

Feasibility and cost-effectiveness of genetic counselling for all patients with newly diagnosed ovarian cancer: a single-centre retrospective study

Saskia Schlootz^a, Flurina A. M. Saner^b, Manuela Rabaglio^a, Sara Imboden^b, Julian Wampfler^a

^a University Clinic for Medical Oncology, Inselspital, University Hospital of Bern, University of Bern, Bern, Switzerland

^b Department of Gynaecology and Gynaecologic Oncology, Bern University Hospital, University of Bern, Bern, Switzerland

Summary

BACKGROUND AND AIMS OF THE STUDY: Due to its importance for treatment and potential prevention in family members, germline testing for *BRCA1/2* in patients with newly diagnosed ovarian cancer is decisive and considered a standard of care. Maintenance therapy with poly(ADP-ribose) polymerase (PARP) inhibitors substantially improves progression-free survival in patients with *BRCA* mutations and homologous recombination-deficient tumours by inducing synthetic lethality. In Switzerland, they are licensed only for these patients. Therefore, it is crucial to test patients early while they are receiving adjuvant chemotherapy. This study aimed to determine whether genetic counselling followed by homologous recombination deficiency testing is feasible for initialising maintenance therapy within eight weeks and cost-effective in daily practice in Switzerland compared to somatic tumour analysis of all patients at diagnosis.

METHODS: This single-centre retrospective study included 44 patients with newly diagnosed high-grade serous ovarian cancer of a Federation of Gynaecology and Obstetrics (FIGO) stage of IIIA-IVB diagnosed between 12/2020 and 12/2022. It collected the outcomes of genetic counselling, germline testing, and somatic Geneva test for homologous recombination deficiency. Delays in initiating maintenance therapy, total testing costs per patient, and progression-free survival were examined to assess feasibility and cost-effectiveness in clinical practice.

RESULTS: Thirty-seven of 44 patients (84%) with newly diagnosed ovarian cancer received counselling, of which 34 (77%) were tested for germline *BRCA* and other homologous recombination repair gene mutations. Five (15%) *BRCA* and three (9%) other homologous recombination deficiency mutations were identified. Eleven of the remaining 26 patients (42%) had tumours with somatic homologous recombination deficiency. The mean time to the initiation of maintenance therapy of 5.2 weeks was not longer than in studies for market authorisation (SOLO1, PAOLA, and PRIMA). The mean testing costs per patient were 3880 Swiss Franks (CHF), compared to 5624 CHF if all

patients were tested at diagnosis with the myChoice CDx test ($p < 0.0001$).

CONCLUSION: Using genetic counselling to consent patients with newly diagnosed ovarian cancer for germline testing fulfils the international gold standard. Subsequent somatic homologous recombination deficiency analysis complements testing and identifies more patients who will benefit from PARP inhibitor maintenance therapy. Contrary to previous health cost model studies, the procedure does not increase testing costs in the Swiss population and does not delay maintenance therapy. Therefore, all patients should be offered a primary germline analysis. The challenge for the future will be to ensure sufficient resources for prompt genetic counselling and germline testing.

Introduction

High-grade serous ovarian cancer is often diagnosed at advanced stages and associated with a high risk of recurrence despite initially high chemosensitivity. For many years, there has been no improvement in the standard chemotherapy consisting of carboplatin and paclitaxel [1]. Maintenance therapies with poly(ADP-ribose) polymerase inhibitors (PARPi), such as olaparib or niraparib, have been introduced into routine clinical practice [2, 3].

Approximately 15%–20% of all high-grade serous ovarian cancers are associated with a germline mutation in *BRCA1* or *BRCA2* and are considered an inherited disease, also known as hereditary breast and ovarian cancer syndrome [1]. Homologous recombination deficiency (HRD) leads to impaired DNA damage repair and thereby contributes to ovarian cancer progression. Pathogenic mutations in *BRCA1* and *BRCA2*, regardless of whether they are somatic and acquired upon tumorigenesis or inherited in the germline, are the leading cause of homologous recombination deficiency among other gene mutations. Genetic alterations such as loss of heterozygosity or copy number variations can arise due to homologous recombination deficiency.

The prevalence of homologous recombination deficiency in high-grade serous ovarian cancer is estimated to be

Dr Julian Wampfler, MD, PhD
Consultant Medical Oncologist
Inselspital, University Hospital of Bern
CH-3010 Bern
[julian.wampfler\[at\]insel.ch](mailto:julian.wampfler[at]insel.ch)

around 50% [4]. This proportion is lower in daily practice, with a recent real-world analysis of 2829 patients finding that 37% of tumours had a genomic instability score of over 42, implicating homologous recombination deficiency, and 16% had *BRCA* mutations [5]. The gold standard to determine homologous recombination deficiency is functional tests such as myChoice CDx or Geneva, which have been validated by the PAOLA trial [6–8].

Maintenance therapy with a PARPi after adjuvant chemotherapy doubles disease-free survival rates and enhances clinically meaningful overall and progression-free survival, especially in patients with *BRCA* mutations [9]. This effect is also observed in patients with homologous recombination-deficient ovarian cancer. However, in patients with homologous recombination-proficient tumours, niraparib maintenance therapy prolonged progression-free survival by only 2.7 months [10] and olaparib combined with bevacizumab had no effect [11, 12]. Therefore, the Swiss regulatory authority licensed maintenance with niraparib or olaparib combined with bevacizumab only for treating ovarian cancer with homologous recombination deficiency.

Blood testing patients for germline *BRCA* mutations (gBRCAmt) is expensive and requires prior genetic counselling for consent. However, it is the only way to identify inherited ovarian cancer and *BRCA* mutations, and it predicts clinical benefit from PARPi maintenance therapy. Next-generation sequencing (NGS) of tumour biopsies can detect somatic *BRCA* mutations (sBRCAmt) and mutations in other genes that cause homologous recombination deficiency. Like the functional tests, it can identify homologous recombination deficiency and predict the clinical benefit of PARPi maintenance therapy but does not identify inherited cancer predisposition [1, 8, 13–15].

