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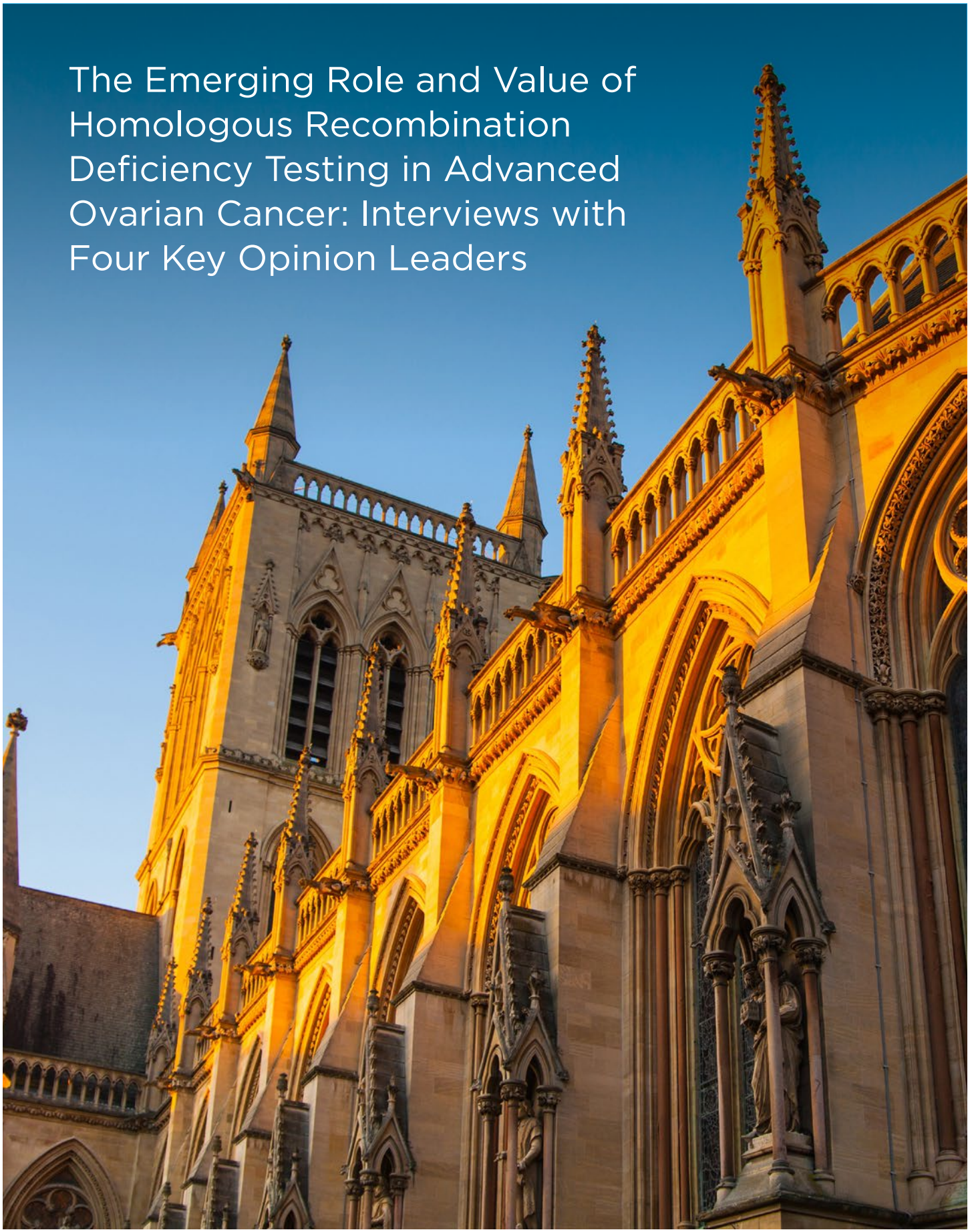

