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REVIEW

Implementation of preventive and predictive BRCA testing in patients with breast, ovarian, pancreatic, and prostate cancer: a position paper of Italian Scientific Societies☆

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Constitutional *BRCA1/BRCA2* pathogenic or likely pathogenic variants (PVs) are associated with an increased risk for developing breast and ovarian cancers. Current evidence indicates that *BRCA1/2* PVs are also associated with pancreatic cancer, and that *BRCA2* PVs are associated with prostate cancer risk. The identification of carriers of constitutional PVs in the *BRCA1/2* genes allows the implementation of individual and family prevention pathways, through validated screening programs and risk-reducing strategies. According to the relevant and increasing therapeutic predictive implications, the inclusion of *BRCA* testing in the routine management of patients with breast, ovarian, pancreatic and prostate cancers represent a key requirement to optimize medical or surgical therapeutic and prevention decision-making, and access to specific anticancer therapies. Therefore, accurate patient selection, the use of standardized and harmonized procedures, and adherence to homogeneous testing criteria, are essential elements to implement *BRCA* testing in clinical practice.

This consensus position paper has been developed and approved by a multidisciplinary Expert Panel of 64 professionals on behalf of the AIOM—AIRO—AISP—ANISC—AURO—Fondazione AIOM—SIAPEC/IAP—SIBioC—SICO—SIF—SIGE—SIGU—SIU—SIURO—UROP Italian Scientific Societies, and a patient association (aBRCAdaBRA Onlus). The working group included medical, surgical and radiation oncologists, medical and molecular geneticists, clinical molecular biologists, surgical and molecular pathologists, organ specialists such as gynecologists, gastroenterologists and urologists, and pharmacologists. The manuscript is based on the expert consensus and reports the best available evidence, according to the current eligibility criteria for *BRCA* testing and counseling, it also harmonizes with current Italian National Guidelines and Clinical Recommendations.

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Key words: *BRCA*-related cancer, *BRCA* testing, *BRCA1*, *BRCA2*, genetic counseling, PARP inhibitors, pancreatic ductal adenocarcinoma

INTRODUCTION

The presence of a constitutional deleterious variant [pathogenic or likely pathogenic variant (PV)] in the *BRCA1/BRCA2* (*BRCA*) genes is associated with an increased risk for developing breast and ovarian cancers. Current evidence indicates that *BRCA1/2* PVs are also associated with pancreatic cancer, and that *BRCA2* PVs are associated with prostate cancer risk, but with lower penetrance.[1-4] Following the introduction of poly(ADP)ribose polymerase (PARP) inhibitors in clinical practice, the demand for *BRCA* genetic testing is rapidly and continuously increasing. Knowledge of the presence of a *BRCA* PV provides useful information of prognostic and predictive value, to predict the efficacy of cancer treatment and estimate individual and familial risk.[5]

However, the recent expansion of approved therapies, deeper knowledge on *BRCA*-related cancers, and rapid technological progress for germline and tumor analysis produce a strong clinical need for *BRCA* testing optimization.

The aim of this document is to provide an update on *BRCA* testing and to support implementation in clinical practice, focusing on the following points:

- the identification of individuals carrying constitutional (germline) *BRCA* PVs, associated with an increased risk of tumors, who may benefit from genetic counseling, dedicated screening programs and risk-reducing strategies addressed to the individuals (carriers) and, when indicated, to the family members (preventive purpose);
- the provision of *BRCA* testing as a predictive tool of the efficacy of specific anticancer therapies, helping clinicians in decision making on treatment options;
- the need to incorporate *BRCA* testing as a fundamental routine part of specific clinical diagnostic paths;
- the importance to use standardized and harmonized procedures for germline and tumor DNA sequencing and for the interpretation of results.

