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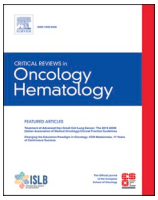

Matching BRCA and prostate cancer in a public health system: Report of the Italian Society for Uro-Oncology (SIUrO) consensus project

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ABSTRACT

The recent approval of PARP inhibitors for the treatment of metastatic –castration-resistant prostate cancer (mCRPC) patients with BRCA mutations firstly introduced the possibility of proposing a targeted treatment in this disease. However, the availability of this therapeutic option raises a number of questions concerning the management of prostate cancer in everyday clinical practice: the timing and method of detecting BRCA mutations, the therapeutic implications of the detection, and the screening of the members of the family of a prostate cancer patient with a BRCA alteration. These challenging issues led the Italian Society for Uro-Oncology (SIUrO) to organise a Consensus Conference aimed to develop suggestions capable of supporting clinicians managing prostate cancer patients. The present paper described the development of the statements discussed during the consensus, which involved all of the most important Italian scientific societies engaged in the multi-disciplinary and multi-professional management of the disease.

1. Introduction

The aggressiveness of prostate cancer, the solid tumour with the highest incidence rate and one of the leading causes of death among adult males (Rawla, 2019; Siegel et al., 2022), ranges from indolent disease that can be managed by means of active surveillance to potentially lethal cases (Cornford et al., 2021; Mottet et al., 2021). However, increasing knowledge of its biology has led to an evolution in grading from classical Gleason scores to the new grading system suggested by Epstein et al. (2005), and the development and testing of innovative treatment options capable of providing further gains in life expectancy. One of the most important of these advances is the discovery that somatic and germline breast cancer (*BRCA*) 1/2 gene mutations, which were already known to play a prognostic and predictive role in ovarian and breast cancers (Goldgar et al., 1994; Miki et al., 1994; Wooster et al., 1995; Wooster et al., 1994), also play a similar role in about 15 % of prostate cancer patients, and this has led to the approval of the first targeted treatment of the disease (Abida et al., 2020b; de Bono et al., 2020; Smith et al., 2022).

However, the availability of this therapeutic option based on poly-ADP ribose polymerase (PARP) inhibitors has raised a number of new questions concerning the management of prostate cancer in everyday

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clinical practice. For this reason, the Italian Society for Uro-Oncology (SIUrO) organised a Consensus Conference involving all of the leading Italian scientific societies engaged in the multi-disciplinary and multi-professional management of the disease with the aim of addressing such issues.

2. Material and methods

Fig. 1 shows the workflow of the consensus process, which started using the estimate-talk-estimate (ETE) or "mini-Delphi" method (Gustafson et al., 1973; Rowe and Wright, 2001). ETE (a formal means of reaching consensus that was developed in an attempt to overcome some of the negative aspects of group dynamics) facilitates group decision making (Jones and Hunter, 1995; Kaplan, 1987) by combining activities that restrict verbal interactions with face-to-face meetings (Gallego and Bueno, 2014).

The nine members of a selected multi-disciplinary board (three medical oncologists, and one pharmacologist, geneticist, clinical biochemist, pathologist, urologist, and radiation oncologist) individually identified 49 points of interest (or *items*) that, in their opinion, deserved exploration and discussion. These were then harmonised and grouped by a senior urologist (GNC) trained in developing group consensus (the *facilitator*) into 22 items that were proposed to the board members at a face-to-face meeting. The harmonised items were discussed in order to reach agreement between the facilitator's work and the experts' opinions, after which the board members individually drew up one or more statements concerning each of 13 agreed items. This led to the proposal of 61 statements, which were again subsequently harmonised by the facilitator. At a second face-to-face meeting, the board members and the facilitator reviewed and further discussed the harmonised statements, and finally agreed on a total of 25 statements.

The statements generated in this way were then presented via an online scoring platform to the 30 members of an extended multi-disciplinary panel of experts who expressed their degree of consensus by means of a 9-point numerical rating scale ranging from 1 = totally disagree to 9 = totally agree (Fitch et al., 2001). A median score of ≥ 7 was considered the threshold of consensus for each statement.

A final face-to-face meeting allowed the members of the board and the expert panel to come to a final shared formulation of 23 statements.

It is worth noting that all of the members of the board and the panel were involved in the global care of prostate cancer patients at different Italian centres with heterogeneous multi-disciplinary teams of urologists, medical and radiation oncologists, geneticists, laboratory staff, pharmacologists, and pathologists in order to ensure the broadest possible discussion.

Given the nature of the consensus technique, a senior clinical epidemiologist (GP) assured scientific and methodological accuracy.

3. Statements and related rationales

The statements (listed in Table 1) were discussed and approved during the plenary session of the SIUrO Consensus Conference held on 2 December 2021.

3.1. Tumour material for BRCA1/2 testing

3.1.1. Statements

1.1 BRCA1/2 status should preferably be determined using the most representative material, and therefore the most recent and readily available tumour tissue.

1.2 BRCA1/2 somatic testing (upon diagnosis, during a biochemical recurrence, or in non-pharmacologically treated patients) can be carried out using formalin-fixed, paraffin-embedded (FFPE) material obtained from an initial prostate biopsy and/or surgical specimen in the absence of visceral or lymph node material. Upon the appearance of metastatic castration-resistant prostate cancer (mCRPC), it is preferable to obtain biological material from a new biopsy whenever possible.

1.3 In the absence of qualitatively and temporally adequate tumour tissue, it is possible to carry out BRCA1/2 testing on circulating tumoral DNA (ctDNA) using validated assays.

1.4 Bone biopsy specimens are not optimal for the determination of BRCA1/2 status because of the marked DNA degradation caused by extraction procedures.

When choosing the optimal tumour material for *BRCA1/2* testing in mCRPC patients, it is necessary to consider a number of strictly interconnected biological, clinical, and technical factors. The main problem is that bone is the principal site of metastatic spread (Gandaglia et al., 2014), and so the only way of obtaining a tumour sample is by means of a skeletal biopsy, which is not routinely carried out because of technical difficulties and the fact that it may be uncomfortable for patients.

An alternative means of determining *BRCA1/2* status is to analyse archival tissue, but this raises a number of other critical issues. From a biological point of view, the expression of *BRCA1/2* in archival material may not reflect the current molecular profile of the disease because it is largely obtained from the primary tumour and often a number of years old. The rate of *BRCA1/2* mutations seems to increase as the disease progresses, from 3 % in primary tumours (Cancer Genome Atlas Research, 2015) to 12.7 % in mCRPC patients (Robinson et al., 2015), and it has been confirmed that *BRCA2* levels are higher in metastatic tissue than in primary tumours (Armenia et al., 2018).

Furthermore, as primary prostate cancer is genetically heterogeneous and involves different foci that only rarely share any somatic gene mutations (Lovf et al., 2019), there is a risk that a biopsy of a primary tumour may not include the cell clone that will eventually lead to the development of castration resistance. Mateo et al. (2020b) found good concordance between the rate of *BRCA2* alterations in a series of 61 patients, but the limited number of cases with *BRCA2* mutations (only four) or other alterations in DNA damage repair genes did not allow any definite conclusions.