The Emerging Role and Value of Homologous Recombination Deficiency Testing in Advanced Ovarian Cancer: Interviews with Four Key Opinion Leaders

Interviewees: Frederik Marmé,[1] Christina Fotopoulou,[2] Ursula Matulonis,[3] David Bowtell[4]

1. Department of Obstetrics and Gynaecology, Medical Faculty Mannheim, Heidelberg University, University Hospital Mannheim, Germany
2. Department of Gynaecologic Oncology, Faculty of Medicine, Imperial College London, UK
3. Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA
4. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

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Introduction

Ovarian cancer is the seventh most common cancer in females,[1-3] and the most lethal gynaecologic malignancy globally because of its vague presentation, insidious nature, recurrence, and drug resistance.[3-7] Genetic factors, such as family history and breast-related cancer antigen (*BRCA*) gene mutations, are among the most important patient factors affecting the occurrence of ovarian cancer.[1]

For decades, first-line therapy for patients with newly diagnosed advanced ovarian cancer has been a combination of debulking surgery and platinum-based chemotherapy as standard of care.[8-10] The

latest breakthrough in the management of patients with advanced ovarian cancer is therapy with poly(ADP-ribose) polymerase (PARP) inhibitors.[8,11]

Tumours with homologous recombination deficiency (HRD), including those in *BRCA* mutation carriers, are sensitive to base excision repair blockade via PARP inhibitors.[12] Diagnostic tests that determine HRD status using tumour tissue from patients with ovarian cancer provide information on the magnitude of benefit for PARP inhibitor therapy. HRD testing provides an opportunity to optimise the use of PARP inhibitors in patients with ovarian cancer, but methodologies are diverse and clinical application remains controversial.[13]

For this article, the EMJ conducted interviews in April, May, and June 2021 with four key opinion leaders (KOLs), Frederik Marmé from Germany, Christina Fotopoulou from the UK, Ursula Matulonis from the USA, and David Bowtell from Australia, all of whom have a wealth of experience and expertise in managing ovarian cancer, to gain their perspectives on the emerging role of HRD testing in advanced disease. The experts gave valuable insights into several pertinent issues in advanced ovarian cancer treatment and discussed significant recent developments in the field.

This article discusses the impact of late diagnosis and delayed treatment on patient outcomes in ovarian cancer, genetic screening, and risk-reduction strategies. The evolving landscape of HRD testing, the importance of HRD testing at diagnosis, and the level of knowledge and understanding of HRD-positive advanced ovarian cancer are also explored.

LATE DIAGNOSIS AND DELAYED TREATMENT IN OVARIAN CANCER

No Public Health Screening Programme

There is no public health screening programme for early detection of ovarian cancer; therefore, most patients with ovarian cancer are diagnosed with advanced disease (when the disease has spread within the entire abdomen or to distant organs), which is associated with significant mortality.[2,4] Marmé highlighted several large studies that have researched screening strategies in the general population[14-23] and in those at risk of developing ovarian cancer because they have a pathogenic germline mutation and family history.[24-26]

For example, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial[14-19] showed that among females in the general population, simultaneous screening with cancer antigen 125 (CA125) and transvaginal ultrasound (TVUS) compared with usual care did not reduce ovarian cancer mortality. Also, in a prospective, randomised controlled trial of ovarian cancer screening in Japan, the Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS),[20] the rise in the detection of early-stage ovarian cancer in asymptomatic postmenopausal females was not significant.

Fotopoulou acknowledged the recent publication by Menon et al.[22] of the final results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS),[21,23] an extensive screening programme that invited >1 million females to participate and was described by Bowtell as "a beautifully run trial, very carefully thought out and executed, and essentially state-of-the-art with what was then current technology." Preliminary data from this study (2016)[21] showed no compelling evidence for an impact of screening on survival. Furthermore, the results from longer follow-up (2021)[22] showed that even though there was a significant reduction in the diagnosis of late-stage ovarian cancer through screening, this did not translate to an increase in overall survival. Menon et al.[22] concluded that, as screening did not significantly reduce ovarian and tubal cancer deaths, general population screening cannot be recommended. Fotopoulou thought that further screening studies with a similar design in the near future were unlikely and more innovative screening approaches would emerge.

