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Integrating BRCA testing into routine prostate cancer care: a multidisciplinary approach by SIUrO and other Italian Scientific Societies

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Abstract

Prostate cancer (PCa) ranks among the most prevalent malignancies in men, with notable associations to Hereditary Breast and Ovarian Cancer Syndrome (HBOC) and Lynch Syndrome, both linked to germline likely pathogenetic variant/pathogenetic variant (LPV/PV) in genes involved in DNA repair. Among these genes, *BRCA2* in PCa patients is the most frequently altered. Despite progresses, challenges in *BRCA* carriers detection persist, with a quarter of PCa cases lacking family history.

To address these challenges, a multidisciplinary expert panel from six Italian Scientific Societies, formulated a care pathway to integrate *BRCA* testing into routine clinical practice in different Italian geographical areas.

The development process, promoted by the Italian Society of Uro-Oncology (SIUrO), involved three key stages. A preliminary meeting convened teams from different Italian regions to establish minimal requirements for a mini-counseling program (defined as a pre-test consultation carried out by clinicians responsible of patients' management) and propose care pathway models. At the same time, a comprehensive survey was launched to highlight regional variations in *BRCA* testing and identify eventual obstacles to testing activities. A subsequent meeting synthesized care pathway proposals and formulated a unified framework, acknowledging regional legislative variations as enriching factors. Lastly, implementation of the unified framework was promoted by the project faculty and identified regional team leaders.

Survey results revealed significant regional disparities in *BRCA* testing, reimbursement policies, and access to genetic counseling. The proposed mini-counseling program outlined essential steps for patient identification, information provision, and multidisciplinary review, aiming to streamline *BRCA* testing processes.

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Expert recommendations emphasized offering tumor genetic testing to metastatic PCa patients eligible for PARP-i treatment and outlined criteria for genetic counseling and germline testing. Key considerations included family history and tumor characteristics.

In conclusion, the proposed care pathway represents a critical step towards integrating *BRCA* testing into routine PCa care, aiming to optimize patient management and familial risk assessment within the constraints of the Italian healthcare system.

Highlights

• *BRCA* likely pathogenetic/pathogenetic variants significantly increase the risk of developing prostate cancer (PCa) and enhance sensitivity to PARP-inhibitor treatment, underscoring the clinical need to incorporate genetic testing into the routine management of PCa patients.

• A comprehensive survey revealed significant regional disparities in *BRCA* testing availability, reimbursement policies, and access to genetic counseling across different geographical regions of Italy.

• A multidisciplinary panel from six Italian Scientific Societies, led by the Italian Society of Uro-Oncology (SIUrO), developed a care pathway to integrate *BRCA* testing into routine clinical practice within the Italian healthcare system.

Keywords BRCA, Prostate cancer, Mini-counseling, Genetic counseling, Care pathway

Introduction

Prostate cancer (PCa) is the second most common malignancy in man worldwide, with an estimated 1,414,000 new cancer cases and 375,304 deaths in 2020 [1]. Advancing age, black race, and family history are well known risk factors for prostate cancer [2, 3]. This neoplasm is also associated with Hereditary Breast and Ovarian Cancer Syndrome (HBOC) [4], linked to germline likely pathogenetic variants/pathogenetic variants (LPV/PVs) in Homologous Recombination Repair (HRR) genes, primarily *BRCA1* and *BRCA2*, and with Lynch Syndrome [5], caused by inherited LPV/PVs in Mismatch Repair (MMR) genes.

Approximately 12% of patients with metastatic PCa are carriers of germline LPV/PVs affecting genes involved in DNA repair [6]. Germline LPV/PVs are most commonly found in the *BRCA2* gene (5.3%), which increases PCa relative risk of 2.5–8.6-fold by the age of 65 years [7]. Referring to the tumor genetic testing, LPV/PVs in genes involved in DNA repair pathways have been identified in 19% of localized PCa and 23% of mCRPC (metastatic Castration-Resistant Prostate Cancer) [8, 9]. These alterations involved mainly *BRCA2* (13%) and *ATM* (7.3%) genes [9].

The Homologous Recombination Deficiency (HRD) condition appears to increase tumor sensitivity to platinum-based chemotherapy [10–12] and poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors (PARPi) [13]. In mCRPC patients, carriers of LPV/PV in genes involved in HRR, PARPi has demonstrated efficacy both as monotherapy, particularly in patients who progressed during ARSI (Androgen-Receptor Signaling Inhibitor) treatment [14–20], and in combination with ARSIs [21–24].