In addition to these clinical and biological considerations, it is necessary to evaluate various technical concerns mainly relating to DNA yields and the quality of the samples. Such technical problems are reflected in the success rate of the *BRCA1/2* analyses of the patients screened in the PROFOUND study (Hussain et al., 2022). This study

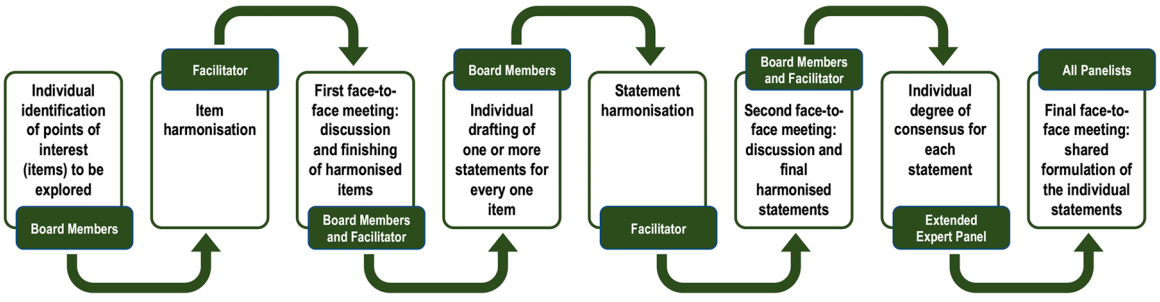

Fig. 1. Project workflow.

Table 1
Approved statements.

Item	Statements
1. **Tumour material for *BRCA1/2* testing**	*1.1 BRCA1/2 status should preferably be determined using the most representative material, and therefore the most recent and readily available tumour tissue. BRCA1/2 somatic testing (upon diagnosis, during a biochemical recurrence, or in non-pharmacologically treated patients) can be carried out using formalin-fixed, paraffin-embedded (FFPE) material obtained from an initial prostate biopsy and/or surgical specimen in the absence of visceral or lymph node material. Upon the appearance of metastatic castration-resistant prostate cancer (mCRPC), it is preferable to obtain biological material from a new biopsy whenever possible. In the absence of qualitatively and temporally adequate tumour tissue, it is possible to carry out BRCA1/2 testing on circulating tumoral DNA (ctDNA) using validated assays. Bone biopsy specimens are not optimal for the determination of BRCA1/2 status because of the marked DNA degradation caused by extraction procedures.*
2. **Disease setting for *BRCA1/2* testing and treatment**	*2.1 Tissue testing should be carried out at a time when, or in a specific setting in which there is an indication for pharmacological treatment (e.g. PARP inhibition) 2.2 The analytical reliability of BRCA1/2 testing is high in the case of material stored for < 5 years after diagnosis, moderate in the case of that stored for 5–10 years, and low in the case of that stored for > 10 years. However, the quantity and quality of intact DNA should always be checked before analysis.*
3. **Variants to be tested: germinal vs somatic variants, BRCA1/2 vs other genes**	*3.1 All patients with metastatic prostate cancer harbouring a somatic BRCA1/2 variant should also be screened for germinal variants because of the implications of possible inheritance. 3.2 Given the limited evidence that PARP inhibitors are effective in patients with mutations other than BRCA mutations, the analysis should be limited to BRCA1/2 genes. Any extension of testing to other genes must consider the available evidence of efficacy and the PARP inhibitor reimbursement criteria in different countries.*
4. **Homologous Recombination Deficiency (HRD) test extension**	*4.1 There is currently no indication for HRD testing in prostate cancer patients.*
5. **Clinical significance of *BRCA* mutations**	*5.1 There is currently no evidence of differences in the response to PARP inhibitors between patients with BRCA1/2 germline mutations and those with somatic mutations.* *5.2 BRCA1/2 status must be determined using a recognised and validated method (ENIGMA, IARC, or ATCC criteria).* *5.3 The type of BRCA1/2 variant should be systematically described in the final report, including bibliographical references and correlations with clinical risk.*
6. **Management and surveillance of patients with inherited *BRCA* disease and their family members**	*6.1 BRCA1/2 germline testing should be considered in the presence of one of the following criteria:* *• Three or more first-degree relatives (including the patient), of whom at least two have been diagnosed as having prostate cancer* *• A diagnosis of grade group 4 or 5 prostate cancer, and/or ductal histotype (also after prostatectomy), and/or the presence of an intraductal component* *• A diagnosis of grade group 4 or 5 prostate cancer, and a family history of ≥ 2 relatives with breast, ovarian, or pancreatic cancer* *• A personal history of early-onset prostate cancer (≤55 years)* *• A personal history of metastatic prostate cancer at the time of diagnosis* *6.2 Systematic prostate-specific antigen (PSA) screening is indicated in subjects aged > 40 years at inherited familial risk and their relatives carrying the pathogenic BRCA1/2 variant* *6.3 Patients with germline BRCA1/2 PVs who undergo local treatment with radical intent must be adequately monitored because of the higher risk of recurrence.*
7. **Selectivity and potency of PARP inhibitors**	*7.1 Although PARP inhibitors are characterised by their different levels of selectivity, potency, and ability to trap enzymes of the PARP family (PARP 1–16), there are insufficient data to support favouring the use of one PARP inhibitor over another.*
8. **PARP inhibitor activity and efficacy against different types of mutation**	*8.1The available data relating to PARP inhibitors demonstrate that they are more active and efficacious in patients with BRCA1/2 mutations.*
9. **On- and off- target effects of PARP inhibitors**	*9.1 It is conceivable that the different inhibition of PARP enzyme isoforms by different agents also predicts differential PARP inhibitor toxicity. However, the data are currently insufficient to support favouring the use of one PARP inhibitor over another.*
10. **Metabolic profile of PARP inhibitors and their drug-drug interactions**	*10.1 Given the different metabolic profiles of PARP inhibitors, it is suggested that any concomitant drugs taken by a patient should be carefully assessed at the beginning of PARP inhibitor treatment in order to identify possibly important pharmacological interactions and allow appropriate dose adjustments or drug changes whenever possible.*
11. **PARP inhibitors and the therapeutic sequence**	*11.1 PARP inhibition should be considered the first possible treatment option in mCRPC patients with BRCA 1/2 mutations when clinically indicated (according to the EMA, in cases progressing after at least one new hormonal agent)* *11.2 PARP inhibitors should be considered the preferred treatment choice in patients harbouring BRCA1/2 PVs with a clinical or prescriptive indication for disease staging.*
12. **Platinum-based chemotherapy in *BRCA1/2* patients**	*12.1 In the absence of other therapeutic alternatives, platinum-based chemotherapy can be considered in patients harbouring BRCA1/2 PVs.*
13. **Accessibility and appropriateness of *BRCA1/2* testing in diagnostic and therapeutic care**	*13.1 It is recommended that BRCA1/2 somatic testing be included in the diagnostic and therapeutic care of patients with advanced/metastatic disease, patients aged < 55 years at the time of diagnosis, and patients at documented genetic risk.* *13.2When indicated, BRCA1/2 testing should be requested (preferentially by a multidisciplinary team or a clinician with documented experience of prostate cancer management) even without an evaluation by a clinical geneticist, which becomes*

(*continued on next page*)

Table 1 (*continued*)

Item	Statements
	mandatory whenever a BRCA1/2 germinal variant is detected.

screened 4047 patients with available tissue samples, but only 2792 samples were successfully analysed (a failure rate of 31 %). Most of the samples came from archived tissue (89.9 %), and the majority of these (79.7 %) came from the primary tumour. The reasons for the test failures were DNA extraction failures (13.2 %), failures after DNA extraction (6.9 %), and pathology review failures (e.g. an estimated tumour fraction of <20 % or a tumour volume of <0.2 mm^2) (6.8 %), with 4.1 % of the samples failing for more than one reason. The success rate was lower in bone samples (42.6 %) than in other tissues, and progressively decreased with sample age (68.1 % in the case of tissue collected within the previous 12 months, and 47.3 % in the case of tissue collected more than 10 years before analysis).