METHODS: DOCUMENT DEVELOPMENT AND COMPOSITION OF THE MULTIDISCIPLINARY WORKING GROUP

The document has been developed, discussed, reviewed, and approved by a multidisciplinary Expert Panel of 64 professionals representing the AIOM—AIRO—AISP—ANISC—AURO—Fondazione AIOM—SIAPEC/IAP—SIBioC—SICO—SIF—SIGE—SIGU—SIU—SIURO—UROP Italian Scientific Societies, and a patient association (aBRCAdaBRA Onlus). It is based on the expert consensus and reports the best available evidence, harmonizing the current eligibility criteria for *BRCA* testing, in agreement with Italian National Guidelines and Clinical Recommendations.[6,7]

The working group included medical, surgical, and radiation oncologists; medical and molecular geneticists; clinical molecular biologists; surgical and molecular pathologists; organ specialists such as gynecologists, gastroenterologists and urologists, and pharmacologists.

The document was ultimately reviewed and approved by the Expert Panel prior to publication, and three additional experts reviewed and proofread the final version.

BRCA TESTING FOR THE DIAGNOSIS OF HEREDITARY CANCER PREDISPOSITION

Eligibility criteria for BRCA testing

The eligibility to *BRCA* testing is generally based on personal and family history, and takes into account the elements usually considered for the identification of tumors related to hereditary predisposition: number of affected relatives, type of neoplasm, multiple primary tumors, age at diagnosis, sex, histological, and immunohistochemical and molecular characteristics of tumors. These variables were organized into tabular criteria corresponding to a substantially increased chance of finding a PV (>20-fold compared with the estimated prevalence in the general population; Table 1) and are used to evaluate the referral to genetic counseling and testing, in agreement with national and international guidelines.[6-8]

The identification of a deleterious germline *BRCA* (g*BRCA*) mutation allows the proband's relatives to access genetic counseling in order to perform *BRCA* predictive testing for the known familial mutation (so-called cascade testing). Genetic counseling should be performed before and after the *BRCA* genetic testing for preventive purposes. If the familial mutation is identified in the relatives, screening programs and risk-reducing strategies for the *BRCA*-related tumors will be proposed.[8]

A current emerging issue is the universal testing of patients with breast, pancreatic, and prostate cancer, in addition to patients with ovarian cancer. We think that although highly desirable, this point is hampered in Europe and even in Italy by heterogeneity in the logistics and coverage policy, including the prevention strategies. Considering the rapid technology improvement and lowering costs of genomic testing, the panelists underline the relevance of this goal for the next near future.

BRCA TESTING AS A PREDICTIVE TOOL FOR EFFICACY OF ANTICANCER THERAPIES

It has been shown that both germinal and somatic *BRCA* PVs represent predictive biomarkers of greater sensitivity to treatment with inhibitors of the PARP enzyme, which is involved in the repair of damaged single-filament DNA.[9,10] The efficacy of PARP inhibitors as a therapeutic option in tumors of patients carrying a *BRCA* PV is considered to

Table 1. Eligibility criteria for the oncological genetic counseling

Personal history:
Male breast cancer
Woman with breast cancer and ovarian cancer
Woman with breast cancer <36 years
Woman with triple negative breast cancer <60 years
Woman with bilateral breast cancer <50 years
Woman with non-mucinous and non-borderline ovarian cancer at any age
Metastatic pancreatic adenocarcinoma
Metastatic prostate cancer
Personal history of breast cancer <50 years and first-degree familiarity[a,b] for:
Breast cancer <50 years
Non-mucinous and non-borderline ovarian cancer at any age
Bilateral breast cancer
Male breast cancer
Locally advanced or metastatic pancreatic cancer
Metastatic prostate cancer
Personal history of breast cancer >50 years and family history of breast cancer, ovarian cancer, metastatic prostate cancer or locally advanced/ metastatic pancreatic cancer in 2 or more first-degree relatives[a,b] among them (including one in first degree with her[a,b])
Personal history of prostate cancer and familiarity[c]:
At least one first-degree relative[a] with non-Grade Group 1 prostate cancer aged <60 years
At least two family members with non-Grade Group 1 prostate cancer aged <50 years
Family history of pancreatic cancer:
At least two first-degree relatives[a] with pancreatic adenocarcinoma[d]
At least three family members with pancreatic adenocarcinoma[e]
If present, testing eligibility criteria for genetic syndromes with an increased risk of pancreatic cancer
Family history of:
Known pathogenic variant in a predisposing gene in a family member