Recent studies have reported a prevalence of germline *BRCA* LPV/PVs in PCa higher than previously recognized and a lack of family history of cancer in a quarter of PCa patients identified as carriers [6, 25]. Therefore, increasing the number of genetic tests could be relevant for an optimal therapeutic management of PCa patients and for cancer prevention in at risk family members [26].

European Society for Medical Oncology (ESMO) guidelines suggest considering tumor testing for hereditary prostate cancer genes and mismatch repair (MMR) defects in all mCRPC patients [27]. Moreover, germline testing for *BRCA2* and other DNA repair genes is recommended in patients with a family history of cancer (mainly breast, ovarian, prostate, pancreatic and colorectal cancer) and should be considered in all patients with metastatic prostate cancer [27].

Certainly, implementing a universal testing strategy could identify more individuals with *BRCA* LPV/PVs. However, this approach would inevitably increase costs and evaluation time, rendering it financially unsustainable for the current healthcare system [28]. Therefore, it is essential to identify criteria that enable clinicians to preselect high-risk patients, optimizing the pathways for *BRCA* testing within the real-world constraints of the Italian public health system [28].

The aim of this document is to provide a care pathway which includes *BRCA* testing as an essential element of clinical practice for patients affected by PCa.

Methods

This document, promoted by SIUrO, has been written, discussed, and approved by a multidisciplinary expert panel of 42 professionals, belonging to five Italian Scientific Societies (SIUrO, SIGU, AIOM, SIPO, SIAPEC). The working group included medical oncologists, urologists, radiation oncologists, medical geneticists, and pathologists. The development of this document occurred in the three following steps:

- A preliminary meeting in Bologna on September 6^{th} –7^{th}, 2022. The working group was divided into six teams, two teams for each Italian geographical macro-area: North, Center, and South. The teams included at least one specialist from all disciplines. They were asked to define the minimal requirements for a mini-counseling program and to formulate three care pathway proposals dedicated to *BRCA* testing in patients affected by PCa in the North, Center and South part of Italy.
- In a subsequent meeting conducted in Bologna on March 3^{rd}, 2023, the team leaders from each macro-area (North, Center, and South) presented the three care pathway proposals. These proposals were examined and discussed by the panel of experts, focusing on issues of significant disagreement among the teams. By the conclusion of the meeting, the panel formulates a cohesive document framework recognizing the geographic disparities in *BRCA* testing and what eventually needed for an upgrade in different areas. It is important to note that in Italy, regions have the authority to legislate on health matters, resulting in variations that have been recognized as a source of realistic enrichment for the project, both in the development of the care pathway and in the drafting of the document.
- The unified document skeleton has been subsequently implemented by the team leaders of each macro-area and the faculty of the project, which included 2 urologists, 3 medical oncologists, 1 radiation oncologist, 1 medical geneticist and 1 methodologist.

In addition, a survey consisting of 23 questions was proposed to Italian specialists before the first meeting in September 2022 to collect baseline information about local organization for *BRCA* testing in PCa patients (see Additional File 1). Answers were collected anonymously. Provider data were collected using an electronic survey platform (Survio.com) and imported into the IBM Statistical Package for Social Science (SPSS) for descriptive analysis. Results can be accessed at link: https://www.survio.com/p/qL53YFL9.

The document was written in agreement with Italian Societies National Guidelines [29] and Clinical Recommendations [30], reviewed and approved by the Expert Panel prior to publication.

Results of the first meeting (6th-7th September 2022, Bologna)

Survey results

The survey results revealed significant regional disparities in *BRCA* testing, reimbursement policies, and access to genetic counseling. Specifically, 38% of participants reported that germline testing is not reimbursed in their region, while 36.6% reported a lack of reimbursement for tumor genetic testing. Regarding obstacles to *BRCA* testing, the most reported issues were difficulties in correctly identifying patients, a lack of established pathways for test requests and reporting, and challenges in accessing genetic counseling. Details of the survey results are provided in the Additional File 2.

