Genetic testing practices among specialist physicians who treat prostate cancer

A Canadian, cross-sectional survey

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Cite as: Yip SM, Morash C, Kolinsky MP, et al. Genetic testing practices among specialist physicians who treat prostate cancer: A Canadian cross-sectional survey. *Can Urol Assoc J* 2023;17(10): 326-36. http://dx.doi.org/10.5489/cuaj.8403

Published online July 21, 2023

Appendix available at *cuaj.ca*

ABSTRACT

INTRODUCTION: In patients with prostate cancer (PCa), the identification of an alteration in genes associated with homologous recombination repair (HRR) has implications for prognostication, optimization of therapy, and familial risk mitigation. The aim of this study was to assess the genomic testing landscape of PCa in Canada and to recommend an approach to offering germline and tumor testing for HRR-associated genes.

METHODS: The Canadian Genitourinary Research Consortium (GURC) administered a cross-sectional survey to a largely academic, multidisciplinary group of investigators across 22 GURC sites between January and June 2022.

RESULTS: Thirty-eight investigators from all 22 sites responded to the survey. Germline genetic testing was initiated by 34%, while 45% required a referral to a genetic specialist. Most investigators (82%) reported that both germline and tumor testing were needed, with 92% currently offering germline and 72% offering tissue testing to patients with advanced PCa. The most cited reasons for not offering testing were an access gap (50%), uncertainties around who to test and which genes to test, (33%) and interpreting results (17%). A majority reported that patients with advanced PCa (74–80%) should be tested, with few investigators testing patients with localized disease except when there is a family history of PCa (45–55%).

CONCLUSIONS: Canadian physicians with academic subspecialist backgrounds in genitourinary malignancies recognize the benefits of both germline and somatic testing in PCa; however, there are challenges in accessing testing across practices and specialties. An algorithm to reduce uncertainty for providers when ordering genetic testing for patients with PCa is proposed.

INTRODUCTION

Prostate cancer (PCa) is the third leading cause of cancer-related death among Canadian males, with an age-standardized mortality rate of 22.6 per 100 000 in 2022.[1,2] Patients diagnosed with advanced, life-limiting disease have a median five-year survival rate of 30%.[3,4]

KEY MESSAGES

- In a survey of academically oriented multidisciplinary specialist physicians, 84% offer genetic testing to PCa patients.
- Most physicians have access to germline genetic testing, with fewer having access to tissue testing; access gaps and uncertainty around how to order genetic tests were the most common reasons for not offering them.
- Surveyed physicians indicated that germline and tissue testing should be offered to all PCa patients with metastatic disease and primarily to patients with high-risk localized disease when there is a family history of cancer.
- For metastatic PCa, germline and somatic testing is recommended in parallel to identify targets for treatment and to inform future cancer risk in patients and their biological relatives.

Inevitably, patients with advanced disease will develop metastatic castration-resistant prostate cancer (mCRPC), with current standard-of-care systemic therapy options including androgen receptor pathway inhibitors (ARPIs; abiraterone acetate, enzalutamide); taxane-based chemotherapies (docetaxel, cabazitaxel); and bone-targeted therapies (radium-223).[5-14]

Furthermore, alterations in genes associated with homologous recombination repair (HRR), such as *BRCA1* and *BRCA2,* have been shown to confer sensitivity to poly adenosine diphosphate–ribose polymerase (PARP) inhibition in mCRPC.[15-22] Consequently, the PARP inhibitor, olaparib, was approved by Health Canada for use in patients with mCRPC harboring a *BRCA1, BRCA2*, or *ATM* genetic alteration, who have progressed after at least one line of ARPIs, based upon the results of the phase 3 PROfound trial.[13 15,16]

Genomic studies have reported that approximately 20–30% of metastatic PCa (mPCa) patients harbor HRR pathway alterations,[13,16,17,23-27] with approximately 10–15% being germline (inherited) in origin and 20–25% somatic (acquired)[14] in origin. Response to standard-of-care therapies, such as ARPIs, also differs in mPCa patients with HRR gene alterations, in contrast to patients with wild-type HRR status.[13]

Since a variant in the HRR gene pathway will have prognostic and treatment implications, Ontario and international guidelines recommend germline and tissue testing in men with metastatic and high-risk localized PCa (LPCa).[17,28-30] The overall objective of this cross-sectional survey of a largely academic, multidisciplinary (urologic oncology, medical oncology, radiation oncology) group was to: 1) evaluate current practices in genetic testing in PCa in the context of the Canadian healthcare system; 2) evaluate recommended genetic testing practices from Canadian healthcare providers; 3) define the patient population who should ideally be offered genetic testing; and 4) understand physician perceptions of when genetic testing should first be offered. Furthermore, a proposed genomic testing algorithm was developed to guide clinician-initiated genetic testing for mPCa, high-risk PCa, and patients with a family history of PCa.

