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Tumour Review

PREDICTIVE *BRCA* GENETIC TESTING IN ITALIAN PATIENTS WITH BREAST CANCER: A POSITION PAPER OF ITALIAN SCIENTIFIC SOCIETIES [Italian Association of Medical Oncology(AIOM); Italian Association of Radiotherapy and Clinical Oncology (AIRO); Italian National Association of Breast Surgeons (ANISC); Italian Society of Pathological Anatomy and Diagnostic Cytology (SIAPeC-IAP); Italian Society of Surgical Oncology (SICO); Italian Society of Human Genetic (SIGU); Italian Society of General Practice (SIMG); Italian Society of Medical and Interventional Radiology (SIRM)]

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ABSTRACT

The introduction of Poly (ADP-ribose) Polymerase (PARP) inhibitors in both metastatic and early-stage breast cancer (BC) treatment has led to the emergence of Mainstreaming Cancer Genetics (MCG) as a new approach to genetic counselling, predictive of therapy outcomes. Therefore, the *BRCA* testing criteria for therapeutic purposes require further implementation. This position paper outlines the Italian indications for predictive genetic testing, approved by a multidisciplinary Expert Panel representing major scientific societies involved in BC treatment in Italy.

We utilized the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, and framed clinical questions as population, intervention, comparison and outcome (PICO). The final recommendations were determined through a voting process, covering key topics such as eligibility criteria for onco-genetic counselling, the role of contralateral prophylactic mastectomy (CPM) in patients harboring *BRCA1/2* germline pathogenic variants (gPV), and the positioning of predictive *BRCA1/2* test.

As results, the Expert Panel defined three distinct patient groups eligible for onco-genetic counselling, based on the *a priori* likelihood of carrying a gPV and the purpose of testing (predictive vs preventive). A conditional recommendation in favor of CPM in patients with a history of surgically treated BC and a *BRCA* gPV was suggested. Finally, a multidisciplinary pathway for *BRCA* testing was proposed, for patients with triple negative and hormone receptor-positive (HR+)/HER2-negative (HER2−) BC.

In conclusion, the predictive *BRCA* testing inside the onco-genetic framework marks an important step-forward in BC management. However, the integration of somatic testing, digital pathology, and artificial intelligence-driven models could refine patient selection for tailored treatments.

Introduction

Germline pathogenic variants (gPV) in BReast CAncer (*BRCA*)*1* and/or *BRCA2* genes are associated with an increased risk of developing breast cancer and ovarian cancer [1]. *BRCA2* gPV may also increase the risk of male breast cancer with an estimated lifetime risk of approximately 13 % for male carriers. Other genes associated with increased breast cancer risk include *TP53, PTEN, CDH1, STK11, MSH6, BARD1, ATM, CHEK2, RAD51C, RAD51D* and *PALB2* [2,3]. With the introduction of poly (ADP-ribose) polymerase (PARP) inhibitors firstly in advanced and then in early-stage settings, a new approach to genetic counselling – the Mainstreaming Cancer Genetics (MCG) – has been introduced into the clinical practice. This model enables medical oncologists and others specialists involved in breast cancer diagnosis and treatment to directly refer patients for *BRCA* genetic testing when it has therapeutic implications. While somatic testing is increasingly being explored as a potential screening tool for *BRCA* gPV detection, current supporting evidence remains limited (level IIB in the ESCAT score) [4]. Therefore, peripheral blood analysis continues to be the standard reference test.

This document aims to provide an update on predictive *BRCA* testing and support its implementation in clinical practice, with a focus on the following patient groups:

1. Patients with clinical characteristics associated with an increased likelihood of *BRCA1/2* gPV, regardless of family history.
2. Patients without clinical characteristics associated with an increased likelihood of *BRCA1/2* gPV but who are eligible for specific treatments if a gPV is detected.
3. Patients with family history suggestive of a high likelihood of *BRCA1/2* gPV.

Furthermore, the document also addresses surgical and radiotherapeutic treatments in patients already affected by breast cancer.

Methods

Document development and composition of the multidisciplinary working group

The document has been developed, discussed, reviewed, and approved by a multidisciplinary Expert Panel composed of 33 clinicians representing major Italian scientific associations of Italian Association of Medical Oncology (AIOM), Italian Association of Radiotherapy and Clinical Oncology (AIRO), Italian National Association of Breast Surgeons (ANISC), Italian Society of Pathological Anatomy and Diagnostic Cytology (SIAPeC-IAP), Italian Society of Surgical Oncology (SICO), Italian Society of Human Genetic (SIGU), Italian Society of General Practice (SIMG), Italian Society of Medical and Interventional Radiology (SIRM). It is based on expert consensus and incorporates the best available evidence, aligning and harmonizing the current eligibility criteria for *BRCA* testing in accordance with Italian National Guidelines and Clinical Recommendations.

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

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) recommendations

After identifying specific outcomes of benefit and harm deemed critical for decision-making, the GRADE approach was applied to assess the certainty of evidence for each selected outcome, evaluating five key domains: study limitations, imprecision, indirectness, inconsistency, and publication bias.

The overall quality of evidence, which forms the basis for the final recommendations, is classified into four levels: high, moderate, low, or very low.

The strength of the final recommendation is determined through a voting process, with four possible outcomes: strong in favor, conditional in favor, conditional against, and strong against.

The clinical recommendation reflects the practical clinical significance of the procedure.

In the Appendix A are presented literature search, PRISMA flow diagram and evidence to decision framework for the GRADE query on contralateral prophylactic mastectomy.

