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REVIEW

European experts consensus: BRCA/homologous recombination deficiency testing in first-line ovarian cancer

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Background: Homologous recombination repair (HRR) enables fault-free repair of double-stranded DNA breaks. HRR deficiency is predicted to occur in around half of high-grade serous ovarian carcinomas. Ovarian cancers harbouring HRR deficiency typically exhibit sensitivity to poly-ADP ribose polymerase inhibitors (PARPi). Current guidelines recommend a range of approaches for genetic testing to identify predictors of sensitivity to PARPi in ovarian cancer and to identify genetic predisposition.

Design: To establish a European-wide consensus for genetic testing (including the genetic care pathway), decision making and clinical management of patients with recently diagnosed advanced ovarian cancer, and the validity of biomarkers to predict the effectiveness of PARPi in the first-line setting. The collaborative European experts' consensus group consisted of a steering committee ($n = 14$) and contributors ($n = 84$). A (modified) Delphi process was used to establish consensus statements based on a systematic literature search, conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Results: A consensus was reached on 34 statements amongst 98 caregivers (including oncologists, pathologists, clinical geneticists, genetic researchers, and patient advocates). The statements concentrated on (i) the value of testing for *BRCA1/2* mutations and HRR deficiency testing, including when and whom to test; (ii) the importance of developing new and better HRR deficiency tests; (iii) the importance of germline non-*BRCA* HRR and mismatch repair gene mutations for predicting familial risk, but not for predicting sensitivity to PARPi, in the first-line setting; (iv) who should be able to inform patients about genetic testing, and what training and education should these caregivers receive.

Conclusion: These consensus recommendations, from a multidisciplinary panel of experts from across Europe, provide clear guidance on the use of *BRCA* and HRR deficiency testing for recently diagnosed patients with advanced ovarian cancer.

Key words: ovarian cancer, *BRCA1/2*, homologous recombination deficiency, PARP inhibition, genetic counselling, mainstream genetic testing

INTRODUCTION

Ovarian cancer is the leading cause of death among all gynaecological cancers in developed countries. Surgical debulking and platinum- and taxane-based chemotherapy result in complete clinical remission in up to 75% of cases, and the 5-year survival rate for patients with ovarian cancer is ∼30%.[1] Next-generation sequencing (NGS) has enabled

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systematic investigations of genomic and molecular alterations that drive ovarian cancer with the aim of identifying patients who may respond to targeted therapies. In normal cells, DNA damage occurs continuously due to a range of factors including intracellular metabolism, replication, and exposure to genotoxic agents. If unrepaired, this damage could result in mutations within the cell genomic material and therefore necessitates a complex network of repair pathways for the maintenance of genomic integrity.[2]

Homologous recombination repair (HRR) is the critical eukaryotic pathway that enables fault-free repair of double-stranded DNA breaks. HRR relies on a number of proteins including BRCA1 and BRCA2, proteins of the Mre11-Rad50-Nbs1 (MRN) complex, CtIP, MRE11, RAD51, ATM, H2AX, PALB2, RPA, RAD52, and the Fanconi anaemia pathway proteins.[3,4] In cells where HRR is non-functioning, for example, due to *BRCA1* or *BRCA2* deficiency, other pathways are utilised such as non-homologous end joining (NHEJ). However, because NHEJ can result in error-prone repair, it can lead to the accumulation of additional DNA amplifications or deletions resulting in chromosomal instability.[5-7]

Until recently, hereditary ovarian cancer was thought to be the result of mutations in *BRCA1* and *BRCA2* genes (*BRCA1/2m*), with a minor contribution from aberrations in DNA mismatch repair (MMR) genes.[8] Further characterisation of the homologous recombination (HR) pathway has revealed multiple protein co-factors that are necessary for functional HRR including RAD51C, RAD51D, BRIP1, PALB2, and BARD1, and mutations in the genes that encode these proteins could also contribute to hereditary ovarian cancer.[8,9] Deficiency in DNA damage repair due to dysfunctional HRR is referred to as HRR deficiency.