METHODS

Study and survey design

A cross-sectional survey was developed by the core faculty of the Canadian Genitourinary Research Consortium (GURC) to assess the real-world genomic testing landscape for PCa in Canada. The survey was sent to GURC cohort study principal investigators (PIs) and sub-investigators (sub-Is) practicing in the fields of urologic oncology, medical oncology, and radiation oncology[31] between January 2022 and June 2022.

This GURC PCa genetic testing investigator survey contained 20 questions focusing on five key components, with the aims to:

1. Determine current testing practices among specialist physicians treating PCa, including the type and form of testing performed (hereditary/germline, somatic tumor tissue next-generation sequencing [NGS], circulating tumor/cell free DNA [ctDNA/cfDNA] NGS, in situ hybridization [ISH]), accessibility of testing, referrals to genetic specialists (for patients with genomic alterations), genetic testing of potentially impacted family members, impact on treatment (treatment plan and sequencing), and biobanking.
2. Examine the respondents' recommended ideal type and form of genetic testing, as well as which specialists should offer genetic testing.
3. Identify the profile of patients (LPCa, metastatic castrate-sensitive prostate cancer [mCSPC], non-metastatic castrate-resistant prostate cancer [nmCRPC], and mCRPC) who should ideally be offered genetic testing either for germline, somatic, or both types of mutations.

Table 1. Current practices for the genomic testing of patients with prostate cancer

Survey questions	n (%)
Province (n=38)	
Alberta	8 (21%)
British Columbia	11 (29%)
Manitoba	5 (13%)
Nova Scotia	1 (3%)
Ontario	8 (21%)
Quebec	5 (13%)
Investigator role (n=38)	
Principal investigator	21 (55%)
Sub-investigator	17 (45%)
Do you practice at an academic or a non-academic center?* (n=38)	
Academic	33 (87%)
Non-academic	9 (24%)
Is mainstream genetic testing initiated by clinicians or is a referral necessary? (n=38)	
Referral to specialist	17 (45%)
Initiated by clinician	13 (34%)
Other	8 (21%)
Do you offer genetic testing to family members of patients with a positive genomic alteration? (n=33)	
Yes	8 (24%)
No	24 (73%)
Missing	1 (3%)
If no, who offers this? (n=24)	
Genetics	17 (71%)
Missing	7 (3+%)
What form of genetic testing is currently available to you?* (n=33)	
Germline	30 (91%)
Somatic	19 (58%)
Archival tissue testing	4 (12%)
ISH	0
ctDNA/cfDNA	10 (30%)
Other	3 (9%)
I do not know	2 (6%)
Do you currently perform/offer genetic testing in PCa patients?* (n=38)	
Yes	32 (84%)
No	6 (16%)

Table 1 (cont'd). Current practices for the genomic testing of patients with prostate cancer

Survey questions	n (%)
If yes, which type of testing do you perform/offer?* (n=32)	
Germline DNA damage repair genetic testing	30 (94%)
Somatic DNA damage repair genetic testing	23 (72%)
Other	1 (3%)
If yes, How do you arrange for testing?* (n=32)	
Clinical trials	20 (63%)
Private pay	10 (31%)
Compassionate use programs	6 (19%)
Provincially funded testing	20 (63%)
Other	9 (28%)
If no, why?* (n=6)	
Access gap	3 (50%)
Uncertain how to order	2 (33%)
Uncertain how to interpret results	1 (17%)
Results will not affect patient management at this time	1 (17%)
Other	2 (33%)
Do results of genomic testing impact your patient management? (n=33)	
Yes	32 (97%)
No	1 (3%)
If yes, it will change my patient's treatment plan and sequencing of the following (n=32):	
Chemotherapy	2 (6%)
PARP inhibitor therapy	9 (28%)
Trials	2 (6%)
I will refer patients with positive actionable mutations to another specialty to treat	1 (3%)
Other	14 (44%)
Missing	4 (13%)
Do you refer to a genetics specialist for *BRCA1/2* or *ATM*? (n=33)	
Yes	31 (94%)
No	2 (6%)
Do you refer to a genetics specialist for *BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C*? (n=33)	
Yes	21 (64%)
No	10 (30%)
Missing	2 (6%)

