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Homologous Recombination Deficiency Should Be Tested for in Patients With Advanced Stage High-Grade Serous Ovarian Cancer Aged 70 Years and Over

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Homologous recombination deficiency should be tested for in patients with advanced stage high-grade serous ovarian cancer aged 70 years and over

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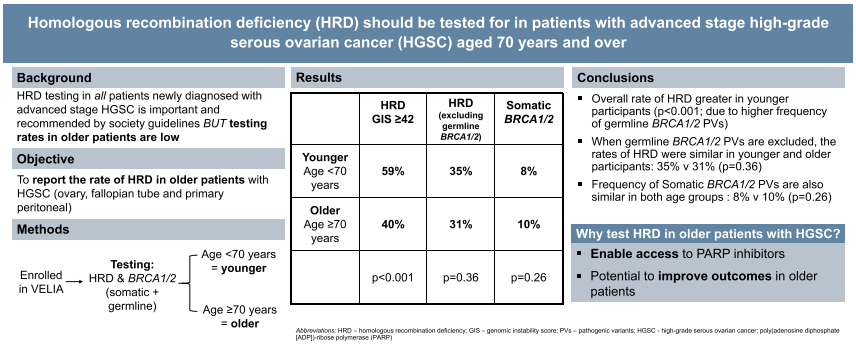
HIGHLIGHTS

- 48% of high grade serous ovarian cancers (HGSC) in older patients are homologous recombination deficient (HRD).
- Somatic or germline *BRCA1/2* pathogenic variants (PVs) contribute to almost half of HGSC tumors with HRD.
- Excluding the contribution of germline *BRCA* PVs, the frequency of HRD is similar in younger vs older patients with HGSC.
- The frequency of somatic *BRCA1/2* PVs is independent of age (8% younger v 10% older participants).
- HRD testing should not be restricted by patient age.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective. Due to limited data on homologous recombination deficiency (HRD) in older patients (≥ 70 years) with advanced stage high grade serous ovarian cancer (HGSC), we aimed to determine the rates of HRD at diagnosis in this age group.

Methods. From the Phase 3 trial VELIA the frequency of HRD and *BRCA1/2* pathogenic variants (PVs) was compared between younger (< 70 years) and older participants. HRD and somatic(s) *BRCA1/2* pathogenic variants (PVs) were determined at diagnosis using Myriad myChoice® CDx and germline(g) *BRCA1/2* PVs using Myriad BRACAnalysis CDx®. HRD was defined if a *BRCA* PV was present, or the genomic instability score (GIS) met threshold (GIS ≥ 33 & ≥ 42 analyzed).

Results. Of 1140 participants, 21% were ≥ 70 years. In total, 26% ($n = 298$) had a *BRCA1/2* PV and HRD, 29% ($n = 329$) were HRD/*BRCA* wild-type, 33% ($n = 372$) non-HRD, and 12% HR-status unknown ($n = 141$). HRD rates were higher in younger participants, 59% ($n = 476/802$), compared to 40% ($n = 78/197$) of older participants (GIS ≥ 42) [$p < 0.001$]; similar rates demonstrated with GIS ≥ 33, 66% vs 48% [$p < 0.001$]. g*BRCA* PVs observed in 24% younger vs 8% of older participants ($p < 0.001$); s*BRCA* in 8% vs 10% ($p = 0.2559$), and HRD (GIS ≥ 42) not due to g*BRCA* was 35% vs 31% ($p = 0.36$).

Conclusions. HRD frequency was similar in participants aged < 70 and ≥ 70 years (35% vs 31%) when the contribution of g*BRCA* was excluded; rates of s*BRCA* PVs were also similar (8% v 10%), thus underscoring the importance of HRD and *BRCA* testing at diagnosis in older patients with advanced HGSC given the therapeutic implications.