[a]First-degree relatives = parents, brothers/sisters, and children.
[b]For breast and ovarian cancers, on the paternal side of the family, also consider second-degree relatives (grandmother, aunts).
[c]Grade Group 1 according to World Health Organization/International Society of Urological Pathology.
[d]The condition does not affect the situation in which both parents are/have been affected.
[e]On the same bloodline and with at least one first-degree relative.

occur mainly through a mechanism of 'synthetic lethality' in the presence of a concomitant loss of function of double-stranded DNA repair mechanisms by homologous recombination, in which BRCA1/2 proteins play an essential role.[10,11]

BRCA testing has to be carried out as part of a multidisciplinary pathway.[7,8] The professionals involved, based on their expertise, should provide:

- the indication to *BRCA* testing according to validated criteria;
- the indications on the type of sample to be used for the analysis (peripheral blood, oral mucosa, or tumor tissue);
- the methods to be used for *BRCA* sequencing;
- the interpretation of *BRCA* genetic variants identified;
- adequate information to the patients on all genetic and clinical aspects related to the possible test results, to be included in the written informed consent;
- information regarding the clinical significance of the findings of *BRCA* analysis and the potential integration of the results in the care and therapeutic path of the individual.
- If *BRCA* testing is performed for therapeutic purposes, a path in which oncogenetic testing can be requested directly by the caring clinicians should be implemented, in order to ensure a rapid process.

In this case, the patient should be informed of the same genetic aspects and clinical implications related to the negative, positive, or non-informative test result. In fact, the tumor PVs findings in a tumor *BRCA* testing could be related to a constitutional predisposition.[8]

Clinicians, such as medical or surgical oncologists who are involved in the multidisciplinary patient's management pathway, should be trained to provide patients with the most appropriate initial information on (i) the medical implications of the *BRCA* testing results, and (ii) the pros and cons of risk-reducing strategies, in coordination with the genetics team. Therefore, adequate education and the achievement of the best qualification for clinician team members in this preliminary setting of the *BRCA* testing administration are crucial for the success of the patient care pathway.[7,8,12]

Breast cancer

The presence of a *BRCA* PV has therapeutic implications for women with a breast cancer diagnosis, both in the non-metastatic and in the metastatic settings. For individuals with newly diagnosed breast cancer who have a high likelihood (i.e. ≥10%) of detection of a *BRCA* PV, *gBRCA* testing should be considered.[8]

Women with non-metastatic breast cancer. The finding of *BRCA* PV in women with newly diagnosed non-metastatic breast cancer can influence the choice of both locoregional treatment (radical versus conservative surgery with complementary radiotherapy; monolateral or bilateral mastectomy) and adjuvant/neoadjuvant systemic therapy.[13]

When *BRCA* status can affect the management of breast cancer, *BRCA* testing should be offered as a fast-track process after receiving complete information regarding the possible outcome of the test.[8]

BRCA assay may have an impact on the patient's family members: in presence of a positive result, in fact, it allows to extend the test to the relatives at risk of being carriers of the same *BRCA* PV.

- To date, the available data on the benefit of adding the platinum derivatives in the neoadjuvant treatment of patients with *BRCA*-related breast cancer remain controversial and do not allow the definition of a personalized treatment. The current guidelines recommend basing the clinical decision on the type of chemotherapy or endocrine therapy according to available prognostic and predictive factors for sporadic cancers.[8,13,14]

  In the neoadjuvant setting, the addition of platinum salts to the standard chemotherapy (containing anthracyclines and taxanes) can be considered in patients with triple-negative breast cancer.

  The use of PARP inhibitors in the neoadjuvant setting remains under evaluation in clinical trials.[13,15]
- In the adjuvant setting, there are no solid prospective data on the use of platinum derivatives in patients with *BRCA*-related breast cancer.

The potential role of PARP inhibitors has been shown in the Olympia trial, where adjuvant olaparib after completion of local treatment and neoadjuvant or adjuvant chemotherapy was associated with significantly longer invasive- or distant disease-free survival than placebo.[16]

Women with metastatic breast cancer. The results of two randomized phase III studies that evaluated the efficacy of two different PARP inhibitors, olaparib and talazoparib, in patients with HER-2-negative metastatic breast cancer and PV *BRCA* have been recently published.[17,18]

The presence of a *BRCA* PV in women with metastatic breast cancer may have an impact on the choice of systemic anticancer treatment.