High-grade serous ovarian carcinoma, also known as high-grade serous tubo-ovarian carcinoma, includes cancers that originate from fallopian tube epithelium and arise primarily from the ovaries, fallopian tubes, or the peritoneum.[10] Depending on the population studied, up to 30% of high-grade serous ovarian carcinomas harbour germline or somatic HRR mutations.[11,12] Of note, 13%-21% harbour germline *BRCA1/2* mutations (*gBRCA1/2m*) and an additional 6% harbour somatic *BRCA1/2* mutations (*sBRCA1/2m*).[11,13-15] For patients with HRR deficiency caused by *BRCA1/2m*, future treatment options are augmented by poly-ADP ribose polymerase inhibitors (PARPi) and a growing list of other possible targeted therapies. However, although HRR mutations are detected in 30% of patients, up to half of high-grade serous ovarian carcinomas are predicted to be defective in HRR.[16] Ovarian cancers harbouring such HRR deficiency typically also respond to platinum-based chemotherapy regimens and exhibit sensitivity to PARPi.[17,18] The establishment of an infrastructure for widespread HRR deficiency testing is therefore imperative for the effective management of these patients. In recent years, PARPi have changed the ovarian cancer treatment landscape in both the first-line and relapsed disease settings.[19-24] However, reversion mutations, which confer resistance to PARPi, have been reported in some *BRCAm* ovarian cancer patients after long-term exposure to PARPi.[25,26]

While it has been established that *BRCA1/2m* are effective predictors of sensitivity to PARPi in ovarian cancer, current guidelines recommend a range of approaches with regard to *gBRCA1/2* testing. Knowledge about a germline pathogenic variant may have not only therapeutic and prognostic implications but also clinical implications for relatives, who are at risk of carrying the same variant. The American Society for Clinical Oncology (ASCO) recommends that all patients diagnosed with epithelial ovarian cancer should undergo germline genetic testing of *BRCA1/2* genes, and also other known ovarian cancer susceptibility genes. ASCO further recommends that patients who do not carry a *gBRCA1/2m* should undergo genetic tumour testing for somatic mutations in *BRCA1/2* and other commonly mutated genes. Patients with epithelial ovarian cancer should have testing at the time of diagnosis.[27] The Society of Gynecologic Oncology (SGO) recommends *BRCA1/2* testing for all patients with epithelial ovarian, tubal, and peritoneal cancers, even in the absence of a familial history.[28] The European Society of Gynaecological Oncology (ESGO) and the European Society of Medical Oncology (ESMO) joint guidelines recommend testing for *BRCA1/2m* for all patients with non-mucinous ovarian cancer.[2] Whilst the current ESMO and ASCO guidelines indicate that HRR deficiency tests are useful for predicting benefit from PARPi, they acknowledge that current biomarkers of non-*BRCA* HRR mutations are insufficient for guiding use of PARPi in high-grade serous ovarian cancer.[12,27]

The focus of this policy review was to establish a European-wide consensus with regard to molecular testing (including the genetic care pathway), decision making, and clinical management of patients with recently diagnosed advanced ovarian cancer, and also the validity of biomarkers to predict the effectiveness of PARPi in the first-line setting. Our ambition was to establish a consensus based on the opinions of experts from a large cross-section of specialties all over Europe. Our emphasis was optimisation of the genetic testing and treatment pathway to identify recently diagnosed patients who would likely benefit from PARPi, based on the current scientific understanding and available data and not what is possible, or current practice, in the individual countries of the contributing specialists.

OVERVIEW OF CONSENSUS METHODOLOGY

A European experts' consensus group was convened to review the role of *BRCA* and HRR deficiency testing in ovarian cancer. Our approach was collaborative, incorporating a panel of experts including a chairperson, steering committee ($n = 13$), and contributors ($n = 84$) from a range of specialties, e.g. oncologists involved in the care of ovarian cancer patients ($n = 66$), geneticists ($n = 13$), pathologists ($n = 9$), patient advocates ($n = 5$), molecular biologists ($n = 4$), as well as an expert in pharmacoeconomics. The steering committee members were selected based on their expertise as documented by topic-relevant publications. The chair and steering committee selected the contributors based on their knowledge and

experience within specialisms and from across 27 European countries, with one contributor based in the United States. The roles and responsibilities of the different members of the consensus group are provided in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.11.013.

A (modified) Delphi process was used to establish consensus as outlined in Figure 1. A systematic literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines to gather data on the use of biomarkers, such as g*BRCAm*/s*BRCAm*/HRR deficiency, for determining the effectiveness of PARPi in patients with recently diagnosed ovarian cancer. Full details of the literature search methodology, search terms, search strategy and evidence grading strategy can be found in the Supplementary Appendix, Supplementary Tables S2-S4, respectively, available at https://doi.org/10.1016/j.annonc.2021.11.013.

