Gynecologic Oncology Reports 48 (2023) 101246

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

The impact of an educational and information systems initiative on somatic *BRCA* testing rates in patients with high grade serous tubo-ovarian cancer in Western Australia

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ARTICLE INFO

Keywords:
High grade serous ovarian cancer
BRCA testing
PARP inhibitor
Genetics
Mainstreaming

ABSTRACT

Objective: Poly-ADP ribose polymerase inhibitors (PARPi) have expanded the management armamentarium against high grade serous tubo-ovarian cancer (HGSOC) in patients with germline and somatic *BRCA* pathogenic variants (PVs). Germline testing has been available in Western Australia (WA) since July 2015, whilst somatic *BRCA* testing was previously only available through interstate laboratories. We hypothesized that due to complexity of referral, testing rates for somatic *BRCA* would be low. We aimed to demonstrate that improving education and information systems would improve testing rates in our service.

Methods: Retrospective data were collected for all patients with HGSOC reviewed between June – November 2021. *BRCA* testing for this period was discussed at multi-disciplinary tumor board. Patients eligible to commence PARPi that had not received somatic testing were referred. Changes were implemented to patient outcome reports, the results application was adjusted to flag clinicians, departmental guidelines were developed, and teaching sessions conducted. Testing rates from March – August 2022 were compared.

Results: From June – November 2021, 98% of patients had germline *BRCA* testing performed. PVs in *BRCA1/2* were detected in 18% of patients. Of those without germline PVs, further somatic *BRCA* testing was referred in 42% of patients. One somatic PV was detected. From March – August 2022, 99% of patients had germline *BRCA* testing and 17% had PVs detected. Further somatic *BRCA* testing was referred in 72% of patients. No somatic PVs were detected.

Conclusion: Testing rates for germline *BRCA* variants in patients with HGSOC in WA are high. Focused education and information systems improved somatic *BRCA* testing rates.

1. Introduction

High grade serous tubo-ovarian cancer (HGSOC) is frequently associated with homologous recombination deficiency (HRD), including and not limited to pathogenic variants (PVs) in *BRCA1* and *BRCA2*. Germline *BRCA* PVs are present in around 15% of cases of HGSOC (Alsop et al., 2012; Zhang et al., 2011). Clinically significant *BRCA* PVs can also develop sporadically in the tumor itself (acquired or somatic PVs) and may additionally be present in a further 5–10% of HGSOC patients (Network, 2011; Hauke et al., Sep 2019). Furthermore, HRD is not limited to variants in *BRCA* genes. Definitions of HRD vary, but broadly, PVs in multiple genes in the homologous recombination pathway including *BRIP1, PALB2, RAD51, ATM*, and others, have been identified as relevant, in addition to gene promoter hypermethylation and other epigenetic modifications (Yang et al., 2005; Catteau et al., 1999; McMullen et al., 2020). It is thus estimated that HRD in some form may be present in up to 50% of HGSOC (Fuh et al., 2020).

Poly-ADP ribose polymerase inhibitors (PARPi) exploit the concept of synthetic lethality to target cancers which harbor HRD (Iglehart and Silver, 2009). Initial trials in HGSOC focused largely on patients with *BRCA* PVs and this appears to be the population of patients who derive the largest magnitude of benefit from PARPi. The Phase III SOLO2 (Pujade-Lauraine et al., 2017) and SOLO1 (Moore et al., 2018) trials first revealed a benefit for using the PARPi olaparib as a maintenance therapy

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https://doi.org/10.1016/j.gore.2023.101246
Received 31 May 2023; Received in revised form 6 July 2023; Accepted 14 July 2023
Available online 16 July 2023

post completion of platinum-based chemotherapy in patients with germline or somatic *BRCA* PVs. Both trials met their primary endpoint of improved progression free survival (PFS) in the recurrent (SOLO2) and first line (SOLO1) setting (Pujade-Lauraine et al., 2017; Moore et al., 2018) and subsequently reported statistically non-significant but numerical improvements in overall survival (OS) (Poveda et al., 2021; DiSilvestro et al., 2022). Despite the benefit seen in those with *BRCA* PVs, subsequent first line trials including PAOLA-1, VELIA, ATHENA MONO, PRIMA and PRIME have revealed that those with non-*BRCA* somatic HRD still seem to derive a significant, albeit lesser, benefit from maintenance PARPi treatment (Ray-Coquard et al., 2019; González-Martín et al., 2019; Monk et al., 2022; Coleman et al., 2019; Li et al., 2022). On this basis, multiple guidelines recommend the routine testing of all patients with HGSOC for both germline *BRCA* status and somatic HRD analysis. Despite this, PARPi are only subsidized in Australia for patients with germline or somatic *BRCA* PVs, and not in those with non-*BRCA* HRD. Likewise, only somatic *BRCA* variant analysis is subsidized in Australia.

