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ORIGINAL RESEARCH

Cost-Effectiveness Analysis of HRD Testing for Previously Treated Patients with Advanced Ovarian Cancer in Italy

Carla Rognoni · Domenica Lorusso · Francesco Costa · Patrizio Armeni

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ABSTRACT

Introduction: Ovarian cancer (OC) is the eighth most common cancer among women, and homologous recombination deficiency (HRD) is present in approximately 50% of these patients. For this group, poly(ADP-ribose) polymerase (PARP) inhibitors are more likely to be effective. The aim of the study was to investigate the cost-effectiveness of HRD testing versus *BRCA* testing (which identifies mutations present only in 25% of patients) in Italy to optimize the treatment management, possibly with PARP inhibitors.

Methods: A cost-effectiveness partition survival model was developed to estimate the expected costs and outcomes (life years, LYs; quality-adjusted life years, QALYs) with lifetime horizon of HRD testing versus *BRCA* testing alone in women with high-grade serous or endometrioid advanced ovarian cancer. The option to perform the tests in sequence, that is, the *BRCA* test followed by the HRD test, in patients with *BRCA*-negative test was also considered, and the model accounted for the National Healthcare Service (NHS) perspective in Italy. The treatments represented the best available options according to the initial test results and according to PARP inhibitors available in Italy. A 3% discount rate was applied. Both deterministic and probabilistic sensitivity analyses were performed to test the robustness of the model results.

Results: HRD testing was shown to be a cost-effective strategy compared to *BRCA* testing (incremental cost-utility ratio 22,610€/QALY) and a cost-saving strategy compared to the sequence of tests. The probabilistic sensitivity analysis showed that the HRD test is cost-effective compared to *BRCA* testing in 98.5% of model simulations considering a willingness-to-pay threshold of 50,000€/QALY.

Conclusion: The identification of genetic anomalies in patients with advanced OC is a costly process. Regardless, HRD upfront testing compared to *BRCA* testing had a cost-effective profile, allowing the efficient use of healthcare resources and better life expectancy and quality of life for patients.

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C. Rognoni (✉) · F. Costa · P. Armeni
Centre for Research on Health and Social Care Management (CERGAS), SDA Bocconi School of Management, Bocconi University, Via Sarfatti 10, 20136 Milan, Italy
e-mail: carla.rognoni@unibocconi.it

D. Lorusso
Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Catholic University of Sacred Heart, Rome, Italy

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PLAIN LANGUAGE SUMMARY

Ovarian cancer has been the most lethal gynecological tumor for years. Recently, there have been notable advances due to the introduction of poly(adenosine diphosphate-ribose polymerase) (PARP) inhibitor drugs, which have significantly increased the survival rates of women affected by advanced-stage disease. At least 50% of ovarian tumors have a defect in the DNA repair mechanism, known as homologous recombination deficiency, and the mechanism of action of these drugs involves blocking the DNA repair mechanisms implemented by neoplastic cells. The identification of patients with homologous recombination deficiency through a genetic test, with consequent optimized treatment management, possibly with PARP inhibitors, resulted in better life expectancy, even when adjusted for the quality of life, than the management of patients starting from *BRCA* testing alone. The homologous recombination deficiency testing strategy can be considered cost-effective from the National Healthcare Service perspective in Italy. These findings provide evidence of the value of a new diagnostic option for clinicians and payers to optimize the management of women with high-grade serous or endometrioid advanced ovarian cancer.

Keywords: Ovarian cancer; HRD test; *BRCA* test; PARP inhibitors

Key Summary Points

Ovarian cancer (OC) is the eighth most common cancer among women. A homologous recombination deficiency (HRD) is present in approximately half of them. For this group of patients, poly(ADP-ribose) polymerase (PARP) inhibitors are more likely to be effective.

The identification of patients with HRD through a genetic test, with consequent optimized treatment management, possibly with PARP inhibitors, is a cost-effective strategy compared to *BRCA* testing (germline or tissue) alone, showing an incremental cost-utility ratio of 22,610€/quality-adjusted life years (QALY) from the National Healthcare Service perspective in Italy.

These findings provide evidence for clinicians and payers on the value of a new diagnostic option to optimize the management of women with high-grade serous or endometrioid advanced ovarian cancer.

INTRODUCTION

Ovarian cancer (OC) ranks as the eighth most prevalent tumor in women, with 295,414 new cases and 184,799 deaths per year reported globally [1]. Roughly 90% of cases are epithelial ovarian cancers, predominantly manifesting in women in postmenopausal period. As early-stage disease often lacks symptoms and late-stage symptoms are non-specific, over 75% of affected women are typically diagnosed at an advanced stage [2]. Moreover, even today, screening procedures for early detection of epithelial ovarian cancer are not well established [3].

The most critical risk factor for ovarian cancer is a family history of breast or ovarian tumor [4]. DNA mutations in tumor suppressor genes contribute to over 20% of ovarian cancers [5], and germline mutations in *BRCA* genes are responsible for 65–85% of inherited ovarian tumors [6]. The cumulative risk of ovarian cancer up to the age of 80 is estimated to be 49% and 21% in individuals harboring mutations in *BRCA1* and *BRCA2* genes, respectively [7].