Results of the literature search were used to develop consensus statements on the following topics:

1. *BRCA* testing following a diagnosis of ovarian cancer
2. HRR deficiency
3. Non-*BRCA* HRR genes
4. Mutations in MMR genes
5. Genetic testing in the clinic

Consensus statements were agreed by the chair and steering committee for inclusion in a survey. A multiple-choice format was chosen for collecting responses, and a five-point Likert scale (strongly agree, agree, undecided, disagree, and strongly disagree) was applied where appropriate. All panel members were invited to complete the survey before attending the consensus meeting. Consensus was defined according to the survey results, with a minimum agreement threshold of 75% of respondents agreeing (strongly agree/agree) with a survey statement. Statements not receiving consensus were discussed and refined during the consensus meeting.

In June 2021, all contributors attended a virtual meeting to discuss the results of the consensus survey. Statements for which there was consensus agreement were not discussed unless specific questions were raised. Statements that were close to reaching a consensus (65%-<75% agreement) were discussed, and restructured in some cases (for clarity of understanding), before the statements were voted on again. All changes were agreed by vote. Statements without consensus (<65% agreement) were discussed during breakout sessions and revisions to the statements made. Revised statements were then voted on by all contributors in a second survey round post-meeting. Overview of the agreement at each stage is outlined in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.11.013.

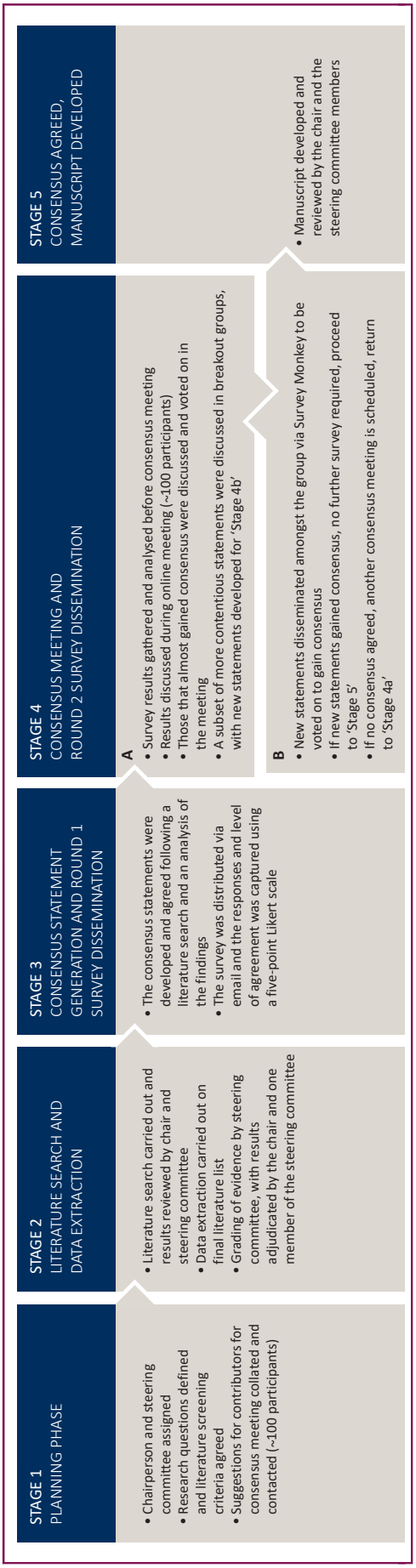

Figure 1. Overview of the Delphi process.

RESULTS

Following the literature search and article screening, 160 articles/meta-analyses/recent conference abstracts were

identified (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2021.11.013) in the following categories: sensitivity to PARPi, phase II and III studies, phase I studies, meta-analyses, testing/assays of interest, health economics, quality of life, genetic counselling/testing, clinical and laboratory testing. A full list of all articles retrieved from the literature search, along with their level of evidence, is provided in the Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2021.11.013.

Consensus statements are grouped by category, followed by supporting evidence from the literature search and, where appropriate, comments from the discussions at the consensus meeting.

BRCA testing following a diagnosis of ovarian cancer

Consensus statements are shown in Table 1.