Table 1 (cont'd). Current practices for the genomic testing of patients with prostate cancer

Survey questions	n (%)
Do you refer when any other genetic alteration** is identified? (n=33)	
Yes	13 (39%)
No	19 (58%)
Missing	1 (3%)
Do you refer when any VUS are identified? (n=33)	
Yes	9 (27%)
No	23 (70%)
Missing	1 (3%)
Do you biobank or maintain a database/registry when the following are identified? (n=33)	
BRCA/ATM	
Yes, biobank	12 (36%)
Yes, database/registry	9 (27%)
No	11 (33%)
Missing	1 (3%)
BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L alteration	
Yes, biobank	12 (36%)
Yes, database/registry	6 (18%)
No	14 (42%)
Missing	1 (3%)
VUS	
Yes, biobank	9 (27%)
Yes, database/registry	6 (18%)
No	16 (49%)
Missing	2 (6%)

*Investigators were allowed to select more than one option. **Example, HOXB. ATM: ataxia telangiectasia mutated; BARD1: BRCA associated RING domain 1; BRCA1/2: breast cancer type ½ susceptibility gene; BRIP1: BRCA1 interacting protein C-terminal helicase 1; CDK12: cyclin-dependent kinase inhibitor 12; CHEK: checkpoint kinase; ctDNA/cfDNA: circulating tumour/cell free DNA; FANCL: Fanconi anemia, complementation group L; IHC: immunohistochemistry; ISH: in-situ hybridization; PALB2: Partner and localizer of BRCA2; PARP: poly (ADP-ribose) polymerase; PCa: prostate cancer; PPP2R2A: Serine/threonine-protein phosphatase 2A regulatory subunit B55α; VUS: variants of unknown significant.

4. Elucidate the timing of genetic testing based on disease and patient characteristics.
5. Assess the proportion of patients currently receiving genetic testing stratified by disease stage (mCRPC, mCSPC, nmCRPC, high-risk PCa, or any PCa).

The intent to use a survey and collect data from study investigators was approved as a protocol amendment by research ethics boards at all GURC sites. The survey itself did not involve data collection from patients and, therefore, did not require ethics approval.

Finally, based on the findings of the GURC survey and further consultation with both the GURC investigators and multidisciplinary experts in genetics (one clinical molecular geneticist, two genetic counsellors, one bioinformatician), a proposed genetic testing algorithm was developed to guide clinician-initiated genetic testing for mPCa, high-risk PCa, and patients with a family history of PCa.

Study participants

A total of 22 multidisciplinary, primarily academically oriented PIs (13 urologic oncologists, eight medical oncologists, one radiation oncologist) and 49 sub-Is of the GURC cohort study from 22 sites across Canada were invited to complete the survey. To encourage maximal response rates, sites were provided with several reminders through emails, newsletters, the investigator portal, and by clinical research associates during monitoring visits. Participation in the survey was optional.

Statistical analysis

The survey data was stored using a Study Data Tabulation Model standards tool and shared through a secured cloud platform. Response data were described using frequencies and percentages. All analyses were descriptive; no inferential analyses were conducted. All statistical analyses were performed using Microsoft Excel and SAS v9.4 (SAS Institute, Cary, NC, U.S.).

RESULTS

Respondent characteristics

A total of 21/22 (95%) multidisciplinary PIs and 17/49 (35%) sub-Is responded to the survey, resulting in an overall response rate of 54%. The majority (87%) of physicians who completed the survey practice in an academic setting and were associated with a university or a teaching hospital (Table 1).

Current practices in genetic testing for prostate cancer

The results for current practices are presented in Table 1. Germline testing was the most common form (91%) of genetic testing currently available to physicians, followed by somatic testing (58%). Of the 58% of