Minimal requirements for a "Mini-Counseling" program in prostate cancer

It is known that pre-test Genetic Counseling (GC) is the standard of care for individuals at risk for hereditary cancer and assists patients in making informed decisions about testing and eventual cancer risk reduction strategies [31]. Recent research revealed that in U.S. the demand for geneticist has seen a steady increase over the past two decades. In 2005, geneticists saw an average of six new patients per week and performed four follow-up visits. By 2015 the number of new patients per week had increased to an average of 10.2 new patients per week and 7.8 follow-up visits per week, resulting in waiting times that are unacceptable to the public [32]. Particularly, 62% of geneticists reported that their current wait time for a nonemergency new patient appointment was longer than one month [32]. These new challenges also highlight the need for viable alternative counseling models, including telephone counseling, pre-counseling education sessions, and group genetic counseling (GGC) [33].

"Mini-Counseling" is defined as a pre-test consultation carried out by health care providers responsible for an individual's care (medical oncologists, surgeons, and radiation oncologists). The "mini" counseling model should be used when the aim of *BRCA* testing is "mainly" therapeutic, with the purpose to speed up patients' access to targeted therapies (PARPi). According to this, a plan in which *BRCA* tests could be requested directly by the caring clinicians should be implemented, also to avoid an excess of genetic consultations in absence of familial risk factors with a consequent useless saturation.

During the preliminary meeting, held in Bologna on 6–7 September 2022, the six teams representing the

Italian geographical Macro-Area, considered Mini-Counselling as the first step of the pathway. To perform "Mini-Counseling" the following needs were defined:

- a multidisciplinary team which includes a geneticist (not necessarily present during all the meetings but eventually available on consultancy), responsible for selecting patients eligible for testing;
- at least one accredited reference laboratory for each multidisciplinary team, with a predefined and simplified sample submission path;
- a continuous and adequate medical education program to perform preliminary counselling for *BRCA* testing, through initial training courses and subsequent annual updates. Identified Hub centers of Medical Genetics for each Macro-area will be responsible for organizing the training courses.

According to experts panel, Mini-Counseling requires four basic steps:

1. Healthcare providers (medical oncologists, urologists, and radiation oncologists) identify patients with PCa eligible for testing. Patients will be asked to complete a proposed standardized questionnaire (Annex 1, see Additional File 3) to gather information about family health history and non-familial risk factors.
2. If the patient is eligible for tumor genetic testing, the attending clinician collects specific written informed consent, providing detailed information about the clinical and therapeutic implications of potential test outcomes negative, positive, or non-informative, as well as the genetic implications of identifying a somatic *BRCA* LPV/PV.
3. If somatic *BRCA* LPV/PVs are identified germline testing must be offered by the caring clinicians or the medical geneticists (if required). They should provide information on (i) genetic aspects and clinical impact of the test result; (ii) risks and benefits of risk-reducing strategies. In particular, the patients should be informed that the testing may identify a genetic variant associated with an elevated risk of developing certain cancers for themselves and their relatives who also carry the variant. The timing and modalities to obtain consent for genetic test must be respectful of patient's will, with a complete discussion about decisional aspects, as the choice to communicate or not the test results to at risk family members. It is crucial to use an appropriate communication protocol with eventual psychological support and the collection of written consent or dissent for testing.
4. If germline *BRCA* LPV/PVs are detected, or familial risk criteria are met, patients will be referred for genetic counseling.

Care pathway proposals

At the end of the preliminary meeting, the six teams formulated three care pathway proposals, one for each Italian geographical Macro-Area (North, Center, and South). The primary issues of proposals were: (i) selection of patient populations eligible for the care pathway; (ii) protocols for *BRCA* testing; (iii) sequencing methods and reporting (iv) criteria for genetic counselling. Proposals from experts are summarized in Table 1.

Selection of patient populations

The expert panel outlined a care pathway targeting two populations: (1) patients affected by metastatic PCa; (2) patients affected by non-metastatic PCa with familial risk (Fig. 1).

For the first population, the primary purpose is predictive, to identify potential candidates for PARPi treatment. The teams consider patients eligible for *BRCA* testing and consequently for PARPi treatment, if they exhibit a preserved Eastern Cooperative Oncology Group (ECOG) performance status and have an adequate life expectancy to undergo other available treatments. In Italy, PARPi are currently reimbursed as monotherapy for the treatment of patients affected by mCRPC, carriers of *BRCA* LPV/PVs in germline and/or somatic line, who have progressed after previous treatment including at least a new hormonal agent. The approval of new hormonal agent in metastatic Castration Sensitive Prostate Cancer (mCSPC) highlights the need to anticipate *BRCA* testing, which may present economic and organizational challenges.