HRR deficiency in ovarian cancer, through *BRCA1/2m*, has been well characterised. Cumulative ovarian cancer risk ranges from 39% to 65% for carriers of *gBRCA*1 and from 11% to 37% for *gBRCA2* carriers,[29-32] compared with only 1.4% of women in the general population.[33] Although, as mentioned above, ESMO—ESGO, ASCO, and SGO recommendations for determination of *BRCA* status are not fully aligned, *BRCA* testing is recommended for patients with ovarian cancer, with ASCO guidelines recommending germline testing for all patients diagnosed with epithelial cancer and ESMO—ESGO guidelines recommending testing for all patients with non-mucinous ovarian cancer.[2,27,28] Such recommendations are based on clinical implications for family members when a germline mutation is detected and prognostic implications for the patient as *BRCA* status is predictive of response to targeted therapies, such as PARPi.

Our literature review captured high-quality data, published from clinical trials of PARPi in patients with platinum-sensitive recurrent ovarian cancer, including olaparib (Study 19), niraparib (NOVA and NSGO-AVANOVA2/ENGOT-ov24), and rucaparib (ARIEL3 and ARIEL2).[20,34-37] Results from these studies show that clinical outcomes are similarly improved in patients with *sBRCAm* and *gBRCAm*, compared with patients with wild-type (WT) *BRCA*. Furthermore, two open-label, randomised phase II studies suggest that when a PARPi is compared with the combination of PARPi with an anti-angiogenic, a more pronounced effect is seen with the combination in *BRCA* WT/unknown patients than in *BRCAm* patients.[37,38]

Table 1. BRCA testing following a diagnosis of ovarian cancer: consensus statements

Consensus statements	Level of contributor agreement (%)[a]
Tumour mutations in *BRCA1/2* are effective at predicting sensitivity to PARP inhibitors	95
Tumour *BRCA1/2* testing should be carried out at primary diagnosis	95
Tumour *BRCA1/2* testing should be carried out at disease recurrence (if not carried out earlier)	95
After primary diagnosis tumour *BRCA1/2* mutation testing should be carried out before the end of first-line chemotherapy	98
Germline and/or tumour *BRCA* testing should be used (in either order) to determine *BRCA* status at primary diagnosis	96
BRCA1/2 tumour testing should be carried out in all invasive epithelial cancers, particularly in those with high-grade non-mucinous disease	95

PARP, poly-ADP ribose polymerase.
[a] Proportion of contributors agreeing (strongly agree/agree) with a survey statement.

Homologous recombination repair deficiency (HRR deficiency)

Consensus statements are shown in Table 2.

The current ESMO guidelines recommend consideration of HRR deficiency testing to identify the patients most likely to gain benefit from a PARPi.[12] Our literature search identified high-quality evidence, including two recent meta-analyses, that PARPi improves the prognosis of patients with primary and recurrent ovarian cancer. Both studies

Table 2. Homologous recombination repair deficiency (HRR deficiency): consensus statements

Consensus statements	Level of contributor agreement (%)[a]
Biomarkers of HRR deficiency are effective at predicting sensitivity to PARP inhibitors as maintenance therapy after first-line chemotherapy for ovarian cancer	88
HRR deficiency tumour testing should be carried out at primary diagnosis	92
HRR deficiency tumour testing should be carried out at disease recurrence (if not carried out earlier)	75
HRR deficiency tumour status, in *BRCA* WT patients, is not effective for predicting familial risk of ovarian cancer	84
HRR deficiency tumour testing should be carried out in all epithelial cancers, particularly in those with high-grade non-mucinous disease	88
HRR deficiency testing either following, but preferably together with *BRCA* testing, should be carried out before the end of first-line chemotherapy	91
There is a need for the development of new, alternative validated HRR deficiency tests	92
The main drivers for the development of a new, alternative validated HRR deficiency test are cost implications, the requirement to send samples for testing abroad, and the ability to develop an HRR deficiency test that outperforms commercially available tests	≥75[b]
Clinically validated genomic instability HRR deficiency tests are important for evaluating HRR deficiency status before the end of first-line chemotherapy	93
Biological overlap with commercially available tests and validation of clinical utility in a clinical trial are required when developing a new, alternative validated HRR deficiency test	≥75[c]