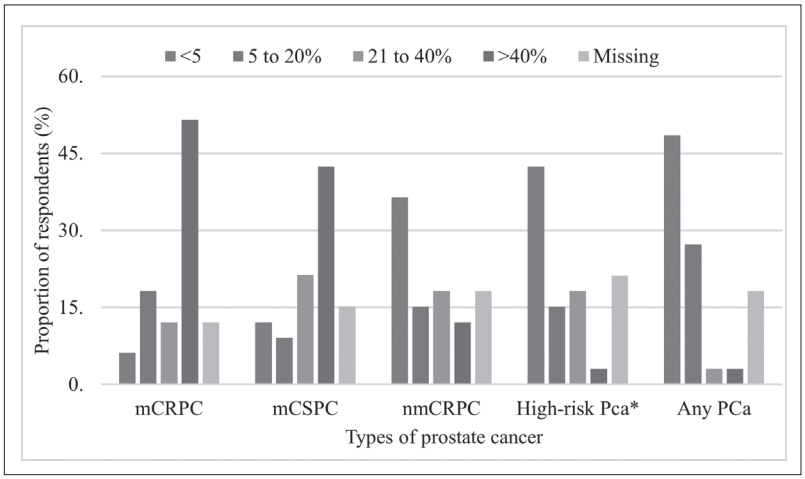

Figure 1. Proportion of prostate cancer patients that are currently receiving genetic testing (n=33). *T3 or higher staging (grade group 4 or 5 – Gleason score 8–10) lymph node involvement, prostate-specific antigen ≥20. mCRPC: metastatic castration-resistant prostate cancer; mCSPC: metastatic castration-sensitive prostate cancer; nmCRPC: non-metastatic castration-resistant prostate cancer; PCa: prostate cancer.

physicians who had somatic testing available, 30% had access to ctDNA/cfDNA, 12% to archival tumor tissue testing, and 9% to other methods of testing (6% did not know). Nearly half of the physicians (45%) required referral to a genetics specialist to initiate hereditary genetic testing for PCa at their current practice, while for 34%, genetic testing was initiated by the clinicians themselves, via a mainstream germline genetic testing approach.[32] When genetic testing was offered to family members of patients with positive results, it was typically performed by genetics specialists (71%), rather than the treating clinician.

Among the physicians who offered genetic testing (84%), the vast majority performed both germline (94%) and tissue (72%) testing. Of the 16% of physicians who did not offer genetic testing, the main reason was a lack of access to testing (50%), followed by uncertainty around how to order tests (33%) and interpret results (17%). Although 63% of respondents have some form of provincially funded genetic testing, genetic testing programs vary greatly by region and center; and a significant proportion also access testing through clinical trials (63%), private pay (31%), or through compassionate access programs (19%).

Almost all respondents (97%) felt that genetic testing impacts patient management. Twenty-eight percent of physicians expressed that the results of testing would affect the sequence and timing of introduction of PARP inhibitor therapy; 44% specified that the treatment plan and sequencing would be impacted by the introduction of other therapies (e.g., platinum-based chemotherapy).

Table 2. Recommended practices for genetic testing of patients with prostate cancer

Survey question	n (%)
In your opinion, should genetic testing be offered to PCa patients in your practice? (n=38)	
Yes, ideally germline DNA damage repair genetic testing alone is sufficient	3 (8%)
Yes, ideally both germline and somatic DNA damage repair testing are needed	31 (82%)
No, it will not change my patient management	1 (3%)
I do not have an opinion on this topic at this time	2 (5%)
Missing	1 (3%)
In your opinion, what is the ideal form of genetic testing that should be offered?* (n=33)	
Germline	26 (79%)
Somatic	25 (76%)
Archival tissue testing	3 (9%)
ISH	2 (6%)
ctDNA/cfDNA	17 (52%)
Other	1 (3%)
I do not know	2 (6%)
Should combination genetic testing be performed? (n=33)	
Yes, liquid biopsy followed by tumor tissue testing	14 (42%)
Yes, tumor tissue testing followed by liquid biopsy	8 (24%)
Yes, but only in certain circumstances	1 (3%)
I do not know	8 (24%)
Missing	2 (6%)
What specialties do you feel should offer genetic testing for patients diagnosed with PCa?* (n=38)	
Non-academic urologist	9 (24%)
Non-academic medical oncologist	13 (34%)
Non-academic radiation oncologist	7 (18%)
Academic urologist	17 (45%)
Academic medical oncologist	20 (53%)
Academic radiation oncologist	14 (37%)
All clinicians who treat PCa	18 (47%)
All clinicians who treat PCa who have training with genetic testing	14 (37%)
Genetics specialists	14 (37%)
Only genetics specialists	1 (3%)

*Investigators were allowed to select more than one option. ctDNA/cfDNA: circulating tumor/cell free DNA; ISH: in-situ hybridization; PCa: prostate cancer.

