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2023 Canadian Urological Association guideline: Genetic testing in prostate cancer

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Appendix available at *cuaj.ca*

INTRODUCTION

Genetic testing in prostate cancer (PCa) is becoming standard of care, as it can provide key information for clinical management, as well as offering crucial insights into familial cancer risk. Knowledge of genetic alterations present in prostate tumors offers prognostic insight and can aid with therapeutic decision-making.[1] In addition, PCa can be hereditary, and patients with PCa may carry germline (inherited) gene alterations that affect their risk of additional cancers.[2] Identification of germline gene alterations in PCa patients provides an opportunity for cascade testing in family members, opening up avenues for cancer prevention and early diagnosis in family members who may also carry the same germline gene alterations.[3]

Genes within the homologous recombination repair/DNA damage response (HRR/DDR) pathway are frequently altered in PCa, and these alterations are involved in disease development and progression. Deleterious alterations in HRR genes, such as *ATM*, *BRCA1*, and *BRCA2*, predict response to poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors.[4] These alterations may be somatic in origin, meaning that they are acquired by tumor cells during tumorigenesis and progression, or they may be germline. Germline or somatic alterations in mismatch repair (MMR) pathway genes, such as *MLH1, MSH2, MSH6*, and *PMS2*, also play roles in the development of PCa, and pathogenic alterations in these genes may predict response to immune checkpoint inhibitor therapy.[5-7] Germline alterations in HRR or MMR genes affect an individual's risk of developing cancer, hence the importance of identifying germline alterations that may also be carried by other family members.[8,9] Both germline and somatic alterations are potentially actionable in terms of treatment with PARP inhibitors or immunotherapy.

Different specimens are used to evaluate germline and somatic alterations in PCa. Patient samples for germline testing are typically obtained from peripheral blood, but saliva is an alternative sample type. Somatic testing, which is also known as tumor testing (genomic profiling of the tumor), is commonly performed using formalin-fixed paraffin-embedded tumor tissue obtained from primary prostate tumor biopsies or metastases, or from radical prostatectomy specimens. Fresh frozen specimens may also be used. It is important to note that tumor testing identifies both somatic and germline alterations and cannot distinguish between the two. Tumor testing can also be done via liquid biopsy, in which tumor DNA is obtained from a peripheral blood specimen. This is achieved by isolating cell-free DNA (cfDNA) shed from cells undergoing apoptosis. A portion of the cfDNA is tumor-derived and is termed circulating tumor DNA (ctDNA). Genomic profiling of the tumor can be performed using ctDNA.[10,11] Next-generation sequencing is the standard method for both germline and tumor testing in PCa This approach allows the simultaneous assessment of multiple genes and the evaluation of different types of variants, including single nucleotide variants, small insertions and deletions, and copy number variants.

Guidelines on genetic testing in PCa in Canada are needed to ensure that PCa patients consistently receive appropriate and timely genetic testing, that healthcare

SUMMARY OF RECOMMENDATIONS

1. Germline testing should be performed in prostate cancer patients with metastatic disease *(Strong, level of evidence [LE] 2)*.

2. In the context of localized prostate cancer, germline testing should be performed in the following patients:
   a. those with a positive family history of prostate or related cancers (most commonly breast, ovarian, colorectal, and endometrial cancers; occasionally pancreatic, upper tract urothelial, stomach, small bowel, and brain cancers; rarely melanoma) *(Strong, LE 2)*;
   b. those with a personal history of related cancers (most commonly colorectal cancer; occasionally pancreatic, upper tract urothelial, stomach, small bowel, brain, and male breast cancers; rarely melanoma) *(Strong, LE 2)*;
   c. those with Ashkenazi Jewish ancestry *(Strong, LE 2)*;
   d. those with high risk or very high-risk disease (Gleason score 8 or higher, clinical stage T3a or T3b or higher, or prostate-specific antigen [PSA] higher than 20 ng/ml) *(Moderate, LE 2)*;
   e. those with ductal, intraductal, or cribriform histology *(Moderate, LE 2)*.

3. Germline testing should be performed in patients with actionable or potentially actionable variants identified with tumor testing to determine whether the variant is germline in origin, to inform future cancer risk, and to initiate cascade testing in family members *(Strong, LE 1)*.

4. Germline testing may be performed at any time after a patient is diagnosed with prostate cancer but is ideally performed as soon as the patient is determined to be a candidate for testing *(Good practice point)*.

5. Genomic profiling of the tumor should be performed in patients with metastatic castration-resistant prostate cancer (mCRPC) to inform the selection of therapy *(Strong, LE 1)*.