Matulonis acknowledged the negative results of the UKCTOCS trial, after nearly two decades of work, and >200,000 females enrolled into the study with either no screening, ultrasound, or the risk of ovarian cancer (ROCA) test. She highlighted that even though there was a shift downward from higher stage to lower stage in

the ROCA test, there was no improvement in survival and concluded: "The bottom line is that the CA125 blood test, as tested in the UKCTOCS trial using the ROCA algorithm, unfortunately does not improve survival."

Marmé emphasised the relatively low incidence and uncharacteristic symptoms of ovarian cancer, the not uncommon occurrence of false positive results on TVUS, and the huge effort required to run screening studies, with large numbers of participants and long follow-up. As none of the studies to date have proven that mortality can be decreased through a screening programme, including TVUS and CA125 serial measurements, the KOLs considered it very unlikely that there will be effective screening programmes for the general population in routine clinical practice in the near future.

Bowtell summarised: "Even though the negative result [of UKCTOCS] is disappointing, the fact that it is conclusive is valuable as women are not falsely reassured that they can be screened." Despite having a "never say never" approach regarding screening programmes in the distant future, Bowtell considered the "door is shut" for blood-based protein biomarkers and low-resolution imaging based on the UKCTOCS trial. He suggested that other molecular methods (e.g., GRAIL's mutation screening, exosomes, RNAs released in the circulation) combined with a high-resolution imaging approach may enable screening in the future. According to Bowtell, "the problem is the biology is stacked against us" as ovarian tumours are deep within the body and relatively inaccessible compared with other cancers (e.g., melanoma, colorectal cancer) and there is no anatomical barrier to prevent spread from the fallopian tubes throughout the peritoneal space.

Similar to the results in the general population, Marmé noted that there is no evidence of significantly reduced mortality by cohort screening studies in the at-risk population, but risk-reducing prophylactic surgery is effective.[24,25,26]

Impact of Diagnosis with Advanced Disease on Patient Outcomes

According to Marmé, staging identifies patients with different prognoses who require different treatments, and the most important prognostic factor is quality of surgery, with post-operative macroscopic tumour residuals the key factor for prognosis. He suggested that macroscopic tumour-free surgery is easier to achieve in earlier-stage cases than in advanced, metastatic disease (e.g., with visceral metastases); however, the presence of visceral metastases does not preclude a surgical approach that results in no macroscopic residual tumour and patients in whom this is achieved derive substantial benefit from radical surgery.

Fotopoulou emphasised the importance of tumour volume and load, adding that "traditional staging classification does not really capture the entire picture in ovarian cancer." She cited Stage IIIC ovarian cancer as an example: in one patient, Stage IIIC may involve a 2.5 cm nodule on the omentum with no other upper abdominal disease; in another patient, Stage IIIC may comprise extensive carcinosis in the entire abdomen. These are both Stage IIIC patients, but the tumour load and expected outcomes are completely different.

In accordance with this, Bowtell expressed that it is underappreciated how important the volume of disease is. He gave an example of a rapid autopsy patient with extensive disease and a *BRCA2* mutation who had received only chemotherapy (no surgery) and died 3 years after diagnosis with >15 independent *BRCA* reversion mutations. He suspected that having a very large pool of tumour provided multiple opportunities for rare cells to evolve and quickly overwhelm the patient.