Germline PVs carry an inheritable genetic risk and implication for family members and thus germline testing requires consenting and genetic counselling. Mainstreaming, a process of allowing surgeons, oncologists and clinical nurses to consent and refer for germline genetic testing, rather than via genetic services; has been available in Western Australia (W.A.) since July 2015. Mainstreaming has been shown to substantially increase the uptake of germline *BRCA* testing in ovarian cancer populations in W.A (Stearnes et al., 2019). Somatic *BRCA* testing remains important even in those without detectable germline PVs as somatic alterations in *BRCA1/2* are still prevalent in germline wild-type patients (Hauke et al., Sep 2019). Reflex somatic testing, where tumor testing occurs automatically as part of the standard pathology review protocol, is not currently routine in Australia. In addition, somatic *BRCA* testing only became available in W.A. in July 2022. Prior to this, somatic testing required pathology specimens being sent interstate to Victoria; creating an administrative and logistical barrier to access. Clinician and patient consent were required to extract specimens from the local pathology providers, and adequate samples needed to be sent across Australia for mutational analysis. The estimated time for testing was several weeks to months whilst patients completed their frontline chemotherapy.

We hypothesized that due to the complexity of somatic *BRCA* testing referral requirements, rates of testing would be low. Studies have highlighted how policy frameworks, guidelines, clinical decision support tools and education and training of health staff are pivotal in improving genomic testing (Alarcón Garavito et al., 2023). We aimed to show that an educational and information systems initiative would improve testing rates in our service and inform service planning to highlight barriers to testing in W.A.

2. Methods

This was a retrospective study approved by the North Metropolitan Health Service Quality Assurance Committee (reference number 43963). A waiver of consent was granted. Data were collected for all patients with a confirmed histological diagnosis of HGSOC treated at Sir Charles Gairdner Hospital, Western Australia (W.A.) during two six-month periods – June to November 2021 and March to August 2022. As Sir Charles Gairdner Hospital is the only publicly funded hospital in W.A. that provides medical oncology services for ovarian cancer, this single institution does represent a majority of HGSOC seen in W.A. The following variables were collected: diagnosis, stage, ECOG performance status, treatment, relapse status, germline and somatic *BRCA* testing, and prescription of PARP inhibitor.

At the time of study, germline *BRCA* testing including consent, blood sample collection, analysis and reporting were all done locally in W.A. Digital medical record was used to report results. Testing was performed using targeted parallel sequencing with the Illumina TruSight ovarian cancer panel (*BRCA1*, *BRCA2*, *BRIP1*, *RAD51C*, *RAD51D* and truncating variants in the *PALB2* gene) hereon referred to as 'germline *BRCA* testing'. Somatic *BRCA* testing was available via Peter MacCallum Cancer Centre in Melbourne, Victoria. Testing was performed via the QIASeq targeted DNA panel (CDHS-33478Z) which targets PVs in *BRCA1* and *BRCA2*. In Australia, patients with class 4 or 5 *BRCA* variants are eligible for government subsidized PARPi. Class 4 or 5 variants are classified as 'likely pathogenic' and 'pathogenic' variants respectively, as per the American College of Medical Genetics and Genomics nomenclature (Richards et al., 2015).