6. Genomic profiling of the tumor should be performed in patients with metastatic castration-sensitive prostate cancer (mCSPC) and patients with non-metastatic castration-resistant prostate cancer prior (nmCRPC) to progressing to mCRPC *(Good practice point)*.

7. The minimum set of genes for germline testing in patients with prostate cancer who meet criteria for germline testing should include *ATM, BRCA1, BRCA2, CHEK2, EPCAM* (large deletions), *HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2, TP53*, and *RAD51D*. Additional genes may be important depending on the clinical context considering the patient's personal and family history *(Strong, LE1)*.

8. The minimum set of genes for genomic profiling of the tumor in patients with prostate cancer who meet criteria for tumor testing should include *BRCA1, BRCA2*, and *ATM*; however, tumor testing panels should be aligned with germline testing panels as much as possible and ideally would also include *CHEK2, EPCAM* (large deletions), *HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2, TP53*, and *RAD51D*. *CDK12* may also be included for prognostic purposes. Additional genes may be included for research purposes, prognostic purposes, or inclusion of patients in clinical trials *(Strong, LE1)*.

9. All patients with de novo metastatic prostate cancer should have a biopsy performed so that tissue is available for next-generation sequencing, to determine candidacy for PARP inhibitors in the future. The biopsy should be performed as early as possible relative to the start of therapy, without compromising the care of the patient *(Strong, LE1)*.

10. A tiered approach is recommended for the choice of specimen for genomic profiling of the tumor:
    a. The first choice of specimen is an archival primary or archival metastatic tumor biopsy *(Good practice point)*.
    b. If archival tissue is not available or testing fails, alternate choices are a contemporary metastatic tumor biopsy or "liquid biopsy" for testing of plasma-derived ctDNA. There are advantages and disadvantages to both options *(Good practice point)*.

resources are used efficiently, and that patient outcomes are optimized. The objective of this guideline is to provide evidence-based recommendations for clinicians treating PCa patients in Canada regarding germline and tumor genetic testing to aid in optimal management and decision-making.

METHODS

Four guideline questions were identified by the authors:

1. At what stage of disease and in which patient populations should germline genetic testing be performed in patients with PCa?
2. At what stage of disease and in which patient populations should genomic profiling of the tumor (tumor testing) be performed in patients with PCa?
3. What genes should be assessed in germline testing and tumor testing in patients with PCa?
4. What is the optimal specimen for genomic profiling of the tumor?

A search of the Medline database was performed to identify articles published in 2019 or later that addressed the guideline questions, with the rationale of finding articles that may not have been included in previous guidelines. The following keyword search strategy was used: "prostate cancer" and "hormone sensitive" or "castration-naive" or "castration-sensitive" or "metastatic" or "high-risk" or "locally advanced" or "poorly differentiated" or "neuroendocrine" and "germline mutation" or "germline test" or "somatic mutation" or "somatic test" or "tumor test" or "DNA repair" or "homologous recombination repair" or "*BRCA*" or "whole exome sequencing" or "next-generation sequencing" or "gene panel."

There were 605 articles imported from the database search for screening. Predefined inclusion and exclusion criteria were used to screen studies. The types of evidence included were randomized controlled trials, systematic reviews, cohort studies, case control studies, cross-sectional studies, and longitudinal studies, whereas pilot studies, case studies, case series, guidelines, reviews, editorials, letters, and other non-research sources were excluded. After screening titles and abstracts, then full-texts, 142 articles fitting the inclusion criteria were selected for data extraction. Reference lists of evidence-based guidelines that included information about genetic testing in PCa were reviewed to identify additional relevant literature prior to 2019 and provided an additional 43 sources for data extraction.

Data was extracted from 185 peer-reviewed articles, and recommendations were drafted based on the evidence. An expert multidisciplinary panel composed of uro-oncologists, medical oncologists, a radiation oncologist, a pathologist, a medical geneticist, a clinical molecular geneticist, and a PCa genomics expert was used to develop the recommendations. Three virtual meetings were convened with the expert panel to review the evidence and to discuss and refine the draft recommendations. The panel then voted via SurveyMonkey to indicate whether they agreed or disagreed with each recommendation. Recommendations were accepted if 75% of the expert panel voted in favor of the recommendation.