In patients with localized prostate cancer, germline *BRCA* status could influence treatment strategies, particularly in low-risk populations. Recent studies indicate that men with inherited BRCA LPV/PVs, undergoing active surveillance, are at higher risk of grade reclassification [34] and present short-term oncologic outcomes [35]. These findings could guide decision-making between active surveillance and curative treatment.

In both populations, testing aims to identify patients who carry germline BRCA LPV/PVs classified as class IV and V, according to the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) criteria [36], to select individuals at increased cancer risk for surveillance. In Italy tumor genetic testing is not reimbursable for patients with locoregional PCa. Therefore, patients with a personal history of non-metastatic PCa, who meet the AIOM-SIGU criteria, will be referred

Table 1 Care pathway proposals

Care Pathway Eligibility		NORTH	CENTER	SOUTH
		Patients affected by metastatic PCa **Patients affected by metastatic or localized PCa with family history at risk**		
Somatic test	Population	Patients affected by metastatic PCa		
	Preferred sample	Prostate (archival material)	Metastasis (archival or re-biopsy)	Prostate (archival material)
	Sequencing method (Gene Panel)	Next Generation Sequencing (Panel: *BRCA 1/2*)		
	Timing	mCRPC mCSPC	mCRPC mCSPC HV or HR (Charteed/ Latitude)	mCRPC mCSPC (who received ARSIs as first line therapy)
Germline test	Population	Patients affected by metastatic PCa found positive for BRCA LPV/PV at somatic testing Patients affected by metastatic or localized PCa with family history at risk		
	Sequencing method (Gene Panel)	Next Generation Sequencing (panel selected by geneticist according to familial risk)		
Criteria for Genetic Counseling		AIOM criteria[a]	-AIOM criteria[a] -PCa (GG > 1) < 55 ys -PCa and familial risk (HBOC, Lynch) -Personal history of multiple tumors	-AIOM criteria[a] -Familial risk: BC < 50 ys, MBC, OC, PaC, CC, EC. -Intraductal or Cribriform histology

Legend: [a]AIOM criteria: (a) Patients with a personal history of metastatic prostate cancer; (b) Patients with a personal history of non-metastatic prostate cancer and a family history involving: i) at least one first-degree relative with non-Grade Group 1 prostate cancer diagnosed at age < 60. Ii) At least 2 family members with non-Grade Group 1 prostate cancer diagnosed at age < 50 (c) History of a pathogenic variant in a predisposing gene in a family member

Abbreviations: *AIOM* Italian Association of Medical Oncology, *PCa* prostate cancer, *LPV/PV* likely pathogenetic variant/pathogenetic variant, *mCRPC* metastatic castration resistant prostate cancer, *mCSPC* metastatic castration sensitive prostate cancer, *HV* high volume, *HR* high risk, *ARSIs* androgen receptor signaling inhibitors, *BC* breast cancer, *MBC* male breast cancer, *OC* ovarian cancer, *PaC* pancreatic cancer, *CC* colonrectal cancer, *EC* endometrial cancer

for genetic counseling and BRCA germline testing [30, 37] (Table 2).

Pathways for BRCA testing

Patients affected by metastatic PCa

For *predictive* purposes, the three proposals asserted that tumor genetic testing test should be prioritized over a germline test, given the higher likelihood of detecting *BRCA* LPV/PVs, approximately 13% and 5.3%, respectively [6, 8].

A wide spectrum of different sample sources may be available for tumor testing including biopsies, surgical material (fresh or frozen tissue, paraffin embedded tissue, formalin-fixed), circulating tumor DNA (ctDNA) [38]. The expert panel considered the tumor tissue as the gold standard, offering a broader range of genomic material (including DNA, RNA, and protein analysis), and enabling the direct assessment of sample quality for Next-Generation Sequencing (NGS).

BRCA LPV/PVs have been found to arise early in tumors from patients who eventually develop metastatic disease [39]. Consequently, archival tissue from prostatectomy or prostate biopsy should be considered for NGS analysis. Re-biopsy of metastatic sites remains a subject of debate, particularly in cases where DNA quality of archival tissue from the primary tumor is inadequate for NGS analysis. Challenges frequently reported by experts include the risks associated with the procedure and the sites, mainly bones, of PCa metastasis [40]. Detailed data of NGS-molecular analysis from PROfound study, reported a failure rate of NGS analysis close to 42%, which progressively increases 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. Moreover, DNA extracted from lymph nodes metastases had the highest rates of NGS read-out obtained (74.7%), while bone samples had the lowest rate (42.6%) except for trephine bone biopsies (87%) [40].