Results of baseline *BRCA* testing between June to November 2021 were presented in March 2022 at our weekly multi-disciplinary tumor board including gynecologic oncologists, radiation oncologists, medical oncologists, clinical nurses, junior medical staff and genetic services. As a result of this meeting, germline and somatic *BRCA* status were added to the multi-disciplinary tumor board patient outcome reports to facilitate communication to both surgeons and oncologists that testing was still outstanding. Furthermore, a "new results" flag and prompt were added to the tumor board's meeting software (Microsoft Teams) to alert clinicians when germline testing had returned. This would prompt that germline testing was negative, even outside of usual tumor board meeting times, and thus better enforce when further somatic testing was required. A departmental guideline was developed to outline the process of *BRCA* testing (Fig. 1*)*, and teaching sessions were conducted with the Medical Oncology Advanced Trainees within our department. Trainees were educated on the testing processes involved, patient counselling, use of digital medical record and result reporting. Pivotal trials of PARP inhibitors were also reviewed to highlight the impact of testing on clinical outcomes and to increase confidence with patient discussions.

The proportion of patients who underwent somatic *BRCA* testing between June – November 2021 was then compared to the March – August 2022 period. Data cut off for the two time periods was one month post the inclusion period, December 2021 and September 2022 respectively. For ethical reasons, where somatic *BRCA* testing had not been requested previously but the patient was eligible to commence PARPi, a request was made by the investigator at the time of record review. As these patients may have also been cared for during the second time period, it may have artificially inflated the proportion of patients who had somatic testing performed. Therefore, to assess if there had been an increase in uptake a further comparison was made between only new patients seen in the two corresponding time frames.

3. Results

Between June – November 2021, 97 patients with HGSOC attended the outpatient Medical Oncology service at Sir Charles Gairdner Hospital. Nineteen of these patients were new patients to the service and the remaining were patients under existing follow-up. Eighty-two of the patients (85%) had at least Stage III disease. Regarding genetic testing for germline *BRCA* status, 3 patients had declined genetic testing, leaving 94 patients eligible for referral (Table 1). Of these 94 patients, 92 patients (98%) had germline testing performed. Most referrals (89%) were ordered in the first line setting, with the remaining ordered at recurrence. The mean time to germline testing in the first line setting was 76 days (±90 days). Two patients who did not undergo germline testing were still undergoing neoadjuvant chemotherapy at the time of data cut off, and both had a poor performance status of 2 or greater and were considered ineligible for surgical debulking.

Of the 92 patients who had germline testing, 17 patients (18%) had a detected germline pathogenic variant. Olaparib was subsidized in Australia from the 1st Feb 2017 in the recurrent setting and from the 1st Nov 2020 in the front-line setting for patients with class 4/5 *BRCA* PVs. Three patients were diagnosed after 1 Nov 2020, and 2 had eligible *BRCA* PVs to receive government subsidized therapy. Both patients received olaparib in the front-line setting. The other 14 patients were therefore eligible only at recurrence as they had completed first line