Matulonis proposed that there are commonly two scenarios in ovarian cancer diagnosis in symptomatic females. In the first scenario, the early-stage mass has become large enough to result in pelvic symptoms, including urinary frequency, bowel issues, and pain, and patients who seek medical attention at this point can be early stage. In the second scenario, a patient who has abdominal bloating, breathlessness, and gastrointestinal symptoms has more advanced disease (Stage III–IV). She pointed out that Stage I and Stage III–IV are likely two different cancers. Detecting early (non-invasive) disease at the serous tubal intraepithelial carcinoma[27] stage is currently rare, as early-stage disease is usually an incidental finding, e.g., during surgery for an ovarian cyst. In contrast, most patients are

diagnosed with Stage III–IV disease in which the cancer is developing in the fallopian tubes and ovary and, instead of a single focus, there are multiple cancer foci in the abdominal cavity.

Marmé noted that treatments can be effective even in frail, elderly patients with advanced ovarian cancer, and referred to the EWOC1 trial,[28-30] in which vulnerable older patients with advanced ovarian cancer benefited substantially from treatment with carboplatin plus paclitaxel, with the standard combination 3-weekly proving the most efficacious regimen.

Delay in Symptomatic Patients Seeking Medical Help and Timing of Diagnosis

A review of global trends in ovarian cancer indicated that just under half of patients visited a doctor within 1 month of experiencing symptoms and one-quarter waited ≥3 months, with only three-quarters of symptomatic patients seeking medical help.[31] Fotopoulou remarked that this delay has been exacerbated by the COVID-19 pandemic as people who have developed symptoms have not sought medical help because of fears over visiting hospital during the crisis. Such a delay has, therefore, caused a shift in disease burden and how ill the patient is from the disease at diagnosis. Matulonis noted that the longer symptomatic patients wait before seeking medical help, the more physically ill they become, and the greater the tumour bulk, risk of obstructions and blood clots, weight loss, and drop in performance status. As ovarian cancer symptoms are vague, the timing of diagnosis depends on how both patients and healthcare professionals (HCPs) interpret the symptoms. Matulonis conveyed that it is sometimes difficult to define low-volume peritoneal carcinomatosis on ultrasound, CT, or PET scan as it can present as bowel wall thickening rather than a mass, or the mass is there but is too small to identify using these methods. She described ovarian cancer as "unfortunately a stealth cancer" and noted that it was not clear whether picking up symptoms early would impact on prognosis.

Following this theme, Bowtell referred to the results of the Australian Ovarian Cancer Study,[32] which indicated that reducing time to diagnosis does not greatly alter stage of disease at diagnosis or improve survival outcomes. Once a cancer becomes symptomatic, he considered, the substantial burden of disease has already been there for months or years, so it makes sense that a few more months is unlikely to significantly alter the outcome. Although patients who ignored symptoms may feel guilty for doing so, it would perhaps alleviate some of the guilt if they were informed that reducing time to diagnosis appears not to make a difference to outcome.

Educational Gaps about Signs and Symptoms of Ovarian Cancer for Patients and Healthcare Professionals

Fotopoulou thought that there are large geographical disparities in the awareness and adequate access to information and knowledge about ovarian cancer. She described how patients in the UK with frequent abdominal pain and bloating visit their general practitioners (GP) who, with their broad, generalist approach, understandably do not necessarily have deep knowledge of the subtle nature of the "chameleon" symptom profile of ovarian cancer. She suggested that gaps in knowledge are through not only lack of awareness but also limited exposure to the disease, and they also depend on the mindset of the patient and HCP and the frame of reference. For example, a female patient aged ≥60 years presenting with abdominal bloating, distension, and pain may be considered by their GP to have irritable bowel syndrome or menopause and, despite symptoms persisting even after diet modification, the GP may not suspect to investigate about ovarian cancer because it is so rare. On the contrary, when such a patient presents to a gynaecological oncology specialist, they may be more inclined to consider ovarian cancer.

Bowtell summarised that HCPs may not have much awareness of ovarian cancer signs and symptoms because it is a rare disease; however, they would work on first principles and continue to investigate until diagnosis. He questioned the use of ovarian cancer symptom awareness as symptoms are non-specific, and thought a clinical trial to prove that increased symptom awareness improves outcome is not feasible and unlikely to be effective.