Results

Eligibility criteria for onco-genetic counselling

The criteria for onco-genetic counselling in breast cancer patients are outlined below and in Table 1. The pathway for genetic testing in breast cancer patients should be tailored according to the "a priori" likelihood of gPV and the primary objective of testing, whether predictive (for treatment decision) or preventive" (for risk assessment and management).

Patients with clinical characteristics associated to an increased likelihood of harboring a BRCA1/2 gPV, regardless of family history

- woman with breast and ovarian cancer;
- woman with breast cancer diagnosed at ≤40 years;
- woman with triple negative breast cancer (TNBC) diagnosed at any age;
- woman with bilateral breast cancer diagnosed at ≤50 years;
- man with breast cancer.

For this group of patients, *BRCA* testing can be requested as a fast-track procedure to guide the most appropriate treatment decisions, both locoregional and systemic, based on the test results. This request can be made not only by geneticists but also by oncologists and surgeons, at a multidisciplinary team (MDT) level discussion, provided they have received adequate training to ensure that patients receive accurate and comprehensive information. Whenever a gPV or a variant of unknown significance (VUS) is identified, genetic counselling must be promptly activated. Conversely, in patients who do not carry a gPV or VUS, testing for other predisposing genes may be considered (either as part of the same multigene panel or at a later stage).

AIOM guideline update has revised the diagnostic criteria for all breast cancer cases, raising the age threshold from 36 to 40 years at the time of diagnosis. This adjustment aligns with the increased prevalence of gPV observed in this age group [5–7]. To assess the feasibility of this amendment, the Italian Cancer Registry estimated the number of breast cancer diagnoses in Italy among patients aged 36–40 years, identifying approximately 1,800 additional patients eligible for testing [8]. Based on the current capacity of national laboratories, this increase in *BRCA* testing volume was deemed sustainable. Additionally, the age criterion—previously set at 60 years—has been removed for patients diagnosed with TNBC. As a result, TNBC itself is now considered a standalone indication for *BRCA* testing, regardless of the patient's age at diagnosis [9].

Patients without clinical characteristics suggesting a high likelihood for BRCA1/2 gPV but eligible for specific treatments if a gPV is detected:

- Any patient affected by hormone receptor-positive (HR+), HER2-negative (HER2−) early breast cancer and ≥4 lymph nodes involved;
- Any patient affected by HR+/HER2− early breast cancer, with residual disease after neoadjuvant chemotherapy and a clinical and pathological stage/estrogen receptor status and histologic grade (CPS/EG) score ≥ 3;
- Any patient affected by advanced/metastatic HR+/HER2− breast cancer, previously treated with anthracycline and/or taxane-based chemotherapy (or deemed ineligible for it), progressing after

Table 1
Eligibility criteria for performing germline *BRCA* genetic testing.

Patients with clinical characteristics associated to an increased likelihood of *BRC1/2* gPV, regardless of family history
Woman with breast and ovarian cancer
Woman with breast cancer diagnosed at ≤40 years
Woman with triple negative breast cancer (TNBC) diagnosed at any age
Woman with bilateral breast cancer diagnosed at ≤50 years
Man with breast cancer
Patients without clinical characteristics associated to an increased the likelihood of *BRCA1/2* gPV, but eligible for specific treatments in case a gPV is identified:
Early breast cancer patient with hormone receptor-positive (HR+), HER2-negative (HER2−) disease and ≥4 lymph nodes involved
Breast cancer patient with HR+/HER2− disease, with residual disease after neoadjuvant chemotherapy and a CPS/EG score (clinical and pathologic stage/estrogen receptor status and histologic grade) ≥3;
Metastatic breast cancer patient with HR+/HER2− disease, previously treated with anthracycline and/or taxane-based chemotherapy (or deemed ineligible for it), progressing after Cycline D Kinase 4/6 inhibitors (CDK4/6i) for advanced disease
Patients with family history associated with a high likelihood of *BRCA1/2* gPV
BC patient diagnosed between 41 and 50 years with a first degree relative* with:
• Breast cancer diagnosed before the age of 50 years
• Ovarian cancer (excluding mucinous and borderline histologies), diagnosed at any age
• Bilateral breast cancer
• Pancreatic cancer
• Prostate cancer
Breast cancer patient diagnosed after the age of 50 years with two first-degree relatives* (related to each other), including one who is a first-degree relative of the patient, affected by breast, ovarian, or pancreatic cancer.
Presence of a gPV already identified in a relative.

* First-degree relative (parent, brother/sister, son/daughter) with breast cancer, ovarian cancer or pancreatic cancer. In the paternal lineage, second-degree relatives (grand-mother, aunts) must be considered.

cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) for advanced disease.

For this patient category, *BRCA* testing is requested for therapeutic purposes (to assess eligibility for PARP-inhibitors) by a trained oncologist, ensuring that patients receive accurate and comprehensive information. Genetic counselling must be promptly activated if a gPV or VUS is detected.

Patients with family history associated with a high likelihood of BRCA1/2 gPV

a) Breast cancer patient diagnosed between 41 and 50 years with a first degree relative affected by:
- Breast cancer, diagnosed within the age of 50 years;
- Ovarian cancer, excluding mucinous and borderline histologies, diagnosed at any age;
- Bilateral breast cancer;
- Pancreatic cancer;
- Prostate cancer.

b) Breast cancer patient diagnosed after the age of 50 years with two first degree relatives (related to each other, including one who is first-degree relative of the patient), affected by breast, ovarian or pancreatic cancer.

c) Presence of a gPV already identified in a relative.

For patients who may have a paternally inherited *BRCA* gPV, due to the male interposition, the second-degree relatives can be considered as first-degree ones.