The American Society of Clinical Oncology (ASCO) recommends initial genetic counselling and germline *BRCA* testing for patients without pathogenic germline mutations, followed by somatic analysis [16]. This approach is favourable and is consistent with Swiss law, which requires detailed counselling for germline testing and somatic analysis that could identify *BRCA* mutations. It enables the patient to decline any testing for personal reasons and allows the detection of gBRCAmt that are not found by somatic testing for technical reasons. In a Korean cohort of 98 patients with high-grade ovarian cancer, three (3.1%) carried a gBRCAmt without evidence of a sBRCAmt based on next-generation sequencing (13% of BRCAmt) [17]. This approach is time-consuming since germline testing is strictly regulated by law. It requires an individual request for coverage from a patient's health insurance, which can delay testing [18]. In addition, a health economic model study concluded that germline testing of patients with ovarian cancer for *BRCA* mutations followed by somatic tumour-based next-generation sequencing was not cost-efficient compared to somatic testing at diagnosis, challenging its use from a health cost perspective [19].

The first aim of this study was to determine whether providing genetic counselling and germline analysis to all patients with newly diagnosed ovarian cancer followed by functional somatic homologous recombination deficiency testing was feasible in clinical practice, assessed as initiating maintenance therapy not later than eight weeks after

completion of chemotherapy, as in the SOLO1 market access study; it was nine weeks in the PAOLA trial and 12 weeks in the PRIMA trial [8–11].

The second aim of this study was to determine whether this testing approach increased testing costs in Switzerland compared to a model in which all patients newly diagnosed with ovarian cancer are provided with a functional homologous recombination deficiency test (myChoice CDx and Geneva), followed by genetic counselling for those with positive tests.

Materials and methods

Bernese testing approach

In accordance with Swiss law, regulations on germline diagnostics, and healthcare insurance policy, in 2021, we implemented a *BRCA*/homologous recombination deficiency status testing approach for patients with newly diagnosed advanced high-grade ovarian cancer at the Inselspital (The University Hospital of Bern) to fulfil the requirements for prescribing PARPi maintenance therapy [18]. Patients are referred for genetic counselling by a multidisciplinary team (MDT). The germline test panel (Twist Bioscience Custom Panel v3) contains six known homologous recombination genes (*BRCA1*, *BRCA2*, *BRIP1*, *PALB2*, *RAD51C*, and *RAD51D*) and four mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). If those results are negative, an evaluation of tumour homologous recombination deficiency using the Geneva test is recommended if the patient still fulfils the clinical criteria for PARPi maintenance therapy [6]. If DNA quality is insufficient for a Geneva test, a conventional somatic tumour next-generation sequencing (Illumina TSO500 panel) was performed to detect sBRCAmt whenever possible. No further somatic tumour testing is conducted once a patient progresses or stops responding to platinum-based chemotherapy.

Patients and treatments

This study included patients newly diagnosed with high-grade serous ovarian, fallopian tube, or primary peritoneal cancer between 1 December 2020 and 31 December 2022. Data were censored on 31 March 2023. All patients had at least a Federation of Gynecology and Obstetrics (FIGO) Stage IIIA. Diagnosis included a diagnostic laparoscopy with tumour sampling. All patients were planned for surgery (primary, interval, or delayed debulking) and recommended for (neo-)adjuvant chemotherapy with six cycles of carboplatin and paclitaxel. Patients with FIGO Stage III and a BRCAmt were treated for two years of olaparib. Maintenance therapy with olaparib/bevacizumab was preferred for patients with FIGO Stage IV. Olaparib/bevacizumab or niraparib was recommended for patients with homologous recombination-deficient tumours. Maintenance therapy with bevacizumab was suggested for patients with homologous recombination-proficient tumours of FIGO Stage III with residual disease or Stage IVA.

Study design

Patients with newly diagnosed ovarian cancer underwent *BRCA* and homologous recombination deficiency testing by the Bernese testing approach (figure 1). We assessed

the time from completion of chemotherapy to initiation of maintenance therapy as the hallmark of clinical feasibility. The testing approach was considered clinically feasible if maintenance therapy was initiated no later than eight weeks. The SOLO1, PAOLA, and PRIMA market access studies started maintenance therapies no later than 8, 9, or 12 weeks, respectively.