Recommendations were assigned a level of evidence (LE) based on the overall body of literature using criteria from the Oxford Center for Evidence-Based Medicine,[12] and then assigned a grading of strong, moderate, or weak, depending on the level of evidence supporting the recommendation. A grade of "strong" was assigned if the recommendation was supported by consistent, high-quality evidence such that further research is unlikely to change the confidence in the strength of the recommendation. A grade of "moderate" was assigned if the recommendation was supported by some evidence, but further research is likely to change the confidence in the strength of the recommendation. A grade of "weak" was assigned if the recommendation was supported by low-quality evidence and there is uncertainty regarding the recommendation. "Good practice points" are recommendations that the expert panel deemed helpful to the clinician and have biological plausibility, but there is no direct evidence to support the recommendation.

RECOMMENDATIONS

Recommendations for question 1: At what stage of disease and in which patient populations should germline genetic testing be performed in patients with PCa?

■ RECOMMENDATION 1

Germline testing should be performed in PCa patients with metastatic disease *(Strong, LE 2).*

■ RECOMMENDATION 2

In the context of localized PCa, germline testing should be performed in the following patients:

a. **those with a positive family history of prostate or related cancers (most commonly breast, ovarian, colorectal, and endometrial cancers;**

occasionally pancreatic, upper tract urothelial, stomach, small bowel, and brain cancers; rarely melanoma) *(Strong, LE 2)*;

b. those with a personal history of related cancers (most commonly colorectal cancer; occasionally pancreatic, upper tract urothelial, stomach, small bowel, brain, and male breast cancers; rarely melanoma) *(Strong, LE 2)*;
c. those with Ashkenazi Jewish ancestry *(Strong, LE 2)*;
d. those with high-risk or very high-risk disease (Gleason score 8 or higher, clinical stage T3a or T3b or higher, or prostate-specific antigen [PSA] higher than 20 ng/ml) *(Moderate, LE 2)*;
e. those with ductal, intraductal, or cribriform histology *(Moderate, LE 2)*.

■ RECOMMENDATION 3

Germline testing should be performed in patients with actionable or potentially actionable variants identified with tumor testing to determine whether the variant is germline in origin, to inform future cancer risk, and to initiate cascade testing in family members *(Strong, LE 1)*.

■ RECOMMENDATION 4

Germline testing may be performed at any time after a patient is diagnosed with PCa but is ideally performed as soon as the patient is determined to be a candidate for testing *(Good practice point)*.

Purposes of germline testing

Germline testing is now the standard of care for patients with metastatic, and/or high-risk PCa, as it can provide information that has implications for the patients themselves, as well as for their family members. Disease-associated genetic alterations that occur in the germline are also known as pathogenic or likely pathogenic (P/LP) variants. Germline genetic alterations that have been observed in PCa patients may be associated with Lynch syndrome, or hereditary breast and ovarian cancer syndrome, depending on the specific mutation.[8,9] Hereditary cancers associated with genes that may be altered in PCa most commonly include breast, ovarian, colorectal, prostate, pancreatic, and endometrial cancers. Others that are occasionally associated with these alterations include urothelial, stomach, small bowel, and brain cancers.[13] Family members of PCa patients who have germline P/LP variants should undergo genetic testing (cascade testing) to determine whether they also carry the same variant. There is an opportunity to reduce the burden of hereditary cancers in family members through screening, early diagnosis, and prophylactic strategies.[3]

Ordering germline testing

Traditionally, germline testing has been done through cancer genetics services, but as genetic testing has become part of routine clinical care in diseases such as breast and ovarian cancer, alternate models of care have been developed. Mainstreaming refers to the incorporation of genetic testing into the standard practices of clinical care. In this model of care, germline testing is initiated by a non-genetics clinician, such as a urologist or oncologist, who does the pre-test counselling and orders the test.[14] Incorporation of this model into care for PCa patients could result in a faster turnaround time for testing and decrease the burden on genetics services, as has been demonstrated for other disease sites.[15,16] Models where the clinician orders germline testing and is responsible for communicating the results to patients have the most impact on reducing the burden on genetics services. In this model, only patients with P/LP variants or relevant variants of uncertain significance (described in more detail below), or patients with a significant family or personal history of cancer are prioritized for referral to the cancer genetics service.[17]

Results of germline testing

Results of germline testing provide prognostic information and may affect clinical management of patients who have P/LP variants. The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) standards and guidelines for the interpretation and reporting of sequence variants from germline testing classifies variants into five categories ['pathogenic', 'likely pathogenic', 'uncertain significance', 'likely benign', and 'benign'] based on criteria using different types of evidence; this is described in more detail in the Supplementary Materials (Supplementary Table 1; available at *cuaj.ca*).[18] Some HRR P/LP variants are associated with more aggressive disease, shorter time to castration-resistance, and worse outcomes after standard therapy, particularly BRCA2 mutations.[19-31] Germline P/LP variants can also be actionable in terms of determining patient eligibility for PARP inhibitor therapy or immune checkpoint inhibitor therapy.[32]