1. Introduction

The Cancer Genome Atlas (TCGA) first reported that approximately 50% of all high-grade serous ovarian cancer (HGSC) was homologous recombination deficient (HRD) which was subsequently confirmed in multiple studies [1–3]. Germline and somatic *BRCA1/2* pathogenic variants (PVs) are responsible for about 40% of cases of HRD. Patients with HRD HGSC potentially benefit from maintenance treatment with poly (adenosine diphosphate [ADP])-ribose polymerase (PARP) inhibitors after a response to 1st line platinum-based chemotherapy [4–6]. Universally, guidelines and consensus statements recommend that all patients with epithelial ovarian cancer (EOC) should be offered *BRCA1/2* and HRD testing at diagnosis [5–8] to identify patients who may benefit from maintenance PARP inhibitor therapy [2,3,9]. There has been a steady increase in the proportion of patients who are offered testing for germline *BRCA1/2* pathogenic variants (PVs) over time [10], but most patients who are offered germline *BRCA1/2* testing tend to be younger with a mean age of 63 years [11]. Despite the guideline recommendations, testing rates for germline *BRCA1/2* PVs in patients with ovarian cancer are variable and seems dependent on local practices [12]. Actual testing rates of patients diagnosed with EOC in Europe can occur in up to 80% [12] of patients such as in the Netherlands, and reported to be approximately 34% based on USA health insurance and registry data [10,13]. Reasons for inequity in genetic testing have been highlighted recently in the Society for Gynecologic Oncology (SGO) clinical practice statement and include a patient's ethnic and racial background, lower socioeconomic status, and type of health insurance [14]. Furthermore, real-world studies demonstrate that only a minority of patients are offered somatic *BRCA1/2* [11,15] and HRD testing [16]. In data from the Flatiron longitudinal database which included 2557 patients diagnosed with ovarian cancer between 2011 and 2018, the germline *BRCA1/2* testing occurred in 63% ($n = 1154$) of patients whereas only 11% ($n = 197$) of patients had somatic *BRCA1/2* testing [11]. In older patients (age ≥ 70 years), somatic *BRCA1/2* testing rates are lower [17], and HRD testing rates in older patients in the real-world setting are likely to be similarly low. In addition to the patient populations highlighted by the SGO [14], the paucity of data in older patients suggests that genetic testing is underutilized in this group. Further data from the Flatiron Health EHR-derived database showed that uptake of first-line maintenance PARP inhibitors has increased from 6% of eligible patients in 2017 to 53% in 2021 [16]; however, this indicates that almost half of eligible patients were still not receiving first-line maintenance PARP inhibitor therapy despite considerable evidence showing improvement in patient outcomes in those that do [16]. We are not aware of any real-world studies that have reported on the proportion of patients with advanced EOC who have HRD testing and who are subsequently offered maintenance therapy with a PARP inhibitor.

Data from randomized trials consistently report that older patients derive similar benefit as younger patients from maintenance PARP inhibitor therapy with comparable frequencies of adverse effects including dose interruptions, dose reductions and discontinuation of treatment [2,9]. Older patients enrolled into clinical trials are highly selected and not necessarily representative of the real-world population. However, the data from clinical trials suggests that maintenance therapy with a PARP inhibitor should be considered in older patients with advanced HGSC and HRD who are treated with, and respond to, 1st line platinum-based chemotherapy. Approximately 70% of deaths from ovarian cancer occur in patients over the age of 65 years of age [18]. This disparity highlights the importance of optimal management of older patients which includes *BRCA1/2* and HRD testing at diagnosis.

The Myriad myChoice® CDx assay which was used in VELIA defines HRD according to the genomic instability score (GIS) which is a combination of the sum of loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transition (LST) scores in the tumor [19]. The original threshold to define HRD was set by Myriad laboratories as a score of 42 or above after analysis of breast and ovarian tumors showed a bimodal distribution of tumors which had a high GIS with *BRCA1/2*, and those with a low GIS and the absence of *BRCA1/2*. A GIS cut-off of 42 and above represented the 95% percentile of HRD scores in patients with *BRCA1/2* [20]. However, retrospective analysis of clinical trials showed that patients with a GIS of 33 and above also derived clinical benefit [21,22], and therefore this lower score was used to define HRD in the VELIA trial in order to include as many patients as possible that may benefit from treatment with a PARP inhibitor [23]. We performed our analysis using both GIS thresholds, ≥ 33 and ≥ 42, to define HRD.