Similarly, Marmé described symptoms of advanced ovarian cancer as really uncharacteristic, with observations such

as changes in bowel habit, stomach-ache, and weight gain through ascites indicating a gastrointestinal investigation route with gastroscopy, colonoscopy, and MRI. He predicted that actively increasing patient awareness of a link between these common symptoms and the "silent killer"[33] that is ovarian cancer would result in many concerned patients.

The KOLs recounted their patients' experiences of visits to the GP and being told their symptoms were related to their stage of life and not to worry, or being referred to gastroenterologists and other medical specialists, with some patients feeling their symptoms were not being taken seriously. Importantly, Matulonis noted, there are several studies indicating patients with ovarian cancer can develop post-traumatic stress disorder,[34-36] which she suggested may be related to feeling that they are not being listened to by HCPs about their symptoms.

GENETIC SCREENING AND RISK-REDUCTION STRATEGIES

Genetics Provide an Opportunity to Intervene

Bowtell emphasised the issue of early detection/prevention in ovarian cancer and proposed that genetics (including screening of *BRCA* and other risk genes) provides an opportunity to intervene, although this is an evolving space and there is more to be done in terms of prevention. He highlighted the many patients who have missed out on ovarian cancer genetic screening because their diagnosis predated improvements in genetic testing and changes to the guidelines. A publication by Samimi et al.[37] described a conceptual framework for identifying and genetically testing previously diagnosed but unreferred patients with ovarian cancer and other unrecognised *BRCA1* or *BRCA2* mutation carriers to improve the detection of families at risk for breast or ovarian cancer. Samimi et al.[37] considered that the failure to identify mutation carriers among probands represents a lost opportunity to prevent cancer in unsuspecting relatives through risk-reduction intervention in mutation carriers and to provide appropriate reassurances to non-carriers.

Prophylactic Surgery for Risk Reduction

Matulonis depicted prophylactic surgery to reduce the risk of ovarian cancer as a highly effective strategy that is conducted in females in whom family planning has already been fulfilled. She commented that a good proportion of high-grade serous ovarian cancer comes from the distal end of the fallopian tubes[38-40] and referred to a strategy in which the fallopian tubes (but not ovaries) are removed to reduce the risk of ovarian cancer.[41,42] Matulonis referred to a study in British Columbia, Canada, by Hanley et al.[43] that reported no significant differences in minor complications between females at general population risk who underwent opportunistic salpingectomy and those who underwent hysterectomy alone or tubal ligation. Hanley et al. also reported that hysterectomy with bilateral salpingectomy was not associated with increased risks of postoperative complications[44] or earlier age of onset of menopause.[45] Matulonis commented that it will be interesting to see what happens to ovarian cancer incidence in British Columbia in the future.

THE EVOLVING LANDSCAPE OF HOMOLOGOUS RECOMBINATION DEFICIENCY TESTING

Homologous Recombination, *BRCA* mutations, and PARP Inhibitors

Homologous recombination and base excision repair are two of the major DNA repair pathways. The proteins encoded by *BRCA* genes and PARP enzymes are involved in homologous recombination and base excision repair, respectively.[12] *BRCA1* and *BRCA2* genes play a vital role in cell repair and maintaining genomic stability.[46] Germline mutations in *BRCA1* and *BRCA2* account for a large proportion of inherited breast and ovarian cancers.[46] PARP enzymes have essential roles in cellular processes, including the regulation of transcription, apoptosis, and DNA damage response.[47] Inhibition of PARP in damaged cells, such as ovarian cancer cells, prevents the DNA repair process and results in disruption of cellular homeostasis and cell death. PARP inhibitors were the first approved cancer drugs that specifically target the DNA damage

response in *BRCA1/2*-mutated breast and ovarian cancers[7,47-51] and have transformed the management of advanced ovarian cancer.[11,52-55]

What Is Homologous Recombination Deficiency Testing and Why Is It Important?