PARP, poly-ADP ribose polymerase; WT, wild type.
[a] Proportion of contributors agreeing (strongly agree/agree) with a survey statement.
[b] Level of agreement was 82% for cost implications, 75% for the requirement to send samples for testing abroad, and 81% for the ability to develop an HRR deficiency test that outperforms commercially available tests.
[c] Level of agreement was 75% for biological overlap with commercially available tests and 81% for validation of clinical utility in a clinical trial.

analysed data from >5000 patients across randomised studies (3 phase II and 7 phase III;[39] 12 phase II/III[40]) and found that PARPi can improve the prognosis of primary or recurrent ovarian cancer patients, with and without *BRCAm,* with a manageable safety profile.

Development of testing protocols to define the HRR deficiency status of patients with ovarian cancer would serve to optimise the clinical benefit of PARPi. Clinical tests aim to predict the presence of HRR deficiency based on genomic features. Specifically, HRR deficiency can be characterised using 'cause (HRR loss of function)' and 'effect (genomic instability)' assays.[41] Commercially available effect assays, such as the 'myChoice CDx' assay by Myriad, test for genomic instability via the presence of loss of heterozygosity (LOH), telomeric allelic imbalance, and large-scale state transitions across the genome.[42] In the myChoice assay, HRR deficiency is typically defined by the presence of *BRCA1/2m*, or when a tumour surpasses a given threshold of genomic instability score (GIS).[19,43,44] In the VELIA/GOG-3005 trial of veliparib, in patients with newly diagnosed high-grade serous ovarian cancer, tumours with GIS ≥33 were considered to be HR deficient (HRd) and tumours with a GIS <33 were considered to be HR proficient (HRp).[19] A higher GIS threshold of 42 is more commonly used, and was the adopted score in PAOLA-1/ENGOT-ov25 and PRIMA/ENGOT-ov26.[24,43,44] The 'FoundationFocus CDx *BRCA* LOH' detects the presence of mutations in the *BRCA1/2* genes and the percentage of the genome affected by LOH in DNA from tumour tissue samples. Tumours with a score ≥16 are categorised as 'LOH-high'.[20] This test was validated in the ARIEL3 trial in a second-line, platinum-sensitive setting,[20] but it has not been evaluated in first-line randomised studies. However, HRR deficiency tests vary in terms of the specific genomic features being measured, and the means used to determine the thresholds that define HRR deficiency. As such, the 'myChoice CDx' and the 'FoundationFocus CDx *BRCA* LOH' assays are not interchangeable.

Non-BRCA homologous recombination repair (HRR) genes

Consensus statements are shown in Table 3.

Our literature search retrieved studies indicating that heritable mutations in ovarian cancer risk genes are present in 13%-28%[13,45-47] of ovarian cancer patients, and that germline genetic testing is recommended for all such patients, ideally with pre-test genetic counselling. It has also been shown that 50% of high-grade serous ovarian cancers are characterised by HRR deficiency.[11] Thus, beyond *BRCAm*, HRR deficiency may also occur as a result of germline and somatic mutations or deregulation of other genes related to HRR. There is increasing literature around ovarian cancer risk associated with a growing group of genes (such as *BRIP1*, *BARD1*, *PALB2*, *NBN*, *RAD51C*, and *RAD51D*).[48,49] One study investigated the role of *RAD51D* in cancer susceptibility and identified eight inactivating *RAD51D* mutations from 911 breast–ovarian cancer families (unrelated individuals) compared with 1 in 1060 controls ($P = 0.01$). The association was principally with ovarian cancer with three mutations identified in the 59 pedigrees with three or more ovarian cancer cases ($P = 0.0005$).[50] Germline variants in *RAD51C*, *RAD51D*, and *PALB2* are associated with a significantly increased risk of ovarian cancer,[51,52] and during our discussions there was agreement that these variants are effective predictors for familial risk of ovarian cancer. A group of contributors regarded *BRIP1* status as a predictor of family risk,[53,54] but consensus was not reached.

Whilst germline mutations in non-*BRCA* HRR genes may have clinical implications for family members, overall, there appear to be insufficient data to support the mutation status of non-*BRCA* HRR genes to reliably predict PARPi response in patients with ovarian cancer. Our literature search identified one report of partial responses[36] to rucaparib in four of five patients with *RAD51C* mutations; however, in the CLIO trial comparing patients with HRd versus HRp ovarian cancer receiving olaparib, only 2 of 10 confirmed responses were recorded in patients with *RAD51* mutations, and none in the other non-*BRCA* HRR mutations.[55] This might be due to the fact that, based on current understanding, pathogenic mutations cannot generally be separated out from harmless single-nucleotide polymorphisms or variants of unidentified significance.