Around 25% of women diagnosed with high-grade serous ovarian carcinoma have germline deleterious mutations in *BRCA1* or *BRCA2* [8].

In the context of genetic mutations, one characteristic of DNA is that it is able to repair itself, a process known as homologous recombination. Homologous recombination deficiency (HRD) refers instead to the situation in which the body cannot effectively restore double-strand breaks in DNA. This means that in patients with HRD with a diagnosis of ovarian malignancy, the cancer cells damaged by treatments are induced to apoptosis in the lack of maintaining genomic stability. The treatments that take advantage of this mechanism are called poly(ADP-ribose) polymerase (PARP) inhibitors and are particularly effective.

Although the prevailing belief was that *BRCA1* or *BRCA2* gene variants were the primary causes of HRD, it was recently found that HRD can be caused by alteration in many other genes. In particular, approximately 50% of women diagnosed with advanced high-grade serous ovarian cancer are HRD positive [9].

According to published ESMO 2023 guidelines, all patients with high-grade ovarian cancer should be tested for germline and/or somatic *BRCA1*/*BRCA2*-mutation at diagnosis. Moreover, testing for HRD is recommended in advanced high-grade ovarian cancers [10]. Systemic therapy decisions should be informed by *BRCA1*/*BRCA2* (germline and/or somatic) and HRD status testing carried out at primary diagnosis allowing more appropriate and specific target therapies like PARP inhibitors.

PARP inhibitors represent a recent milestone as maintenance treatment after first-line therapy [11]. PARP inhibitors have been under development for the last 10 years, with the first US Food and Drug Administration (FDA) approval achieved in 2014 for olaparib (Olap) [12, 13], followed by approvals for rucaparib and niraparib (Nirap) [14].

In Europe the monotherapy with Olap has been approved on the basis of the results of the SOLO-1 trial [15]. The study showed an advantage for Olap in progression-free survival (PFS) with a median PFS of 56.0 months vs. 13.8 months in the placebo arm (HR 0.33, 95% CI 0.25–0.43). The 7-year follow-up showed an advantage also in overall survival (OS) with median not reached in the Olap arm versus 75.2 months in the placebo arm (HR 0.55, 95% CI 0.40–0.76).

For the combination of olaparib plus bevacizumab (Olap + Beva) the approval was based on the findings of PAOLA-1 study [13, 16]. This study showed for the combination as maintenance therapy a substantial clinical advantage in PFS when compared with bevacizumab alone in patients with HRD-positive cancers, with a median PFS of 46.8 months compared to 17.6 months (HR 0.41, 95% CI 0.32–0.54). The study showed also an advantage in OS with a median of 75.2 months for the combination versus 57.3 for bevacizumab (HR 0.62, 95% CI 0.45–0.85).

The PRIMA randomized, double-blind, phase 3 trial assigned patients with newly diagnosed advanced ovarian cancer to receive Nirap or placebo once daily after response to platinum-based chemotherapy [14]. The trial included women with and without HRD, and the HRD-positive group included women who were *BRCA* positive. In the overall population, the median PFS time was significantly longer in the Nirap group than in the placebo group, with 13.8 months versus 8.2 months respectively (HR 0.62, 95% CI 0.50–0.76). Among the subgroup of patients with HRD median PFS was 21.9 months for Nirap versus 10.4 months (HR 0.43, 95% CI 0.31–0.59).

Whereas in clinical trials HRD testing is generally assessed by centralized next-generation sequencing (NGS), in clinical practice it can be executed in structures that have specialist know-how and suitable equipment and, for this reason, its use in this setting is still limited [17] compared to the wide diffusion of *BRCA* testing. The aim of the study was to investigate the cost-effectiveness of the treatment of patients with advanced ovarian cancer by comparing HRD testing to *BRCA1*/*BRCA2* testing alone from the National Healthcare Service (NHS) perspective in Italy. The option to perform the tests in sequence, that is, the HRD test after the *BRCA* test in patients with negative *BRCA* test, was also considered. The identification of patients with HRD through HRD testing allows one to extend the use of an optimized

treatment with effective drugs like PARP inhibitors to a larger set of patients (e.g., olaparib in combination with bevacizumab for HRD+, *BRCA*−) compared to standard *BRCA* testing.

The literature, to our knowledge, reports only two studies investigating the cost-effectiveness of HRD testing for OC. Elsea and colleagues [18] evaluated the cost-effectiveness of biomarker testing and maintenance treatments with PARP inhibitors in platinum-sensitive advanced ovarian cancer in the USA. The authors showed that HRD testing followed by Olap + Beva for patients with positive HRD test and Beva for patients with negative HRD test is a cost-effective strategy (52,948$/QALY) compared to *BRCA* testing followed by Olap + Beva for patients with *BRCA* mutation and Beva for patients without *BRCA* mutation. Another study [19], still in the US setting, assessed the cost-effectiveness of a "PARPi-for-all" strategy versus a targeted approach through biomarker analysis for the setup of a frontline maintenance therapy for OC. In this case, the authors concluded that OC maintenance treatment in this setting should be reserved for patients with germline or somatic HRD mutations until the cost of therapy is significantly reduced.