For this patient category, traditional genetic counselling is activated to optimize the genetic evaluation. This process involves verifying tumor characteristics in affected relatives, assessing their distribution within the family tree, determining the appropriateness of genetic testing, and identifying the most informative index case. A comprehensive evaluation should also include differential diagnosis among other hereditary syndromes, cancer risk estimation, and prevention strategies in case of uninformative results. In addition, co-segregation and *in silico* analyses should be considered to better interpret VUS

When *BRCA* genetic testing is required for therapeutic decisions, genetic counselling should be conducted within one week of the request. If geneticists are unavailable, a trained medical or clinical/radiation oncologist or surgeon may request the test ensuring that patients receive accurate information. The results must then be reviewed by the MDT, including a geneticist, to ensure proper interpretation.

The *BRCA* test must be integrated into a structured genetic pathway, conducted by health providers with both oncological and genetic expertise. These skills are essential for both pre-test and post-test counselling. A predictive *BRCA* testing for therapeutic decisions can be prescribed not only by geneticist, but also by oncologists and breast surgeons with oncological skills, who are responsible for providing adequate information on the implications of the results.

The test results can be:

- Informative: the predisposing variant has been identified;
- Uninformative: the predisposing variant has not been detected, but its presence cannot be entirely excluded, or a VUS has been identified with no confirmed clinical significance.

Germline pathogenic variants are categorized into five classes according to the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) classification:

- Category 1: benign = no clinical significance
- Category 2: likely benign = unlikely to be associated with disease.
- Category 3: variant of unknown significance = Insufficient evidence to determine clinical relevance.
- Category 4: likely pathogenic = strong evidence suggests an association with disease.
- Category 5: pathogenic = confirmed to be disease-causing

A true negative result occurs only when a pathogenic variant previously identified in a family member is not detected in the tested subject. The test can be extended to other family members, who wish to undergo testing, only in case of an informative result, starting at 18 years of age. *BRCA* test in minors is currently not recommended, as the associated risk begins to increase in adulthood. In case of VUS, extending the test to other family members is not indicated outside of research projects. Surveillance programs should be based on family history and other established risk factors.

Positioning of predictive gBRCA1/2 test for the use of PARP inhibitors

The availability of PARP inhibitors in both early and advanced settings for patients with HER2-negative breast cancer carrying a *BRCA1/2* gPV [10–12] has necessitated a revision of the *BRCA* testing framework, as shown in Fig. 1.

The presence of *BRCA* gPV has crucial implications at multiple levels. From a surgical perspective, BRCA gPV patients should be offered bilateral mastectomy (even in case of radiological complete response after neoadjuvant treatment). From a medical standpoint, 1 year of adjuvant olaparib represents a priority treatment option for patients at high-risk of relapse, as shown in Fig. 1.

In patients with early TNBC, *BRCA* testing should be performed before initiating any treatment, whether in the neoadjuvant or adjuvant setting. Within 7 days, the MCG should be conducted by an oncologist or surgeon, along with blood sample collection for the *BRCA* test. A psychologist can be involved upon request. The genetic analysis should be completed within a maximum of 3 weeks and the final result should be released within 2 days. In case of a positive result, the discussion should take place in the presence of a breast surgeon and an oncologist, along with a plastic surgeon and psychologist, as needed.

In TNBC with a radiological diameter of less than 1 cm, surgery should be the first therapeutic choice and bilateral mastectomy should be considered. If after primary surgery the pathological stage is ≥II, adjuvant chemotherapy should be administered for at least six cycles followed by Olaparib therapy for one year. In case of bilateral prophylactic mastectomy an early plastic surgery consultation is warranted to plan in advance the best reconstructive options to be shared with the patient.

In tumours with a clinical diameter between 1 and 2 cm, neoadjuvant treatment with anthracyclines, cyclophosphamide and taxane (with or without platinum-derived drugs) may be considered. In stage II-III tumours at diagnosis, pembrolizumab combined with chemotherapy (carboplatin and paclitaxel for 4 cycles followed by anthracycline and cyclophosphamide for 4 cycles) should be the standard of care according to the results of the Keynote-522 study [13]. However, it should be discussed with the patient the opportunity to receive only neoadjuvant chemotherapy without pembrolizumab, followed by Olaparib in case of residual disease, due to a limited benefit in pathological complete response (pCR) rate from the addition of pembrolizumab (69.1 % vs.62.1 % in the placebo arm). Furthermore, the Olaparib treatment in adjuvant setting shows a better toxicity profile compared to pembrolizumab and achieves an OS advantage in 4 years follow-up period compared to 75 months in the Keynote-522 study.

For patients who are undergoing neoadjuvant chemotherapy and carry a *BRCA* gPV, bilateral mastectomy with immediate reconstruction should be discussed and considered, even in cases of radiological complete response. If residual disease is present, adjuvant Olaparib should be prioritized over pembrolizumab (see Fig. 2).