Current ESMO guidelines state that there is insufficient evidence to determine the clinical validity of individual or panels of non-*BRCA* HRR mutations to predict response to PARPi and additional prospectively collected data are required.[12] We identified clinical data in support of this guidance: with the exception of *BRCA*, HRR mutation gene panels were not predictive of the efficacy of maintenance olaparib plus bevacizumab in the first-line PAOLA-1/ENGOT-ov25 trial.[23] Furthermore, there is good evidence to suggest

Table 3. Non-*BRCA* homologous recombination repair (HRR) genes: consensus statements

Consensus statements	Level of contributor agreement (%)[a]
There is currently insufficient evidence to recommend tumour testing for other HRR mutations (e.g. *RAD51C, ATM, BRIP1, BARD1, CDK12, BLM, CHEK1/2*) besides *BRCA1/2*, for predicting sensitivity to first-line PARP inhibitors	83
If it is decided to perform non-*BRCA* HRR tumour mutation testing, it could be considered in all invasive epithelial cancers, particularly in those with high-grade non-mucinous disease	86
If non-*BRCA* HRR tumour mutation status is examined, the following genes could be considered: *RAD51C/D, BRIP1, PALB2*, and *BARD1*. The value of mutations in other genes (*ATM, ATR, BLM, CDK12*, and *CHECK1/2*) remains to be established	90
Non-*BRCA* HRR mutation tumour testing could be beneficial for clinical research	100
If germline non-*BRCA* HRR gene mutations are identified, relatives should be notified by the ovarian cancer patient and advised that they may be referred for genetic counselling and genetic testing (if they wish)	82

PARP, poly-ADP ribose polymerase.
[a] Proportion of contributors agreeing (strongly agree/agree) with a survey statement.

that non-*BRCA* HRR pathway gene mutations are rare;[36] while testing for non-*BRCA* HRR mutations may identify a subset of ovarian cancers with HRR deficiency, HRR mutations are not considered to be predictive of HRR deficiency or sensitivity to PARPi in the first-line setting.[36,56]

We identified high-quality evidence from randomised trials using gene panels including Study 19, ARIEL3, NOVA, and CLIO.[20,55,57,58] These data show that mutations in less than half of non-*BRCA* HRR genes had a median GIS $\geq$42, and non-*BRCA* HRR mutations were not predictive of improved progression-free survival in first-line treatment, regardless of the gene panel used. As an example, data from the PAOLA-1 study used a gene panel with 13 pre-defined genes involved in HRR, an expanded panel with 5 additional genes involved in HRR, a restricted panel using 5 selected genes with the highest median GIS, and 3 published panels. Using the Myriad myChoice CDx plus assay to analyse patient samples from 806 patients randomised in PAOLA-1, 235 (29.2%) had a *BRCA*-mutated tumour, and patients harbouring deleterious mutations involved in HRR, excluding tumours with *BRCAm*, ranged from 3.7% to 9.8% depending on the HRR gene panel used.[59]

However, we also identified other data to suggest that mutations in HRR genes may predict response to PARPi in some cases. A study of tumour samples from Study 19 (olaparib maintenance therapy) included classification of mutations in genes involved in HRR, *BRCA1* promoter methylation status, measurement of BRCA1 protein, and Myriad CDx assay score. Patients with tumours harbouring *BRCA* mutations gained most benefit from olaparib. A similar treatment benefit was observed in 21/95 patients with *BRCA* WT tumours, but with loss-of-function HRR mutations, compared to patients with no detectable HRR mutations (58/95). These data suggest that patients with tumours harbouring loss-of-function mutations in HRR genes, other than *BRCA1/2*, may constitute a small but identifiable population who derive treatment benefit from olaparib, similar to patients with *BRCAm*.[57]

Mutations in mismatch repair (MMR) genes

Consensus statements are shown in Table 4.