The extension of these analyses to other geographical contexts may give a broader picture of the assessment of tailored treatments in the setting of OC.

METHODS

The Model

A cost-effectiveness model was developed with TreeAge Software (TreeAge Software, Inc., Williamstown, MA, USA) to estimate the expected costs and outcomes (life years, LYs; quality-adjusted life years, QALYs) of (1) HRD testing versus *BRCA1*/*BRCA2* (*BRCA*) testing (germline or tissue) alone or (2) HRD testing after *BRCA* testing in patients with negative *BRCA* test with high-grade serous or endometrioid advanced ovarian cancer in Italy. The analysis followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [20]. The CHEERS checklist is reported in the Supplementary Materials Appendix 1.

A mean patient age of 60 years was applied in accordance with the study on olaparib [13]. The model structure is reported in Fig. 1.

With the *BRCA* test option, the assumption is that 25% of patients will have a positive result [21], but with HRD testing, the assumption is that 50% of women will have a negative or unknown HRD status and that the remaining women will be HRD+ [22], with patients being *BRCA* positive or negative at a rate of 50% each [23]. Both options consider a population split between high risk (HR, 74%) and low risk (LR, 26%). Patients with high risk are classified as (1) stage III with upfront surgery and residual disease or neoadjuvant chemotherapy or (2) stage IV; however, patients with low risk are classified as stage III with upfront surgery and no residual disease [24].

The treatments represent the best available options according to the initial test results and according to drug availability in Italy. In particular, in Italy, olaparib (Olap) is approved as monotherapy for maintenance treatment of adult patients with advanced *BRCA1*/*BRCA2*-mutated high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer with a complete or partial response following completion of first-line platinum-based chemotherapy. Olap in combination with bevacizumab is approved for the maintenance treatment of adult patients with advanced high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer with a complete or partial response following completion of first-line platinum-based chemotherapy and whose cancer has a HRD positive status, excluding patients with *BRCA* mutation. Niraparib (Nirap) is indicated for the maintenance treatment of adult patients with high-risk advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer with a complete or partial response to first-line platinum-based chemotherapy.

Another possible treatment is bevacizumab, which can be administered alone (Beva) or in combination with olaparib (Olap + Beva).

When two treatments are both available for a specific indication, in the model, we assumed 50% of prescriptions for each of them.