Germline testing in patients with metastatic prostate cancer

It is not currently practical or necessary to perform germline testing in every patient with PCa, as the

Table 1. Prevalence of germline pathogenic variants in prostate cancer

	Canadian cohort (metastatic disease), n=879[39]	U.S. commercial laboratory cohort (patients referred for germline testing), n=3607[41]	Multisite U.S. and U.K. cohort (metastatic disease), n=692[2]
Size of gene panel	73 genes	Up to 80 genes*	53 genes
All tested genes	6.5%	17%	12%
BRCA2	3.9%	4.7%	5.4%
ATM	0.7%	2.0%	1.6%
BRCA1	0.3%	1.25%	0.9%

Note that each study used gene panels of different sizes, but all tested core genes **BRCA1**, **BRCA2**, and **ATM**. *The gene panel analyzed was chosen at the discretion of the ordering clinician and ranged from 2–80 genes.

prevalence of germline mutations varies according to the stage of disease, histological characteristics, patient ethnicity, and personal and family history of cancer; thus, germline testing will have less utility in certain patient subgroups due to a much lower rate of actionable alterations. The expert panel recommends germline testing in patients with metastatic disease, as multiple studies have found a significantly higher prevalence of P/LP variants in patients with metastatic disease compared to patients with localized disease.[2,33-37] The prevalence of germline P/LP HRR variants is similar in metastatic castration-sensitive prostate cancer (mCSPC) and metastatic castration-resistant prostate cancer (mCRPC).[38] The overall prevalence of germline mutations varies with the size of the gene panel used; using a targeted panel that included 22 DNA damage repair genes, the prevalence was 6.5% in liquid biopsies from unselected patients with metastatic PCa in a study with patients living in Canada (Table 1).[39] *BRCA2* is the most frequently altered HRR gene in the germline for patients with PCa (Table 1).[33,39-41] In some populations with metastatic PCa, the frequency of germline P/LP variants can be as high as 18%, but this very high rate is not expected for most unselected Canadian patient populations.[2]

Germline testing in patients with localized prostate cancer

To align with other criteria that are used in Canada for hereditary cancer testing eligibility,[42] the expert guideline panel used a threshold of a ≥5% likelihood of carrying a P/LP variant for patient subgroups in which germline testing should be recommended. In general, the prevalence of germline P/LP variants in patients with localized PCa is such that the likelihood of picking up a P/LP variant would fall below the 5% threshold, but the prevalence is higher in certain patient subgroups. Patients with localized PCa with a personal or family history of certain cancers have a higher likelihood of carrying a P/LP variant and should receive germline testing[32,35,36,43-45] (Figure 1).

Relevant family history has been extensively described in the guidelines from the National Comprehensive Cancer Network (NCCN)[46] and takes into account how many first-, second-, or third-degree relatives have hereditary breast and ovarian cancer syndrome cancers or Lynch syndrome cancers, how many relatives have PCas (considering the stage and risk level), and the age of onset of cancers. Germline mutations are found in up to 10% of PCa patients meeting strict criteria for germline testing based on family history.[35] Even following negative germline testing, patients with a personal or family history of cancer that remains suspicious for hereditary cancer should be referred to their local cancer genetics service. Cancer genetics services may offer access at the time or in the future to additional clinical testing and will provide tailored residual risk information and screening recommendations for the family. Research opportunities to identify the potential inherited susceptibility may also be available through clinical genetics services.

Other patient subgroups with localized PCa in which germline testing is recommended are those with Ashkenazi Jewish ancestry; those with high-risk or very high-risk disease (defined by grade group, T stage, and serum PSA levels at diagnosis); and those with ductal, intraductal, or cribriform histology (Figure 1). Ashkenazi Jewish ancestry significantly increases the risk of carrying a germline P/LP variant: in a cohort of patients with a personal history of PCa that were referred for germline testing, tested at a U.S. commercial laboratory with a large gene panel, 23% of patients with Ashkenazi Jewish ancestry had germline P/LP variants.[41]

Patients with high-risk or very high-risk localized PCa according to NCCN criteria have an increased risk of carrying P/LP variants, which includes patients with Gleason score 8 or higher, clinical stage T3a or T3b or higher, or PSA higher than 20 ng/ml.[35,44,46]

In addition, although evidence is somewhat limited, PCa tumors with ductal or intraductal histology have a stronger association with HRR P/LP variants. In one study, 20% of patients with ductal PCa had germline P/LP variants,[47] and in another study, presence of ductal or intraductal histology was associated with germline pathogenic variants.[48] There are even more limited data on the association between cribriform histology and HRR status: one study reported no association, while others have found that cribriform histology was asso-