Similar to the HR pathway, the MMR pathway plays an important role in DNA damage repair.[60] MMR deficiency is rare in high-grade serous carcinoma but is present in ~5%-10% of endometriosis-derived clear-cell and endometrioid ovarian carcinomas.[61] We found clinical evidence from a study using targeted sequencing to study 16 HR-associated genes and 4 MMR-associated genes, in germline and somatic samples from 207 patients with ovarian cancer, that revealed a positive correlation between the mutation status of HR and MMR genes ($P = 0.0072$).[62] Another study investigating sensitivity to olaparib in a panel of 18 high-grade serous epithelial ovarian cancer cell lines showed that sensitivity to PARPi is not associated with HR defects alone. Results from this preclinical study demonstrated that down-regulation of genes in the nucleotide excision repair (NER) and MMR pathways increased response to PARPi; the most highly sensitive cell lines were those where HR and NER, or HR and MMR pathways, were concomitantly down-regulated.[63] However, in a study of 523 unselected patients with ovarian cancer, <1% harboured germline mutations in MMR genes (*MHS2* and *MHS6*).[13] In a recent study of clinical samples from patients with non-serous/non-mucinous ovarian cancer, Lynch syndrome was detected in 11/28 (39%) of MMR deficiency cases (7 ovarian cancer and 4 synchronous): 7 *MSH6*, 2 *MLH1*, 1 *PMS2*, and 1 *MSH2*.[64]

Table 4. Mutation in mismatch repair (MMR) genes: consensus statements

Consensus statements	Level of contributor agreement (%)[a]
If germline panel testing is indicated, it is recommended to include MMR genes	87
In patients with a family history suggesting Lynch syndrome, germline testing of MMR genes is strongly recommended	97
If in the tumour mismatch repair deficiency (MMRd)/microsatellite instability-high (MSI-H) is detected, germline MMR testing is recommended	92
Mutations in MMR genes (e.g. *MSH6, MSH2, MLH1* and *PMS2*) or MSI are not proven to be effective predictors of sensitivity to PARP inhibitors in the clinic	90

PARP, poly-ADP ribose polymerase.
[a] Proportion of contributors agreeing (strongly agree/agree) with a survey statement.

Genetic testing in the clinic

Consensus statements are shown in Table 5.

We found high-quality evidence in meta-analyses of data from randomised trials to support the statement that PARPi is appropriate for patients with platinum-sensitive, relapsed ovarian cancer.[65,66]

The phenotype of HRR deficiency can be detected in tumour samples, with 'cause' and 'effect' assays. These include HRR gene panel tests (cause of HR loss) and genomic instability (effect of HR loss).[41] In addition to commercial germline tests for hereditary ovarian cancer, 'academic' laboratory tests such as the BROCA cancer risk panel use NGS to detect most of the recognised mutations in a large group of genes.[18] The panel commented that some tests [e.g. Myriad and 'academic tests' (e.g. used by the PAOLA Consortium)] analyse both *BRCA* and HRR deficiency simultaneously.[67,68] Simultaneous testing of *BRCA* and HRR deficiency is optimal if this capability is available. Furthermore, during the consensus meeting, it was expressed that some authorities will give reimbursement for one test only; in such cases, determination of *BRCA* status and HRR deficiency status simultaneously might be an efficient approach. An interesting study of triple-negative breast cancer samples from a population-based study using whole-genome and RNA sequencing data found that hypermethylation may be an early event in tumour development that progresses along a common pathway with *BRCA1*-mutated disease. This may represent a promising DNA-based biomarker for early-stage disease.[69]

Table 5. Genetic testing in the clinic: consensus statements

Consensus statements	Level of contributor agreement (%)[a]
Germline and/or tumour *BRCA* status and, if *BRCA* WT, tumour HRR deficiency status should be determined after primary diagnosis and ideally before the end of first-line chemotherapy	97
Tumour tissue and germline testing can be used to characterise *BRCA* status, and tumour tissue testing can be used to characterise HRR deficiency, non-*BRCA* HRR status, and MMR status	≥78[b]
Germline genetic testing should be a routine part of cancer patient care and should be integrated into the cancer patient genetic care pathway	83
Mainstreaming (making germline cancer gene testing part of cancer patient care by integrating testing into the treatment pathway) is a valuable option, and patients with germline *BRCA* mutation(s) should receive genetic counselling. If mainstreaming is not available, the patient should be referred for genetic counselling before germline testing	91
Oncologists (if appropriately trained/educated) should be able to counsel patients with regard to tumour and/or germline testing	90
Educational material, websites/videos, information on patient groups, and further counselling should be a routine part of cancer patient care and should be integrated into the cancer patient pathway following genetic counselling appointments	≥81[c]
Educational materials and formal training support should be available to staff responsible for counselling	≥94[d]
Genetic counselling should be made available to patients undergoing genetic testing at primary diagnosis with a family history of breast/ovarian cancer and in patients requesting specific information on genetic risk	≥94[e]
Support and genetic counselling in the clinical setting of ovarian cancer patients could be provided by genetic counsellors OR medical geneticists OR the patients' treating physician OR appropriately trained nursing staff	≥78[f]