Patients positive for *BRCA1*, *BRCA2*, or *ATM* mutations following tumor tissue testing were referred to a genetics specialist by 94% of the respondents, and *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, or *RAD51C* mutations by 64%. Similarly, current practices around referrals for other genetic alterations (e.g., *HOXB13*) were more mixed, with 58% of physicians electing not to refer to a specialist. Most physicians (70%) did not refer patients with any variant of unknown significance (VUS) to a genetics specialist (variant classification is defined in Supplementary Figure 1; available at *cuaj.ca*). Lastly, biobanking was not common among physicians despite the academic focus of the group, with just over a third of physicians (36%) banking samples when *BRCA/ATM* or *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PLAB3*, *PPP2R2A*, *RAD51B*, or *RAD51C* alterations were identified.

Proportion of patients that are currently receiving genetic testing

The results around the current proportion of patients receiving genetic testing stratified by type of PCa are presented in Figure 1. In general, genetic testing rates were higher for patients with advanced disease (mCRPC and mCSPC), as compared to localized disease (nmCRPC and high-risk PCa). Approximately 40–50% of the physicians indicated that more than 40% of their mCRPC or mCSPC patients were currently receiving genetic testing; however, 36% and 48% reported that fewer than 5% of patients with nmCRPC or high-risk PCa currently received genetic testing, respectively. In addition, 75% of physicians also stated that currently up to 20% of patients with any PCa received genetic testing.

Recommended practices for genetic testing in prostate cancer

Respondents were surveyed regarding recommended practices (Table 2). It was consistently recognized among physicians that both germline and tissue testing were important, with 82% of physicians indicating that ideally both germline and tissue testing would be provided to PCa patients. When asked about the ideal form of genetic testing, 79% of physicians selected germline testing, while 76% and 52% selected tissue testing with tumor and plasma-derived cfDNA NGS testing, respectively. There were mixed responses regarding the order in which tissue NGS testing were performed, with most physicians (42%) preferring plasma cfDNA testing followed by tumor tissue testing if the first test does not yield an adequate result (e.g., low

Table 3. Profile of patients who should ideally be offered genetic testing*

Patient characteristics (n=38)	Diagnosis			
	LPCa n (%)	mCSPC n (%)	mCRPC n (%)	nmCRPC n (%)
All PCa patients				
Germline and somatic	6 (16%)	28 (74%)	30 (80%)	25 (66%)
Germline	3 (8%)	1 (3%)	1 (3%)	3 (8%)
Somatic	0	0	0	0
High-risk PCa patients only**				
Germline and somatic	20 (52%)	–	–	21 (55%)
Germline	5 (13%)	–	–	0
Somatic	0	–	–	0
Patients with a primary relative*** with PCa				
Germline and somatic	10 (26%)	21 (55%)	21 (55%)	20 (53%)
Germline	14 (37%)	2 (5%)	4 (11%)	3 (8%)
Somatic	0	0	0	0
Patients with any relative with PCa				
Germline and somatic	7 (18%)	18 (47%)	19 (50%)	17 (45%)
Germline	5 (13%)	3 (8%)	4 (11%)	3 (8%)
Somatic	0	0	0	0
Patients with a primary relative with ovarian, breast or pancreatic cancer				
Germline and somatic	13 (34%)	22 (58%)	21 (55%)	21 (55%)
Germline	13 (34%)	4 (11%)	5 (13%)	3 (8%)
Somatic	0	0	0	0
Patients with any relative with ovarian, breast of pancreatic cancer				
Germline and somatic	8 (21%)	20 (53%)	21 (55%)	16 (42%)
Germline	6 (15%)	4 (11%)	4 (11%)	3 (8%)
Somatic	0	0	0	0
Patients with a family history of another cancer				
Germline and somatic	5 (13%)	15 (40%)	16 (42%)	13 (34%)
Germline	4 (11%)	3 (8%)	4 (11%)	3 (8%)
Somatic	0	0	0	0

*Investigators were allowed to select more than one option. **High-risk nmCRPC: prostate cancer antigen (PSA) doubling time ≤10 months. ***Primary relative: first degree relative. LPCa: localized prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; mCSPC: metastatic castration-sensitive prostate cancer; nmCRPC: non-metastatic castration-resistant prostate cancer; PCa: prostate cancer.