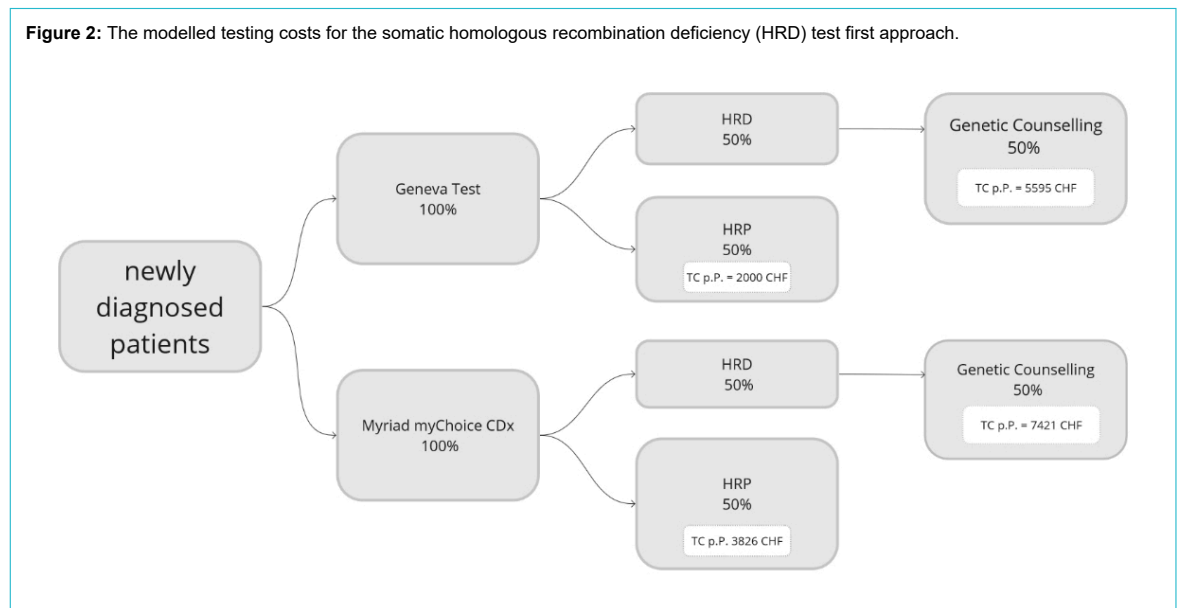
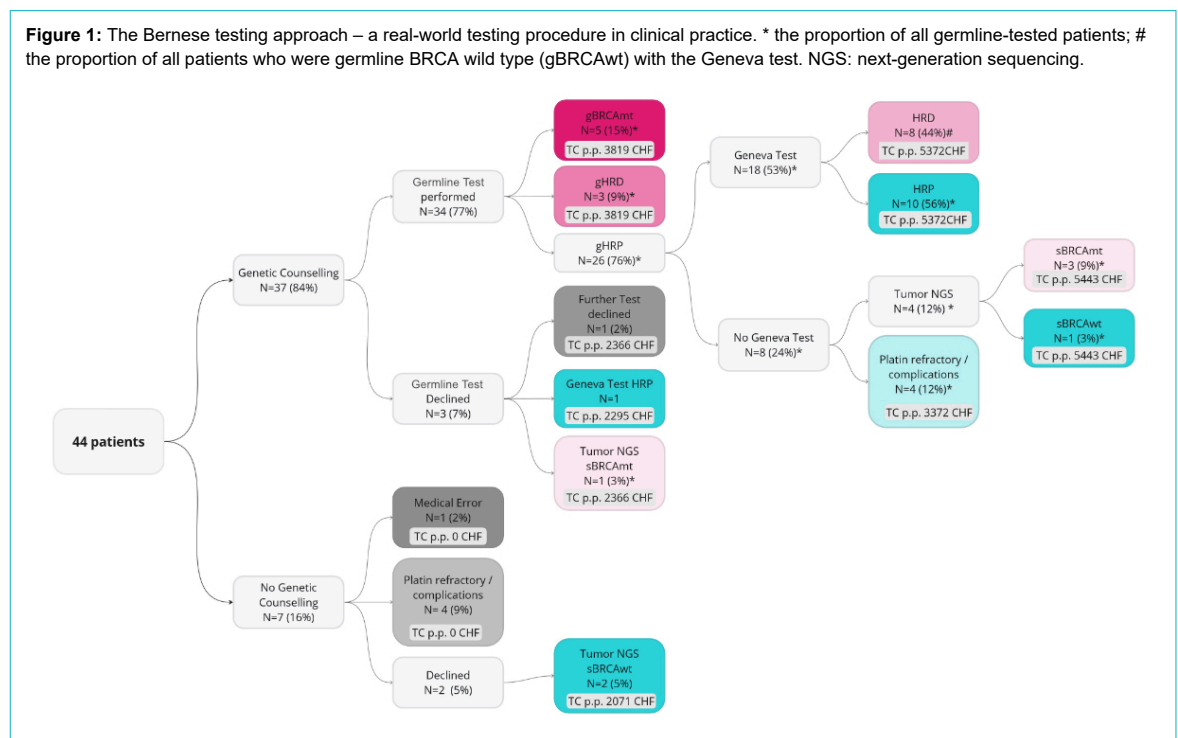
To assess cost-effectiveness, we calculated the total testing costs of the entire population. We compared these costs to a modelled approach in which all patients are given an initial Geneva HRD or myChoice CDx test at diagnosis, ordered at the first multidisciplinary team meeting, followed by germline testing for those with homologous recombination deficiency tumours (figure 2).

Ethical considerations

This study was reviewed and approved by the Local Ethical Committee of the canton of Bern (KEK Bern: 2023-00071).

Endpoints

We examined the numbers and proportions of patients with gBRCAmt, sBRCAmt, homologous recombination-deficient tumours, and homologous recombination-proficient tumours, and the numbers of patients that did not undergo testing for medical or personal reasons. We explored the times from diagnosis, defined as the date of the multidisciplinary team meeting, to genetic counselling, homologous recombination deficiency analysis, chemotherapy completion, and maintenance therapy initiation to deter-



mine whether our testing approach was feasible in clinical practice. Disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS) from diagnosis and the initiation of maintenance therapy were examined. In addition, total testing and treatment costs per patient were calculated.

Statistical analyses

All statistical analyses were performed with GraphPad Prism (version 9.5.1). A 95% confidence interval (95% CI) was calculated for the mean in all graphs. Mean costs were compared with an unpaired *t*-test. Kaplan-Meier survival functions and corresponding *p*-values were calculated with the Log-rank (Mantel-Cox) test. Hazard ratios (HRs) and their 95% CIs were calculated using the Mantel-Haenszel method.

Costs

The costs were calculated based on the sum of all costs invoiced to health insurers in the Swiss healthcare system. Medical and nursing services are billed based on the uniform tariff structure called TARMED (Tarmed Browser 01.09_BR). Laboratory diagnostics costs were calculated according to the Swiss list of analyses [20], including genetic counselling, germline analysis, the Geneva test, and somatic next-generation sequencing. To determine the expenses on maintenance therapy, we recorded all regularly scheduled medical consultations, including nursing services, laboratory analyses, and medication costs. Total maintenance therapy costs were adjusted to the median duration of treatment of the ICON7, PRIMA, PAOLA, and SOLO1 studies [10, 11, 21, 22]. The medication prices correspond to the approved official price (table S1 in the appendix).