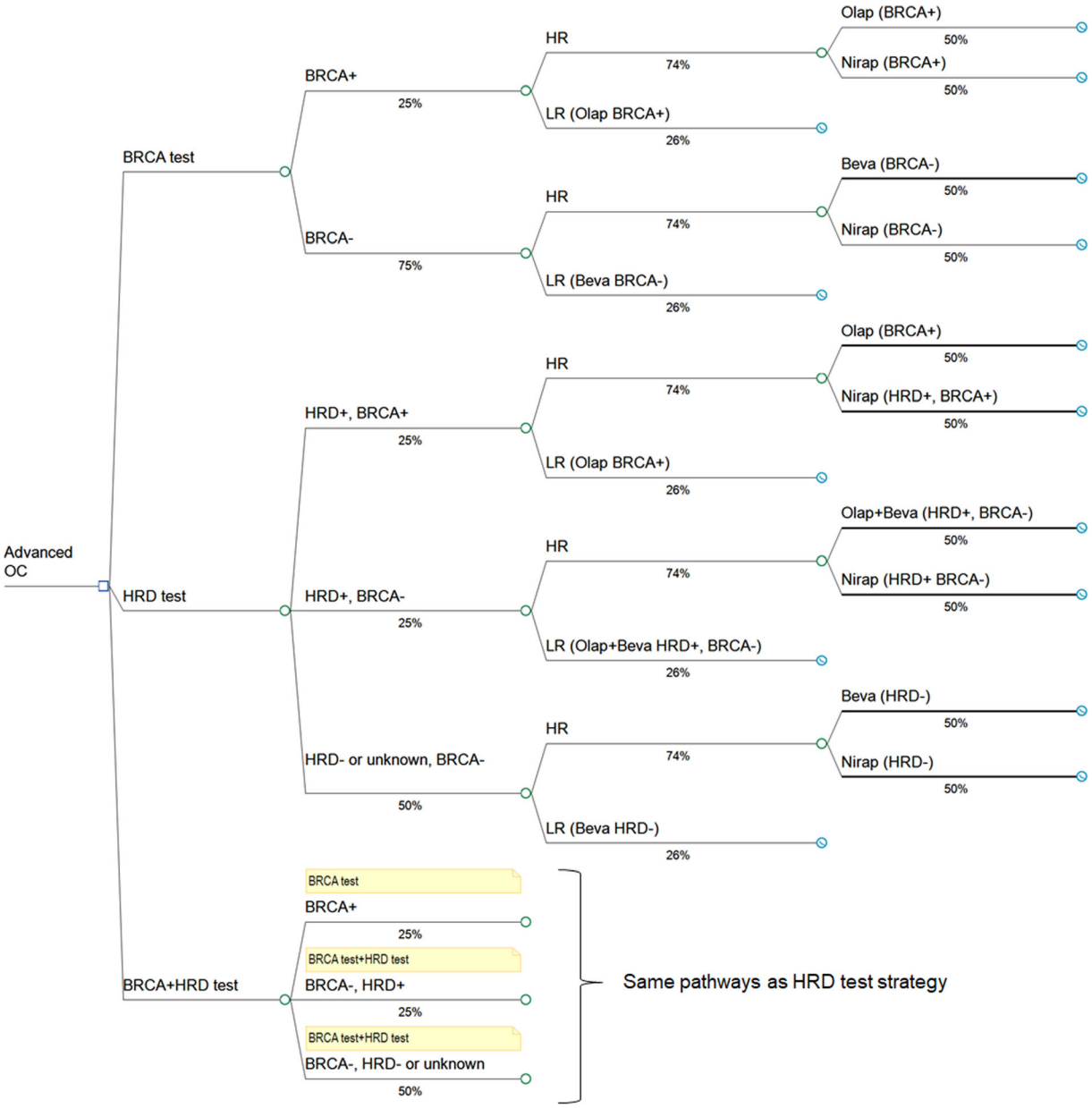

Fig. 1 Structure of the decision model. *OC* ovarian cancer, *HR* high risk, *LR* low risk, *HRD* homologous recombination deficiency

The option of the sequence of tests considers the use of HRD testing in *BRCA*− patients. In this case, the treatment choices are the same as in the HRD strategy (leading to the same health outcomes) since the genetic information obtained is the same. This pathway takes into consideration the additional cost of HRD testing performed on the subset of *BRCA*− patients.

A partitioned survival model was applied to each therapy to follow patients from an initial line of treatment after diagnosis until disease progression or death. The model considers three states for each treatment: progression-free, progression, and death. This kind of model is accepted by health technology assessment (HTA) bodies and frequently used in peer-

Table 1 Clinical data for overall survival (OS) and progression-free survival (PFS) used to populate the model

Treatment	Outcome	Study FUP (months)	Time point (months)	Survival at time point (%)	Kaplan–Meier curve reported (yes/no)	Reference
Olap + Beva (HRD+, *BRCA*−)	OS	60	60	54.7%	Yes	PAOLA-1 final OS analysis [16]
Olap + Beva (HRD+, *BRCA*−)	PFS	60	60	41.0%	Yes	PAOLA-1 5 years (ESMO) [31]
Nirap (HRD+, *BRCA*−)	OS	24	24	91.0%	No	PRIMA [14]
Nirap (HRD+, *BRCA*−)	PFS	42 (mean)	19.4	50.0%*	Yes	PRIMA 3.5 years [32]
Nirap (HRD+, *BRCA*+)	OS	24	24	91.0%	No	PRIMA [14]
Nirap (HRD+, *BRCA*+)	PFS	42 (mean)	31.5	50.0%*	Yes	PRIMA 3.5 years [32]
Nirap HRD−	OS	24	24	81.0%	No	PRIMA [14]
Nirap HRD−	PFS	42 (mean)	8.4	50.0%*	Yes	PRIMA 3.5 years [32]
Olap (*BRCA*+)	OS	84	84	67.0%	Yes	SOLO1 7 years [15]
Olap (*BRCA*+)	PFS	60	60	48.0%	Yes	SOLO1 5 years [12]
Beva (HRD−)	OS	60	60	32.30%	Yes	PAOLA-1 final OS analysis [16]
Beva (HRD−)	PFS	60	16	50.00%	No	PAOLA-1 final OS analysis [16]
Beva (BRCA−)	OS	60	43.4	50.0%*	Yes	GOG218 [33]
Beva (BRCA−)	PFS	60	24	50.0%*	Yes	GOG218 [33]

FUP follow-up, *HRD* homologous recombination deficiency
*Time point refers to median survival

reviewed publications for the target indication of this analysis [25–27].

Overall survival (OS) and progression-free survival (PFS) curves were obtained through fittings starting from Kaplan–Meier curves published in the literature related to drug approval studies. This approach allowed us to extrapolate OS and PFS curves to a time horizon longer than those reported for the reference clinical trials [28]. Different curve functions

(e.g., Weibull, Gompertz, exponential) have been fitted for OS and PFS curves emerging from the different treatments. The performance of the different fittings was assessed according to standard evaluation criteria (Akaike information criterion and Bayesian information criterion). For Beva (HRD−), the survival curve was not presented; therefore, an exponential curve was implemented considering the reported value of median survival.