The KOLs explained that the inability to repair DNA through homologous recombination creates a specific pattern of mutations on the genome, also known as a footprint, signature, or 'genomic scar',[56] which can be detected with molecular analysis. This scar remains even if there have been reversion mutations or other mechanisms of resistance. HRD testing picks up these genetic alterations, thereby revealing past mutations that remain even if they may no longer be functionally important.

Marmé proposed that there is considerable knowledge of the pathogenic mutations in *BRCA1* and *BRCA2* genes, which constitute the majority of genomic alterations; however, there are several less-frequently mutated genes of significance in this process (e.g., partner and localiser of *BRCA2* [*PALB2*], *RAD51*), about which there is substantially less knowledge. Marmé estimated that in the early days of *BRCA1* and *BRCA2* sequencing, the proportion of findings that were classified as variants of unknown significance was in the order of 30% and this has decreased to 5–6% because of the considerable data collected from many families that have been followed.

Tumours with HRD, including those in *BRCA* mutation carriers, are sensitive to base excision repair blockade via PARP inhibitors.[12] Approximately 50% of ovarian carcinomas present with HRD and these tumours are more sensitive to platinum-based chemotherapy and PARP inhibitor therapies.[57] Defects in one or both *BRCA1* and *BRCA2* genes and the resulting deficiency in BRCA1 and/or BRCA2 proteins induces profound cellular sensitivity to the inhibition of PARP activity.[58] HRD and platinum sensitivity are therefore prospective biomarkers for predicting the response to PARP inhibitors in ovarian cancers.[59]

HRD testing is important because it identifies patients who are specifically sensitive to platinum-based treatments and PARP inhibitors. Response to platinum, according to Marmé, is the only useful clinical factor apart from HRD and *BRCA* mutations in the recurrent setting.

Increasing Interest in Homologous Recombination Deficiency Testing

Marmé explained that HRD testing only really gained interest in late 2020, so currently there is only a short history of its use. However, the KOLs described increasing interest and demand for testing (and longer turnaround times), particularly across large centres. Accessibility of HRD testing also appears to be dependent on geography, with fewer tests available in remote areas and less-developed countries. Fotopoulou recognised the substantial progression and increased awareness in HRD testing. She acknowledged that HRD testing is now a standard approach in countries including the UK and Germany, particularly in patients with high-grade serous ovarian cancer; however, it is not standard in all countries in Europe or globally.

HRD testing is used to identify which patients should receive PARP inhibitors, but even in the first-line setting PARP inhibitor therapy is not always restricted to patients who are HRD-positive. Notably, Marmé described the benefit of PARP inhibitors as less pronounced in patients who are HRD-negative in the first-line setting, so the benefit—toxicity balance has to be carefully considered as other options like bevacizumab (Avastin®)[60] are available. He also noted that a positive HRD test may point to heritable disease; therefore, any use of or discussion about HRD testing should be accompanied by genetic testing for heritable disease and genetic counselling, although there are ongoing discussions about the optimal strategy (e.g., should HRD or *BRCA* and other homologous recombination repair [HRR] tests be conducted first?).

Methods of Homologous Recombination Deficiency Testing in Current Use

Two commercially available tests, myChoice® CDx (Myriad Oncology, Salt Lake City, Utah, USA)[61] and Foundation Medicine's loss of heterozygosity (LOH), have been prospectively validated in Phase III studies: myChoice® CDx in PRIMA/ENGOT-OV26/GOG-3012[62,63] and PAOLA1,[64-66] and LOH in ARIEL3.[67-69] These

tests enable stratification of patients based on sensitivity to PARP inhibitors.