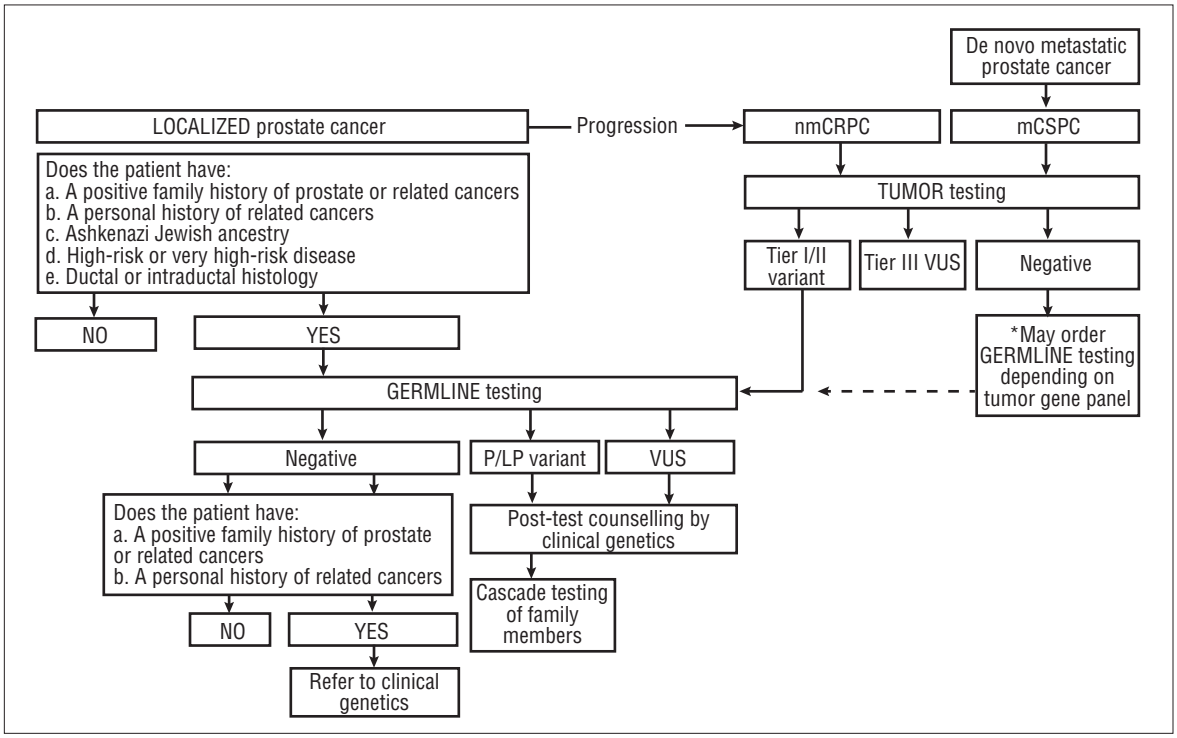

Figure 1. Overview of genetic testing in prostate cancer. LP: likely pathogenic; mCSPC: metastatic castration-sensitive prostate cancer; nmCRPC: non-metastatic castration-resistant prostate cancer; P: pathogenic; VUS: variant of uncertain significance.

ciated with increased genomic instability and biallelic somatic *BRCA2* loss.[49,50]

Disease stage at which to perform germline testing

The results of germline testing have important immediate implications for both patients and their family members; therefore, the guideline panel recommends performing germline testing as soon as possible after the diagnosis of PCa, once the patient is determined to be a candidate for germline testing as outlined above. Given the potential for the results of testing to influence clinical management and provide prognostic information, it is useful to perform germline testing early after diagnosis. From a hereditary cancer testing perspective, even if patients do not have any living parents, siblings, or children, there is utility in the information being available for extended family members like aunts, uncles, and cousins, which hereditary cancer/cancer genetics services can help the patient or next-of-kin share.

Recommendations for question 2: At what stage of disease and in which patient populations should genomic profiling of the tumor (tumor testing) be performed in patients with PCa?