The model calculations ensure that, irrespective of the parametric distribution used to extrapolate survival curves, OS is always higher or equal to PFS, and OS is never above the background mortality curve for the Italian population (female) [29]. Table 1 shows the health outcomes used to populate the model.

As the aim of the study was to compare the different testing modalities, only first-line and second-line treatments were modeled, accounting for the complexity of the different treatment pathways for subsequent treatments. A lifetime horizon has been applied. A discount rate of 3% has been considered for costs and health outcomes [30].

For the adequate modeling of treatment-related costs, treatment status (i.e., on and off treatment) in a progression-free health state was tracked over time. Patients who start first-line treatment experience a PFS interval. Patients who experience disease progression and do not die during the initial modeled line of treatment continue to progress to a health state in which we assume they receive a second-line treatment. In this case, the same patient pathway was considered for all patients after the second-line therapy. Patients may die at any time in the model. Costs and utilities were assigned to each health state and were accrued and summarized for each cycle of the model (1 month) so that the difference in cumulative cost and utilities could be analyzed and compared between the testing options.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Healthcare Resource Consumption and Costs

The model considered only direct healthcare resource consumption (direct costs, euros, 2023) according to the NHS perspective in Italy. Costs were considered for genetic testing, initial treatment and second-line therapies, for follow-up visits and exams, and for the management of major adverse events.

Regarding the initial genetic test, in Italy, the corresponding tariff currently does not distinguish between HRD and *BRCA*, and a recent publication [34] proposed different tariffs (1150€ for NGS *BRCA* test and 1850€ for HRD test), which were considered for the purpose of the present study (conservative assumption considering a higher cost for HRD test).

Olaparib has an oral formulation (film-coated tablets, 100 mg or 150 mg); the recommended dose in monotherapy or in combination with bevacizumab for ovarian cancer is 300 mg (two 150-mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. In general, patients may continue treatment until radiological disease progression, unacceptable toxicity, or up to 2 years if there is no radiological evidence of disease after 2 years of treatment [35].

Niraparib is available as capsules (100 mg); the recommended starting dose is 200 mg (two 100-mg capsules), taken once daily. However, for those patients who weigh at least 77 kg and have a baseline platelet count of at least 150,000/μL, the recommended starting dose is 300 mg (three 100-mg capsules), taken once daily [36]. Treatment is performed for 36 months or until disease progression [14].

Bevacizumab is available in vials, for which 1 mL of concentrate contains 25 mg of bevacizumab. This drug is administered as an intravenous infusion [37]. The administration cost is reimbursed according to diagnosis-related group (DRG) 410, which is reduced by 90% [38].

For treatment dosages dependent on the patient body weight or surface, a mean weight of 64.8 kg and mean height of 161 cm are

Table 2 Summary of healthcare resource use and related costs

Cost item	Frequency/schedule	Reference	Cost (€)	Reference
BRCA test	Initial test	–	1150	[34]
HRD test	Initial test	–	1850	[34]
Olaparib (per mg)	600 mg/day	[13]	0.29	[44]
	(Maximum duration 2 years)		(Annual cost 62,640€)	
	Median duration alone 24.6 months			
	Median duration combined with bevacizumab 17.3 months			
Niraparib (per mg)	200–300 mg/day depending on body weight	[14, 45]	0.92	[46]
	(Maximum duration 3 years)		(Annual cost in the range 66,240–99,360€ depending on body weight)	
	(Mean time on treatment 2 years)			
	Median duration 11.1 months			
Bevacizumab (per mg)	15 mg/kg every 3 weeks	[13]	2.90	[47]
	(Maximum duration 15 months)		(Annual cost 48,324€)	
	Median duration 11 months			
Drug administration (intravenous infusion)	In case of bevacizumab administration	[38]	37.10	[41]
Second-line treatment	Monthly	–	1714	[43]
Specialist visit	Every 3 months	Clinical practice in Italy	20.66	[42]
Urinalysis			2.17	[42]
Blood test			3.17	[42]
CA-125			12.98	[42]
Computed tomography scan			79.47	[42]

CA-125 ovarian carcinoma antigen, *HRD* homologous recombination deficiency

assumed according to the mean values for women in Italy [39]. The corresponding body surface is 1.68 m^2 [40].

Relative dose intensity was applied to treatment costs to consider dose reductions and interruptions. The mean relative dose intensities for bevacizumab were 91.20% and 90.50% for Olap + Beva and Beva, respectively. The mean relative dose intensity for Olap was 86.7% in the safety analysis set population [28]. For

Table 3 Frequency of adverse events for the treatments considered and related management costs

Adverse event	Olap + Beva [13]	Nirap [32]	Olap [12]	Beva [13]	DRG	Cost (€)
Fatigue or asthenia	5.00%	–	4.00%	–	463—SIGNS & SYMPTOMS W CC	2870
Hypertension	19.00%	7.20%	–	30.00%	134—HYPERTENSION	963
Anemia	17.00%	31.60%	22.00%	–	395—RED BLOOD CELL DISORDERS AGE > 17	1676
Lymphopenia	7.00%	–	–	–	399—RETICULOENDOTHELIAL & IMMUNITY DISORDERS W/O CC	1704
Neutropenia	6.00%	21.30%	9.00%	3.00%	574—MAJOR HEMATOLOGIC/ IMMUNOLOGIC DIAG EXC SICKLE CELL CRISIS & COAGUL	3738
Thrombocytopenia	–	39.70%	–	–	397—COAGULATION DISORDERS	2748
Diarrhea/gastrointestinal	–	–	3.00%	–	572—MAJOR GASTROINTESTINAL DISORDERS AND PERITONEAL INFECTIONS	3484

DRG diagnosis-related group

Nirap, the median relative dose intensity considered was 63.00% [14].