These findings clearly reflect two critical issues when choosing the optimal tissue for assessing *BRCA1/2* alterations. The best source of contemporary tissue is bone metastases, but the frequently used acid-based methods of decalcifying bone biopsy tissue in order to soften it before analysis also degrade nucleic acids (Chen et al., 2015), and are more likely to lead to analytical failure. Better performing protocols for analysing bone tissue are available, but they are expensive, technically complex, and time consuming (Sailer et al., 2018; Van Allen et al., 2014).

In the case of archival tissue, the main technical issue is the age of the formalin-fixed, paraffin-embedded specimens. Although there are no evidence-based data indicating the good or almost perfect quality of archival tissue, that fixed within the previous five years is considered a good source of DNA, that fixed within the previous 5–10 years is considered an average source, and that fixed > 10 years before analysis is considered a poor source (Kokkat et al., 2013; Simbolo et al., 2013).

Given these technical problems, innovative means of evaluating *BRCA1/2* alterations in mCRPC patients have been considered. These include the new-generation sequencing (NGS) of liquid (blood) samples, which is less invasive, easier to perform, and more capable of detecting a patient's contemporary genomic status than tissue-based analyses. The PROFOUND study made an exploratory analysis of *BRCA1/2* (and *ATM*) status using ctDNA taken from the blood samples of 111 patients in cohort A (Matsubara et al., 2021), and found that there was good concordance between the *BRCA1/2* (and *ATM*) alterations found in the blood samples and those detected in tissue samples obtained from the same patients. In particular, the concordance rate was high in the case of nonsense (93 %), splice (87 %), and frameshift/indel alterations (86 %), but lower in the case of deletion/rearrangement (43 %) and missense alterations (25 %).

A recently published study has evaluated the concordance between the genomic profiles of tissue and blood samples collected in two different trials of rucaparib (Tukachinsky et al., 2021). The authors concluded that the genomic analysis of ctDNA reflected the genomic picture detected in tissue biopsies, and that there was a high level of agreement (93 %) in the case of *BRCA1/2* mutations. Interestingly, the genomic analyses of ctDNA were made by Foundation Medicine, Inc. (FMI, a Clinical Laboratory Improvement Amendments-certified, College of American Pathologists-accredited, New York State-regulated reference laboratory) using the FoundationOne CDx test.

3.2. Disease settings for BRCA1/2 testing and treatment

3.2.1. Statements

2.1 Tissue testing should be carried out at a time when, or in a specific setting in which there is an indication for pharmacological treatment (e.g. PARP inhibition).

2.2 The analytical reliability of BRCA1/2 testing is high in the case of material stored for < 5 years after diagnosis, moderate in the case of that stored for 5–10 years, and low in the case of that stored for > 10 years. However, the quantity and quality of intact DNA should always be checked before analysis.

The activity and efficacy of PARP inhibitors in prostate cancer have mainly been tested in patients with mCRPC, and a number of trials have shown that the presence of *BRCA1/2* mutations is associated with an increase in their anti-tumour activity (Abida et al., 2020b; de Bono et al., 2020; Smith et al., 2022). On the basis of the results of these trials, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have both approved the reimbursement of the use of PARP inhibitors in mCRPC patients. With the exception of the need to identify subjects at inherited risk, *BRCA1/2* mutation testing in prostate cancer patients should only be used to identify mCRPC patients suitable for PARP inhibitor treatment.

Ongoing trials are currently testing the role of PARP inhibitors in the early phases of prostate cancer (NCT04497844, NCT04332744) and, if these show a clinical advantage, it will be possible to propose extending *BRCA1/2* testing to these stages.

As underlined in Statement 1, the choice of material for *BRCA1/2* analysis is critical because tissue fixation modifies nucleic acids, thus making it challenging to extract high-quality DNA samples from formalin-fixed tissues. Material obtained within the previous five years can generally be considered good quality material, whereas quality progressively decreases over time, and material obtained more than 10 years before analysis is usually considered poor quality material. The results of the PROFOUND study confirm this: the success rate of the genetic alteration analyses progressively decreased with sample age, being highest in the case of tissue collected within the previous 12 months and lowest in the case of tissue collected > 10 years before analysis (Hussain et al., 2022).

Test reliability clearly depends on the quality of the extracted DNA, which may not only vary depending on its source and/or the extraction method used, but also on the availability of standardised methods of analysis.

3.3. Variants to be tested: germinal vs somatic variants, BRCA1/2 vs other genes

3.3.1. Statements

3.1 All patients with metastatic prostate cancer harbouring a somatic BRCA1/2 variant should also be screened for germinal variants because of the implications of possible inheritance.

3.2 Given the limited evidence that PARP inhibitors are effective in patients with mutations other than BRCA mutations, the analysis should be limited to BRCA1/2 genes. Any extension of testing to other genes must consider the available evidence of efficacy and the PARP inhibitor reimbursement criteria in different countries.

The detectable *BRCA1/2* mutations in tumour tissue include so-called somatic mutations (i.e. the non-heritable mutations associated with the cancer); according to the findings of PROFOUND, the detection rate of somatic mutations is 27.9 % in mCRPC patients (Tukachinsky et al., 2021).

The TOPARP-A study detected alterations in DNA repair genes in 16 patients (33 %) (Mateo et al., 2015). In particular, among the seven patients who showed *BRCA2* aberrations, only three also had a pathogenic germline mutation, which suggests that the detection rate of germline alterations is less than that of somatic mutations. However, the results of the TRITON2 trial indicate that the response of somatic and germline mutations to PARP inhibitors is similar (Abida et al., 2020b). These findings indicate that the search for germline mutations in the presence of somatic alterations does not have any therapeutic implications, although it is clearly important in the case of inherited cancer.

All of the trials of PARP inhibitors involving mCRPC patients have demonstrated that their anti-tumour activity is greater in those with *BRCA1/2* alterations than in those with alterations in other genes

associated with DNA repair mechanisms. The beneficial effect of olaparib in the PROFOUND trial was limited to the patients with mutated *BRCA1, BRCA2*, and *ATM* (de Bono et al., 2020), and an exploratory gene-by-gene analysis found that olaparib was superior to a control agent in the presence of *BRCA1/2*, but not in the presence of *ATM* or *CDK12* alterations (Matsubara et al., 2021).

Similarly, in the TOPARP B trial, the response to olaparib was greater in the patients with *BRCA1/2* alterations than in those with other mutations (Mateo et al., 2020a), and data from the TRITON2 and GALAHAD trials have respectively confirmed that rucaparib and niraparib are less active in patients with mutations other than *BRCA* mutations (Abida et al., 2020a; Smith et al., 2022).

Nevertheless, the FDA has approved olaparib for the treatment of adult patients with homologous recombination repair (HRR) gene-mutated mCRPC, and rucaparib and niraparib for mCRPC patients with *BRCA1/2* mutations; on the other hand, olaparib is currently the only PARP inhibitor approved in Europe for mCRPC patients, and its use is limited to those with *BRCA1/2* mutations.

3.4. Homologous recombination deficiency (HRD) test extension

3.4.1. Statement

There is currently no indication for HRD testing in prostate cancer patients.

TOPARP-A and TOPARP-B showed that tumours with *BRCA1* or *BRCA2* alterations were more sensitive to olaparib monotherapy than tumours harbouring any of the other homologous recombination repair-related genes considered (Mateo et al., 2015; Mateo et al., 2020a). Furthermore, although the gene-level analyses in the PROFOUND trial were complex and comparisons may be confounded by multiple clinical factors, the findings of exploratory efficacy analyses of genomic sub-groups and patients with genes other than *BRCA1, BRCA2,* or *ATM* suggest that patients with *BRCA1* or BRCA2 alterations receive the greatest benefit (de Bono et al., 2020). However, it has been shown that olaparib is active in patients with alterations in other pre-specified genes that play a direct or indirect role in homologous recombination repair, and further more detailed analyses are ongoing.