■ RECOMMENDATION 5

Genomic profiling of the tumor should be performed in patients with mCRPC to inform the selection of therapy *(Strong, LE 1).*

■ RECOMMENDATION 6

Genomic profiling of the tumor should be performed in patients with mCSPC and patients with non-metastatic (nm)CRPC prior to progressing to mCRPC *(Good practice point).*

Purposes of tumor testing

Targeted therapies are becoming available for patients with advanced PCa. PARP inhibitors, which have been used in patients with breast, ovarian, and pancreatic cancers, are being investigated in clinical trials for patients with PCa,[4,51-62] and PARP inhibitors have been approved by Health Canada as monotherapy or in combination with anti-androgen therapy for patients with mCPRC

who have selected germline and/or tumor HRR gene alterations.[63] In addition, patients with MMR-deficient mCRPC may benefit from immune checkpoint blockade (anti-PD1/PL-L1 therapy).[5-7] Therefore, it is important to perform tumor testing to identify patients who may be eligible for targeted therapy or immunotherapy.

Disease stage at which to perform tumor testing

The guidelines panel recommends that tumor testing be performed prior to progression to mCRPC (i.e., in patients with mCSPC and patients with nmCRPC) so that results are available to the clinician to inform treatment selection once the patient's disease progresses (Figure 1). Tumor testing should also be performed in patients who have previously had germline testing at an earlier stage of disease, since about 50% of genetic alterations that are relevant for PARP inhibitor treatment in PCa are acquired in the tumor(s) during disease development and would not be detected by germline testing alone.[37]

Results of tumor testing

Different guidelines and variant classification schemes are typically used to report the results of germline and tumor testing. The AMP/American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) schema is one of the more frequently used ones for the reporting and classification of variants from tumor testing; this is described in more detail in the Supplementary Materials (Supplementary Table 2; available at *cuaj.ca*).[64] This classification scheme is predicated on a four-tiered system, with significant weight placed upon published evidence for making stratification decisions. Tier I and II variants have evidence of strong clinical significance or potential clinical significance, respectively; these variants are generally considered actionable for treatment with the associated targeted therapy, if there is an approved therapy. Tier III variants have unknown clinical significance and are treated as non-actionable with respect to clinical management.

Germline testing in patients with reportable variants detected with tumor testing

Patients with tier I/II variants detected by tumor testing should also receive germline testing if the variant falls within a gene that is associated with hereditary cancer risk (e.g., *BRCA2, ATM, TP53*). Genomic profiling of tumor tissue does not distinguish whether the origin of an observed variant is germline or somatic. Liquid biopsy can only distinguish between germline and somatic gene alterations if white blood cell DNA is assessed concurrently with ctDNA, which is not typically performed by current commercial test providers. Therefore, typically, tumor testing results need to be followed up with germline testing to determine whether P/LP variants identified by tumor testing are present in the germline (Figure 1). Some patients with tier III/ variant of uncertain significance (VUS) results from tumor testing may need to be referred for germline testing if further evaluation is deemed helpful. In addition, patients with a personal or family history of cancer that raises suspicions about hereditary cancer syndromes should be referred for germline testing regardless of tumor testing results. Post-test genetic counselling should be offered to patients with P/LP variants. Genetic counselling may also be offered to those with VUS results from germline testing, particularly those with a concerning personal or family history. In addition, cascade testing should be offered to family members of patients who carry P/LP germline variants.

Recommendations for question 3: What genes should be assessed in germline testing and tumor testing in patients with PCa?

■ RECOMMENDATION 7: GENE PANELS FOR GERMLINE TESTING

The minimum set of genes for germline testing in patients with PCa who meet criteria for germline testing should include *ATM, BRCA1, BRCA2, CHEK2, EPCAM* (large deletions), *HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2, TP53,* and *RAD51D*. Additional genes may be important depending on the clinical context considering the patient's personal and family history *(Strong, LE1)*.

The expert panel recommends that the minimum set of genes for germline testing in patients with PCa who meet the above criteria, should include *ATM, BRCA1, BRCA2, CHEK2, EPCAM* (large deletions), *HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2, TP53,* and *RAD51D.* This aligns with current recommendations in international guidelines, such as those from the NCCN, the European Society for Molecular Oncology (ESMO), and the Philadelphia Prostate Cancer Consensus Conference,[46,65,66] as well as testing eligibility criteria from Canadian provincial agencies, such as Cancer Care Ontario, that are mandated to facilitate hereditary cancer testing.[42] This panel includes genes in the HRR pathway that are associated with hereditary PCa

(*ATM, BRCA1, BRCA2, CHEK2, PALB2, RAD51D*),[33,37,39] as well as DNA MMR genes that are associated with Lynch syndrome (*EPCAM* [large deletions], *MLH1, MSH2, MSH6, PMS2*).[67-69] In addition, inherited pathogenic variants in *TP53* are associated with Li-Fraumeni syndrome, which predisposes individuals to developing multiple types of cancer at a young age and is associated with more aggressive PCa.[70] The genes on this recommended germline testing gene panel are generally associated with a variety of hereditary cancers, except for *HOXB13*, which has only been implicated in PCa.[71] Clinical geneticists may also support germline testing with an expanded hereditary cancer gene panel if that is appropriate considering the patient's personal and family history.

