nakai H, Miyagawa C, Otani T, Yoshida M, Murakami R, Komiyama S, Tanigawa T, Yokoi T, Takano H, Baba T, Miura K, Shimada M, Kigawa J, Enomoto T, Hamanishi J, Okamoto A, Okuno Y, Mandai M, Matsumura N. Artificial Intelligence-Based Histopathological Subtyping of High-Grade Serous Ovarian Cancer. The American Journal of Pathology 2024;194:1913–23. https://doi.org/10.1016/j.ajpath.2024.06.010.
92. Geng T, Zheng M, Wang Y, Reseland JE, Samara A. An artificial intelligence prediction model based on extracellular matrix proteins for the prognostic prediction and immunotherapeutic evaluation of ovarian serous adenocarcinoma. Front Mol Biosci 2023;10:1200354. https://doi.org/10.3389/fmolb.2023.1200354.
93. Sharma O, Gudoityte G, Minozada R, Kallioniemi OP, Turkki R, Paavolainen L, Seashore-Ludlow B. Evaluating feature extraction in ovarian cancer cell line co-cultures using deep neural networks. Commun Biol 2025;8:303. https://doi.org/10.1038/s42003-025-07766-w.