In patients with HR+/HER2- early breast cancer who do not present clinical characteristics suggesting a high likelihood of *BRCA1/2* gPV, predictive *BRCA* testing should be offered to those eligible for one year

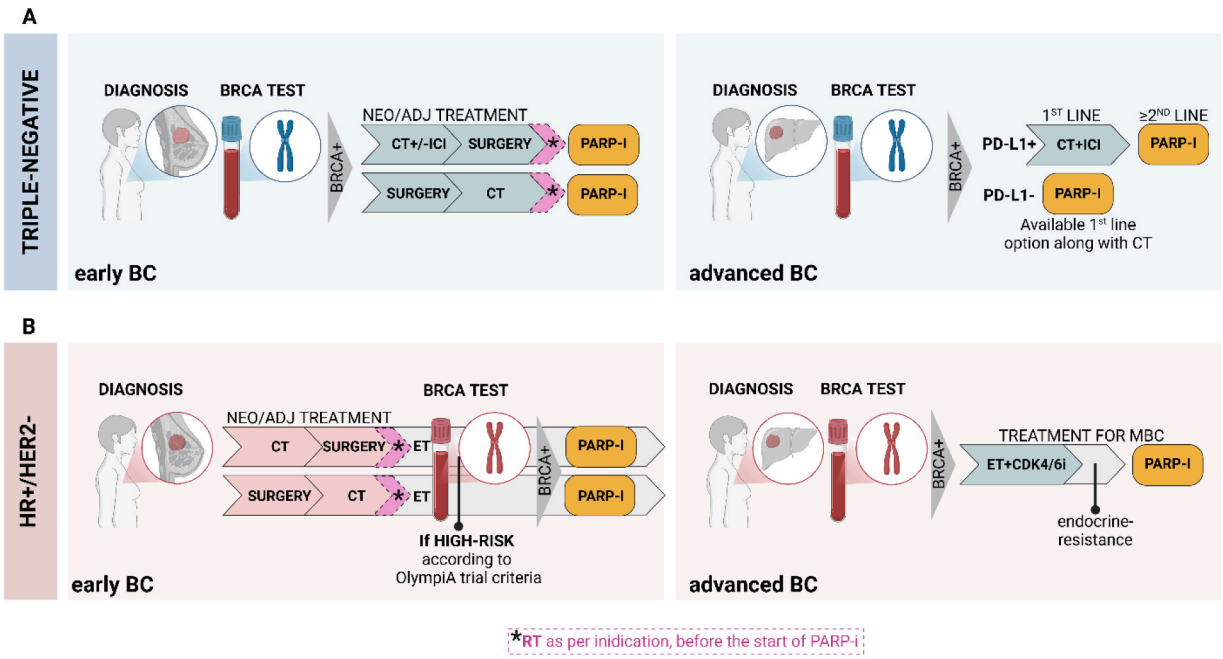

Fig. 1. Possible treatment pathways for gBRCA test in early and advanced breast cancer, either Triple Negative (A) and HR+/HER2− (B) BRCA+: BRCA positive; NEO/ADJ: Neoadjuvant/Adjuvant; CT: Chemotherapy; ICI: Immune Checkpoint Inhibitors; PD-L1+; PD-ligand 1 positive; PARPi: Poly (ADP-ribose) polymerase inhibitors; PD-L1-; PD-ligand 1 negative; BC: breast cancer; HR+:Hormone Receptors positive; HER2−: human epidermal growth factor receptor 2 negative; ET: endocrine therapy; MBC: Metastatic Breast Cancer; CDK4/6i: Cycline D Kinase 4/6 inhibitors; RT: Radiotherapy.

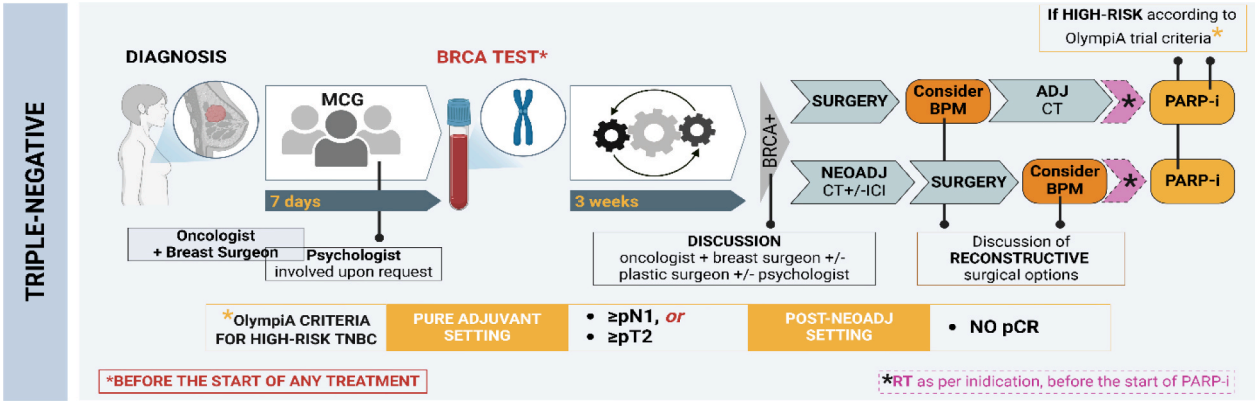

Fig. 2. Multidisciplinary pathway of Triple Negative Breast Cancer at stage I-III diagnosis MCG: Mainstreaming Cancer Genetics; BRCA+: BRCA positive: BPM: Bilateral Prophylactic Mastectomy; ADJ: Adjuvant; CT: Chemotherapy; PARP-i: Poly (ADP-ribose) polymerase inhibitors; NEOADJ. Neoadjuvant; ICI: Immune Checkpoint Inhibitors; pCR: pathological Complete Response, RT. Radiotherapy.

of adjuvant olaparib (in combination with adjuvant endocrine treatment), based on the OlympiA trial eligibility criteria. In these cases, the *BRCA* test should be performed within 4 weeks of surgery or during adjuvant chemotherapy to ensure results are available within the required timeframe to start olaparib within 12 weeks of completing local treatment (see Fig. 3).