Results

Patient characteristics

This study included 44 patients diagnosed with high-grade serous ovarian cancer and a median age of 66 (range: 38–88) years (table 1), of which 14 (32%) had FIGO Stage IV and 30 (68%) had FIGO Stage III. Thirty-eight (86%) patients underwent debulking surgery and received platinum-based chemotherapy. In addition, 23 patients (52%) had started maintenance therapy, and four (9%) had been planned for maintenance therapy but had not initiated it at the data cut-off. Moreover, 17 (39%) patients were assigned for follow-up, mainly those with primary refractory disease or FIGO Stage III homologous recombination-proficient tumours. Only patients carrying a BRCAmt or with homologous recombination-deficient tumours started PARPi maintenance. Combined maintenance therapy with olaparib and bevacizumab was initiated in five patients harbouring a somatic or germline *BRCA* mutation and five patients with homologous recombination-deficient tumours without a *BRCA* mutation. Olaparib was given as a maintenance therapy to four patients with either a sBRCAmt or gBRCAmt. Niraparib was only given to patients with homologous recombination-deficient tumours without a BRCAmt. Bevacizumab maintenance therapy was

only prescribed to patients with homologous-proficient tumours (table 1).

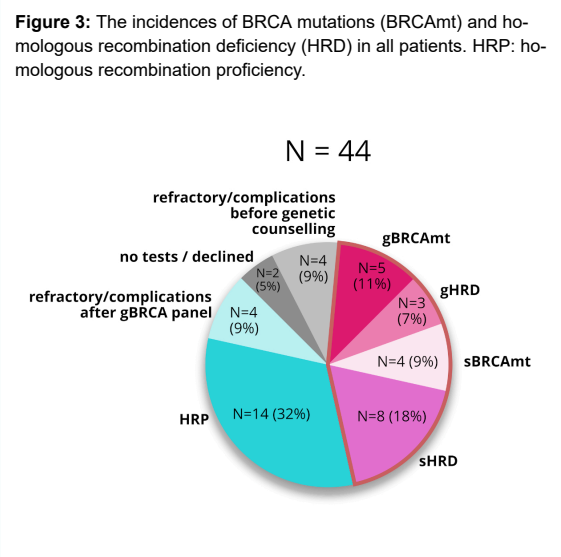
Genetic counselling and homologous recombination deficiency analysis

The multidisciplinary team recommended genetic counselling to all 44 patients, of which seven (16%) received no counselling due to medical reasons such as platinum-refractory disease ($n = 2$, 5%), defined as progression during first-line chemotherapy, complications or death ($n = 2$, 5%), declining the consultation ($n = 2$, 5%), or not being offered a consultation ($n = 1$, 2%); the reason for this could not be determined with certainty in the retrospective data analysis. Of the 37 patients (84%) who received genetic counselling, three declined germline testing and were offered a Geneva test ($n = 1$, homologous recombination-proficient tumour) or somatic next-generation sequencing ($n = 1$, sBRCAmt detected).

Of the 34 patients who underwent germline testing, five (15%) carried a gBRCAmt, and three (9%) carried a germline mutation in a homologous recombination deficiency-causing gene. No further testing was recommended for four (12%) of the remaining 26 patients (76%) because they developed platinum-refractory disease, defined as progression during first-line chemotherapy, or experienced substantial toxicity that contradicted maintenance therapy. Eighteen patients underwent a Geneva test, of which eight (44%) were identified as homologous recombination deficient and 10 (56%) as homologous recombination proficient. The Geneva test was infeasible for four (12%) patients due to tissue quality, and they were examined by somatic next-generation sequencing, which identified an sBRCA in three (9%; figures 1, 3, 4 and 5).

Feasibility in clinical practice

Genetic counselling followed by homologous recombination deficiency testing was initiated at the first multidisciplinary team meeting. The mean time from this meeting to the availability of a germline test result was 15.7 weeks, and the completion of subsequent homologous recombina-



tion deficiency testing was 20.2 weeks. The median time from the completion of chemotherapy to the initiation of maintenance therapy was 5.2 weeks; this estimate includes patients who received a delayed debulking surgery, defined as surgery after the completion of chemotherapy, which prolongs the time between the completion of chemotherapy and the initiation of maintenance. This median was 3.7

weeks when patients with delayed debulking surgery were excluded (figure 6).

Costs of the Bernese testing approach

The total healthcare costs for genetic counselling and homologous recombination deficiency analysis were summarised (figure 1). Seven patients did not undergo genetic

Figure 4: The incidences of BRCA mutations (BRCAmt) and homologous recombination deficiency (HRD) in all patients who received genetic counselling. HRP: homologous recombination proficiency.

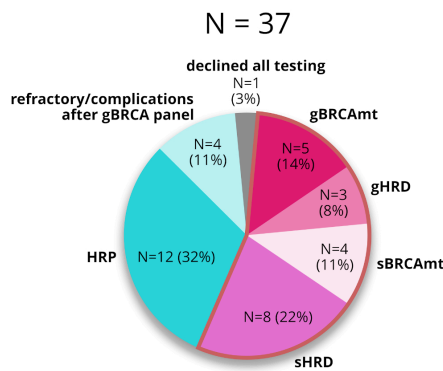


Figure 5: The incidences of BRCA mutations (BRCAmt) and homologous recombination deficiency (HRD) in all patients who received germline testing. HRP: homologous recombination proficiency.

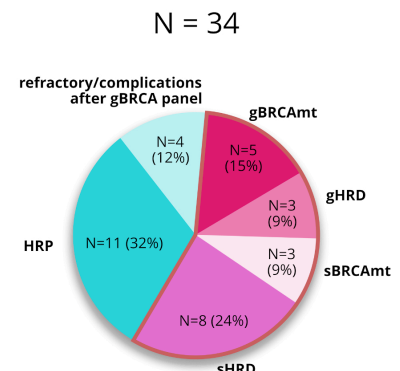


Table 1: Patient characteristics.