Given the paucity of data on the frequency of HRD at diagnosis of HGSCs in older patients and the implications for maintenance therapy with a PARP inhibitor alone or in combination with bevacizumab [2,3,8] for patients with HRD, we used data from VELIA/GOG-3005 (Funded by Abbvie; NCT02470585) to address this question. We analyzed the HRD status of all enrolled participants and report the frequency of HRD in HGSCs according to age, with participants aged

≥ 70 years defined as the older, and age < 70 years as the younger cohort. We also present the rates of germline and somatic *BRCA1/2* PVs in this cohort where somatic PVs are defined as *BRCA1/2* PVs identified in the tumor tissue of a participant without a germline *BRCA1/2* PV.

2. Materials and methods

2.1. Study design

Eligible participants were aged ≥ 18 years with International Federation of Gynecology and Obstetrics Stage III or IV HGSC (ovarian, peritoneum, or fallopian tube) and enrolled from 202 sites in 10 countries. Complete details on the VELIA study design have been reported previously [23,24].

2.2. HRD assessment

Blood and tumor tissue was used to determine the presence of germline or tumor *BRCA1*/2 PVs and HRD status [23]. Assessment of HRD status on DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens was performed using the Myriad myChoice® CDx assay (Myriad Genetics, Inc., Salt Lake City, UT) which provides a genomic instability score (GIS) which is a combination of i) loss of heterozygosity, ii) telomeric allelic imbalance, and iii) large-scale state transitions. Germline *BRCA1/2* PVs were assessed using the Myriad BRACAnalysis CDx®. The myChoice CDx assay was used for tumor sequencing which includes germline and somatic PVs and detects single nucleotide variants (SNVs), variants in homopolymer stretches, indels, and large rearrangements in the *BRCA1* and *BRCA2* genes. To meet the definition of HRD, there needed to be a deleterious or suspected deleterious germline or somatic *BRCA1/2* PV, or a GIS which met the specified threshold. We performed our analysis using two thresholds for GIS, ≥ 42 and ≥ 33. Non-HRD (or HRD-negative) was defined as the absence of *BRCA1/2* PV in either the germline or tumor, or by the GIS and defined as < 42 or < 33 respectively. For inclusion in the trial all patients needed to have pre-treatment tumor tissue available for HRD assessment, in the form of core biopsies for patients undergoing neoadjuvant therapy, or surgical specimens for patients having primary cytoreductive surgery.

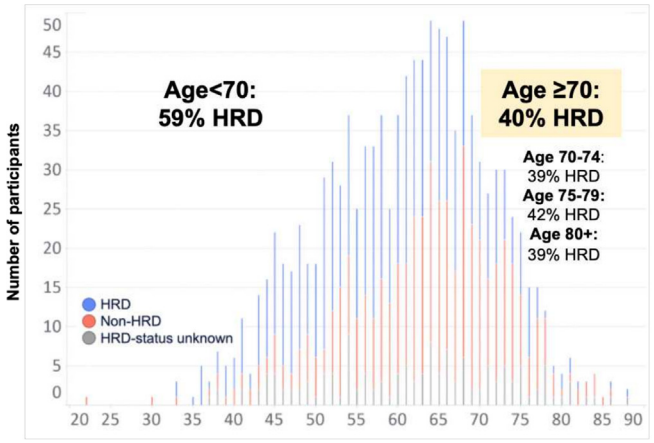
2.3. Statistical analysis

Descriptive statistics are used to present proportions of participants with *BRCA* PVs and HRD. A comparison of the frequency of HRD in younger versus older participants, and *BRCA* PVs in younger versus older participants was calculated using the Fisher's exact test with a significance value of 0.05. Odds ratio (OR) was calculated using the Baptista-Pike method with 95% confidence interval (CI) reported. All statistical analyses were performed using Prism Version 9.3.1 (December 2021).