In centres where there is no access to these validated tests, Marmé explained that HRR gene panel sequencing (which is not validated) is conducted instead. PAOLA-1[65] compared olaparib with bevacizumab versus placebo plus bevacizumab in patients with advanced high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer after first-line, platinum-based chemotherapy. In PAOLA-1,[65] HRD testing identified a larger number of patients who were sensitive to PARP inhibition than HRR gene panel sequencing; also, mutations in HRR panel genes were not predictive for PARP inhibitor benefit. These results indicate non-*BRCA* HRR gene panel sequencing is not an alternative to HRD testing. Marmé noted there is no evidence for LOH testing in the first-line setting, and that the two commercially available tests are not interchangeable. He also mentioned some important efforts in development and validation of academic HRD tests and predicted that validated academic HRD tests may be available in the near future.

Matulonis explained that the HRD test does not always give a conclusive answer (≤25% of results are indeterminate) but testing helps define whether the tumour is HRD or homologous recombination proficient, and these results are then used in decision-making for patients with high-grade tumours that are sensitive and responsive to chemotherapy.

A deficiency of HRD testing, according to Bowtell, is that it reveals nothing about restoration of HRR in a tumour as a result of, for example, *BRCA* reversion mutation. He added that a dynamic protein biomarker that is active under steady state and reflects tumour homologous recombination status may be valuable in the future.

THE IMPORTANCE OF HOMOLOGOUS RECOMBINATION DEFICIENCY TESTING AT DIAGNOSIS

No Value in Homologous Recombination Deficiency Testing in Early Disease

Fotopoulou commented: "I cannot believe that a patient with early ovarian cancer will not benefit from PARP inhibitors; however, there are currently no data to demonstrate or prove this as there are no relevant studies in early disease." Marmé confirmed that HRD testing is not used in Stage I-II ovarian cancer as there are currently no clinical implications. There is no option to give PARP inhibitors to patients with early disease outside of clinical trials as all PARP inhibitor studies have been in advanced disease and these drugs have not been tested or licensed in early disease. Matulonis clarified that in patients with early ovarian cancer, the focus is on germline testing and treating the patient as clinically indicated based on factors such as exact early stage and histology.

The Value of Homologous Recombination Deficiency Testing at Diagnosis in Patients with Advanced Ovarian Cancer

The KOLs acknowledged that HRD testing depends on budget and availability; however, the consensus was that HRD testing has value at diagnosis in patients with advanced disease. HRD status enables treatment to be tailored to provide the best course of therapy and directs which treatment is given to the patient first, with patients with HRD-positive disease recommended PARP inhibitors. Matulonis indicated that it is difficult to judge how common HRD testing is at diagnosis.

In cases where HRD testing is not available, HCPs deal with patients empirically, explained Bowtell. He considered that, generally, if a drug is well-tolerated and available it can still be used even if testing is not conducted (e.g., because of a restricted budget). He advised: "If health budgets are very limited, predictive biomarkers are more important. If drugs are heavily rationed, it is essential to do the testing to direct drug use effectively." Bowtell underlined that HRD

testing should be conducted early on in patient management and may become an essential part of first-line treatment.

Marmé suggested the importance of HRD testing for different HCPs depends on how they judge the role of bevacizumab with or without olaparib in first-line advanced ovarian cancer. If bevacizumab is to be administered, HRD testing should be conducted to indicate whether the patient is eligible for PARP inhibitors**.** If bevacizumab is not to be administered in the front-line setting (e.g., drug not available, spare for later use, contraindications), Marmé considered HRD testing is still important as it enables an estimate of magnitude of benefit from PARP inhibitors and may influence treatment strategy for recurrence (e.g., reintroduction of platinum-based therapy in patients who are HRD-positive). In addition, as PARP inhibitors are associated with low-grade toxicity (fatigue, nausea), which can become a substantial burden for patients on long-term maintenance therapy, knowledge of HRD status will help define the potential benefit of this treatment and perhaps help the patient to maintain compliance.