In the metastatic setting, predictive *BRCA* testing should be performed at the time of diagnosis of HER2− advanced disease given the availability of olaparib and talazoparib as treatment options. More specifically, in patients with advanced TNBC, PARP inhibitors (olaparib or talazoparib) represent a valuable first-line treatment option in case of PD-L1 negative status. In patients with PD-L1 positive tumors, who receive chemotherapy plus immunotherapy in the first line setting, PARP-inhibitors may be considered from the second-line onward. According to the Italian label, both olaparib and talazoparib should be preceded by treatments with platinum-derived drugs, anthracycline and/or taxanes in any disease setting, unless these are contraindicated (Fig. 1A).

In advanced HR+/HER2− breast cancer, the only PARP-inhibitor currently approved by the Italian drug agency (AIFA) and reimbursed by the national health system is talazoparib. This agent represents a key treatment option in endocrine-resistant patients with *BRCA* gPV who have already received endocrine-based therapy, including CDK4/6 inhibitors. Additionally, patients must have previously undergone anthracycline-taxane based chemotherapy either in the early or advanced setting (Fig. 1B).

Treatment of patients with BRCA1/2 gPV and breast cancer: focus on the role of bilateral mastectomy/contralateral prophylactic mastectomy/ bilateral salpingo-oophorectomy

The optimal surgical approach – breast-conserving surgery (plus radiation therapy [RT]) vs radical mastectomy in *BRCA1/2* carriers affected by breast cancer is still debated. Several meta-analyses have

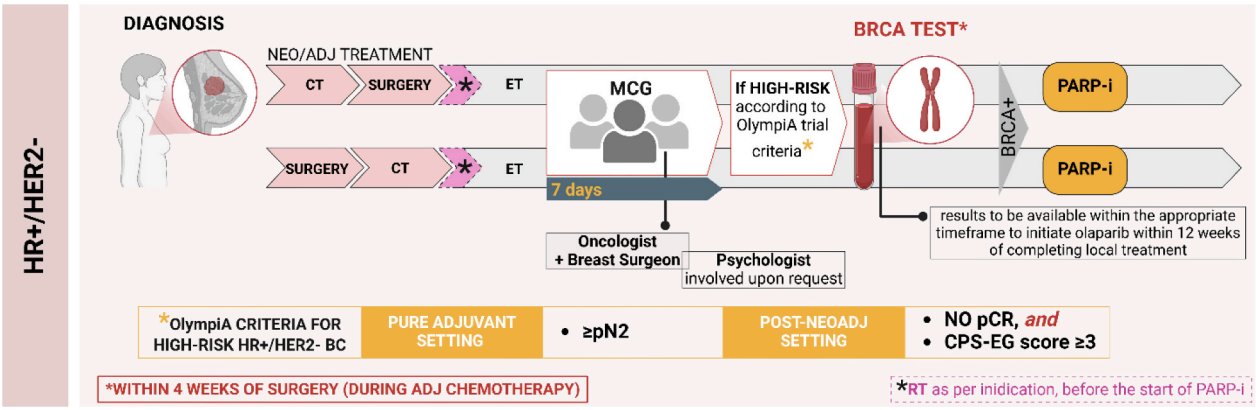

Fig. 3. Multidisciplinary pathway of HR+/HER2− breast cancer at stage I-III diagnosis HR+: Hormone Receptors positive: HER2−: human epidermal growth factor receptor 2 negative; NEO/ADJ: Neoadjuvant/Adjuvant; CT: Chemotherapy; ET: endocrine therapy; MCG: Mainstreaming Cancer Genetic; BRCA+: BRCA positive; PARP-i: Poly (ADP-ribose) polymerase inhibitors; BC: Breast Cancer; pCR: pathological Complete Response; CPS-EG: clinical and pathologic stage and estrogen receptor status and histologic grade; RT: Radiotherapy.

reported that the risk of a second ipsilateral breast cancer is approximately 24 % after 15 years in patients treated with conservative surgery plus RT compared to those undergoing mastectomy [14,15]. However, this increased risk did not impact the mortality rate at 15 years [16]. The use of prophylactic contralateral irradiation has been evaluated in a phase II case/control trial showing a 80 % reduction in breast cancer risk [17].

Compared to non-*BRCA* carriers, the risk of contralateral breast cancer 25 years after the initial diagnosis is increased by 53 % for *BRCA*1 and 65 % for *BRCA*2 gPV carriers. Furthermore, the cumulative ovarian cancer risk to age 80 years is 44 % for *BRCA1* and 17 % for *BRCA2* carriers [18]. The contralateral breast cancer risk remains elevated also in patients who have undergone bilateral prophylactic salpingo-oophorectomy and is influenced by the age at first diagnosis [19]. Given the known increased risk of contralateral breast cancer, many women choose to undergo bilateral mastectomy at the time of breast cancer surgery rather than in a later stage [20]. This underscores the importance of performing the *BRCA* test at the time of breast cancer diagnosis (when criteria for *BRCA* testing are met), ensuring that results are available within 4 weeks. Some retrospective evidence suggests that contralateral prophylactic mastectomy (CPM) in *BRCA*1/2 gPV carriers may reduce mortality, mostly in the second decade after surgery [21–23].