3.5. Clinical significance of BRCA mutations

3.5.1. Statements

5.1 There is currently no evidence of differences in the response to PARP inhibitors between patients with BRCA1/2 germline mutations and those with somatic mutations.

5.2 BRCA1/2 status must be determined using a recognised and validated method (ENIGMA, IARC, or ATCC criteria).

5.3 The type of BRCA1/2 variant should be systematically described in the final report, including bibliographical references and correlations with clinical risk.

Although the role of *BRCA1/2* mutations in promoting tumorigenesis is well established in the case of some tumours, their presence in others seems to be biologically neutral: the discovery of mutant *BRCA1/2* alterations may therefore be unrelated to tumour pathogenesis and is unlikely to be therapeutically relevant in all of the cancer types in which they are found (Jonsson et al., 2019). Consequently, the somatic alterations observed in *BRCA1/2* genes may be passenger rather than driver mutations, and PARP treatment may not be beneficial.

Three of the seven patients with *BRCA2* aberrations in the TOPARP-A study also harboured a pathogenic germline variant (Mateo et al., 2015); however, all seven patients responded to treatment with olaparib. Furthermore, the response rate among patients with germinal alterations was the same as that of those with somatic alterations in the TRITON2 trial (Abida et al., 2020b). These findings have been confirmed by a recent meta-analysis of studies of different cancers (including the two studies involving mCRPC patients): the response rates were the same regardless of whether the patients had somatic or germline *BRCA* mutations (Mohyuddin et al., 2020).

The language used to describe the variants identified in genetic tests of cancer susceptibility still typically reflects the outdated paradigm of Mendelian inheritance and, as this could affect treatment decision making, the use of standardised terminology in the clinical reporting of genetic variants is highly recommended. The term 'pathogenic variant' (PV) is used to describe a germline disease-causing variant in a Mendelian disease gene classified on the basis of the criteria of the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) (Richards et al., 2015) or those of the International Agency for Research on Cancer (IARC) (Tavtigian et al., 2008). A PV is also defined as a *'sequence variant which contributes mechanistically to disease but is not necessarily fully penetrant: that is, it may not be sufficient in isolation to cause disease*' in the context of assessing support of disease causality of variants identified by high-throughput sequencing. In addition, a germline PV considered to be a causal variant of disease risk is also commonly referred to as a 'mutation' in medical management. However, 'mutation' refers to any permanent change in a DNA sequence, regardless of its frequency or disease-causing potential, and is almost exclusively used to define a somatic alteration in the context of tumorigenesis. Spurdle et al. (2021) have recently proposed harmonising such language.

In the case of some *BRCA1/2* variants, there are no published papers supporting clinicians and laboratory specialists with functional data. However, both the IARC and ACMG/AMP classifications can help when reporting molecular findings, and the method of reporting should also take into account the latest published indications (Spurdle et al., 2021).

Further details regarding sample processing and management have been provided by Capoluongo et al. (2017).

3.6. Management and surveillance of patients with inherited BRCA disease and their family members

3.6.1. Statements

6.1 BRCA1/2 germline testing should be considered in the presence of one of the following criteria:

- *Three or more first-degree relatives (including the patient), of whom at least two have been diagnosed as having prostate cancer*
- *A diagnosis of grade group 4 or 5 prostate cancer, and/or ductal histotype (also after prostatectomy), and/or the presence of an intraductal component*
- *A diagnosis of grade group 4 or 5 prostate cancer, and a family history of* $\geq$ *2 relatives with breast, ovarian, or pancreatic cancer*
- *A personal history of early-onset prostate cancer (*$\leq$*55 years)*
- *A personal history of metastatic prostate cancer at the time of diagnosis*

6.2 Systematic prostate-specific antigen (PSA) screening is indicated in subjects aged $>$ *40 years at inherited familial risk and their relatives carrying the pathogenic BRCA1/2 variant.*

6.3 Patients with germline BRCA1/2 PVs who undergo local treatment with radical intent must be adequately monitored because of the higher risk of recurrence.

Various guidelines consider genetic counselling for patients with suspected inherited prostate cancer and their relatives, although there is no full consensus concerning the factors that define possible hereditary prostate cancer (Zhen et al., 2018).

Among the familial factors highlighted by the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors (Hampel et al., 2015), the National Comprehensive Cancer Network (NCCN) guidelines (NCCN, 2022), and the Johns Hopkins Group (Bova et al., 1998), our panellists underlined the importance of a diagnosis of cancer in three or more first-degree relatives (including the patient) with at least two being diagnosed as having prostate cancer, or a diagnosis of high-grade disease in patients with two or more relatives who have been diagnosed as having breast, ovarian or pancreatic

cancer.

Three other factors were also judged to be important: a ductal and intraductal component due to genomic instability (NCCN, 2022); early-onset prostate cancer; and metastatic disease at the time of diagnosis. An age of 55 years represents the bottom decile for a prostate cancer diagnosis (Salinas et al., 2014), and these patients may be genetically predisposed (Carter et al., 1992; Lange et al., 2012); furthermore, approximately 12 % of patients with metastatic prostate cancer at the time of diagnosis show DNA-repair gene mutations (Pritchard et al., 2016).

Germline *BRCA* mutations in prostate cancer patients are associated with poor survival and a high incidence of metastatic nodal or distant disease (Castro et al., 2013). The interim findings of the IMPACT study (Page et al., 2019) showed a higher incidence of prostate cancer in patients carrying *BRCA* PVs after three years of follow-up. During the study, these patients experienced a younger disease onset and had more clinically significant tumours than their non-carrier counterparts. These data underline the role of PSA screening, which should be proposed to over 40-year-olds at inherited risk of prostate cancer and their relatives.

Finally, Castro et al. (2015) analysed data relating to 1302 patients who underwent surgery or radiotherapy for localised prostate cancer after a median follow-up of 64 months. They recorded worse metastasis-free and cancer-specific survival outcomes in the *BRCA* carriers than the non-carriers (the hazard ratio of the risk of developing distant metastases or dying of prostate cancer was $\geq$2), and so such patients must be adequately monitored because of the higher risk of recurrence.

3.7. Selectivity and potency of PARP inhibitors

3.7.1. Statement

7.1 Although PARP inhibitors are characterised by their different levels of selectivity, potency, and ability to trap enzymes of the PARP family (PARP 1–16), there are insufficient data to support favouring the use of one PARP inhibitor over another.

PARP inhibitors not only block the enzymatic activity of PARP, but also (and more importantly) trap PARP1 on damaged DNA, thus leading to stalled replication forks and the subsequent formation of double-stranded breaks (Gourley et al., 2019; Murai et al., 2012). *In vitro* data shows that the clinical efficacy of PARP inhibitors is mainly associated with their PARP-trapping efficiency, and that mutations in PARP1 that affect its trapping can give rise to drug resistance (Murai et al., 2012; Pettitt et al., 2018).

It has been reported that niraparib and talazoparib have greater PARP-trapping potency than rucaparib or olaparib (Thomas et al., 2018). It has also been shown that the four drugs have a similar trapping profile in relation to the PARP1 isoform, but different IC50s in relation to the other PARP isoforms (Antolin et al., 2020). Nevertheless, as no prospective head-to-head trial has been carried out, there is no evidence to support the superiority of one PARP inhibitor over the others.