Follow-up exams and visits (specialist visit, urinalysis, blood test, ovarian carcinoma antigen (CA-125), and CT scan) were performed every 3 months according to clinical practice in Italy.

Adverse events were considered if they were classified as grade 3 or higher, and occurred in at least 3% of patients in the active treatment group. For healthcare resource use, we referred to DRG reimbursement rates [41] and official tariffs at the national level [42]. For the sake of simplicity, we assumed that adverse events occurred in the first month of treatment.

As the focus of the analysis was the cost-effectiveness of genetic tests, for subsequent therapies, we relied on published costs from the

Table 4 Disutilities and durations for the adverse events considered in the model

Adverse event	Disutility value (SD)	Reference	Duration (days)	Reference
Fatigue or asthenia	− 0.073 (0.02)	Nafees 2008 [51]	32	TA310 [52]
Hypertension	− 0.090 (0.02)	ID1652 [48]	11	TA580 [53]
Anemia	− 0.119 (0.01)	Swinburn 2010 [54]	7	TA411 [55]
Lymphopenia	− 0.090 (0.02)	ID1652 [48]	16	TA573 [56]
Neutropenia	− 0.090 (0.02)	Nafees 2008 [51]	7	TA411 [55]
Thrombocytopenia	0	Guy 2019 [45]	–	–
Diarrhea	− 0.090 (0.02)	Casado 2018 [57]	7	Casado 2018 [57]

SD standard deviation

Table 5 Cost-effectiveness results

Option	Costs	LYs	QALYs	ICER	ICUR
BRCA testing	126,084 €	5.66	4.51	–	–
BRCA testing + HRD testing	147,347 €	6.79	5.42	18,817€/LY vs. *BRCA* testing	23,366€/QALY vs. *BRCA* testing
HRD testing	146,659 €			18,208€/LY vs. *BRCA* testing	22,610€/QALY vs. *BRCA* testing
				Cost-saving vs. *BRCA* testing + HRD testing	Cost-saving vs. *BRCA* testing + HRD testing

LY life years, *QALYs* quality-adjusted life years, *ICER* incremental cost-effectiveness ratio, *ICUR* incremental cost-utility ratio, *HRD* homologous recombination deficiency

NHS perspective in Italy [43]. The mean cost, including both surgery and adjuvant chemotherapy, was 17,418€ per year in 2014 (20,571€ after adjustment to 2023). Accordingly, a monthly cost of 1714€ was applied to patients with progressive disease.

Table 2 summarizes the healthcare resource use and related costs. Table 3 reports the details on adverse events (frequencies and management costs).

Quality of Life Estimates

The utility coefficients for patients with OC across the model health states were retrieved from the literature. The values were 0.819 and 0.771 for progression-free and progression, respectively [38]. Since adverse events generally happen during the first treatment cycles, one-off QALY adjustments (disutilities) were applied during the first month to account for the impact of side effects on patients' quality of life [48–50]. These data are summarized in Table 4.

Baseline Analyses

Incremental cost-effectiveness and cost-utility ratios were calculated. In Italy, thresholds vary between 25,000€ and 74,700€ [58–60]. In the context of the present analysis, a willingness-to-pay (WTP) threshold of 50,000€/QALY was applied.

Deterministic sensitivity analyses (DSA) and probabilistic sensitivity analysis (PSA) were performed to evaluate the influence of the uncertainty of the model parameters on the model results. The PSA was performed by assigning distributions to model parameters. Beta distributions were used for probabilities of events, utilities, disutilities, and relative dose intensity, while gamma distributions were applied for healthcare resource use and costs. A standard deviation of 20% of the baseline value was used when the reference studies for input data did not report a specific value. Then, all parameters were randomly sampled from their assigned distributions considering 10,000 Monte Carlo simulations. The results are presented graphically with acceptability curves. One-way sensitivity analyses were performed on the model parameters by applying a variation of ± 20% of their baseline values, except the discount rate, which varied from 0 to 10%, and the time horizon, which varied from 10 years to lifetime. The results of these analyses are shown in a tornado diagram for the incremental cost-utility ratio (ICUR).