3. Results

A total of 1140 participants were recruited to the VELIA trial of whom 21% ($n = 237$) were aged ≥ 70 years. *BRCA1/2* PVs and HRD status could be determined in 91% ($n = 1040$) and 88% ($n = 999$) of the participants respectively, and breakdown by age revealed HRD status was unknown in 17% ($n = 40$) of older participants and 11% ($n = 101$) of younger participants. Fig. 1 demonstrates the age distribution of participants with HRD tumors, non-HRD and where HR status was unknown. In total, 554 participants (49%) had tumors that were classified as HRD (≥ 42) of which 54% ($n = 298$) were due to a *BRCA1/2* PV. Using a GIS ≥ 33, 627 participants (55%) had tumors that were classified HRD. Participant's age at diagnosis according to HRD and non-HRD status is shown for both GIS cut-offs (Fig. 2).

Table 1 shows the frequency of *BRCA1/2* PVs and HRD in younger and older participants. Younger participants had higher rates of HRD compared to older participants (OR 2.228; 95% CI, 1.611–3.041) using



Age	HRD	Non-HRD	Unknown
≤ 69	476	326	101
70-74	48	76	18
75-79	23	32	14
80+	7	11	8

Fig. 1. HRD status (GIS ≥ 42) represented by age. Age distribution of patients with HRD (with or without a *BRCA1/2* PV), non-HRD, and unknown tumor HR-status represented by a blue, red, and grey line respectively. HRD percentages represent the proportion of HRD positive tumors where HR-status could be determined. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Abbreviations: HR (D) = homologous recombination deficient, PV = pathogenic variant, WT = wild-type.

GIS ≥ 42; and similarly for GIS ≥ 33 (OR 2.116 (95% CI, 1.550–2.894). Germline *BRCA1/2* PVs occurred more frequently in younger compared to older participants (OR 3.509; 95% CI, 2.117–5.869), with no significant difference in the rates of somatic *BRCA1/2* PVs in younger and older participants (OR 0.7545; 95% CI, 0.4766–1.209). Table 2 shows the frequency of HRD is similar when the contribution of germline BRCA PVs is excluded, and this applies to both GIS thresholds.

4. Discussion

The frequency of HRD in VELIA was very similar in participants independent of age after excluding the contribution to HRD from germline *BRCA* PVs (Table 2), with rates of 35% in younger vs 31% older participants (GIS ≥ 42), and similarly, 41% vs 40% with a GIS threshold of

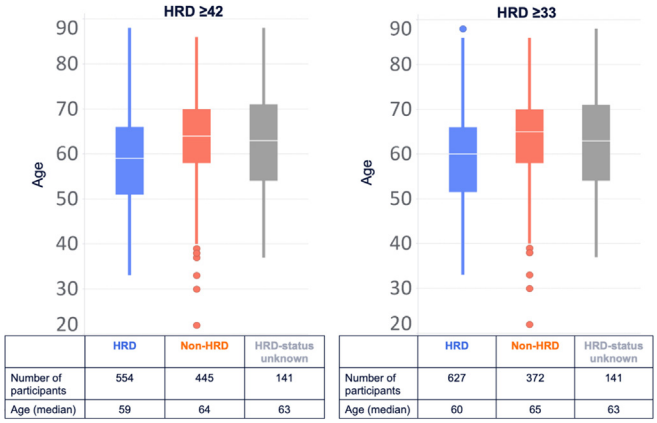


Fig. 2. Age at diagnosis according to HRD status. The median age at diagnosis is lower in participants with HRD tumors as compared to those with non-HRD tumors, using both (A) GIS ≥ 33 and (B) GIS ≥ 42.

Table 1
Frequency of *BRCA1/2* pathogenic variants and HRD using GIS thresholds of ≥ 33 and ≥ 42 according to patient age (< 70 years and ≥ 70 years).