Particular attention should be given to young patients. Women aged ≤40 years who have already been diagnosed with breast cancer and carry a *BRCA* gPV are at higher risk of developing a second malignancy over their lifetime. In the group of women with early--stage breast cancer, metachronous ovarian cancer is a common cause of mortality [24]. In these patients, to undergoing bilateral risk-reducing mastectomy and/or salpingo-oophorectomy appears to have a positive impact on prognosis, leading to lower rates of recurrence, secondary breast and/or ovarian cancers, and mortality compared to those who do not pursue these strategies. Recent data from a cohort study of *BRCA1/2* gPV, show that oophorectomy among patients already affected by breast cancer reduces the specific mortality risk of 56 % (HR = 0.44; 95 % CI, 0.25–0.78; P = 0.005), mostly in *BRCA2* patients (HR = 0.22; 95 % CI, 0.06–0.84; P = 0.03) [25].

To provide recommendations based on the GRADE system, the following clinical question was voted on by the panelists, as reported in Table 2:

For this GRADE query the research evidence is the following:

Breast cancer is the leading cause of cancer-related death among women worldwide, being 522,000 the patients deceased in 2012 (15 % of all female deaths) [26]. Furthermore, it represents the most common cancer in all countries with 1,7 million of women affected [27].

In Italy about 58,000 new breast cancer/year are estimated, among those 5 % arise in genetically predisposed women with *BRCA*1/2 gPV. Since patients with *BRCA*1/2 gPV are at increased risk of ovarian and

Table 2
GRADE clinical question on CPM versus no CPM in patients with a history of surgically treated breast cancer and a *BRCA* gPV.

Is contralateral prophylactic mastectomy indicated in patients with a history of surgically treated breast cancer and *BRCA* gPV?
RECOMMENDATION: In patients with operated breast cancer and gPV *BRCA*, contralateral prophylactic mastectomy may be performed.
Strenght of the recommendation: CONDITIONAL IN FAVOUR
Reasons/Comments to the benefit/risk ratio:
Outcome of benefit. The panel deemed the following outcomes of benefit as critical:
Breast cancer mortality, disease free interval (DFI), breast cancer incidence, quality of life, Patient Reported Outcomes (PROs).Supporting evidence comes from observational studies indicating that contralateral prophylactic mastectomy was associated with a significant improvement of: breast cancer mortality (HR 0,46; IC95% 0,20–0,71), breast cancer incidence (OR 0,08; IC95% 0,03–0,19) DFI (HR 0,42; IC95% 0,26–0,69) compared to no procedure. The procedure was well tolerated with minimal impact on quality of life, as indicated by PROs. Considering this evidence, the impact of the procedure on these benefit outcomes was rated as great by 9 and moderate by 2 panelists (totally 11 voters). The assessment was affected by the low quality of evidence, primarily due to the following biases: study design limitations, including selection, detection, recall, and attrition biases, as well as result imprecision.
Outcome of harms. The panel identified the following outcomes of harms: long terms coping with cosmeticresults, early and late physical morbidity. Five observational studies reported on the effects of contralateral prophylactic mastectomy effects on long term cosmetic results. None of the studies reported on early and late physical morbidity. Due to the low quality of evidence, the impact of the procedure on the outcomes of harms was considered moderate by all voters (totally of 11 voters)
.
Given the limitations of the included observational studies and the low quality of evidence, the panel assessed the balance between benefits and harms as uncertain in favor of the contralateral prophylactic mastectomy.
Future research implications: perspective studies are needed.
Proofs quality: Outcome of benefit: Very low; Outcome of harms: Very low
Global proofs quality: VERY LOW
Declaration of competing interest (COI): no COI to declare

breast cancer, contralateral too, CPM could be considered to prevent the second breast cancer onset. As preventive measure, risk reducing mastectomy remains controversial. Potential benefits include reduction of breast cancer risk and increased psychological wellbeing. Potential disadvantages regard procedure invasiveness and subsequent morbidity, such as reduction of body image satisfaction and reduction of breast tactile sensitivity. It remains clear that this surgery must be performed in high-volume centres with specific experience.

Discussion

BRCA testing is a key component in the management of early and metastatic HER2-negative BC, as the presence of *BRCA* gPV currently serves as a theragnostic biomarker for access to PARP inhibitors. In Italy, the national health system provides *BRCA* testing free of charge, accordingly to National Guidelines. Thus, defining eligibility criteria for *BRCA* test is essential to ensure treatment approval and reimbursement. Beyond the new implications arising from the recent introduction of PARP inhibitors, the predictive role of genetic testing remains well-established in guiding surgical decision-making. In fact, offering bilateral mastectomy at the surgical time seems to provide an overall survival (OS) benefit compared to unilateral mastectomy [28]. Furthermore, the rate of bilateral mastectomy in breast cancer patients is around 75 % when the *BRCA* result is known before the surgery, compared to 15 % when is released after [29,30].

The introduction of MCG, performed by health care providers such as surgeons or oncologists, ensures that test results are delivered within an appropriate timeframe, allowing for optimal medical treatment planning.

On the medical treatment point of view, knowing the *BRCA* status, allows to offer one-year treatment with Olaparib, that provides OS benefit compared to placebo arm [31]. We well know that TNBC patients treated with neoadjuvant therapy according to the Keynote-522 trial derive a benefit in OS by the adjuvant pembrolizumab, mostly in case of Residual Cancer Burden (RCB)-2 [32,33] but not in case of RCB-1 or RCB-3. In Italy, where the Pembrolizumab plus Olaparib combination is not permitted, knowing the *BRCA* status can aid to choose the right adjuvant strategy.

In HR+ tumors, the alternative to Olaparib could be Abemaciclib or Ribociclib, that did not show OS benefit compared to endocrine treatment alone yet. Some retrospective data in the metastatic setting seem to suggest a worse prognosis of gPV *BRCA2* patients treated with CDK4/6i compared to wild-type *BRCA* [34]. However, given the small number of gPV *BRCA* patients included in these studies, caution is warranted in drawing definitive conclusions about potential resistance mechanisms induced by drug exposure and the optimal treatment sequence. Further studies are needed to address these important questions.