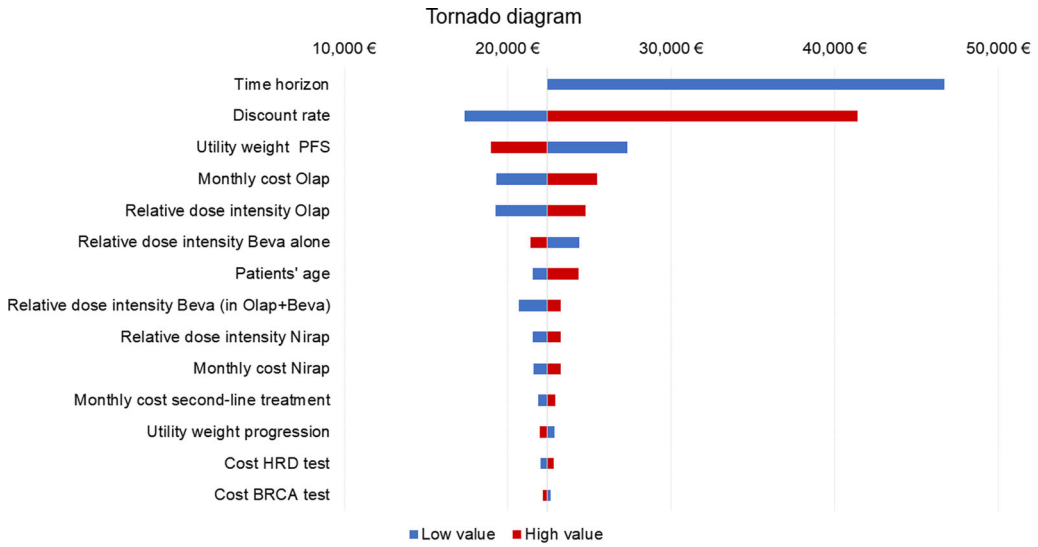

Fig. 2 Tornado diagram reporting the results of deterministic sensitivity analyses on the incremental cost-utility ratio (22,610€/QALY) for the comparison of HRD testing and *BRCA* testing. *QALY* quality-adjusted life years, *HRD* homologous recombination deficiency, *PFS* progression-free survival

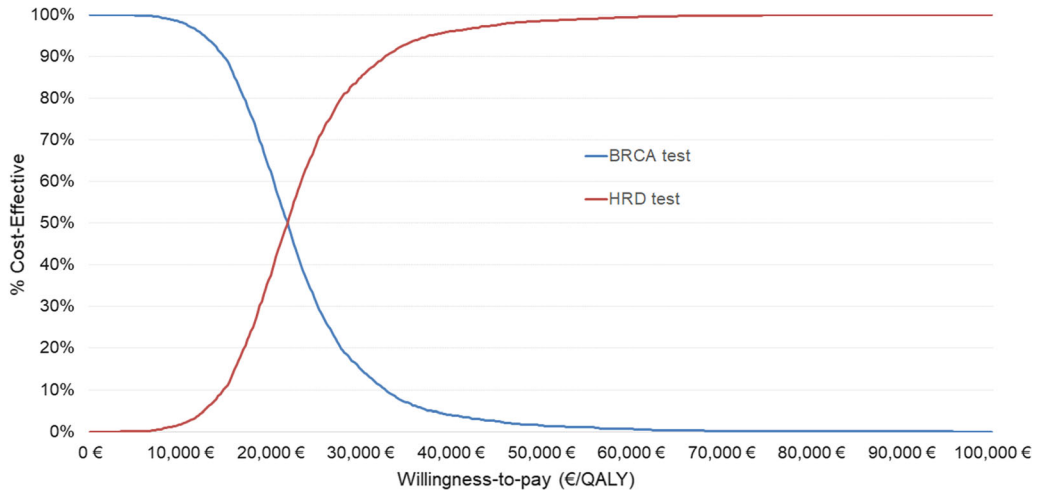

Fig. 3 Acceptability curve for the incremental cost-utility ratio (HRD testing versus *BRCA* testing). *HRD* homologous recombination deficiency, *QALY* quality-adjusted life years

RESULTS

Curve Fittings

For Olap alone, the best fittings for the OS and PFS curves were log-logistic functions, and the best fittings for Olap + Beva HRD+/BRCA− OS and PFS curves were generalized gamma functions. These functions were also better approximations for PFS curves for niraparib for the HRD+/BRCA−, HRD+/*BRCA*+, and HRD− subgroups. OS for Beva BRCA− and HRD− were better fitted by log-normal functions, while PFS for Beva BRCA− was better approximated by a log-logistic function (see Supplementary Materials Appendix 2).

Baseline Results

The mean life expectancy per patient was estimated to be 6.79 (5.42 QALYs) and 5.66 (4.51 QALYs) years for the HRD and *BRCA* testing options, respectively. The mean costs per patient were estimated to be 146,659€ for HRD testing and 126,084€ for *BRCA* testing. The strategy that considers the sequence of tests for patients with negative *BRCA* test (HRD testing + *BRCA* testing) has a cost of 147,347€, and the same health outcomes as the HRD testing strategy, with 6.79 LYs and 5.42 QALYs.