	BRCA1/2 PV[a] ($n = 1040$)		
Age	< 70 years ($n = 831$)	≥ 70 years ($n = 209$)	
Germline	197 (24%)	17 (8%)	$p < 0.001$
Somatic	63 (8%)	21 (10%)	$p = 0.2559$
	HRD[b,c] (n = 999)		
Age	< 70 years ($n = 802$)	≥ 70 years (n = 197)	
GIS ≥ 42	476 (59%)	78 (40%)	$p < 0.001$
GIS ≥ 33	532 (66%)	95 (48%)	$p < 0.001$

Abbreviations: PV = pathogenic variant, HRD = homologous recombination deficient, GIS = genomic instability score.
[a] *BRCA1/2* status was unknown in 72 younger patients (aged < 70 years) and 28 older patients (aged ≥ 70 years).
[b] HRD status was unknown for 101 younger patients (aged < 70 years) and 40 older patients (aged ≥ 70 years).
[c] Frequency of germline PVs, somatic PVs, and HRD were calculated as a proportion of total patients in the respective age group (age < 70 years, ≥ 70 years). The *p* value tests for a difference in rates between the age groups using the Fisher's exact test.

≥ 33. The overall frequency of HRD using both GIS thresholds of ≥ 42 and ≥ 33 was significantly higher in younger participants, 59% and 66%, compared to older participants 40% and 48%, respectively (Table 1). This notable difference in overall HRD rates is to be expected as germline *BRCA* PVs are the major contributor to HRD. In VELIA, a germline *BRCA* PV was detected in 24% of participants under the age of 70 compared to only 8% in those aged 70 years and over. Therefore, when germline *BRCA* PVs are included, there will be a clear difference in HRD rates in younger and older participants. However, the similar rates of HRD when the contribution of germline *BRCA1/2* PVs is excluded underscores the importance of HRD testing in all patients diagnosed with HGSC who are offered platinum-based chemotherapy irrespective of age. An interesting finding in our study was that the frequency of somatic *BRCA1/2* PVs was similar, 8% in younger compared to 10% in older participants. To our knowledge this has not been previously reported and supports testing for somatic *BRCA* PVs in all patients diagnosed with EOC independent of age.

PAOLA-1 is the only other trial that we are aware of which addressed a similar question to our study [25]. However, there are important differences between PAOLA-1 and VELIA in that PAOLA-1 included eligible patients who had responded to at least 6 cycles of platinum-based chemotherapy in combination with bevacizumab. This would have potentially enriched the number of participants with HRD, given that HRD is associated with a higher response to chemotherapy [26] which could impact on the results. In contrast, VELIA included eligible consenting participants and HRD and *BRCA1/2* testing was performed at initial diagnosis of advanced stage HGSC, prior to chemotherapy, which is more consistent with guidelines and clinical practice where HRD and *BRCA1/2* testing is recommended at diagnosis and thus often not known at commencement of therapy. PAOLA-1 used age ≥ 65 as the cut-off to define the older participant cohort and reported the frequency of HRD to be 34.1% in older participants compared to 55.7% in those aged < 65 years [25]. The higher rate of HRD in younger participants can be accounted for by the higher frequency of *BRCA1/2* PVs among younger patients, which was 36.7% compared to 17.1% in patients aged ≥ 65 years. As PAOLA-1 tested tumor *BRCA*, this would have included both germline and somatic *BRCA* PVs [25]. Among the *BRCA1/2* wild-type/HRD subset, the frequency of HRD was 34% ($n = 272/802$) in younger compared with 29% ($n = 57/197$) of older participants, which is very similar to our findings. These results highlight the importance of HRD testing, as well as germline and tumor *BRCA1/2* testing, in patients with advanced EOC independent of age as there are therapeutic implications in selecting which patients should be offered maintenance therapy with a PARP inhibitor in the first line setting.

Table 2
HRD frequency in younger and older participants when germline *BRCA1/2* PVs were excluded.

	HRD (germline *BRCA1/2* W/T) ($n = 999$)		
Age	< 70 years ($n = 802$)	≥ 70 years ($n = 197$)	
GIS ≥ 42	279 (35%)	61 (31%)	$p = 0.36$
GIS ≥ 33	335 (42%)	78 (40%)	$p = 0.63$

The *p* value tests for a difference in rates between the age groups using the Fisher's exact test.
Abbreviations: PV = pathogenic variant, HRD = homologous recombination deficient, W/T = wild-type, GIS = genomic instability score.