The isolation and analysis of ctDNA from patients with PCa has recently emerged as promising method to understand the molecular and genomic mechanisms driving the disease. While liquid biopsies yield less tumor material compared to soft tissue or bone biopsies, they offer several significant advantages. These include being noninvasive, associated with lower morbidity, quicker to perform, and providing a practical means for serial monitoring of tumor dynamics over time. Nowadays, liquid biopsy for ctDNA represents a valid alternative to metastatic site re-biopsy, boasting a concordance rate close to 90% [38]. However, only a few laboratories in Italy are currently validated to perform this procedure.

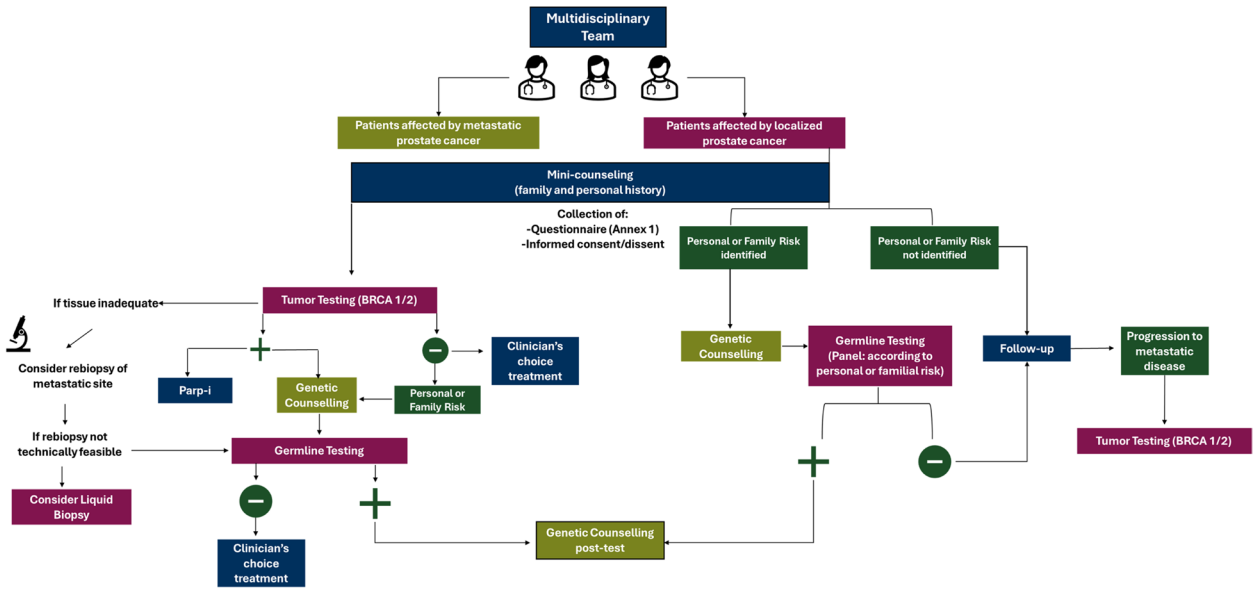

Fig. 1 Flowchart of care pathway Patients affected by metastatic Prostate Cancer: The multidisciplinary team selects patients affected by metastatic prostate cancer eligible for PARP inhibitor treatment. Caring clinicians conduct pre-test mini counseling, gathering personal and family history through a proposed questionnaire (Annex 1) and obtaining written informed consent or dissent. Regardless of familial risk clinicians will proceed with a BRCA tumor testing. If archival tissue is inadequate for analysis, clinicians should consider re-biopsy of the metastatic site. Alternatively, liquid biopsy or germline testing should be considered. If BRCA (likely) pathogenetic variants are detected at the somatic level (+), patients will have access to PARP inhibitor treatment and genetic counseling for germline testing. In the case of positive (+) germline testing, patients and family members will be referred to a geneticist for testing and eventual surveillance. Patients affected by localized Prostate Cancer: The multidisciplinary team selects patients affected by localized Prostate Cancer who meet criteria for personal or familial risk. Caring clinicians conduct pre-test mini counseling, gathering personal and family history through a proposed questionnaire (Annex 1), and require genetic counselling. The geneticist will decide whether to perform germline testing and which panel to use based on the familial risk. In case of a positive germline test, patients and family members will be referred to a geneticist for testing and surveillance

It's well established that tumor testing cannot distinguish between tumor or constitutional variants. Therefore, if a BRCA LPV/PV in tumor tissue, germline testing must be proposed to confirm or exclude a constitutional variant. Conversely, patients with metastatic PCa whose tumor testing show no *BRCA* LPV/PVs require referral to a geneticist only in the case of familial risk or personal multiple cancers history. In such instances, genetic counseling aimed at further molecular analyses should be considered.