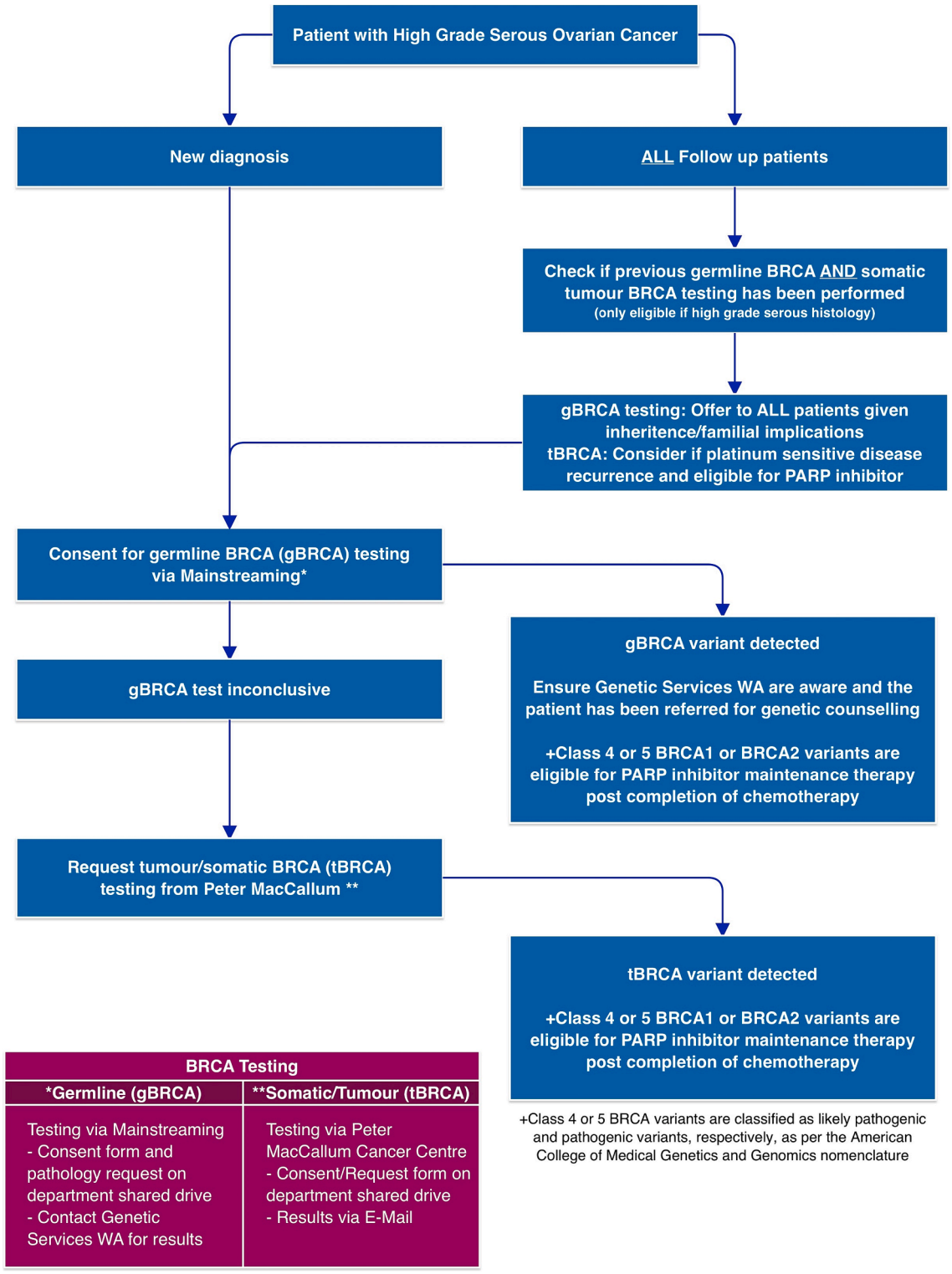

Fig. 1. Department Testing Guide.

treatment and were in follow-up. Eleven of these patients had eligible *BRCA* PVs, eight of whom had recurrent disease and 100% of whom received olaparib. A breakdown of the detected genetic variants is reported below.

Of the total 94 patients eligible for *BRCA* testing in the first six-month period, 77 patients had either no germline variant detected (and therefore would have been suitable for further somatic testing) or had not yet received any germline testing. Of these patients, 32 (42%) were referred for somatic *BRCA* testing to the interstate laboratory. Only 1 patient (3% tested) returned a pathogenic somatic variant (*BRCA1*) which was not present in germline testing. This patient subsequently received olaparib in the first line setting. The reasons for patients not undergoing somatic testing are shown in Table 2. Of the 45 patients who did not undergo somatic testing, 26 patients had no identifiable reason for the test not being performed. At least 16 of these patients (21% of the total 77 eligible) were considered missed as they had already completed

Table 1
Germline and Somatic BRCA testing over the two time periods.

	June to November 2021 Total eligible patients (n = 94)	**March to August 2022 Total eligible patients (n = 106)**
Underwent germline *BRCA* testing	92 patients **(98%)**	105 patients **(99%)**
Pathogenic variant detected	17 patients (18%)	18 patients (17%)
Variant of unknown significance	0 patients	0 patients
No pathogenic variant detected	75 patients	87 patients
Suitable for further somatic *BRCA* testing	77 patients	88 patients
Underwent somatic *BRCA* testing	32 patients **(42%)**	63 patients **(72%)**
Unable to test (sample limitations)	6 patients (19%)	7 patients (11%)
Pathogenic variant detected	1 patient (3%)	0 patients
Variant of unknown significance	3 patients	2 patients

Table 2
Reasons somatic testing was not performed in the two time periods.