[a] Proportion of contributors agreeing (strongly agree/agree) with a survey statement.
[b] Level of agreement for using tumour and germline tissue for *BRCA* status was 92% and 86%, respectively. Level of agreement for using tumour tissue for HRR deficiency, non-*BRCA* HRR status, and MMR status was 98%, 78%, and 96%, respectively.
[c] Level of agreement was 97% for educational material, 88% for directing to websites/videos, 86% for information about patient groups, and 81% for further counselling.
[d] Level of agreement was 98% for educational materials and 94% for formal training support.
[e] Level of agreement was 98% for patients with a family history of breast/ovarian cancer, and 94% for patients requesting specific information.
[f] Level of agreement was 89% for genetic counsellors, medical geneticists, and the patients' treating physician, and 78% for appropriately trained nursing staff.

Panel germline testing should factor into decisions about cascade testing to family members. For example, mainstreaming (making germline genetic testing part of cancer patient care through integration of testing into the treatment pathway, with non-clinical geneticists performing pre-test counselling) allows for timely detection of *gBRCA1/2*, which is important for both the patient and her relatives. We identified publications in support of mainstreaming,[70,71] including a study where a genetic testing pathway was established, and genetic testing undertaken by the trained cancer team with cascade testing to relatives carried out by the genetics team.[70] Of 207 patients who accepted testing through this pathway, 33 (16%) had a *BRCAm* and 121/154 (79%) had active disease. The authors reported a 4-fold reduction in time and a 13-fold reduction in resource requirement compared to a conventional testing pathway.[70] In another recent study, Jordan et al.[72] found that by initiating in-office germline testing, time to testing and receipt of results were meaningfully shortened, improving access to maintenance therapy following front-line treatment.

In addition to tumour sample analyses, we identified emerging literature around the characterisation of circulating tumour DNA (ctDNA) as a contemporaneous and non-invasive alternative, or additional measure, to define HRR deficiency status. In one study, ctDNA was identified in plasma from 29/33 (87%) blood samples; further analysis of ctDNA from ascites in 17 of these patients revealed that 10 had a high GIS (HRd) and 7 a low GIS (HRp).[73]

Genetic counselling is an essential element of patient care and should be available to any patients who have a family history of breast and/or ovarian cancer, hereditary germline mutations associated with increased cancer risk, or an abnormal tumour test (such as *sBRCAm*), as well as for those who request specific information. This approach is consistent with recent clinical practice guidelines for *BRCA1/2* genetic testing, in which identifying individuals who may benefit from genetic counselling and risk-reducing strategies is listed as the first aim of *BRCA* testing.[74] In our discussions around who is/are the appropriate professional/s to give genetic counselling, there was agreement that it does not necessarily need to be a genetic counsellor or clinical geneticist, and that an appropriately trained oncologist or expert nurse could also provide the counselling if this is permissible within local regulations. Some panellists advised that nurses would not be considered suitable in their country as they were not routinely trained for this work and may therefore lack the required specialist knowledge. We also agreed that those engaged in necessary counselling, if not professional counsellors, should be appropriately trained/supported with access to educational material and formal training support (online training modules or local interactive materials were discussed and the panel thought that these methods may be most suitable). During the consensus meeting we discussed the dramatic increase in *BRCA* testing in the last two decades, for both preventive and therapeutic assessment. We agreed that these changes have, in many European countries, contributed to a bottleneck in access to genetic counsellors and genetic test results, with the latter being a requirement for treatment of ovarian cancer. Alternative pathways to perform genetic testing in patients with ovarian cancer are thus needed.

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APPENDIX: THE EUROPEAN CONSENSUS GROUP

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