■ RECOMMENDATION 8: GENE PANELS FOR TUMOR TESTING

The minimum set of genes for genomic profiling of the tumor in patients with PCa who meet criteria for tumor testing should include *BRCA1, BRCA2,* and *ATM*; however, tumor testing panels should be aligned with germline testing panels as much as possible and ideally would also include *CHEK2, EPCAM* (large deletions), *HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2, TP53*, and *RAD51D*. *CDK12* may also be included for prognostic purposes. Additional genes may be included for research purposes, prognostic purposes, or inclusion of patients in clinical trials *(Strong, LE1)*.

The expert panel recommends that the minimum set of genes for tumor testing in patients with PCa should include *BRCA1, BRCA2,* and *ATM*, as these are sufficient to identify patients who are eligible for and may benefit from consideration of PARP inhibition therapy; however, ideally, the tumor testing gene panel would include additional genes, such as *CHEK2, EPCAM* (large deletions), *HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2, TP53,* and *RAD51D,* to provide information that may be relevant at the time of testing or in the near future for consideration of immunotherapy or targeted therapy as new therapies and/or new indications of current therapies become available. In addition, *CDK12* may be included, as it is associated with aggressive disease and poor outcomes in response to standard therapies.[72-74] Additional genes may also be included for prognostic or research purposes, or for inclusion of patients in clinical trials. In a Canadian cohort of patients with metastatic disease undergoing liquid biopsy testing with a targeted panel that included 22 DNA damage repair genes, approximately 22% had a pathogenic gene alteration (inclusive of both somatic and germline alterations), with *CDK12, BRCA2,* and *ATM* being the most common (Table 2).[39] Mutation prevalence varies according to the population tested and the size of the gene panel used (Table 2).[33,39]

Table 2. Prevalence of pathogenic gene alterations identified from tumor testing in prostate cancer

	Canadian cohort (metastatic disease), n=635[39]	Prospective U.S. cohort (all stages of disease), n=451[33]
Size of gene panel	73 genes	53 genes
All genes	21.7%	22%
CDK12	4.4%	5.3%
ATM	3%	7%
BRCA2	8.5%	11%

Tumor testing identifies both somatic and germline alterations. Note that the Canadian study used plasma ctDNA, while the U.S. cohort used metastatic tissue biopsy.

A larger next-generation sequencing (NGS) panel for tumor testing that overlaps with the genes recommended for germline testing may provide the highest yield of findings. It may identify P/LP variants in patients who would not otherwise meet the criteria for germline testing alone. Patients with P/LP variants from tumor testing should still undergo germline testing to ascertain whether the variant is inherited or acquired (Figure 1); however, alignment of tumor panel content with germline panels could decrease the likelihood of patients having a germline variant after a negative tumor test result, as long as the assay meets sufficient performance metrics. It is important to note that, in some cases, tumor testing may miss a germline variant for various reasons, including different variant classification methods for somatic and germline variants, different bioinformatics pipelines for tumor and germline testing, and technical challenges associated with the detection of certain variant types, particularly when analyzing specimen types often used in oncology (e.g., formalin-fixed, paraffin-embedded biopsy specimens). Therefore, if there is a strong personal or family history of cancer, germline testing could be considered even after a negative result from tumor testing.[75,76]

An ideal gene panel design for tumor testing would distinguish between monoallelic and biallelic pathogenic variants in the *BRCA* genes, i.e., pathogenic gene alterations in one copy or in both copies of the *BRCA1* or *BRCA2* gene. Because of the mechanism of action of PARP inhibition, pathogenic biallelic gene alteration in *BRCA1* or *BRCA2* results in more complete inactivation

of the HRR pathway and would be expected to lead to greater PARP inhibitor efficacy. Emerging evidence suggests that this is the case.[75,76]

Recommendations for question 4: What is the optimal specimen for genomic profiling of the tumor?