3.8. PARP inhibitor activity and efficacy against different types of mutation

3.8.1. Statement

8.1 The available data relating to PARP inhibitors demonstrate that they are more active and efficacious in patients with BRCA1/2 mutations.

The PROFOUND trial enrolled patients with known or suspected deleterious alterations in at least one of the 15 pre-specified genes selected on the basis of their direct or indirect role in HRR: *BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L* (de Bono et al., 2020). Patients with *BRCA1/2* and *ATM* alterations were enrolled in cohort A, and those with alterations in the other genes were enrolled in cohort B. The results showed that the patients in cohort A clearly benefitted more from olaparib than from the control arm agent in terms of all of the trial endpoints, whereas the patients in cohort B showed no such advantage. This seems to suggest that the efficacy of olaparib depends on the type of HRR gene alteration, and that it is better in the case of *BRCA1/2* mutated patients. An exploratory gene-by-gene analysis of the outcomes of the patients with the most frequently altered HRR genes has supported this hypothesis, thus confirming the superiority of olaparib in terms of radiographic progression-free survival, overall survival, objective response rate, biochemical response rate, and circulating tumour cell conversion rate in the presence of *BRCA1/2* alterations, but not in the presence of *ATM* or *CDK12* alterations (Matsubara et al., 2021).

These findings also confirmed the results of the TOPARP-B trial, which prospectively validated the association between DNA damage response and repair (DDR) gene aberrations and responses to olaparib in 98 mCRPC patients. A composite overall response (a radiological objective response, a >50 % decrease in PSA levels from baseline, and the circulating tumour cell conversion rate) was observed in respectively 83.3 %, 36.8%, 25 %, 57.1 %, and 20 % of the patients with *BRCA1/2*, *ATM, CDK12, PALB2*, and other DDR alterations (Mateo et al., 2020a).

In addition, the phase II TRITON2 trial of rucaparib confirmed its good activity in the presence of *BRCA1/2* alterations (an objective response rate of 43.5 %, and a PSA response rate of 54.8 %) (Abida et al., 2020b), and its marginal activity in patients with genomic alterations in DNA damage-repair genes other than *BRCA* (Abida et al., 2020a).

The open-label, phase II GALAHAD trial of niraparib in patients with mCRPC and DNA repair defects led to similar results: the objective and composite response rates among the *BRCA1/2* patients were respectively 41 % and 63 %, whereas the same figures among the non-*BRCA1/2* patients were respectively 9 % and 17 % (Smith et al., 2022).

No difference in the relative efficacy of PARP inhibition in mCRPC patients with *BRCA1* or *BRCA2* alterations has yet been fully demonstrated. Data from the sub-group analysis of the olaparib registration study (de Bono et al., 2020) and a multicentre retrospective genomic and clinical analysis of 123 mCRPC patients with *BRCA1/2* alterations treated with PARP inhibitors (Taza et al., 2021) show that PARP inhibition was less efficacious in the patients with *BRCA1* alterations, possibly because there were more mono-allelic mutations and/or concurrent TP53 alterations in the *BRCA1* group (Taza et al., 2021).

In conclusion, PARP inhibitors are more active and efficacious in patients with *BRCA1/2* mutations, and the evidence is not strong enough to support an analysis of HRD as a predictive biomarker of the response to PARP inhibition.

3.9. On- and off-target effects of PARP inhibitors

3.9.1. Statement

9.1 It is conceivable that the different inhibition of PARP enzyme isoforms by different agents also predicts differential PARP inhibitor toxicity. However, the data are currently insufficient to support favouring the use of one PARP inhibitor over another.

The four FDA-approved PARP inhibitors have similar profiles in relation to the PARP1 isoform, but different IC50s in relation to the other isoforms (Gourley et al., 2019). Moreover, the kinome profiling of 392 unique human kinases has revealed that rucaparib and niraparib seem to have a broader spectrum of kinase inhibition, whereas olaparib and talazoparib seem to be the most specific inhibitors (Antolin et al., 2020).

3.10. Metabolic profile of PARP inhibitors and their drug-drug interactions

3.10.1. Statement

10.1 Given the different metabolic profiles of PARP inhibitors, it is suggested that any concomitant drugs taken by a patient should be carefully assessed at the beginning of PARP inhibitor treatment in order to identify possibly important pharmacological interactions and allow appropriate dose adjustments or drug changes whenever possible.

PARP inhibitors are all metabolised by the liver, but their different metabolic profiles may be responsible for different drug-drug interactions. Olaparib is primarily metabolised by CYP3A4, and caution is advised when prescribing medications that inhibit or induce CYP3A4 (Murthy and Muggia, 2019). Moreover, as it also seems to be a mild CYP3A inhibitor in vivo, care should be taken when it is co-administered with CYP3A-sensitive substrates or substrates with a narrow therapeutic index. The induction of CYP2B6 by olaparib may be clinically relevant, and may also induce CYP2C9, CYP2C19 and P-gp.

Rucaparib is primarily metabolised via CYP2D6 and, to a lesser extent, CYP1A2 and CYP3A4. It may therefore theoretically interact with drugs such as antidepressants that inhibit CYP2D6 (Murthy and Muggia, 2019). It is a moderate inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP3A, P-gp and BCRP, and a weak inhibitor of CYP2C8, CYP2D6 and UGT1A1. At clinically relevant concentrations, it can induce CYP1A2 and reduce the activity of CYP2B6 and CYP3A4 in human hepatocytes.

Niraparib is metabolised by carboxylesterase enzymes to form a major inactive metabolite that is subsequently conjugated with glucuronic acid and, therefore, has limited drug interactions (Murthy and Muggia, 2019).

Talazoparib has minimal hepatic metabolism and therefore limited drug interactions at metabolic level. However, it is a P-gp substrate and in vivo studies have demonstrated that its concomitant administration with P-gp inhibitors significantly increases plasma talazoparib concentrations. Its co-administration with strong P-gp inhibitors should therefore be avoided and, if this is not possible, the talazoparib dose should be reduced. Caution is also required when talazoparib is administered with strong PgP inducers (Murthy and Muggia, 2019).

However, in addition to a drug's metabolic profile, it must be remembered that the risk of drug-drug interactions also depends on the therapeutic index of the "victim" drug, the genetic profile of the enzymes involved in drug metabolism, liver and/kidney function, and any significant patient co-morbidities.

3.11. PARP inhibitors and the therapeutic sequence

3.11.1. Statement

11.1 PARP inhibition should be considered the first possible treatment option in mCRPC patients with BRCA 1/2 mutations when clinically indicated (according to the EMA, in cases progressing after at least one new hormonal agent).

11.2 PARP inhibitors should be considered the preferred treatment choice in patients harbouring BRCA1/2 PVs with a clinical or prescriptive indication for disease staging.

Trials testing PARP inhibition monotherapy in mCRPC patients have shown that it offers significant advantages: the most relevant data come from cohort A of the PROFOUND study (de Bono et al., 2020; Hussain et al., 2020), but the findings of other studies also support the view that PARP inhibition is currently the most promising treatment option for this selected group of patients (Abida et al., 2020b; Mateo et al., 2020a; Smith et al., 2022).

It is worth noting that the design of the PROFOUND study has recently been criticised because cabazitaxel should have been the treatment in the control arm (Van Wambeke et al., 2022) but, on the basis of the published data, PARP inhibition should still be considered the preferred treatment option.

3.12. Platinum-based chemotherapy in BRCA1/2 patients

3.12.1. Statement

12.1 In the absence of other therapeutic alternatives, platinum-based chemotherapy can be considered in patients harbouring BRCA1/2 PVs.