Patient characteristics		
Age at diagnosis (years), median (range)		66 (38–88)
FIGO Stage at diagnosis, n (%)	III	30 (68%)
	IV	14 (32%)
Surgery, n (%)	Primary debulking surgery	16 (36%)
	Interval debulking surgery	18 (41%)
	Delayed debulking surgery	4 (9%)
	No debulking surgery (Laparoscopy only)	6 (13%)
Resection status, n (%)	R0	33 (87%*)
	R1	2 (5%*)
	R2	3 (8%*)
	N/A (no debulking)	6 (13%)
Systemic treatment, n (%)	Neoadjuvant chemotherapy	22 (50%)
	– Carboplatin/paclitaxel	9 (20%)
	– Carboplatin/paclitaxel/bevacizumab	13 (30%)
	Adjuvant chemotherapy	16 (36%)
	– Carboplatin/paclitaxel	10 (23%)
	– Carboplatin/paclitaxel (including nab-paclitaxel)/bevacizumab	5 (11%)
	– Carboplatin monotherapy	1 (2%)
	Palliative first-line chemotherapy	6 (14%)
	– Carboplatin/paclitaxel	3 (7%)
	– Carboplatin/paclitaxel/bevacizumab	2 (5%)
	– Carboplatin monotherapy	1 (2%)
	Maintenance therapy	23 (52%)
	– Bevacizumab and olaparib	10 (23%)
	– Olaparib	4 (9%)
– Niraparib	3 (7%)	
– Bevacizumab	6 (14%)	
No maintenance therapy	17 (39%)	
Not yet started	4 (9%)	
Follow-up (months), median (range)		13.6 (2.0–27.9)

* percentage of patients with (interval-)debulking surgery

counselling. Two patients who were not germline tested underwent tumour next-generation sequencing (2071 CHF per patient [p.p.]). One patient who was not germline tested had received prior genetic counselling and later underwent tumour next-generation sequencing (2366 CHF p.p.). One patient had received genetic counselling but then underwent a Geneva test instead of a germline test (2295 CHF p.p.). Eight patients carried a gBRCAmt or another mutation causing homologous recombination deficiency and underwent no further testing (3819 CHF p.p.). Four patients underwent no further testing after a non-mutated germline result (3372 CHF p.p.). Four patients underwent tumour next-generation sequencing and a germline test (5443.6 CHF p.p.). Eighteen patients underwent both a GENEVA test and a germline analysis (5372 CHF p.p.; figure 1).

The mean testing cost across the 44 patients was 3880 CHF p.p. If we had used the Myriad myChoice CDx test instead of the Geneva test, the mean total testing cost would have been 4669 CHF p.p. Estimates were calculated to compare the cost-effectiveness of our testing approach to giving a somatic homologous recombination deficiency test to all patients at diagnosis. If all patients first undergo a Geneva test, total test costs would be 3798 CHF p.p. If they instead first undergo a Myriad myChoice CDx test, total testing costs would be 5624 CHF p.p. There was no statistically significant difference if the Geneva test was used ($p = 0.8357$). However, the mean test costs were significantly lower if a myChoice CDx test was used ($p = 0.0467$; figure 7).

Clinical cancer-related outcomes of the studied cohort

At 12 and 24 months after diagnosis, 84% and 65% were disease-free, respectively (data maturity was 59% and 16%, respectively; figure 8). The median follow-up time was 13.6 months. Patients with homologous recombination-deficient tumours had a significantly longer DFS than

patients diagnosed with homologous-proficient tumours ($HR = 0.25$, 95% CI = 0.07–0.82; $p = 0.022$; figure 9). One year after diagnosis, 90% were alive (64% data maturity), and two years after diagnosis, 76% were alive (data maturity 18%; figure 10). The PFS with maintenance therapy was significantly longer in patients with homologous recombination-deficient tumours than in patients with homologous recombination-proficient tumours ($HR = 0.09$, 95% CI = 0.01–0.81; $p = 0.032$; figure 11).

Total therapy costs

At our centre, the resulting total healthcare costs p.p. for maintenance therapy were 133,513 CHF for 24 months of olaparib monotherapy, 126,241 CHF for 24 months of niraparib monotherapy, 197,576 CHF for combined olaparib (24 months) and bevacizumab (15 months) therapy, and 38,628 CHF for bevacizumab monotherapy. Adjusted to the median treatment durations in the SOLO1, PRIMA, PAOLA, and ICON7 studies, these costs become 133,513 CHF, 58,761 CHF, 164,511 CHF, and 34,769 CHF (table S1).

Figure 6: The mean time from the multidisciplinary team (MDT) meeting to the test results and from the completion of chemotherapy to the initiation of maintenance therapy.

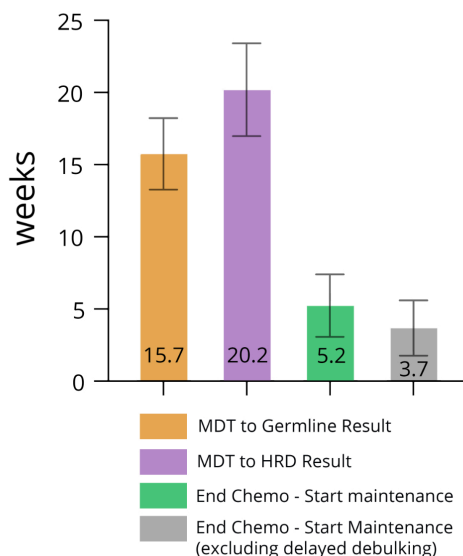


Figure 7: The mean testing costs per patient.

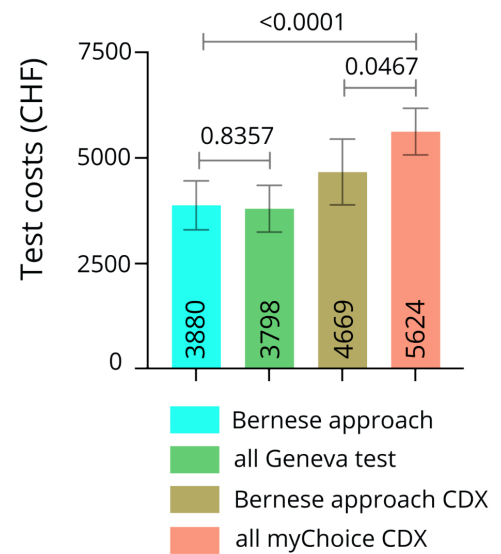
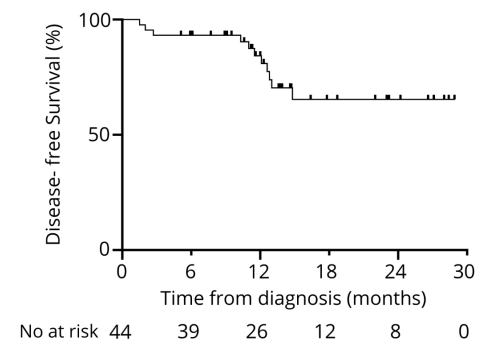


Figure 8: Disease-free survival from diagnosis.