Studies have shown older patients with HGSCs consistently have inferior outcomes compared to their younger counterparts [27,28]. The age used to define older patients in clinic trials varies slightly, with both age ≥ 65 years and ≥ 70 years used [27]. We used age ≥ 70 years as the cut-off to define older patients as this represents 42% of the overall cancer population [27] and they are not well represented in clinical trials despite comprising 40% of patients diagnosed with advanced stage HGSC [18]. Irrespective of which age cut-off is used, what is certain is that the proportion of older adults with HGSC is projected to increase over time given the aging population, and offering optimal treatment to older patients is of utmost importance [29].

Although approximately 20% of patients enrolled in VELIA were over the age of 70 years [23], they are likely a highly selected subset considered suitable for platinum-based combination chemotherapy in combination with a PARP inhibitor. An important limitation of our analysis is that the criteria for enrolment into VELIA excluded patients with inadequate organ function including hematological, renal and hepatic function, poor ECOG performance status, ≥ Grade 1 peripheral neuropathy, symptomatic congestive failure, bowel obstruction and a psychiatric condition that would preclude participation in study requirements. In addition, those with *BRCA*-related breast cancer may have been excluded as any participants with a history of malignancy apart from a non-melanoma skin cancer in the past 3 years would not be eligible. We cannot rule out differences in the frequency of HRD in an unselected real-world population of older patients.

Older patients tend to receive suboptimal treatment regardless of their performance status or lack of comorbidities that would preclude treatment [30,31]. In addition, the rate of inclusion of older patients in clinical trials is lower than the burden of cancer in that age group, and a significantly lower proportion of patients aged ≥ 70 years are screened, offered, or included a clinical trial compared to younger patients [32,33]. All these factors translate to poorer clinical outcomes for older patients. In an effort to counter this the US FDA has issued a guide on the "Inclusion of Older Adults in Cancer Clinical Trials". They place a particular emphasis on including patients aged 75 years and over to allow generalizability of trial results to the aging population [34].

The frequency of germline *BRCA1/2* pathogenic variants in patients with HGSC ranges from 13 to 21% and approximately 6–8% have somatic *BRCA1/2* pathogenic variants [1,35,36]. An additional 30% of patients have HRD due to other genomic alterations [37]. To determine HRD status, the United States (US) Food and Drug Administration (FDA) approved diagnostic tests for HRD include the FoundationOne®CDx [38] or Myriad myChoice® CDx [39] assay, which have overlapping sensitivity in detecting genomic scars, but are not entirely equivalent [40]. Both tests use next generation sequencing to determine HRD and are costly and a deterrent to universal testing. In view of the costs of HRD testing using FDA approved assays, surrogate measures for HRD include germline or somatic testing for *BRCA1/2* and a panel of other HR-related genes [40]. The most common genetic causes of HRD are due to biallelic inactivation of *BRCA1/2*, *RAD51C* or *PALB2* [41]. However, gene sequencing alone may miss HRD secondary to epigenetic events, for example promoter methylation of *BRCA1* [40]. As alternative HRD assays are developed and validated, the cost of HRD testing is likely to decrease in the near future leading to greater accessibility.

In VELIA, HRD testing failed in 12% of participants' tumor specimens. The most common reasons for this are poor quality DNA, or inadequate tumor in the specimen. In VELIA, approximately 28% of patients received neoadjuvant therapy prior to interval debulking surgery. For these patients to be included in the trial they required a core biopsy specimen to be available for HRD testing prior to commencing the first cycle of chemotherapy as it is often not possible following neoadjuvant chemotherapy particularly when there is a good response to treatment as there may be no viable tumor tissue for assessment of HRD at interval debulking surgery. As older patients are more likely to undergo neoadjuvant chemotherapy prior to interval debulking surgery [18], it is essential that an adequate number of core biopsy specimens are obtained prior to neoadjuvant chemotherapy in order to permit testing for HRD.