By this way, our guidelines assure the *BRCA* test to all patients responding to eligibility criteria for early and metastatic breast cancer, regardless the family history or the patient characteristics'.

In the case of indications for RT (both after breast-conserving surgery and mastectomy) and adjuvant PARP-i or CDK4/6i, there is no recommendation to administer concomitant RT outside the context of a clinical trial, due to the potential increase in toxicity and the lack of robust data on combination treatments. The consensus statement endorsed by the European Society for Radiotherapy and Oncology (ESTRO) recommends starting adjuvant PARP-i or CDK4/6i after the completion of the postoperative RT course [35].

The MCG process has enabled a more efficient redistribution of resources, optimizing the pathway at a time when the demand for genetic testing is steadily increasing, while ensuring the appropriate level of oversight and support for patients with a positive result.

The new *BRCA* test paradigm necessarily needs to be integrated in a multidisciplinary medical practice. Such an approach would not only promote adherence to test criteria, but also facilitate the monitoring of target treatments. There is widespread consensus on the crucial role of the MDT in discussing the timing of the test, taking into account the unique characteristics of each patient and their disease. To allow proper effective discussion at MDT meetings especially in the pre-operative scenario all experts of the MDT should be fully aware of the MCG process and promptly request the test when seeing patients at the beginning of their diagnostic analyses. This would allow to mitigate the turn around time of *BRCA* testing and to obtain the information in a timely way. Finally, the role of psychosocial support is part of the *BRCA* test since depression, anxiety, stress, social and economic challenges, should be assessed and addressed for a comprehensive counselling, mostly in case of young patients who are worried for their kids.

In this context, the AIOM Guidelines Panel identified the redefinition of *BRCA* testing eligibility criteria as a fundamental and urgent priority. One of the most debated topics within this working group was the potential incorporation of the universal genetic testing into the Italian Breast Cancer Guidelines, an approach that has been endorsed since 2019 by the Consensus Guidelines on Genetic Testing for Hereditary Breast Cancer from the American Society of Breast Surgeons [36]. While universal genetic testing may be considered an ideal strategy, its implementation faces several critical challenges, including: costs and, in general, sustainability within publicly funded healthcare systems, scarcity of genetic counselling services, increased detection of VUS, limited utility of *BRCA* testing in patients diagnosed with breast cancer at ≥65 years of age, especially for HR+/HER2− subtype. Among these challenges, sustainability is particularly crucial in Italy, where a universal healthcare system ensures equitable access to medical services, but demands strategic resource allocation. A cost-effectiveness analysis demonstrated that universal *BRCA* testing for breast cancer patients becomes cost-ineffective when the test cost exceeds a certain threshold [37]. To improve cost-effectiveness, it is essential to increase the number of tests processed per laboratory, centralizing genetic testing in high-volume Hub centers while ensuring a regionally balanced distribution of services. In the Emilia-Romagna region, where 4500 new breast cancer at year are estimated, 4 Hub centers are able to provide all predictive *BRCA* test, accordingly to National guidelines, corresponding to about 53 % of all new breast cancer diagnosed [38]. As reported by Cortesi et al., an intensive surveillance program has been provided, with annual mammography, combined with semi-annually ultrasound ± annual magnetic resonance imaging, accordingly to moderate and high risk for breast cancer development, calculated by the Tyrer-Cuzick model [39]. By this, we can ensure an adequate follow-up for at risk people, even in the absence of a *BRCA* gPV.

While universal *BRCA* testing is likely the future direction, at present, this approach is not considered sustainable within the Italian healthcare system. Therefore, the AIOM multidisciplinary guidelines panel opted for a gradual expansion of *BRCA* testing eligibility rather than an immediate shift to universal testing—an approach that will eventually become inevitable.

This progressive transition has been facilitated through three key modifications: abolition of the age threshold for TNBC, making it a standalone criterion for *BRCA* testing, raising the age threshold for non-TNBC cases from 36 to 40 years and formal introduction of predictive *BRCA* testing in patients who, despite lacking a strong personal or family history, suggestive of a high mutation probability, may still be eligible for specific targeted therapies, particularly PARP inhibitors.

The low percentage of TNBC among the breast cancer subtypes (15–20 %) made possible to test all patients belonging to this category, having the highest gPV *BRCA* rate (13–15 %). Otherwise, testing all HR+/HER2− breast cancer, that represent the vast majority of cases, would have meant unsustainable costs for our Public Health System, given the low mutation rate in this population (5–6 %). Similarly, the low rate of gPV *BRCA* in HER2+ subtype does not justify extending testing to all those patients. Nowadays, we think that this incremental expansion of *BRCA* testing criteria ensures greater accessibility to precision oncology treatments while maintaining sustainability within the current healthcare framework. As testing costs become more affordable,

we intend to extend the analysis to all breast cancer patients. This will also allow us to expand the test indication to patients with multiple tumors in addition to breast cancer, especially in case of association with pancreatic carcinomas.

The introduction of MCG for predictive *BRCA* testing has proven effective in reducing the reliance on geneticists, limiting specialist genetic services primarily to patients with significant and suggestive family/personal history. A prospective study demonstrated that MCG provided by surgeons or nurses delivered sufficient information for most breast cancer patients to make informed decisions about genetic testing, with minimal distress, compared to traditional geneticist-led pre-test counselling [40]. The only statistically significant difference regarded the less frequent discussion about second breast cancer or ovarian cancer in the MCG compared to the traditional genetic counselling. However, in both groups, genetic knowledge and patient satisfaction levels were comparable.