Although platinum-based chemotherapy has been tested in a number of trials (Hager et al., 2016), it is not routinely included in the therapeutic algorithm for mCRPC patients. However, as its activity is mainly related to its ability to cross-link with purine bases in DNA (thus interfering with DNA repair mechanisms), responses to this treatment may increase in the presence of concurrent DNA repair alterations (Dasari and Tchounwou, 2014).

Three published case series including 14 mCRPC patients with DNA repair gene alterations have shown that platinum-based chemotherapy has encouraging anti-tumour activity (Cheng et al., 2016; Pomerantz et al., 2017; Zafeiriou et al., 2019).

More recently, two larger retrospective studies have considered clinical data relating to mCRPC patients treated with platinum-based chemotherapy and evaluated the impact of DNA repair gene alterations on their therapeutic outcomes. Slootbeek et al. studied a series of 30 mCRPC patients treated with a platinum-based chemotherapy whose DNA repair gene profiles were available (Slootbeek et al., 2021), and found that the biochemical response rate of the 14 patients with DNA repair gene alterations was higher than that of the 13 patients without alterations (71 % vs 31 %; $p = 0.028$), although there was no between-group difference in terms of their best radiographic response. However, when comparing seven *BRCA1/2* patients and 23 patients without *BRCA* mutations, both the biochemical response rate (100 % vs 35 %; $p = 0.006$) and the best radiographic response rate (partial response 100 % vs 16 %; $p < 0.001$) were higher among the *BRCA1/2* patients.

The second retrospective study involved the largest published series of 178 patients (Schmid et al., 2020) and confirmed that *BRCA* status is a major predictor of response to platinum-based treatment. Comparison of the patients with and without DNA repair gene alterations showed no differences in biochemical and objective responses or overall survival, whereas there were clear differences in outcomes when considering the individual genes. Biochemical responses were more frequent among the *BRCA1/2* patients (63.9 %) than among the patients with other mutations (no response in *BRCA1* patients, a 36.4 % response rate among *ATM* patients, and a 28.6 % response rate among patients with other aberrations). Similarly, median overall survival from the start of platinum-based therapy was significantly longer in the *BRCA2* patients (15 months) than in those showing alterations in *BRCA1, ATM* or other genes (respectively 4.1, 9.3, and 4.9 months).

3.13. Accessibility and appropriateness of BRCA1/2 testing in diagnostic and therapeutic care

3.13.1. Statements

13.1 It is recommended that BRCA1/2 somatic testing be included in the diagnostic and therapeutic care of patients with advanced/metastatic disease, patients aged < 55 years at the time of diagnosis, and patients at documented genetic risk.

13.2 When indicated, BRCA1/2 testing should be requested (preferentially by a multidisciplinary team or a clinician with documented experience of prostate cancer management) even without an evaluation by a clinical geneticist, which becomes mandatory whenever a BRCA1/2 germinal variant is detected.

At the end of the Consensus Conference, on the basis of the available data and the state of the art, it was recommended that testing for *BRCA1/2* mutations be included in the diagnostic, therapeutic and assistance pathways of patients at particularly high risk in order to make it available through the Italian National Health System.

It was also pointed out that the presence of a multidisciplinary team with extensive clinical experience is important as a means of optimising the prescription of testing, and that it is necessary to request the evaluation of a geneticist whenever a *BRCA1/2* germline variant is found.

4. Discussion

Alterations in breast cancer susceptibility genes 1 and 2 (better known as *BRCA1* and *BRCA2*) were first described and related to the risk of developing breast and ovarian cancer more than 30 years ago

(Goldgar et al., 1994; Miki et al., 1994; Wooster et al., 1995; Wooster et al., 1994). This discovery led to the genetic testing of breast and ovarian cancer patients in order to identify their familial/inherited cancer risk and subsequently develop the therapeutic strategy of PARP inhibition, which is capable of inducing synthetic killing in the absence of *BRCA*-related DNA repair mechanisms.

It has more recently been reported that there is an association between *BRCA1* and *BRCA2* mutations and the development of cancer in patients with other tumours, including prostate and pancreatic tumours (particularly in the case of *BRCA2*) (Breast Cancer Linkage, 1999; Thompson et al., 2002). In the case of prostate cancer, *BRCA1* and *BRCA2* mutations are respectively associated with approximately 4-fold and 3–8.6-fold increases in the risk of developing the disease (Gallagher et al., 2010; Giusti et al., 2003; Kote-Jarai et al., 2011; Leongamornlert et al., 2012; Mersch et al., 2015; Thompson et al., 2002; Venkitaraman, 2002), and the rate of *BRCA1/2* mutations varies depending on its stage: 3 % in patients with primary tumours (Cancer Genome Atlas Research, 2015) and 12.7 % in those with mCRPC (Robinson et al., 2015). These findings provided a strong rationale for the development of a PARP inhibition-based therapeutic strategy also in the case of prostate cancer.

A number of studies have confirmed the role of rucaparib (Abida et al., 2020a; Abida et al., 2020b), niraparib (Smith et al., 2022), and talazoparib (de Bono et al., 2021) in prostate cancer, but olaparib is currently the only agent with mature data coming from a phase III trial (de Bono et al., 2020). This trial involved mCRPC patients with an alteration in one of the genes involved in DNA repair who had previously been treated with one androgen receptor signalling inhibitor (ARSI, abiraterone or enzalutamide). The patients were divided into two cohorts on the basis of whether the alterations affected the *BRCA1/2* or *ATM* genes (cohort A) or the other screened HRD genes (cohort B), and randomised to receive olaparib or the ARSI they had not previously been administered. The trial satisfied the primary endpoint of a lower risk of radiographic progression-free survival among the cohort A patients treated with olaparib than among those treated with an ARSI (HR: 0.34; 95 % CI 0.25–0.47; $P < 0.001$) (de Bono et al., 2020), and olaparib treatment was also associated with a significant reduction in mortality in cohort A (HR: 0.69; 95 % CI 0.50–0.97; $P = 0.02$) (Hussain et al., 2020). However, the use of olaparib did not lead to any advantage in cohort B. On the basis of these findings, the FDA approved olaparib for mCRPC patients progressing after treatment with one ARSI who have one known or suspected deleterious germline or somatic HRR gene mutation. In Europe (including Italy), olaparib is only indicated for *BRCA1/2* mCRPC patients previously treated with one ARSI.

The availability of olaparib in clinical practice clearly raised practical questions concerning the timing and method of detecting *BRCA* mutations, the therapeutic implications of the detection, and the screening of the members of the family of a prostate cancer patient with a germline *BRCA* alteration. These challenging issues were discussed during the course of our consensus project aimed at generating suggestions capable of supporting clinicians managing prostate cancer patients.

The choice of the material used to detect mutations in the genes involved in DNA repair mechanisms is important in the case of mCRPC. The rate of *BRCA1/2* mutations is related to the phase of prostate cancer, and progressively increases as the disease progresses from a localised form to castration resistance. It can therefore be assumed that a tumour sample obtained at the time of the *BRCA1/2* assessment probably better reflects mutational status than archival tissue. This was clearly acknowledged by our panellists, who suggested that *BRCA1/2* status should preferably be determined using the most recent, readily available tumour tissue (statement 1.1), and that the assessment can be made using primary tumour tissue in the absence of visceral or lymph node material during the initial stages of the disease (statement 1.2). However, after the development of castration resistance, the panellists suggested that it is preferable to obtain biological material from a new biopsy (statement 1.2).