The current indications in Italy are listed below.

To date, olaparib has a reimbursable indication as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer, which is HER2 negative and hormone receptor (HR) negative, carrying g*BRCA* PVs. Patients must have been previously treated with anthracycline and taxane and with platinum in the (neo) adjuvant or metastatic setting, unless they had been ineligible for these treatments (Determine no. DG/1265/2020 of 3 December 2020, Official Gazette general series n.308 of 12 December 2020).

Currently, talazoparib has a reimbursable indication as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer, HER2-negative and both HR negative and HR positive, carrying *gBRCA* PVs. These patients must have been previously treated with anthracycline and/or taxane in the (neo)adjuvant or metastatic setting, unless they had been ineligible for these treatments. Patients with HR-positive tumors must have previously received an endocrine treatment, unless ineligible for this therapy (Determine no. DG/765/2021 of June 2021, Official Gazette general series n.158 of 03 July 2021).

Summary of expert opinion

- For patients with primary breast cancer meeting the eligibility criteria for the oncological genetic counseling (Table 1), *gBRCA* testing could affect the management of breast cancer, and should be offered as a fast-track process.
- In HER2-negative metastatic breast cancer, *gBRCA* testing has therapeutic value: two PARP inhibitors (olaparib and talazoparib) should be offered according to previously mentioned indications.

Types of assays. The currently available evidence does not support *BRCA* tumor tissue testing in breast cancer. At present, *BRCA* testing is indicated on peripheral blood, while the somatic assay can be performed within experimental context.[19,20] Possible evolutions are emerging from studies on homologous recombination deficiency (HRD) and PARP inhibitor sensitivity, where the assessment of the HRD status can be performed only at the tissue level in triple-negative breast cancers.

Ovarian cancer

Retrospective studies showed that patients with ovarian cancer who are carriers of a g*BRCA* PV have higher pharmacologic sensitivity to therapeutic combinations containing platinum derivatives,[21,22] even when administered at high doses, like in intraperitoneal chemotherapy, and also susceptibility to pegylated liposomal doxorubicin[23] and trabectedin.[24] Furthermore, several studies showed that the presence of germline or somatic *BRCA* PVs represents a predictive biomarker of increased sensitivity to the treatment with PARP inhibitors.[9,25,26]

The PARP inhibitors, recently, demonstrated their effectiveness after the first line of platinum-based therapy, even in the setting of patients without *BRCA* genes alterations (wild-type).[27,28] However, it remains important to consider that *BRCA* genes should be analyzed in all patients with ovarian cancer (excluding mucinous and borderline tumors) because: (i) the patients with a *BRCA* PV derive a greater benefit from the PARP inhibitors treatment, compared with the wild-type patients; (ii) a PV disclosed on *BRCA* testing has relevant implications on personal and family cancer risk prevention.[7]

Summary of expert opinion

The *BRCA* testing is recommended at the first diagnosis of non-mucinous, non-borderline ovarian epithelial carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma, regardless of the patient's age and family history.[7]

Types of assays. The panel recommends to analyze, in the first instance, the tumor tissue, particularly because g*BRCA* testing would miss clinically meaningful somatic mutations. The nature of the variant identified (constitutional or somatic) will be subsequently established by analyzing a normal tissue (blood and other tissues).[7,8,29]

In the case of a somatic mutation, the patient will have access to the PARP inhibitor treatment, when indicated.

In the case of a constitutional variant, in addition to the access to a PARP inhibitor treatment, the patient and her family will have access to the preventive path, through the oncogenetic counseling and subsequent clinical-instrumental surveillance programs and/or risk-reduction strategies[7,8] (Figure 1).

Metastatic pancreatic cancer

In Italy, from September 2019 to February 2022, the PARP inhibitor olaparib was available in the context of an Early Access Program for the treatment of patients with metastatic pancreatic adenocarcinoma selected on the basis of the enrollment criteria of the POLO study.[29] This clinical trial evaluated olaparib as maintenance therapy in patients with pancreatic adenocarcinoma and *gBRCA* VP, with response/stability of tumor after a platinum-containing first-line treatment.[30]

On the available evidence, in patients with metastatic pancreatic adenocarcinoma potentially treated with a platinum derivative, *BRCA* testing offered to the patients with

BRCA PV, if not progressing to first-line therapy with platinum, the opportunity of maintenance with olaparib[§].