Nevertheless, genetic counselling remains essential in cases of gPV or VUS, for cascade testing in relatives, for a comprehensive discussion of surgical options and ovarian cancer risk, and for further risk assessment in other inherited cancer syndromes in patients with uninformative results. Unlike predictive testing, post-test genetic counselling in these cases can be conducted without strict time constraints. Nonetheless, a recent survey conducted across the Canadian healthcare system revealed that only 67 % of patients informed their relatives about a positive *BRCA* test, highlighting the need for additional support in result dissemination [41].

Albeit our guidelines have been focused on *BRCA1/2* testing, they do not preclude the test for other hereditary syndromes genes, (i.e. *TP53, PTEN*, *STK11* and *CDH1*), that would impact management decisions such as CPM, or avoiding the use of radiation. At this aim, patients undergone predictive analysis without carrying *BRCA1/2* gPV, can receive testing for other predisposing genes, as part of the same multigene panel or at a later stage, accordingly to specific personal or family history.

The increasing use of multigene panel testing allows for the identification of additional high-and moderate-penetrance genes associated with hereditary breast cancer at the time of initial breast cancer diagnosis. It has been estimated that 8–15 % of patients testing negative for *BRCA*1/2 carry a pathogenic variant in other hereditary cancer genes [42,43]. This expanded genetic profiling not only accelerates the diagnosis of other hereditary syndromes but also facilitates cascade testing in affected families. Furthermore, specific genetic findings can have direct clinical implications, as in the case of *PALB2* gPV, where surgical management aligns with that used for *BRCA1/2* gPV carriers and is also expected to be incorporated into the access criteria for PARP-inhibitors [44]. However, the widespread adoption of multigene panel testing also increases the detection of VUS, which can pose significant challenges. Although, at the beginning of multigene panel adoption, patients could misinterpret uncertain results, developing inaccurate cancer risk perceptions, experiencing prolonged distress despite psychosocial support, or even pursuing prophylactic surgeries inconsistent with current guidelines [45–47], the increasing knowledge of VUS meaning and the improvement into the right choice of genes to include in a test, provided better information on correct cancer-related surgical and screening management. Indeed, more recent data show that VUS carriers received less CPM, prophylactic mastectomy and oophorectomy and less annual breast magnetic imaging resonance compared to gPV ones [48–50]. From a healthcare perspective, the increased detection of VUS also places a burden on genetic services, due to long-term variant reclassification, and recontact protocols. Effective VUS communication involves clarifying the actual probability of future pathogenic reclassification [51]. However, the timeline for VUS reclassification remains undefined, presenting an ongoing challenge for both clinical laboratories and healthcare services. A recent cohort study analyzing 94,453 variants across 3,272,035 individuals reported that 4.5 % of VUS in hereditary disease genes were reclassified over an 8-year period, emphasizing the extensive workload and the role of emerging machine learning-based computational methods in variant resolution [52].

Concerns remain regarding the utility of genetic testing in patients diagnosed with HR+/HER2− breast cancer without family history at ≥65 years, given the high negative predictive value (>99 %) and low positive rate (1.09 %) in this population [53,54].

Emerging technologies, including somatic *BRCA* testing and artificial intelligence (AI)-based digital pathology, could serve as pre-screening tools, requiring confirmation through direct sequencing in peripheral blood. Some studies suggest that AI can accurately predict homologous recombination deficiency, with Relative Operating Characteristic (ROC) curves of 0.86 and 0.81, particularly in HR+/HER2− Breast cancer subtypes [55,56].

Interestingly, the European Society of Medical Oncology (ESMO) Precision Medicine Working Group supports the use of tissue Next Generation Sequencing (NGS) as a substitute for germline *BRCA1/2* testing in patients with endocrine-resistant HR+/HER2− metastatic breast cancer, given the high accuracy of tissue sequencing. However, reflex germline testing is still recommended in cases where no tumor alterations are detected but the probability of harboring a germline *BRCA1/2* gPV remains high, considering that NGS may fail to detect approximately 7 % of germline *BRCA* gPV[4].

Despite these recommendations, regulatory barriers still limit the full adoption of this approach in Italy, where access to PARP inhibitors is restricted to patients with a *BRCA* gPV identified through germline testing, in accordance with the registration trials. Consequently, implementing NGS as a pre-screening tool for drug eligibility would require a more flexible interpretation of current regulatory criteria, a topic that warrants further discussion at the decision-making level in future policy frameworks.

To conclude, the integration of predictive *BRCA* testing into the onco-genetic framework represents an important step-forward, driven by the constantly evolving therapeutic landscape of breast cancer. This process has required epidemiological assessments, structural optimizations and cost-effectiveness evaluations to ensure feasibility within the healthcare system. Despite these advancements, several open questions remain. Notably, even with the incremental expansion of *BRCA* testing criteria, a small subset of patients may still be overlooked, potentially missing the opportunity to access effective treatments such as PARP inhibitors. Additionally, while these targeted agents have been transformative for HER2− BRCA-related breast cancer, several alternative treatment options are available in the same clinical settings (i.e., pembrolizumab/capecitabine for early TNBC or abemaciclib for HR+/HER2− early breast cancer), thus necessitating careful considerations at a single case level. Finally, as precision oncology continues to evolve, the integration of somatic testing, digital pathology, and artificial intelligence-driven models may further refine patient selection, optimizing treatment allocation and ensuring that innovative therapies reach those most likely to benefit.

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Declaration of competing interest

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Appendix A. Supplementary material

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