Discussion

The presented real-world data demonstrate that a testing approach involving germline analysis followed by somatic homologous recombination deficiency testing with the Geneva test for patients with newly diagnosed advanced high-grade serous ovarian cancer is feasible in clinical

Figure 9: Overall survival from diagnosis.

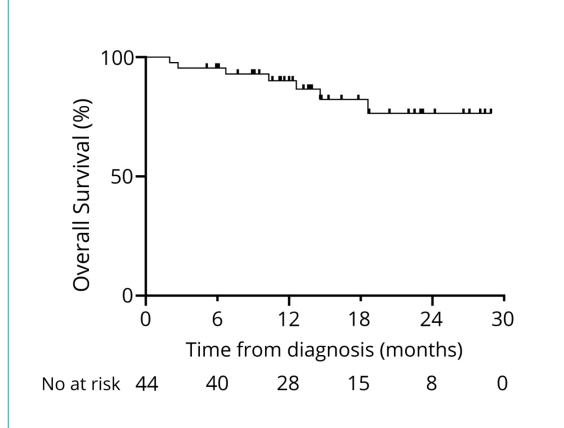


Figure 10: Comparison of disease-free survival with homologous recombination deficiency (HRD) or no homologous recombination deficiency (No HRD).

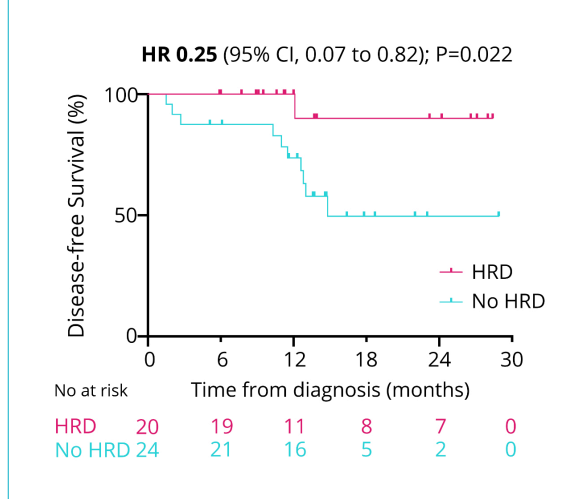
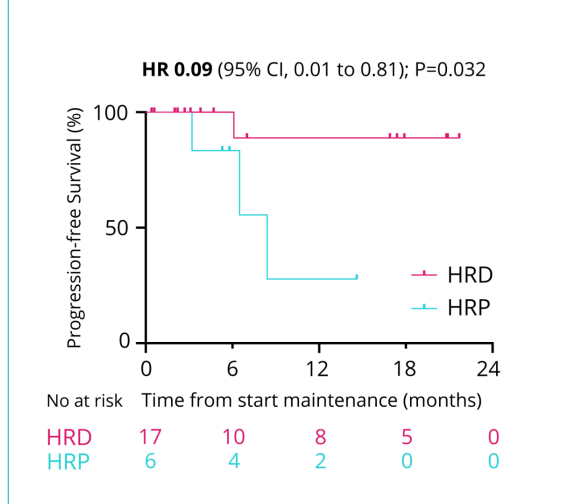


Figure 11: Progression-free survival with maintenance therapy.



practice. It does not lead to clinically meaningful delays in initiating maintenance therapy. Given the prevention of unnecessary testing for patients who would not qualify for a PARPi, such as those with platinum-refractory disease, the total testing costs per patient do not differ from the algorithm-estimated costs of first testing all patients somatically for homologous recombination deficiency followed by genetic counselling. Modelling testing costs with the more expensive myChoice CDx test showed that the Bernese approach is cost-effective compared to a homologous recombination deficiency test at diagnosis. Clinical outcomes were not evidently worse than those in SOLO1, PAOLA, and PRIMA studies. For example, 88% of patients were progression-free at one year and 74% at two years in the SOLO 1 study. In contrast, these proportions were 88% and 65% in our cohort with limited follow-up, but considering that many patients had less favourable prognoses since most did not harbour a BRCAmt [10, 21]. The Bernese testing approach successfully identified candidates for PARPi maintenance therapy since DFS and PFS were significantly longer in those with homologous recombination deficient tumours than those with non-homologous recombination deficiency tumours.

The Bernese testing approach follows the current ASCO guidelines [16] and meets the requirements of Swiss law since homologous recombination deficiency or somatic NGS testing of unconsented patients is unlawful [18]. Despite the high costs of genetic counselling and germline analysis, this approach does not increase the testing costs or is even more cost-effective if the myChoice CDx test is used instead of the Geneva test. Our real-world data demonstrates that an upfront testing strategy with a somatic tumour-based test, such as a next-generation sequencing or homologous recombination deficiency test, indicated at the first multidisciplinary team does not lower testing costs as a Canadian model suggests [19]. Unlike a Dutch study that proposed a reciprocal testing strategy that combined somatic *BRCA* testing with somatic next-generation sequencing but did not address homologous recombination deficiency [23], the Bernese testing approach aims to identify patients with gBRCAmt and homologous recombination deficient ovarian tumours, which ensures no patients risk of missing out on gBRCAmt diagnoses [17]. All patients without gBRCAmt are considered for a Geneva test or, if infeasible, somatic next-generation sequencing. The Swiss label for niraparib and olaparib/bevacizumab requires a validated homologous recombination deficiency test, which can be a Geneva or myChoice CDx test [6]. Despite previous results demonstrating the cost-effectiveness of biomarker-driven PARPi maintenance, we do not observe this in our cohort since total maintenance costs would be higher if niraparib were given to all patients with a gBRCAwt [13, 14, 25]. Compared with a prevalence of a genomic instability score of at least 42 of 37% reported in a recent British study on 2829 patients, we found a higher prevalence of 44%, which could be explained by avoiding testing in patients with primary platinum-refractory disease [5].