■ RECOMMENDATION 9

All patients with de novo metastatic PCa should have a biopsy performed so that tissue is available for NGS, to determine candidacy for PARP inhibitors in the future. The biopsy should be performed as early as possible relative to the start of therapy, without compromising the care of the patient *(Strong, LE1).*

■ RECOMMENDATION 10

A tiered approach is recommended for the choice of specimen for genomic profiling of the tumor:

a. **The first choice of specimen is an archival primary or archival metastatic tumor biopsy** *(Good practice point).*
b. **If archival tissue is not available or testing fails due to a suboptimal specimen, alternate choices are a contemporary metastatic tumor biopsy or "liquid biopsy" for testing of plasma-derived ctDNA, if a metastatic biopsy is not feasible. There are advantages and disadvantages to both options** *(Good practice point).*

Tumour biopsy in de novo metastatic prostate cancer

Tumor testing is required to assist clinicians in the selection of optimal therapy for patients with mCRPC, as described above. As such, the expert panel recommends that all patients with de novo metastatic PCa should have a biopsy performed so that tumor tissue is available for molecular testing. Given that treatments used in patients with mCSPC may decrease the size of tumors and make biopsy more difficult,[77] the panel recommends that biopsy be performed as early as possible after the diagnosis of de novo metastatic disease without compromising the care of the patient.

Considerations for specimen types

Different specimen types may be used for tumor testing, including archived primary or metastatic tumor tissue, newly collected metastatic tumor tissue, and liquid biopsies. Liquid biopsy results have been found to have high concordance with tissue-based tumor testing and can be used to select patients who can benefit from PARP inhibition.[39,78-87] In addition, there is high concordance in HRR gene alterations between primary and metastatic tumors.[33,39,78,87,88]

Each specimen type has advantages and disadvantages for genetic testing in PCa. The expert panel recommends archival tumor tissue as the first choice of specimen due to its availability for most patients; however, for PCa patients, archival tissue can sometimes be 10 years old or more, and the ability to generate an NGS result declines with increasing sample age due to DNA fragmentation. A study of over 4000 tumor samples from patients with mCRPC found that approximately 70% of archival samples that were less than one year old generated NGS results, while approximately 50% of samples older than 10 years generated results.[89] If both an archival primary biopsy and an archival metastatic biopsy are available, testing of the metastatic tissue is preferred. Newly obtained metastatic biopsies can also be used as a source of tumor tissue for genetic testing with a comparable or higher success rate vs. archival tissue for returning an NGS result, but some metastatic sites have a much lower success rate, particularly bone samples.[33] The expert panel recommends newly obtained metastatic tumor biopsies as an alternate choice of specimen for tumor testing if archival specimens are not available for testing or if testing fails due to a suboptimal specimen. The panel recommends experience with bone biopsies because of their additional challenges to maximize the chances of successful testing. Local expertise in taking bone biopsies and processing bone biopsy tissue should be developed.

Liquid biopsy is a feasible alternative to tissue-based testing; however, there is limited availability of clinical liquid biopsy testing for PCa patients in Canada. Liquid biopsy results are dependent on tumor shedding of ctDNA; therefore, optimal timing for a liquid biopsy is when the patient's disease is not under control of therapy, i.e., at the time of clinical progression or before the initiation of systemic therapy for a treatment-naive patient.[85] Measures of disease burden that correlate with higher ctDNA levels and a greater likelihood of successful tumor testing via liquid biopsy include elevated lactate dehydrogenase, high PSA, visceral disease, and a high number of bone metastases.[90]

SUMMARY

Genetic testing has become the standard of care in the management of patients with PCa. Clear guidelines are needed to ensure consistent and timely testing, efficient healthcare resource allocation, and optimal patient outcomes. In this guideline, an expert panel

recommends that germline testing be performed in patients with metastatic disease and in selected patients with localized disease as soon as they are identified to be eligible candidates for germline testing based on the criteria described herein. Tumor testing should be performed to inform the selection of therapy in patients with mCRPC and should be performed in patients with mCSPC and nmCRPC prior to progressing to mCRPC so that results are available when therapeutic decisions need to be made.

The expert panel recommends a germline gene panel containing at a minimum *ATM, BRCA1, BRCA2, CHEK2, EPCAM* (large deletions), *HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2, TP53*, and *RAD51D*, as these genes are associated with various hereditary cancers in patients with PCa. The gene panel for tumor testing should ideally be aligned with the germline gene panel and may contain additional genes for prognostic or clinical trial purposes, but at a minimum, should contain *ATM, BRCA1*, and *BRCA2*.

Most patients with PCa have archival tumor tissue available for tumor testing; therefore, this specimen is the first choice for tumor testing, although the failure rate with older specimens is higher than with more recent specimens. Newly obtained metastatic tumor biopsy tissue may also be used, as well as liquid biopsy for testing of ctDNA, although the latter has limited availability for clinical testing currently.

Multidisciplinary education will be required to support the implementation of these guidelines.

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