Patients affected by non-metastatic PCa with familial cancer risk

Tumor genetic testing is currently not reimbursed for patients with localized PCa in Italy. Therefore, patients identified by attending clinicians as having a high risk of carrying germline BRCA LPV/PVs, based on personal or family cancer history, should be referred to a geneticist, who will assess the indication for germline *BRCA* testing. Various samples are suitable for germline testing, such as blood, saliva, buffy coat, or buccal mucosa.

If *BRCA* germline test produces negative results (no LPV/PVs detected), the geneticist will consider expanding the molecular analysis to include other genes, taking into consideration the patient's risk profile and familial history. Further recommendations are needed for multigene panel genotyping in PCa patients, especially in *BRCA*-negative familial/hereditary conditions.

Additionally, tumor testing should be proposed to patients with a negative *BRCA* germline test result who develop metastases, to assess eligibility for potential PARP-I therapy.

A flowchart of the two pathways is reported in Fig. 1.

Sequencing methods and reporting

Both somatic and germline *BRCA* testing are generally performed using NGS analysis. This method is strongly recommended as the preferred sequencing approach for *BRCA* tumor testing due to the ample availability of DNA from tumor samples, and the substantial size of *BRCA* coding regions [41].

NGS platforms employ massively parallel sequencing, where millions of DNA fragments from a single sample are sequenced simultaneously. This technology enables high-throughput sequencing, enabling the sequencing of an entire genome in less than a day.

Table 2 Eligibility criteria for the oncological genetic counseling [30, 37]

Personal history of:
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
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 for:
At least one first-degree relative with non-Grade Group 1[c] prostate cancer aged < 60 years
At least two family members with non-Grade Group 1[c] prostate cancer aged < 50 years
Family history of pancreatic cancer:
At least two first-degree relatives 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] Do not consider this statement if both parents are/have been affected

[e] on the same bloodline and with at least one first-degree relative

The process comprises several key sequencing steps: DNA fragmentation, library preparation, massively parallel sequencing, bioinformatics analysis, and variant annotation and interpretation. FFPE human tissues are the predominant source of genetic and epigenetic data in oncology for diagnostic and translational research purposes using NGS analysis [42].

The interpretation of variants follows the classification criteria proposed by the ENIGMA Consortium, which categorizes *BRCA* and other gene variants into five classes: (I) benign, (II) likely benign, (III) variant of uncertain significance (VUS), (IV) likely pathogenic, and (V) pathogenic. A VUS denotes a nucleotide sequence alteration whose clinical significance remains unclear, necessitating periodic revision of VUS status by geneticist to guide patient management and follow-up [36].

Laboratory professionals should follow the specific protocols associated with each NGS platform and *BRCA* testing kit. The chosen kit should be an in vitro diagnostic (IVD) medical device comply with the European In-Vitro Diagnostic Medical Devices Regulation (IVDR 2017/746/EU) [43]. Research-use-only (RUO) kits are not considered to be effective IVDs products (21CFR809.10(c)) and are intended for research and development purposes, and not for medical/clinical diagnostic use. RUOs might be purchased by a laboratory and used as components to be further assembled, modified, developed or validated into a Laboratory Developed Test (LDT) subjected to regulatory measures and must be internally validated, before it can be claimed/used for clinical diagnostic purpose [44].

The NGS platform and the *BRCA* testing kit used to perform the molecular test should be reported along with the accreditation program (such as ISO15189 or equivalent) and have external quality control certifications by participation in certified external quality assessment (EQA) programs specific for tumor *BRCA* testing from

FFPE (i.e., EMQN, QuIP or UKNEQAS) to ensure accurate and reproducible molecular profiling [44].

Criteria for genetic counselling

Several hereditary, autosomal dominant syndromes have been associated with a predisposition to PCa, such as HBOC syndrome linked to *BRCA* genes, Hereditary Prostate Cancer (HPC) linked to *HOXB13* gene and Lynch Syndrome associated with MMR genes [45, 46].