Bone is the most frequent site of metastatic spread in mCRPC patients, and this means that a skeletal biopsy is frequently the only means of obtaining contemporary material for *BRCA1/2* analysis. Unfortunately, this procedure is usually uncomfortable for patients, and the process of DNA extraction is difficult because acid-based decalcification methods degrade nucleic acids (Chen et al., 2015). The panellists therefore concluded that bone biopsy specimens are not optimal for determining *BRCA1/2* status (statement 1.4).

Although archival tissue from a prostatectomy specimen or primary tumour biopsy may be a valid alternative in the absence of an adequate contemporary tumour sample, it is also subject to technical problems concerning DNA extraction that are due to the inverse relationship between the analytical reliability of *BRCA1/2* testing and the age of the archived material (statement 2.2). This can be seen in the 31 % failure rate of the *BRCA1/2* analyses of the samples used in the PROFOUND study (Hussain et al., 2022), which was probably due to the fact that 89.9 % of the samples were taken from archived tissue and 57.8 % were obtained more than three years before analysis; the mean success rate was 51.4 %.

Taken together, these limitations suggest the possibility of using an NGS analysis of ctDNA from a liquid (blood) biopsy, which would have the clear advantages of being less invasive and capable of capturing a patient's current genomic status. This approach is not yet considered a standard option for the genomic profiling of prostate cancer patients, but an exploratory analysis of the PROFOUND trial compared the genomic profiles obtained from tumour tissue samples and liquid biopsies and found a high degree of concordance, although the concordance rates varied depending on the type of detected mutation (Matsubara et al., 2021); furthermore, two studies of rucaparib have also found a similar degree of concordance (93 %) in detecting *BRCA1/2* mutations using the two techniques (Tukachinsky et al., 2021). All of these studies used the FoundationOne CDx test of liquid biopsies, which led our panellists to conclude that, in the absence of qualitatively and temporally adequate tumour tissue, a liquid biopsy *BRCA1/2* test may be an option in mCRPC patients as long as the assay has been validated (statement 1.3).

BRCA1 and *BRCA2* are the most frequently altered genes in prostate cancer patients with deficient DNA repair mechanisms, but mCRPC patients may also present alterations in the other genes involved. The results of trials comparing the activity of PARP inhibitors in mCRPC patients with *BRCA1/2* or these other gene mutations have all found that they are more active in the presence of the former, whereas no clinical advantage has been observed in the presence of the latter (Abida et al., 2020a; de Bono et al., 2020). Accordingly, our panellists agreed that PARP inhibitors are more active and efficacious in *BRCA1/2* mutated patients (statement 8.1). Furthermore, on the basis of the available evidence concerning their efficacy and the existing reimbursement criteria applied in Europe (including Italy), they agreed that analyses should be limited to *BRCA1/2* genes, but their extension to other genes should be considered in the case of the publication of new efficacy data or the adoption of different reimbursement rules (statements 3.2 and 4.1).

As mentioned above, olaparib is the agent for which the most mature data are available, but other PARP inhibitors have been tested and shown to be active in mCRPC, and rucaparib and niraparib are currently reimbursed in this setting in the USA. Although PARP inhibitors are different in terms of their selectivity, potency, and ability to trap enzymes of the PARP family, there is insufficient data favouring the use of one over another on the basis of efficacy or their on- and off-target effects (statements 7.1 and 9.1). However, it is also necessary to pay special attention to their different metabolic profiles because potentially relevant pharmacological interactions with concomitant drugs may require appropriate dose adjustments or drug changes (statement 10.1).

PARP inhibitors have mainly been tested in patients with mCRPC as they are more active in patients with *BRCA* mutations. Accordingly, somatic *BRCA* status should be assessed in the specific settings in which it is possible to propose their therapeutic use (statement 2.1). In the

presence of *BRCA1/2* mutations and prescriptive possibility, our panellists suggest that PARP inhibition should be the preferred treatment (statement 11.1), although patients harbouring *BRCA1/2* variants may also benefit from platinum-based chemotherapy in the absence of other therapeutic alternatives (statement 12.1).

Given the role of *BRCA1/2* mutations in increasing the risk of developing cancer, their detection in tumour tissue makes it necessary to screen mutated patients for germline mutations in order to define the inherited cancer predisposition of their families (statement 3.1). The presence of germline mutations does not influence therapeutic choices in mCRPC patients because there is no difference in the activity of PARP inhibitors in patients with germinal or somatic *BRCA1/2* mutations (statement 5.1); however, their detection does imply the development of screening programmes for the patients' families.

More than 7400 *BRCA* variants have been classified by the international ENIGMA Consortium (Tischkowitz et al., 2019), but the BRCA Exchange web portal (the largest public source of information concerning *BRCA1* and *BRCA2* variants) lists more than 68,000 (https://brcaexchange.org/). Given this situation, *BRCA* variants should be reported cautiously, and it is highly recommended to use standardised terminology based on recognised and validated systems (the ENIGMA, IARC or ATCC criteria) (statement 5.2). Moreover, bibliographical references and correlations with clinical risk should be systematically described in final reports (statement 5.3).

A search for germline *BRCA1/2* mutations should be considered in prostate cancer patients under specific conditions regardless of the therapeutic implications, and statement 6.1 clearly describes the conditions that may suggest inherited disease. This information is prognostically relevant because a germline *BRCA1/2* mutated patient who is locally treated with curative intent is at high risk of recurrence, and must be adequately monitored (statement 6.3). Furthermore, healthy subjects at inherited familial risk who show a *BRCA1/2* variant should undergo systematic PSA screening after the age of 40 years (statement 6.2).

It is clear that the complexity of the issues described above means that the optimal approach to the management of subjects with *BRCA1/2* mutations (whether they are healthy or have prostate cancer) is strictly related to a multidisciplinary vision of the different diagnostic and therapeutic strategies (statement 13.2), which should be clearly defined in diagnostic, therapeutic and assistance algorithms (statement 13.1).

A multidisciplinary approach to prostate cancer patients is essential not only as a means of making the most of the therapeutic opportunity offered by PARP inhibitors, but also as a means of managing all of the implications of an inherited risk of developing cancer and disease prognosis (Crocetto et al., 2021). The cooperation of medical oncologists, radiotherapists, urologists and all of the other professionals involved in the management of prostate cancer patients (geneticists, psychologists, etc.) is therefore to be encouraged as much as possible. This is particularly true because the future possibility of detecting the real prevalence of germline *BRCA* mutations could substantially change clinical practice and improve our ability to propose a tailored approach to a larger number of patients.

As emphasised above, the use of PARP inhibitors in prostate cancer patients has led to the unprecedented opportunity of tailoring therapeutic strategies, but has also given rise to new challenges for clinicians who, in the absence of clear evidence, need to be supported in their everyday clinical practice. A number of consensus documents based on experts' opinions and suggestions (Russo et al., 2022; Gillessen et al., 2022) have recently attempted to clarify critical issues relating to the assessment of *BRCA* mutations and the optimal use of PARP inhibitors in prostate cancer patients but, unlike us, these experts did not use a formal consensus methodology to develop their recommendations.

The possibility that even just one DDR alteration is present in a prostate cancer patient opens up a large and increasingly attractive field of future research. The economic implications of DDR gene detection tests and the prescription of PARP inhibitors are being evaluated because of their impact on public health prevention, monitoring, and treatment policies. It has been confirmed that genomic test-directed olaparib is preferable to standard care for mCRPC patients with one of the 15 DDR alterations tested in the PROFOUND trial (Su et al., 2021). Similarly, a study conducted in the United States has assessed the economic value of knowing the *BRCA* status of patients with low-risk localised disease, and provided short- and long-term evidence in favour of *BRCA* testing for the purposes of early screening and optimising treatment (Oh et al., 2023).