This study shows for the first time that genetic counselling followed by germline testing and homologous recombination deficiency analysis for patients without a gBRCAmt is feasible and cost-effective in clinical practice, provided

sufficient resources for prompt genetic counselling exist. Unlike all other models, our data account for some patients not being tested for homologous recombination deficiency for medical reasons and would never qualify for maintenance therapy [19, 23]. The applied and suggested testing approach is consistent with current guidelines and permits an informed-consent-based decision-making process, unlike any routine somatic tumour next-generation sequencing or homologous recombination deficiency automated testing approach [1, 8, 16].

To date, some clinicians and institutes have refrained from consistently conducting primary germline analysis on patients newly diagnosed with advanced high-grade serous ovarian cancer due to assumptions that such an approach would lead to additional costs and delays in initiating maintenance therapy [19, 23].

This study demonstrates that a germline-first testing approach is both cost-efficient and feasible in routine clinical practice in Switzerland. Moreover, it should be routinely offered since it adheres to the international gold standard. It ensures that patients are well-informed about the potential implications of familial inherited cancer syndromes, enabling them to make self-determined decisions regarding the analysis [16]. This approach also maximises the likelihood of detecting a germline mutation since large *BRCA* deletions can be missed with conventional somatic next-generation sequencing panels [17]. It clearly demonstrates that the requirements of Swiss law that informed consent be obtained before genetic analysis are feasible for patients with newly diagnosed ovarian cancer. This testing approach should be applied to all patients newly diagnosed with ovarian cancer since it is based on individual informed consent, enables the detection of potentially homologous recombination deficient tumours, and meets the requirements of the Swissmedic label for maintenance therapies with olaparib, niraparib, or olaparib combined with bevacizumab.

As a real-life retrospective single-centre cohort study with relatively few patients, its results should be interpreted cautiously. Its conclusions are based on local tariffs and apply only to the Swiss healthcare system. Therefore, a larger international, prospective, multicentre, real-world analysis is warranted.

Conclusions

We showed for the first time that germline testing followed by homologous recombination deficiency analysis for those without a gBRCAmt is feasible for patients with newly diagnosed ovarian cancer. This testing approach does not delay the initiation of maintenance treatment, which was initiated within 5.2 weeks after the completion of chemotherapy. The pre-test probability of homologous recombination deficiency, as assessed by the Geneva test, was 44% if patients with primary platinum-refractory disease were not tested. Finally, we demonstrated that this test approach does not increase total testing costs per patient. It can even lower total healthcare costs if homologous recombination deficiency is assessed using the myChoice CDx test based on Swiss prices.

Acknowledgments

The authors would like to thank all patients for consenting to the use of their anonymous healthcare data.

Author contributions: Saskia Schlootz: Project development, data collection and analysis, health care cost calculation, wrote the manuscript. Flurina A.M. Saner: Project development, data analysis and editing the final manuscript. Manuela Rabaglio: Project development, data analysis and editing the final manuscript. Sara Imboden: Project development and editing the final manuscript. Julian Wampfler: Project development, data collection and analysis, seeking ethical committee approval, wrote the manuscript.

Financial disclosure

This study was not supported by any grants or industry contribution.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. The following potential conflicts of interest related to the content of this manuscript were reported: JW: Julian Wampfler: Received travel assistance by AstraZeneca and has taken part in advisory boards for MSD, AstraZeneca, GSK, Daiichi Sankyo and Exact Sciences. All financial compensation was fully donated to the University Clinic for Medical Oncology in favour of educational activities for residents. No other potential conflict of interest related to the content of this manuscript was disclosed.

References

- González-Martín A, Harter P, Leary A, Lorusso D, Miller RE, Pothuri B, et al.; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2023 Oct;34(10):833–48. <http://dx.doi.org/10.1016/j.annonc.2023.07.011>.
- Matulonis U, Herrstedt J, Oza A, Mahner S, Redondo A, Berton D, et al. Long-term safety and secondary efficacy endpoints in the ENGOT-OV16/NOVA phase III trial of niraparib in recurrent ovarian cancer. *Gynecol Oncol.* 2021;162:S24–5. [http://dx.doi.org/10.1016/S0090-8258\(21\)00693-4](http://dx.doi.org/10.1016/S0090-8258(21)00693-4).
- Poveda A, Floquet A, Ledermann JA, Asher R, Penson RT, Oza AM, et al.; SOLO2/ENGOT-Ov21 investigators. Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2021 May;22(5):620–31. [http://dx.doi.org/10.1016/S1470-2045\(21\)00073-5](http://dx.doi.org/10.1016/S1470-2045(21)00073-5).
- Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. *Cancer Discov.* 2015 Nov;5(11):1137–54. <http://dx.doi.org/10.1158/2159-8290.CD-15-0714>.
- Morgan RD, Clamp AR, Barnes BM, Timms K, Schlecht H, Yarram-Smith L, et al. Homologous recombination deficiency in newly diagnosed FIGO stage III/IV high-grade epithelial ovarian cancer: a multinational observational study. *Int J Gynecol Cancer.* 2023 Aug;33(8):1253–9. <http://dx.doi.org/10.1136/ijgc-2022-004211>.
- Christinat Y, Ho L, Clément S, Genestie C, Sehoul J, Martin AG, et al. 2022-RA-567-ESGO The Geneva HRD test: clinical validation on 469 samples from the PAOLA-1 trial. *Int J Gynecol Cancer.* 2022;32 Suppl 2:A238–9.
- Heitz F, Ataseven B, Staniczok C, Denkert C, Rhiem K, Hahnen E, et al. Implementing HRD Testing in Routine Clinical Practice on Patients with Primary High-Grade Advanced Ovarian Cancer. *Cancers (Basel).* 2023 Jan;15(3):818. <http://dx.doi.org/10.3390/cancers15030818>.
- Miller RE, Leary A, Scott CL, Serra V, Lord CJ, Bowtell D, et al. ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. *Ann Oncol.* 2020 Dec;31(12):1606–22. <http://dx.doi.org/10.1016/j.annonc.2020.08.2102>.
- DiSilvestro P, Banerjee S, Colombo N, Scambia G, Kim BG, Oaknin A, et al.; SOLO1 Investigators. Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: the SOLO1/GOG 3004 Trial. *J Clin Oncol.* 2023 Jan;41(3):609–17. <http://dx.doi.org/10.1200/JCO.22.01549>.
- González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al.; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in Patients with Newly Diagnosed Advanced Ovarian