Summary of expert opinion

The g*BRCA* testing should be offered to all patients with metastatic pancreatic adenocarcinoma:

- in patients who can be potentially treated with a platinum derivative, the *BRCA* testing is a predictive biomarker of efficacy to the anticancer therapies and, therefore reporting times should be adequate to the clinical need to plan the best therapeutic strategy[§];
- in all other patients, not candidates to therapy with platinum derivatives, the indication to g*BRCA* testing remains for the screening of a hereditary cancer predisposition and for the assessment of preventive strategies. In this case, the reporting times may differ, on the basis of clinical needs, from those of the therapeutic pathway.
- the panel highlighted the presence of another type of pancreatic exocrine carcinoma associated with alterations in *BRCA* genes, namely, acinar cell carcinoma.[31] Also because of its rarity, specific data on therapeutic strategies of this specific neoplasm in the case of alterations of *BRCA* genes are very limited,[32] but a continuous update on this topic is highly recommended.

Types of assays. To date, to identify *BRCA* PVs in the patients with metastatic pancreatic cancer for therapeutic purposes, the *BRCA* testing must be performed on peripheral blood or oral mucosa (germline test).[8]

The somatic *BRCA* testing on pancreatic tumor tissue is currently used only within clinical studies, being limited by some preanalytical and analytical issues.[33]

Metastatic prostate cancer

The phase III randomized PROfound trial compared the efficacy of olaparib with hormonal therapies (enzalutamide or abiraterone) in patients with metastatic castration-resistant prostate cancer, pre-treated with abiraterone or enzalutamide in all cases and taxanes in two-third of cases.[34]

The results of this study showed, in patients with *BRCA* PVs, an advantage in terms of progression-free survival, for olaparib treatment compared with a second treatment with abiraterone or enzalutamide.[35] These findings led in October 2020 to the registration by the European Medicines Agency (EMA) of the PARP inhibitor olaparib 'indicated, as monotherapy, for the treatment of adult patients with metastatic castration-resistant prostate cancer and *BRCA* gene mutations (germline and/or somatic PV), progressing after previous treatment including a new hormonal agent'.

Patients must have confirmation of a *BRCA* PV (either in the germline or in tumor tissue) before starting treatment with olaparib. In Italy the drug olaparib is available and reimbursed from March 2022 for the treatment of castration-resistant metastatic prostate cancer.

Summary of expert opinion

- The *BRCA* testing is recommended for patients with metastatic prostate cancer;
- The identification of a PV in the *BRCA* genes allows to plan an adequate therapeutic pathway;
- The identification of a g*BRCA* PV in a patient with prostate cancer allows the access to the preventive pathway, the oncogenetic counseling for the family members to identify high-risk carriers, dedicated screening programs for early diagnosis of *BRCA*-related heredo-familial tumors, and risk-reduction strategies.

Types of assays. The panel considers that both somatic and g*BRCA* tests can be offered to patients with metastatic prostate cancer, with the priority given to somatic test due to a larger chance to detect *BRCA* PVs than germline analysis, nearly 13% and 6%, respectively (Figure 2).

- For the somatic testing, the histological samples must be evaluated by a pathologist who identifies the most representative areas of the tumors, with the greatest number of tumor cells.
- The histological samples should not be older than 7 years and possibly not belonging to bone metastasis.
- The somatic test still presents technical issues that limit it to selected specialized laboratories. Laboratories must offer validated testing and quickly available results.
- The somatic test should be proposed to the patients with previous non-informative results of germline test (no PV identified) and who are candidates for the PARP-inhibitors treatment.