Regarding BRCA genes, the present guidelines consider a proband eligible for genetic screening when the pretest probability of identifying a *BRCA* deleterious LPV/PVs is ≥10% [36]. The approximate 10% threshold for probability of carrying BRCA LPV/PV is utilized because of availability of prior probability models, validated only for BRCA 1 and BRCA 2 genes.

Family history is essential in assessing the risk of inherited cancers and should encompass critical information, including the degree of relation, types of cancer, and age at diagnosis. However, among lethal prostate cancer cases, 60% of patients carrying *BRCA* and *ATM* variants have a lack of known familial history [47].

ESMO guidelines recommend germline test in all patients affected by mCRPC and in patients with a family history of cancers [27]. National Comprehensive Cancer Network (NCCN) guidelines enlarged germline test indications as follows: PCa (high-risk, very-high-risk, regional or metastatic) or a history of breast cancer; family history of other cancers, including Lynch syndrome-related cancers; family history of risk LPV/PVs; Ashkenazi Jewish ancestry. Moreover, NCCN guidelines suggest considering germline test in patients with PCa and specific tumor characteristics (intermediate-risk prostate cancer with intraductal histology) or a personal history of other qualifying cancers [48].

As reported earlier, AIOM clinical recommendations suggest genetic counselling in patients affected by mCRPC and in patients with a family history of PCa [30] (Table 2). Building upon the preceding information, the teams explored the feasibility of extending familial criteria to include other type of tumors associated with HBOC syndrome (male breast cancer, ovarian cancer, female breast cancer, pancreatic cancer) [46, 47]. The teams' proposals are summarized in Table 1.

Results of the second meeting (3rd March 2023, Bologna)

Summary of expert opinion: predictive pathway

- Tumor genetic testing should be offered to all patients affected by mCRPC, eligible for PARPi treatment, with an NGS panel including *BRCA* genes. The experts concur in defining eligible patients who meet the following criteria: (i) ECOG performance status 0-1; (ii) adequate life expectancy; (iii) favorable Geriatric evaluation, if requested, assessed by G8 scale (score ≥ 14).
- All patients affected by mCRCP, eligible for PARPis treatment, who progressed on a novel hormonal agent, are candidates for *BRCA* testing. Patients treated with a novel hormonal agent in mCSPC setting, should undergo *BRCA*test before or at the time of progressive disease, to facilitate an eventual subsequent therapy with PARPi.
- Regarding the type of test, priority is given to tumor genetic testing due to a higher chance to detect *BRCA* LPV/PVs compared to germline analysis [6, 8]. In case of *BRCA* LPV/PV detection on tumor testing, germline analysis should be performed.
- For tumor genetic testing, the expert panel suggests the following guidelines:

  (i) The preferred sample for analysis should be the archival material of prostate tissue (prostatectomy or prostate biopsy sample) or metastasis, with a time of tissue storage preferably not older than 5 years [28].
  (ii) The pathologist assesses the sample adequacy in terms of neoplastic cellularity and selects the most representative areas of tumor (higher grade) for testing.
  (iii) If archival material is unsuitable for analysis, clinicians should consider obtaining a biopsy from a metastatic site.
  (iv) If metastatic site is not available or inadequate for biopsy, AIOM Recommendations suggest liquid biopsy [30].
  (v) In cases where the tumor genetic testing (tissue or blood) is non informative for patients affected by metastatic PCa, germline testing should be considered, regardless of familial risk.
  (vi) If a germline *BRCA* test conducted previously for familial risk yields a negative result, tumor genetic testing must be considered if the purpose of testing is therapeutic.
  (vii) If a patient affected by metastatic PCa with personal or familial risk receives a negative *BRCA* testing result, genetic counseling for further molecular analyses should be provided.

Summary of expert opinion: preventive pathway

For preventive purposes, genetic counselling and *BRCA* 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 non-Grade Group 1.
- A diagnosis of non-Grade Group 1 prostate cancer, and a family history of ≥2 first degree relatives with breast, male breast, ovarian, or pancreatic cancer.
- A *BRCA* LPV/PV identified at tumor testing, regardless of familial risk.
- Personal history of multiple tumors. In this case the geneticist will evaluate additional molecular analyses beyond *BRCA*.

To identify more *BRCA* carriers, genetic testing should be evaluated in the case of:

- A diagnosis of grade group 4 or 5 prostate cancer, and ductal histotype, and/or the presence of intraductal and/or cribriform patterns.
- A personal history of early-onset prostate cancer (≤55 years).