- Cancer. *N Engl J Med.* 2019 Dec;381(25):2391–402. <http://dx.doi.org/10.1056/NEJMoa1910962>.
- 11 Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al.; PAOLA-1 Investigators. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *N Engl J Med.* 2019 Dec;381(25):2416–28. <http://dx.doi.org/10.1056/NEJMoa1911361>.
 - 12 Ray-Coquard I, Leary A, Pignata S, Cropet C, González-Martín A, Marth C, et al.; PAOLA-1/ENGOT-ov25 investigators. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. *Ann Oncol.* 2023 Aug;34(8):681–92. <http://dx.doi.org/10.1016/jannonc.2023.05.005>.
 - 13 Gonzalez R, Havrilesky LJ, Myers ER, Secord AA, Dottino JA, Berchuck A, et al. Cost-effectiveness analysis comparing “PARP inhibitors-for-all” to the biomarker-directed use of PARP inhibitor maintenance therapy for newly diagnosed advanced stage ovarian cancer. *Gynecol Oncol.* 2020 Nov;159(2):483–90. <http://dx.doi.org/10.1016/j.ygyno.2020.08.003>.
 - 14 Penn CA, Wong MS, Walsh CS. Cost-effectiveness of Maintenance Therapy Based on Molecular Classification Following Treatment of Primary Epithelial Ovarian Cancer in the United States. *JAMA Netw Open.* 2020 Dec;3(12):e2028620. <http://dx.doi.org/10.1001/jamanetworkopen.2020.28620>.
 - 15 Sessa C, Balmaña J, Bober SL, Cardoso MJ, Colombo N, Curigliano G, et al.; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. *Ann Oncol.* 2023 Jan;34(1):33–47. <http://dx.doi.org/10.1016/jannonc.2022.10.004>.
 - 16 Konstantinopoulos PA, Norquist B, Lacchetti C, Armstrong D, Grisham RN, Goodfellow PJ, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. *J Clin Oncol.* 2020 Apr;38(11):1222–45. <http://dx.doi.org/10.1200/JCO.19.02960>.
 - 17 Eoh KJ, Kim HM, Lee JY, Kim S, Kim SW, Kim YT, et al. Mutation landscape of germline and somatic BRCA1/2 in patients with high-grade serous ovarian cancer. *BMC Cancer.* 2020 Mar;20(1):204. <http://dx.doi.org/10.1186/s12885-020-6693-y>.
 - 18 Stoll S, Unger S, Azzarello-Burri S, Chappuis P, Graffeo R, Pichert G, et al. Update Swiss guideline for counselling and testing for predisposition to breast, ovarian, pancreatic and prostate cancer. *Swiss Med Wkly.* 2021 Sep;151(3738):w30038. <http://dx.doi.org/10.4414/SMW.2021.w30038>.
 - 19 Kwon JS, Tinker AV, Santos J, Compton K, Sun S, Schrader KA, et al. Germline Testing and Somatic Tumor Testing for *BRCA1/2* Pathogenic Variants in Ovarian Cancer: What Is the Optimal Sequence of Testing? *JCO Precis Oncol.* 2022 Oct;6(6):e2200033. <http://dx.doi.org/10.1200/PO.22.00033>.
 - 20 Analysenliste, Krankenpflege-Leistungsverordnung KLV, Anhang 3. In: (EDI) EDdI, editor. Bundesamt für Gesundheit 2023.
 - 21 Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med.* 2018 Dec;379(26):2495–505. <http://dx.doi.org/10.1056/NEJMoa1810858>.
 - 22 Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al.; ICON7 Investigators. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med.* 2011 Dec;365(26):2484–96. <http://dx.doi.org/10.1056/NEJMoa1103799>.
 - 23 Witjes VM, Ligtenberg MJ, Vos JR, Braspenning JC, Ausems MG, Mourits MJ, et al. The most efficient and effective BRCA1/2 testing strategy in epithelial ovarian cancer: Tumor-First or Germline-First? *Gynecol Oncol.* 2023 Jul;174:121–8. <http://dx.doi.org/10.1016/j.ygyno.2023.04.029>.
 - 24 González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al.; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med.* 2019 Dec;381(25):2391–402. <http://dx.doi.org/10.1056/NEJMoa1910962>.
 - 25 Elsea D, Fan L, Mihai A, Moustaid FE, Simmons D, Monberg M, et al. Cost-Effectiveness Analysis of Olaparib in Combination with Bevacizumab Compared with Bevacizumab Monotherapy for the First-Line Maintenance Treatment of Homologous Recombination Deficiency-Positive Advanced Ovarian Cancer. *Pharmacoeconom Open.* 2022 Nov;6(6):811–22. <http://dx.doi.org/10.1007/s41669-022-00338-2>.

Appendix: supplementary table

Table S1:

Total maintenance healthcare costs, including nursing, laboratory, consultations, and medications, adjusted by the median duration of maintenance therapy.

Maintenance regimen	Total costs for entire maintenance in analogous studies (CHF)	Total costs per median treatment duration (CHF)
Olaparib	133,513	133,513
Niraparib	126,241	58,761
Olaparib & bevacizumab	197,576	164,511
Bevacizumab	38,628	34,769