Knowledge and Understanding of Homologous Recombination Deficiency-Positive Advanced Ovarian Cancer

Marmé described the ovarian cancer professional community as very proactive, with lots of educational programmes, state-of-the-art meetings, clinical study groups, and quality assurance efforts. He added that all this activity leads to a high quality of patient care in this setting, including awareness of the importance of surgery and standard-of-care chemotherapy. However, the consensus of the KOLs was that gaps in knowledge of HRD-positive advanced ovarian cancer depend on the HCP. Matulonis proposed that HCPs other than ovarian cancer/gynaecological experts should have increased education about ovarian cancer in general, genetic testing, and HRD testing. Fotopoulou explained that the first concern of GPs in the case of HRD-positive disease is that there is a genetic background and the associated worry about the patient's family. She postulated that perhaps GPs are unaware that HRD-positivity has significant therapeutic implications nowadays, and implications for the patient herself, and is also associated with better response to platinum agents and PARP inhibitors and eligibility for more clinical trials. These gaps in knowledge and understanding and the imbalance of HRD testing through geographical or financial reasons were perfectly summarised by Bowtell in a quote from William Ford Gibson, the American Canadian science fiction writer: "The future is already here; it's just not very evenly distributed."

FUTURE PROSPECTS AND CONCLUSIONS

Marmé emphasised the huge unmet need in patients who are HRD-negative, who derive little or no benefit from PARP inhibitors, and proposed that future research focusing on specific trial strategies is required in this population. New therapies are needed in patients who are HRD-negative as there are no effective standard-of-care therapies for these patients after platinum-based chemotherapy. Also needed is counselling about the magnitude of benefit they should expect with PARP inhibitors, which may guide PARP inhibitor use (benefit versus toxicity) and help compliance. Marmé stressed that he has always considered it important to know the HRD status of the patient as this may influence treatment strategy (current and next lines of therapy) and timing of follow-up. He considers there is room for improvement in HRD testing and is looking forward to new academic HRD tests and development in research areas such as PARP inhibitor–immunotherapy combinations.

Fotopoulou's vision and hope for the future is that HRD testing will be easy, straightforward (with minimal associated paperwork), cost-effective, accessible, and routine in every hospital across the world. She reflected on the incredible recent advances in the treatment of advanced ovarian cancer, including the huge increase in survival compared with 20 years ago; however, she emphasised that there are currently not enough data on PARP inhibitors to determine whether these drugs will actually change overall cure rates from the disease. Fotopoulou classified HRD testing as having a key role in the optimal management and care of patients with ovarian cancer, but remarked that surgery remains crucial, even in patients who are HRD-positive. She advocated a systematic effort comprising

HRD testing, surgery, and treatment, requiring a maximum level approach across all areas to provide a comprehensive and complete package of care for patients with advanced ovarian cancer because, for these patients, "the effort matters across all levels".

Matulonis concluded that the main emphasis of HRD testing is in newly diagnosed patients, where it enables HCPs to define the optimal treatment route for the patient. She considered HRD testing to be less important in relapsed disease where there is no real-time tissue and there is more real-time ability to look at reversion mutations through blood-based assays. Ovarian cancer has no or very few circulating tumour cells but there is circulating DNA, which may enable a more precise treatment strategy. She predicted that there will be better assays in the future, with HRD testing an important component of the clinical picture.

Bowtell commented that there is a need for good biomarkers of resistance in the advanced ovarian cancer population and knowledge about how to use them clinically. He posed several questions: What should be done in the case of *BRCA* reversion in germline/somatic mutation? What level of reversion in circulating tumour DNA predicts failure to respond to the next line of treatment? If a patient has a reversion, are they more likely to respond to a particular conventional agent? These and many more questions on the topic of acquired resistance need to be answered to determine how to detect and manage this more effectively. Bowtell also predicted that much could be learned from highly unusual patients who have exceptionally favourable responses to treatment and/or overall survival,[70] and that research into such "exceptional responders" may provide insights that could ultimately improve the outcome of individuals with more typical disease trajectories.[70]

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