Notwithstanding the underrepresentation of older participants in clinical trials, all the trials of maintenance therapy with PARP inhibitor included a subset of older participants, and they all demonstrated that PFS benefit was independent of age [2,3,9]. A recent meta-analysis which included 4364 participants from 8 Phase III trials including VELIA showed a PFS improvement in older participants treated with a maintenance PARP inhibitor (HR = 0.54; 95% CI 0.45 to 0.65; $p < 0.00001$) compared to participants under the age of 65 years (HR = 0.47; $p = 0.13$) [42]. Moreover, the rates of adverse effects are similar in older and younger participants [25,42]. However, it is possible that these participants are not representative of the older population of patients with advanced stage HGSC. Real world data indicates that the uptake of maintenance PARP inhibitors in the first line setting is lower in patients aged 65 and over compared to younger patients (aged < 65 years), 20% ($n = 86/423$) v 28% ($n = 80/282$) [16]. However, Chan et al observed that real-world clinical outcomes are consistent with trial data, with real world PFS not reached in patients who received maintenance PARP inhibitor therapy compared to patients who did not (9.53 months; $p < 0.001$) [16]. Additionally, patient age does not appear to impact on non-adherence rates [43]. Another area that is lacking is further research into the impact of health-related quality specifically in older patients treated with PARP inhibitors.

Patients with HRD are more likely to benefit from maintenance therapy with a PARP inhibitor and it is relevant that almost half of the older participants in VELIA had tumors that were HRD. This supports HRD testing in older patients fit for platinum-based chemotherapy given the potential benefits. Global access to HRD testing and the relatively high cost of testing almost certainly contributes to the low testing rates reported particularly in regions of the world where HRD testing is not covered by insurance [44]. Nonetheless, it is likely that as newer HRD assays and algorithms are developed and the cost of testing decreases, the frequency of testing should rise in all patients including patients aged 70 years and over. It is important that oncologists caring for patients with HGSC do not restrict HRD and *BRCA1/2* testing to patients based on age if deemed fit for platinum-based chemotherapy. The results of this study should increase awareness regarding the importance and clinical significance of HRD testing in older patients with advanced stage HGSC.

5. Conclusion

The rates of HRD were similar in younger and older participants in VELIA when the contribution from germline *BRCA1/2* PVs was excluded, thus highlighting the importance of HRD testing in all patients newly diagnosed with advanced HGSC. Almost half of older participants were classified as HRD and therefore could potentially benefit from treatment with a maintenance PARP inhibitor. Increasing HRD testing in patients aged ≥ 70 years with advanced stage HGSC has the potential to improve outcomes in older patients. Additionally, the similar rates of somatic *BRCA* PVs in younger and older participants supports *BRCA1/2* PV testing at diagnosis as per current guidelines.

CRediT authorship contribution statement

Omali Pitiyarachchi: Conceptualization, Data curation, Formal analysis, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Peter J. Ansell:** Formal analysis, Data curation, Visualization, Writing – review & editing. **Robert L. Coleman:** Formal analysis, Resources, Writing – review & editing. **Minh H. Dinh:** Conceptualization, Investigation, Writing – review & editing. **Laura Holman:** Resources, Writing – review & editing. **Charles A. Leath:** Resources, Writing – review & editing. **Theresa Werner:** Resources, Writing – review & editing. **Paul DiSilvestro:** Resources, Writing – review & editing. **Mark Morgan:** Resources, Writing – review & editing. **William Tew:** Resources, Writing – review & editing. **Christine Lee:** Resources, Writing – review & editing. **Mary Cunningham:** Resources, Writing – review & editing. **Meredith Newton:** Resources, Writing – review & editing. **Babak Edraki:** Resources, Writing – review & editing. **Peter Lim:** Resources, Writing – review & editing. **Joyce Barlin:** Resources, Writing – review & editing. **Nicola M. Spirtos:** Resources, Writing – review & editing. **Krishnansu S. Tewari:** Resources, Writing – review & editing. **Mitchell Edelson:** Resources, Writing – review & editing. **Thomas Reid:** Resources, Writing – review & editing. **Jay Carlson:** Resources, Writing – review & editing. **Michael Friedlander:** Conceptualization, Data curation, Formal analysis, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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