Another research line is the potential interplay between *BRCA* and hormonal receptor machinery. It is known that estrogen signalling is involved in the carcinogenesis and progression of prostate cancer (Bonkhoff, 2018), although the exact mechanisms involved are still unclear (Di Zazzo et al., 2016; Di Zazzo et al., 2018). Interestingly, *BRCA1* inhibits the transcriptional activity of estrogen receptors in (https,; https,; https,; https,) human prostate cancer cell lines (Fan et al., 1999) and, although this intriguing association has not yet been fully interpreted, it merits further investigation in order to evaluate its potential therapeutic activity. Furthermore, the theoretical interplay between androgen receptors and DDR machinery (Polkinghorn et al.,. 2013) has led to the possibility of combining PARP inhibitors and ARSIs, which may be active in prostate cancer patients with and without mutations (Agarwal et al., 2023; Chi et al., 2022; Clarke et al., 2022). However, despite the clear improvement in progression-free survival, the use of such a combination is still not considered a standard of care. Furthermore, such studies have become the subject of widespread debate because of their immature results in terms of overall survival, different designs, and potential differences in the activity and synergism of the administered PARP inhibitors (olaparib, niraparib or talazoparib) and ARSIs (abiraterone or enzalutamide).

5. Conclusions

The role of *BRCA1/2* gene mutations in prostate cancer patients has led to new therapeutic strategies that provide an opportunity to propose tailored treatments for mCRPC patients. The previously available active therapeutic agents directly or indirectly targeted androgen receptor machinery, but PARP inhibitors have a different target and avoid the risk of cross-resistance with other drugs. However, their availability is raising new questions concerning the methods and timing of testing, and the biological material to test. Our panellists discussed the available evidence regarding these critical issues and drew up their consensus statements in an attempt to guide clinical practitioners in optimising the PARP-based management of prostate cancer.

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Declaration of Competing Interest

Alberto Lapini has received fees or honoraria for acting as an advisor to Medac, Bayer, MSD and Janssen, Orazio Caffo has received fees or honoraria for acting as speaker or as an advisor to AAA, Astellas, Astra Zeneca, Bayer, Ipsen, Janssen, MSD, Pfizer, Giario Natale Conti has received fees or honoraria for acting as an advisor to Janssen, Astellas, Bayer, Recordati, MSD, Astrazeneca and Ipsen, Giovanni Luigi Pappagallo has received fees or honoraria for acting as an advisor to AAA, Astellas, Astrazeneca, Janssen, Marzia Del Re has received fees from Astellas, AstraZeneca, Celgene, Novartis, Pfizer, BioRad, Janssen, Sanofi-Aventis, Roche, MSD, Lilly and Ipsen; and honoraria for acting as an advisor to Astra Zeneca, MSD, Ipsen, Janssen, Sanofi-Aventis, and Amgen, Francesca Castiglione has received fees from AstraZeneca, Novartis, Roche, MSD, GSK, and honoraria for acting as an advisor to Astra Zeneca, MSD, and Amgen, Matteo Brunelli has received fees from MSD, Janssen, Genactis, NTP, Oncotech, Roberto Iacovelli has received

fees or honoraria for acting as an advisor to Astellas, BMS, EISAI, IPSEN, Janssen, MSD, Novartis, Pfizer, Sanofi. Consultant for Astellas, EISAI, MSD, Pfizer, Ugo De Giorgi received honoraria for advisory boards or speaker fees for Pfizer, BMS, MSD, PharmaMar, Astellas, Bayer, Ipsen, Roche, Novartis, Clovis, GSK, AstraZeneca, institutional research grants from AstraZeneca, Sanofi and Roche, Sergio Bracarda has received fees or honoraria for acting as an advisor from or steering committee member from AAA, Astellas, AstraZeneca, Bayer, BMS, Janssen, Ipsen, Merck, MSD, Pfizer, Roche, Sanofi. The other authors did not have conflicts of interest to be declared.

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Marzia Del Re works as Assistant Professor in the Clinical Pharmacology and Pharmacogenetics Unit at the University of Pisa (Italy) and her research programme is focused on the 1) diagnosis of adverse drug reactions by pharmacogenetic analysis of germline DNA and 2) monitoring of acquired resistance to targeted therapies using circulating nucleic acids released from tumours in plasma. Dr. Del Re received her Pharm.D. degree (2009) and became Specialist in Clinical Biochemistry (2014) at the University of Pisa. Dr. Del Re obtained the Master degree in "Clinical trials in Oncology, Hematology and Internal Medicine" (2015) at the University of Pisa and the PhD title of Clinical Pathophysiology. Dr. Del Re received the Merit Awards from the American Society of Clinical Oncology (2011 and 2013) for her studies on DPYD variants and adverse drug reactions by fluoropyrimidines. Dr. Del Re received the Umberto Veronesi Foundation Fellowship (2012) for a project on pharmacogenetics of tamoxifen. Dr. Del Re was the recipient of the special award from the Italian Society of Pharmacology for her contribution to research in pharmacogenetics (2014) and the special award "SIF-Farmindustria for Pharmacological Research" (2016). In 2018 Dr. Del Re has been awarded from the Italian Association of Medical Oncology for her research on circulating tumour DNA in lung cancer.In 2015, 2016, 2018 and 2019 Dr. Del Re worked for a total of 9 months at the Erasmus Medical Center, Rotterdam (Netherlands) as Visiting scientist, on projects revolving around drug resistance in prostate and lung cancer. In particular, it was set up the exosomes isolation from plasma and the RNA extraction, optimized the ddPCR assay and performed expression analyses on a large series of plasma samples. In 2017 Dr. Del Re worked at the NCI/NIH (Bethesda, USA) as Visiting Scientist, on in vitro CRPC models. From November 2022 Dr. Del Re works as a Visiting Professor at the Center for Thoracic Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai Hospital, working on liquid biopsy in lung cancer.

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Ettore Capoluongo, is Full Professor of Clinical Biochemistry and Clinical Molecular Biology. He has been appointed as the Head of the Departmental Oncogenomics Programme on Ovarian, Mammary, Pancreatic, Prostatic and pNET tumours Diagnostics at Federico II University Hospital. He has been also appointed for more than 13 years the Head of the Genomic and Personalized diagnostics Laboratory at Policlinico Gemelli Teaching Hospital. He is currently member of the Expert panel on medical devices and in vitro diagnostics ('Expamed') at the European Commission, as well as member of the "Committee on Clinical Molecular Biology Curriculum (C-CMBC)" and Molecular Diagnostict Division (C-MD) within the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). As the Coordinator of the Operational Group on "Use of genomic technologies in the field of treatment personalization" of the Italian Society of Clinical Biochemistry and Clinical Molecular Biology - SIBioC-Laboratory Medicine, he is playing a reference role in the intersociety activities for the harmonization advanced molecular diagnostics tests. He is currently elected member of the Board of Directors of the Multicenter Italian Trials in Ovarian cancer and gynecologic malignancies (MITO-Group). Prof. Capoluongo is an internationally recognised as molecular geneticist particularly as an expert NGS-based technologiessince he has sequenced and reported thousands of genetic tests. Very recently he has also been nominated as a member of the EFLM-TFG "Circulating Nucleic Acids in plasma and Serum/Circulating Tumour Cells in early detection of cancer" which is an interdisciplinary group (iTFGCNAPS/CTC-EDC) comprising specialists from Laboratory Medicine and Radiology/Imaging. He has published more than 275 peer reviewed papers, with a current H-Index (source Scopus) = 42.

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