Moreover, in case of a family history of ≥2 relatives with endometrial or colorectal cancer, Microsatellite Instability (MSI) testing should be performed to exclude Lynch Syndrome.

The detection of a germline *BRCA* LPV/PV in a patient with PCa enables access to the preventive pathway, genetic counseling for family members to identify high-risk carriers, dedicated screening programs for early diagnosis of *BRCA*-related hereditary tumors, and risk-reduction strategies. The identification of a VUS necessitates periodic review of its status by a geneticist to guide patient management and follow-up.

Conclusions

The recent approval of PARP inhibitors for patients affected by mCRPC, along with the evidence of a steady increase in individuals carrying germline LPV/PVs in *BRCA* genes, emphasizes the importance of establishing dedicated but realistic pathways for conducting both *BRCA* tumor testing and germline testing in high-risk patients. With this work, we aimed to establish the minimal requirements for pre-test mini-counseling sessions and delineate the role of the multidisciplinary team in developing specific testing paths.

Our study has several limitations. First, the care pathway was designed specifically for the Italian healthcare system, which may limit its generalizability to other countries with different policies, resources, or genetic testing structures. Second, while *BRCA* LPV/PVs, particularly *BRCA*2, are a key focus, other HRR gene variants linked to prostate cancer may be underrepresented, potentially limiting comprehensive genetic risk identification. Lastly, the study relies on self-reported survey data to assess regional differences in *BRCA* testing, which may not fully capture all factors affecting access to testing and counseling.

In conclusion, our proposal of a flexible nationwide pathway aims to achieve both therapeutic and preventive objectives, integrating the *BRCA* testing into the multidisciplinary clinical practice of PCa patients, to facilitate clinical and surgical decision-making in a look of improved quality of care, also considering existing geographical differences: a limit that may become a model.

Abbreviations

AIOM	Associazione Italiana di Oncologia Medica
ARSI	Androgen-Receptor Signaling Inhibitor
BRCA 1	tumor suppressor gene on Chromosome 17
BRCA 2	tumor suppressor gene on Chromosome 13
CTC	Circulating Tumor Cells
ct-DNA	Circulating Tumor DNA
ECOG	Eastern Cooperative Oncology Group
ENIGMA	Evidence-based Network for the Interpretation of Germline Mutant Alleles
EQA	External Quality Assessment
ESMO	European Society of Medical Oncology
FFPE	Formalin-Fixation Paraffin-Embedded
GC	Genetic Counseling
GGC	Group Genetic Counseling
HBOC	Hereditary Breast and Ovarian Cancer Syndrome
HPC	Hereditary Prostate Cancer
HRD	Homologous Recombination Deficiency
HRR	Homologous Recombination Repair
IVD	In-Vitro Diagnostic
IVDR	In-Vitro Diagnostic Medical Devices Regulation
LDT	Laboratory Developed Test
LPV/PV	Likely Pathogenetic Variant/Pathogenetic Variant
m-CRPC	Metastatic Castration-Resistant Prostate Cancer
m-CSPC	Metastatic Castration Sensitive Prostate Cancer
MMR	Mismatch Repair
MSI	Microsatellite Instability
NCCN	National Comprehensive Cancer Network
NGS	Next-Generation Sequencing
PARPi	Poly (adenosine diphosphate [ADP]–ribose) polymerase inhibitors
PCa	Prostate Cancer
RUO	Research-use-only
SIAPEC	Società Italiana Anatomia-Patologica e Citologia Diagnostica
SIGU	Società Italiana di Genetica Umana
SIPO	Società Italiana di Psico-Oncologia
SIUrO	Italian Society of Uro-Oncology
SPSS	Statistical Package for Social Science
VUS	Variant of Uncertain Significance

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions
Conception and overall idea of the study: Se.B. Manuscript Writing: G.M., A.C., and P.P. Data Collection: Si.B., N.B., A.C., G.N.C., L.C., R.M.D., G.F., L.I., A.L., L.M., D.T., G.S. Data Analysis: G.P, R.C. All authors reviewed the manuscript. All authors have approved the submitted version.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Survey results can be accessed at link: https://www.survio.com/p/qL53YFL9.
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Declarations

Ethics approval and consent to participate
Not applicable. This manuscript does not report on or involve the use of any animal or human data or tissue.

Consent for publication
Not applicable. This research does not involve human participants.

Competing interests
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