Table 4. Timing of genetic testing*

Patient diagnosis (n=33)	Type of testing	
	Germline n (%)	Somatic n (%)
PCa diagnosis	5 (15%)	2 (6%)
PCa diagnosis for patients with a family history of PCa	10 (30%)	3 (9%)
PCa diagnosis for patients with a primary relative with breast, ovarian, prostate, or pancreatic cancer	16 (49%)	5 (15%)
PCa diagnosis for patients with any relative with breast, ovarian, prostate, or pancreatic cancer	10 (30%)	5 (15%)
High-risk localized PCa patients**	11 (33%)	6 (18%)
All nmCRPC diagnosis	12 (36%)	7 (21%)
All nmCRPC diagnosis at PSA progression	11 (33%)	6 (18%)
All nmCRPC diagnosis at progression to mCRPC	13 (39%)	9 (27%)
All nmCRPC patients with a primary relative with breast, ovarian, prostate, or pancreatic cancer	12 (36%)	6 (18%)
All nmCRPC patients with any relative with breast, ovarian, prostate, or pancreatic cancer	13 (39%)	7 (21%)
High-risk nmCRPC*** diagnosis	12 (36%)	7 (21%)
High-risk nmCRPC*** diagnosis at PSA progression	10 (30%)	6 (18%)
High-risk nmCRPC*** diagnosis at progression to mCRPC	11 (33%)	9 (27%)
High-risk nmCRPC*** patients with a primary relative with breast, ovarian, prostate, or pancreatic cancer	12 (36%)	8 (24%)
High-risk nmCRPC*** patients with any relative with breast, ovarian, prostate, or pancreatic cancer	11 (33%)	8 (24%)
mCSPC diagnosis	21 (64%)	16 (49%)
mCSPC at progression to mCRPC	17 (52%)	18 (55%)
mCSPC patients with a primary relative with breast, ovarian, prostate or pancreatic cancer	19 (58%)	11 (33%)
mCSPC patients with any relative with breast, ovarian, prostate, or pancreatic cancer	15 (46%)	10 (30%)
mCRPC diagnosis	23 (70%)	18 (55%)
mCRPC progression on first-line treatment	18 (55%)	19 (58%)
mCRPC progression on second-line treatment	18 (55%)	18 (55%)
mCRPC patients with a primary relative with breast, ovarian, prostate, or pancreatic cancer	19 (58%)	13 (39%)
mCRPC patients with any relative with breast, ovarian, prostate, or pancreatic cancer	15 (46%)	10 (30%)
Patient's age at diagnosis will impact my decision	6 (18%)	3 (9%)
Other	3 (9%)	1 (3%)

*Investigators were allowed to select more than one option. **High-risk localized PCa: T3 or higher staging (grade group 4 or 5 – Gleason score 8-10) Lymph Node involvement, PSA ≥20. ***High-risk nmCRPC: PSA doubling time ≤10 months. mCRPC: metastatic castration-resistant prostate cancer; mCSPC: metastatic castration-sensitive prostate cancer; nmCRPC: non-metastatic castration-resistant prostate cancer; PCa: prostate cancer; PSA: prostate-specific antigen.

ctDNA fraction), and approximately one-quarter (24%) of respondents selecting tumor tissue testing followed by liquid biopsy. Respondents reported mixed results around which specialties should offer genetic testing, with a slightly higher preference for academic oncology specialties. Just over half of respondents (53%) felt that academic medical oncologists should provide genetic testing as part of their practice.

Patient population recommended for genetic testing

Table 3 contains the data on respondents' recommendations for genetic testing based on patient characteristics. Tissue testing alone was not recommended by any physician, regardless of patient demographic characteristics. Most respondents indicated that advanced PCa patients —mCRPC (80%), mCSPC (74%), and nmCRPC (66%) — should receive both germline and somatic testing, while only 16% stated the same for localized disease. Further, approximately half of the respondents would offer both germline and tissue genetic testing to high-risk patients with LPCa (52%) and nmCRPC (55%).

Approximately half (45–55%) of all respondents proposed testing patients with mCSPC, mCRPC, and nmCRPC who have a family history of PCa (primary or any relative) for both germline and somatic mutations. Similarly, approximately half of the respondents suggested testing for both germline and somatic mutations in mCSPC (53%), mCRPC (55%), and nmCRPC (42%) patients with a family history of ovarian, breast, or pancreatic cancer (primary or any relative).

Timing of genetic testing

The recommended timing of genomic testing for patients with PCa is described in Table 4. Only a small fraction of physicians would offer genetic testing at the time of diagnosis of localized PCa (15% germline and 6% somatic testing); however, this increased to 30% for patients with a family history of PCa or to 49% for patients with a primary relative with breast, ovarian, prostate, or pancreatic cancer. A higher proportion of physicians would offer genetic testing at mCSPC (64% germline, 49% somatic) and mCRPC (70% germline, 55% somatic).