Patients who did not undergo somatic testing	**June to November 2021(n = 45)**	**March to August 2022(n = 25)**
Early Stage (I-II) and no recurrence to date	6	4
Advanced disease or platinum resistant (i.e. no indication for testing)	8	8
Poor ECOG for further treatment	2	4
Declined PARP inhibitor so not tested	1	0
Pending surgery for further tissue for testing	0	1
Pending germline testing at time of data collection	2	1
No reason provided	**26**	**7**
Patients still on chemotherapy at time of audit	10	3
Missed opportunity for testing	**16 (21% eligible)**	**4 (4.5% eligible)**

their platinum-based chemotherapy and may have been eligible to commence maintenance PARP inhibition at data cut off. The final determined somatic *BRCA* testing miss rate was therefore 21% over this period.

Between March to August 2022 following the period of education and adjustment of information systems, 108 patients with HGSOC were seen in the medical oncology outpatient clinic. Nineteen patients were new to the service during this time. 82 patients (76%) had been seen previously between June and November 2021. Ninety-two of the patients (85%) of the patients had at least Stage III disease. Of the 108 patients eligible for germline *BRCA* testing, 2 patients declined testing. 105 of the remaining 106 patients (99%) had germline testing performed (Table 1). The one patient who did not have germline testing had a poor performance status and died before initiation of chemotherapy or any surgical intervention. In 89% of the cases testing was ordered in the first line setting. The mean time to testing in the first line setting was 48 days (±93 days). Eighteen patients had a detected germline PV (17%), of which two patients had not been seen in the previous period, one of whom had recurrent disease and was planned for olaparib maintenance therapy. The other patient had early-stage disease and was thus not eligible for maintenance PARP inhibitor in the first line setting.

Of the total 106 patients eligible for *BRCA* testing during this period, 88 patients had no PV on germline testing or were still eligible for further somatic testing. Of these, 72% (63 patients) were referred for somatic testing compared to only 42% in the June – November 2021 period (OR 3.54, p = 0.0001). Between March – August 2022, no new patients returned a PV on somatic testing, however, two patients had variants of unknown significance detected. Table 2 compares the reasons for patients potentially not undergoing somatic testing during this period. Of the 25 patients who did not undergo somatic testing, only 7 patients had no identifiable reason for the test not being performed. Of these, only 4 patients (4.5% of the total 88 patients eligible) were considered missed as they had already completed their platinum-based chemotherapy and may have been eligible to commence maintenance PARPi at data cut off. The final determined somatic *BRCA* testing miss rate was therefore 4.5% during this period, compared to 21% between June – November 2021.

Patients identified in the June to November 2021 period where somatic testing had not been performed, but who were eligible to commence PARPi, had testing requested by the investigator at the time of review. As these patients may have also been cared for during the second time period, a further comparison was made between only new patients seen in the two corresponding time frames. In both six-month periods there were 19 new patients to the service over each period. In the original period, there were 15 patients eligible for testing (3 already had a detected germline variant and 1 had declined testing) and of these 5 patients received somatic testing for a final testing rate of 33.3%. In the second period, 17 patients were eligible for testing (excluding 2 who had detected germline variants), and 10 patients received somatic testing for a final testing rate of 58.8% (OR 2.85, p = 0.15). It is worth noting that most of these patients were still on front-line chemotherapy at the time of data collection and thus still had time for somatic testing to be performed prior to PARPi initiation.

Over the duration of the study, a total of 22 patients were identified with germline or somatic HRD PVs out of the 123 patients included. This gave a final detected PV rate of 18% across both time periods. Detected variants are shown in Table 3. Of note, only 1 patient had a pathogenic *BRCA1* variant detected on somatic tumor analysis throughout the duration of study which subsequently allowed the prescription of a PARP inhibitor.

4. Discussion

As the treatment paradigm in HGSOC has changed to include maintenance PARPi, testing for both germline and somatic *BRCA* variants has also become a new standard of care. We found high testing rates for germline *BRCA* in our HGSOC patients, with 98% of patients in the first period receiving testing. Rates remained high in the second period with only 1 patient missed who died before ever receiving any treatment or before testing could occur. Over the study period, the mean time to testing improved from 76 days to 48 days in the first line setting.

Regarding somatic *BRCA* testing, there was an increased rate of testing observed between the two periods, improving from 42% of patients to 72%. Although many patients were still on their front line or recurrent chemotherapy at the time of data collection (and thus still had time for testing to be performed), when excluding these patients as

Table 3
Frequency of pathogenic variants observed throughout the study.