BRCA SEQUENCE ANALYSIS

Both somatic *BRCA* and g*BRCA* testing are routinely performed by next-generation sequencing (NGS) analysis, with the latter having become very popular in molecular diagnostic laboratories. Nevertheless, although there are many in-house and commercially available assays, the standardization of the entire path for *BRCA* NGS-based analysis is not completely achieved,[36] due to many factors: (i) the use of different molecular pipelines, where *BRCA* are generally screened within larger gene panels rather than as single genes; (ii) use of different bioinformatic tools that sometimes fail in the identification of large rearrangements or cannot homogeneously cover all the gene regions[37]; (iii) the volume of samples processed that does not allow the bioinformatic pipeline to identify overall of large rearrangements and copy number changes; (iv) the types of sequencing machines used because they can differently perform and could not always provide superimposable results, particularly when somatic and germline results are compared. In addition, somatic pipelines are more sensitive to the quality of the extracted DNA and are generally affected by some pre-analytical conditions, such as (i) time of fixation, (ii) the adequate amount of tumor tissue and the number of tumor cells

[§]Currently, olaparib is not reimbursed by the Italian National Health System.

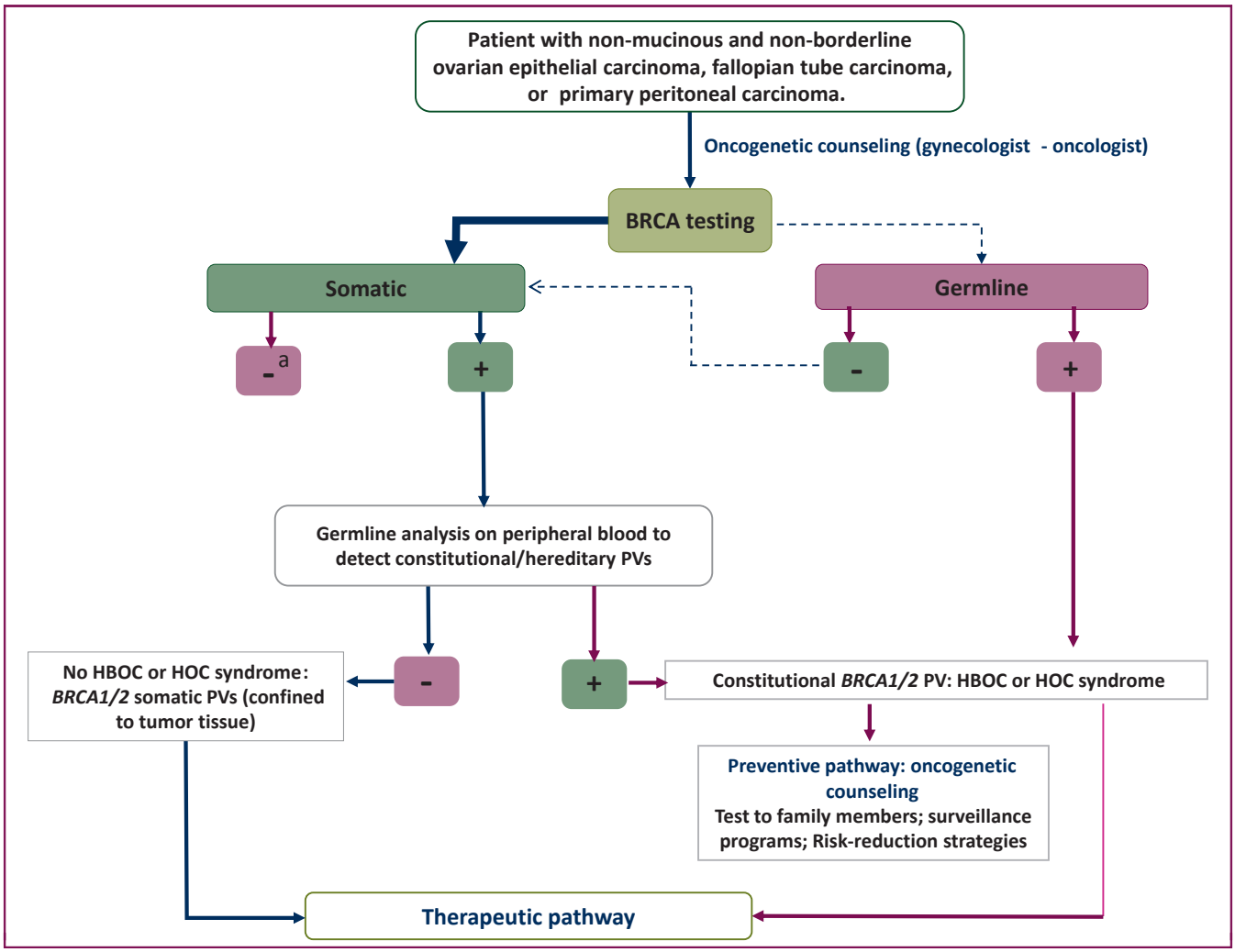

Figure 1. The workflow for the *BRCA1/2* analysis in nonmucinous, nonborderline ovarian epithelial carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma.