The model results are summarized in Table 5 and show that HRD testing, alone or after *BRCA* testing, has a cost-effective profile since the ICUR is in the range of 22,610–23,366€/QALY compared to *BRCA* testing alone for the setup of first-line treatments in patients with advanced OC. The incremental cost-effectiveness ratio (ICER) for HRD testing (alone or combined with *BRCA* testing) is in the range of 18,208–18,817€ per life year saved. The strategy that considers the sequence of genetic tests for patients with negative *BRCA* test, instead of the HRD test only, has a lower cost-effectiveness profile compared to *BRCA* testing alone.

Analyses

Figure 2 reports the results of one-way sensitivity analyses performed on the main model parameters for the comparison of HRD testing versus *BRCA* testing. The discount rate, the utility value for the PFS health state, the time horizon for the analyses, and the monthly cost of olaparib and its dose intensity are the parameters that can greatly influence the ICUR. In particular, a time horizon of 10 years leads to an ICUR of 46,698€/QALY, which is the highest obtainable but lower than the WTP threshold of 50,000€/QALY.

The acceptability curve for the ICUR obtained from the PSA is reported in Fig. 3 and shows that for a WTP higher than 21,800€/QALY, HRD testing may be a cost-effective choice compared with *BRCA* testing alone. The HRD test is cost-effective in 98.5% of the simulations considering a WTP threshold of 50,000€/QALY.

DISCUSSION

Ovarian cancer is a heterogeneous disease with the highest mortality rate and poorest prognosis among gynecological malignancies [61]. As a result of the lack of specific early symptoms, most patients with OC are diagnosed at late stages. Over the last decade, researchers have made considerable efforts to gain deep molecular profiling of OC that can help make more accurate and personalized clinical decisions.

In the present study, we evaluated the cost-effectiveness of genetic testing, in particular HRD vs. *BRCA* or HRD vs. *BRCA* + HRD, for the definition of personalized treatment for women with advanced OC in Italy. The analyses showed that HRD testing may be a cost-effective choice compared to *BRCA* testing, leading to an ICUR of 22,610€/QALY (ICER 18,208€/LY). The sequence of the *BRCA* test followed by the HRD test showed only additional costs with no difference in health outcomes compared to the HRD test alone, showing that the HRD test may be a cost-saving strategy compared to the sequence of tests. Our results are in line with the ones presented in a similar analysis in the US context [28].

The present study has limitations that need to be recognized. As the aim of the study was to compare the different testing modalities and their influence on the choice of first-line treatments, the model presented first-line therapies in detail but did not distinguish following lines. This approach may be justified considering that first-line treatments are reported as the main drivers of survival [62]. On the other hand, considering the entire clinical pathway of the management of patients with advanced OC is a complex task that entails making assumptions to reflect the complexity of the different treatment pathways for subsequent treatments. For the same reason, the model does not distinguish first from second progression and applies the same utility coefficient. A personalized treatment considered in the following lines might

further improve the cost-effectiveness profile of HRD testing.

Another limitation relates to the specific treatments considered after genetic test results. The reference study on niraparib [32] did not report specific survival curves for the whole group of patients with negative *BRCA* test to be considered in the *BRCA* test strategy (BRCA−, HR, Nirap); therefore, we referred to the subgroup analysis for HRD− patients; this was a conservative assumption, the survival being lower than for the other groups.

Third, the results may be influenced by the extrapolation of survival curves over a lifetime horizon. Although robust methods have been applied to select the best fittings, constant data collection will allow us to improve the projections of clinical outcomes to obtain more precise results.

Fourth, in the model, drug costs were retrieved from Italian official documents reporting ex-factory values (*Gazzetta Ufficiale*). These costs were reduced by a cumulative 5% + 5% mandatory manufacturer discount on the ex-factory prices [63]; nevertheless, confidential discounts may be in place, leading to lower baseline drug costs [64]. This scenario would be favorable to the HRD test, as shown in one-way sensitivity analyses, where a lower cost for PARP inhibitors (Olap, Nirap), which are the parameters with the highest impact on the model results, leads to a lower ICUR.

CONCLUSIONS

The leading contributors to cancer-related deaths are ovarian, breast, prostate, and colorectal cancers. A considerable percentage of individuals with these tumors carry inherited mutations. The recognition of these genetic anomalies could provide patients with personalized treatments. Nevertheless, genetic screening requires the use of healthcare resources with additional costs and, in a context of scarce resources, an optimization of their use is necessary. The present study adds new evidence on the cost-effectiveness of HRD testing compared to *BRCA* testing for patients with advanced ovarian cancer, allowing for an efficient use of healthcare resources and improved life expectancy and QALYs.

In the future, enhancements in testing proficiency, a more inclusive panel of genes for the screening of HRD, and advances in the development of inhibitors with increased efficacy will be able to provide robust diagnosis and a broader range of treatments for ovarian cancer.

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Data Availability. All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of Interest. Carla Rognoni, Domenica Lorusso, Francesco Costa, and Patrizio Armeni have nothing to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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