Pathogenic Variants (PV) detected during the study	**Patients with PV(n = 22)**
Clinically significant variants	
BRCA1 germline PV	6
BRCA1 somatic PV (with wild-type germline)	1
BRCA2 germline PV	9
RAD51C germline PV	1
BRIP1 germline PV	1
PALB2 germline PV	2
Variants of unknown significance	
BRCA2 somatic PV (with wild-type germline)	2

described, the rate of missed testing improved from 21% of patients to only 4.5%. Furthermore, when trying to account for potential duplicate patients in the two time periods, albeit with smaller sample size, we were still able to show increased somatic testing rates over the two time periods with near double the patients tested shortly after diagnosis. Our study therefore still revealed an increase in the uptake of somatic testing suggesting a positive impact from our interventions.

Consistent with the Cancer Genome Atlas project (Network, 2011), 18% of our patient population had a germline HRD PV. Interestingly, despite the increase in somatic testing over the two periods, a lower-than-expected rate of somatic *BRCA* PVs was detected, with only one of our 123 patient cohort having a clinically relevant somatic *BRCA* PV. However, it is worth noting that 100% of our patients who had eligible *BRCA* PVs for government subsidized olaparib were offered and received this therapy.

This study represents the first audit of current somatic *BRCA* testing rates in Western Australia. As service implementation for somatic *BRCA* testing has lagged behind the availability of therapy, current testing rates are less than ideal. However, despite this, we have shown that education to our colleagues, instituting changes in reporting methods, and assisting databases to prompt results can have a positive impact on testing rates. Change management strategies were implemented both on a "coalface" level (education for trainees), a department level (guideline development) and a multidisciplinary institutional level (testing strategies, MDT discussion, results flagging). Addressing areas for development at multiple levels enabled significant improvement in testing rates. This study may prompt institutions to review their policies and procedures regarding testing for *BRCA* status in ovarian cancer patients, where results may significantly impact a patient's cancer management and survival.

When this study commenced, it was envisioned that knowledge of current testing rates in Western Australia could be utilized to lobby for funding of somatic *BRCA* testing at local pathology providers. As mentioned, local somatic testing became available on 28th July 2022 toward the end of this study. With somatic *BRCA* analysis now available locally in WA, it is hoped that with faster turn arounds, easier referrals and more physician familiarity, that testing rates will continue to improve. Perhaps in the future, reflex somatic testing at our pathology providers, as is performed in other tumor types (and shown to increase the uptake of germline testing in some settings (McCuaig et al., 2020), is an alternative model of testing that could potentially be explored in this patient population.

5. Conclusion

Testing rates for germline *BRCA* variant status in patients with high grade serous ovarian cancer in Western Australia are high. Somatic tumor testing is not performed as frequently but should be considered standard of care as results may significantly impact a patient's cancer management and survival. Future consideration may be given to exploring reflex testing in this patient population, as well as further defining the role and methods of HRD assessment. Nevertheless, this study demonstrates the importance of education and improvements in reporting at departmental and multidisciplinary levels in enabling change management where a paradigm shift in patient treatment has occurred.

Author Contribution

- Dr Andrew Fantoni: conceived and designed the analysis, collected the data, performed the analysis, manuscript preparation.
- A/Professor Tarek Meniawy: supervision, manuscript preparation.
- Professor Paul Cohen: supervision, manuscript preparation.
- Dr Michelle McMullen: conceived and designed the analysis, supervision, manuscript preparation.
- Dr Andrew Fantoni: no conflicts of interest
- A/Professor Tarek Meniawy: Advisory Boards for AstraZeneca, GSK, Novartis, BMS, MSD, Speaker Fees AstraZeneca, GSK. Travel support AstraZeneca, BMS
- Professor Paul A Cohen: honoraria Astra Zeneca, Seqirus; Advisory Board Clinic IQ Pty Ltd, Stock Clinic IQ Pty Ltd.
- Dr Michelle McMullen: no conflicts of interest

Ethics

This was a retrospective study approved by the North Metropolitan Health Service Quality Assurance Committee (reference number 43963). A waiver of consent was granted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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