HBOC, hereditary breast and ovarian cancer; HOC, hereditary ovarian cancer; PV, pathogenic variant.

[a]When a somatic PV has not been identified, the genetic consultation should be considered taking into account specificities of the family history and personal criteria.

enriched; (iii) the ratio between normal and tumor tissue within the tissue section; (iv) the number of processed samples per batch; (v) the tumor-infiltrating lymphocytes, which can reduce the capability of detecting copy number variants or rearrangements.[38]

Moreover, at the analytical level, the type of laboratory layout can still influence the quality and the tourn around time of assays, particularly when the automated and manual processes are compared.[39] However, the coverage and the filtering criteria of variant can also affect the quality of variant reporting.[40]

Although somatic testing is more informative than the sole germline one, it is not able to distinguish between germline and somatic nature of the deleterious variant identified: therefore the confirmation on blood sample is still necessary to better manage not only the patients but also their family members.[7]

Finally, all laboratory developed tests should fulfill at least the requirements of ISO15189 standards, also taking into account the upcoming new regulation on *in vitro* diagnostic systems.[41]

THE INTERPRETATION OF *BRCA* GENETIC VARIANTS

In general, the classification criteria proposed by the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) consortium (https://enigmaconsortium.org/), according to the International Agency for Research on Cancer (IARC) recommendations,[42] are followed. These criteria systematically classify both *BRCA* and other gene variants into five classes, from I to V.[43] Thanks to NGS technologies, novel variants defined as variants of uncertain significance (VUSs) have been shown to be harbored by 10%-20% of patients undergoing *BRCA* genetic screening.[15] A VUS is a nucleotide sequence alteration with unknown or unpredictable functional consequences on the product of the gene or on the potential risk of causing disease. Consequently, the clinical significance remains unclear, making the overall patient management not very easy, particularly when the laboratory specialists and the molecular team do not periodically revise the status of each VUS. Periodical revision of VUS status is therefore recommended to facilitate the patient's path and follow-up. Regarding tissue variants, unique criteria of filtering and