DISCUSSION

The findings from this study describe current practices and recommendations around genetic testing for PCa patients among Canadian physicians who are largely academically focused. Genetic testing for mPCa has

been endorsed by several international clinical practice guidelines.[28,29,33] (Editor's note: A Canadian guideline is now also available; see this issue of *CUAJ*). As genetic testing becomes standard-of-care in PCa, it is essential to ensure equitable access and awareness among physicians.[3,17] The GURC survey was developed to understand the current framework of genetic testing for patients with mPCa in Canada and the barriers encountered by physicians in accessing these tests.

Our respondents reported that both germline and tissue testing are important for patient management; nevertheless, there are gaps in accessing genetic testing, with approximately half of physicians requiring referral to a genetics specialist, which may be a barrier to having genetic testing performed. Furthermore, access to tissue genomic testing is limited, heterogeneous, and varied. These limitations were similarly identified in renal cell carcinoma (RCC) Canadian genetic testing surveys; yet, the direct impact of genetic testing in RCC is not nearly as well-defined and required in clinical care, in contrast to PCa.[34] This issue in PCa tissue testing access reflects the fact that testing is not yet widely available in Canada and that there is variability in provincial reimbursement.[18,21] Arranging for testing appears to be difficult to navigate, with physicians reporting multiple avenues for access, including compassionate use programs, clinical trials, and private pay, in addition to public funding.

Although there was a mixed spectrum of responses regarding which specialties should offer testing, just over half of respondents reported that academic medical oncologists should initiate genetic testing. Patients identified with *BRCA1, BRCA2*, or *ATM* alterations with tissue testing are currently being appropriately referred for genetic counselling and subsequent testing of potentially impacted family members, but there appears to be a lack of clarity around referrals for VUS and other genomic alterations identified from tissue testing. While a proportion of physicians agreed that identifying mutations would affect patient management, in terms of subsequent PARP inhibitor therapy and enrollment on a clinical trial, a substantial proportion also indicated that the treatment plan and sequencing would be altered for other therapies (e.g., platinum-based chemotherapy).

Physicians recommended both germline and tissue genetic testing for advanced PCa patients, as well as high-risk LPCa patients with a family history of prostate, breast, ovarian, and pancreatic cancer. Most respondents recommended genetic testing for patients at the time of diagnosis of advanced disease (e.g., mCSPC). The GURC 2020 Canadian consensus forum (CCF)[3] reported that 83% recommended germline and somatic testing for patients with PCa, like the 74–80% reported in this study. There was also more limited access to tissue testing, with 59% recommending tissue testing,[3] relative to 66% for germline testing, compared to 49% (tissue) and 64% (germline) in this study. Furthermore, 86% of CCF physicians recommended PARP inhibitor treatment for mPCa if *BRCA1* or *BRCA2* mutations were identified.[3] A prior study also reported that 36% of sites have mainstreaming available,[17] similar to the 34% noted here. The major difference that we noted from prior literature is an increase in awareness or knowledge around testing, as previously, 40% of physicians were unaware of the best method to identify *BRCA1* or *BRCA2* mutations in patients with PCa.[3]

While physicians appreciate the need for genetic testing in PCa, there remain gaps in access and education around testing. These results suggest a strong need for optimization of testing pathways and health technology assessment evaluation of algorithms for germline and somatic testing in Canada that address issues around cost-effectiveness, logistics, and fund-