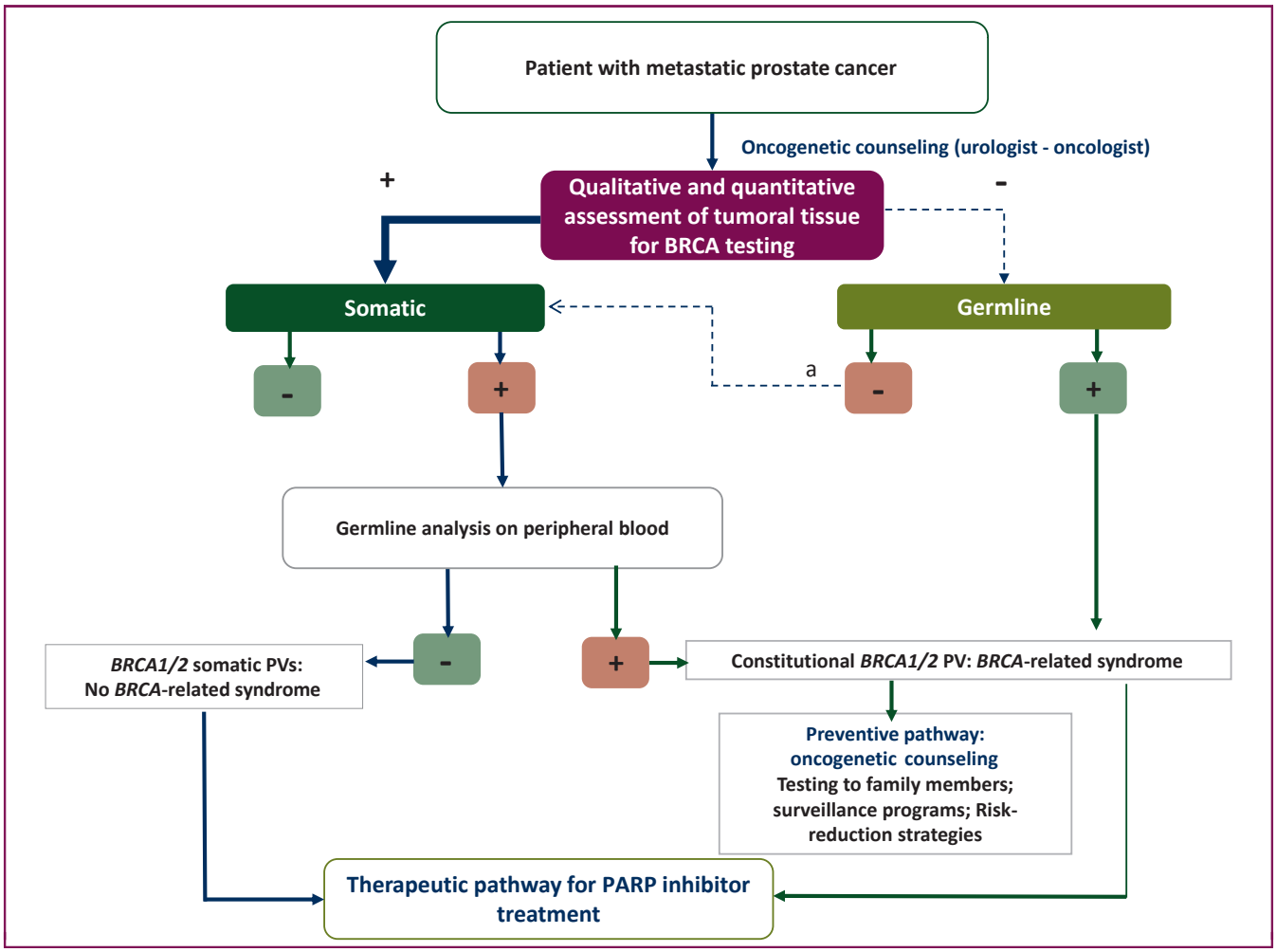

Figure 2. The workflow for the *BRCA1/2* analysis in patients with metastatic prostate cancer.
PV, pathogenic variant.
[a]To consider repeating biopsy if germline testing is not informative.

calling should be assessed to avoid those with equivocal results or at low frequency <5%. Moreover, detection of large copy number variants remains challenging and some issues have been raised around the potential for up to 5% of germline variants to be missed by tumor testing.[44] Noteworthy, variants detected within tumor tissues should be retested at germline level (on blood or buccal mucosa)[36] in a reflex modality.[45] However, the evaluation of sole *BRCA* in the cancer tissue does not allow the identification of deleterious variants in other genes associated with hereditary ovarian cancer risk, which are mutated in 4%-7% of patients with ovarian cancer.[46] Notably, although *BRCA1/2* gene PVs account for the vast majority of the hereditary breast and ovarian cancer, PVs of other genes can be involved, and could explain an HRD status when no *BRCA1/2* PVs are identified. *BRCA1* methylations status should be also considered for a better understanding of HRD status. Further recommendations are needed for multigene panel genotyping, especially in *BRCA*-negative familial/hereditary conditions.[8]

Tumor variants should be evaluated by the 2015 American College of Molecular Genetics (ACMG) germline variant interpretation guidelines and following the updates from the literature.[47,48]

CONCLUSION

Considering the recent availability of approved therapies, and the increased number of individuals and their relatives, carriers of *BRCA* PVs, who may benefit from the preventive pathways and cancer risk-reducing strategies, standardized and harmonized procedures, and testing criteria are needed. The adequate patient selection is essential to address the patients in the appropriate therapeutic paths.[49,50,51] Incorporating *BRCA* testing in the routine management of patients is a key requirement to help medical or surgical decision making. All the professionals involved in the multidisciplinary preventive and therapeutic pathway should be specifically trained to optimize and implement *BRCA* testing in clinical practice.

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DISCLOSURE

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APPENDIX

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