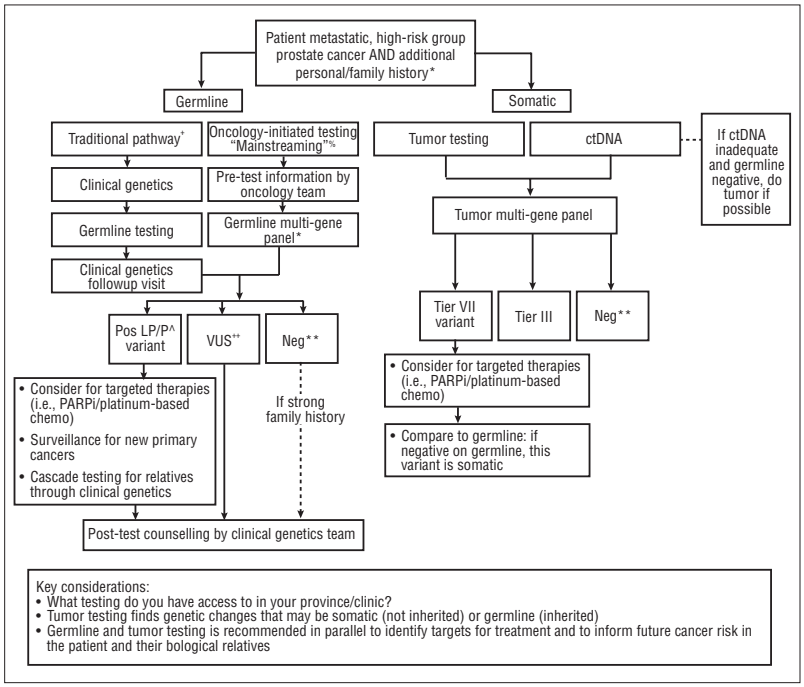

Figure 2. Genetic testing algorithm for metastatic prostate cancer patients (adapted from[28,29,33]). †As explained in13, particularly with patients with a significant family history of malignancies. ‰Refer to clinical genetics for germline testing if mainstreaming pathway not available. *For additional personal/family history criteria, refer to National Comprehensive Cancer Network (NCCN) guidelines.[32] ^Minimum germline panel: *ATM, BRCA1, BRCA2, CHEK2, HOXB13, PALB2, MLH1, MSH2, MSH6, PMS2, EPCAM* (large deletions). #Minimum tumor panel*: BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, CDK12, MLH1, MSH2, MSH6, PMS2,* and *EPCAM* (large deletions). **No variants were detected; tumor testing panel may not cover all genes found in germline testing panel. ctDNA: circulating tumor DNA; LP/P: likely pathogenic/pathogenic variants; Neg: negative; PARPi: poly (ADP-ribose) polymerase inhibitor; VUS: variant of unknown significance.

ing.[17] Although Kolinsky et al discuss clinician-driven mainstreaming and traditional germline HRR genetic testing approaches as options for this disease space,[13] up until now, there were no comprehensive Canadian guidelines for germline and tissue HRR genetic testing in PCa (Editor's note: A Canadian guideline is now available; see this issue of *CUAJ*).

Based upon the findings of this GURC survey and further consultation with multidisciplinary genetics experts, we propose an algorithm to guide genetic testing for mPCa, high-risk PCa, and patients with a family history[28] of PCa (Figure 2). These recommendations are aligned with previously published national and international clinical guidelines for management of PCa.[3, 13,17,28-30,33] Traditional avenues of germline genetic testing require genetic specialist referral to initiate germline testing and conduct a followup with the patient. This model was developed to facilitate testing patients with a strong family history of cancer, where the individual's medical and family history determine the probability of a cancer-predisposing germline mutation.[35] Given the volume of the mPCa population, mainstreaming germline genetic testing by clinician-initiated ordering, guided by specific local criteria or international guidelines,[28] is recommended as a model that ensures timely access to testing while lessening the burden on genetics services. Germline testing using a multi-gene panel that includes a minimum of *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *HOXB13, PALB2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* (large deletions) is recommended. Patients positive for likely pathogenic and pathogenic variants, as well as patients with relevant VUS or negative test results who have a strong family history, should be referred for post-test genetic counselling.

Tumor tissue testing or ctDNA testing with a multigene panel that includes, at a minimum, *BRCA1*, *BRCA2,* and *ATM,* is recommended because of the PARP inhibitor treatment implications, though *MLH1, MSH2,* and *MSH6* may be considered when testing, given potential treatment with immune checkpoint inhibitors.[36-40] Patients positive for likely pathogenic and pathogenic germline variants or tier I/II somatic mutations (strong clinical significance or potential clinical significance, described in Supplementary Figure 1; available at *cuaj.ca)* should be considered for targeted therapies (i.e., PARP inhibitors), with the potential consideration of platinum-based chemotherapy in later lines of therapy.[12] In addition, surveillance for new primary cancers and cascade testing for biological relatives through clinical genetics is also recommended for patients with likely pathogenic or pathogenic germline variants. Ideally, germline and somatic testing should be conducted in parallel to identify targets for treatment and to inform future cancer risk in the patient and their biological relatives.

Implementation of this algorithm should be guided by what is available in the treating physicians practice setting and local practice standards. While mainstreaming hereditary genetic testing represents an ideal model, patients should be offered timely access to germline genetic testing through other pathways if mainstreaming is not possible. Greater access to provincially funded somatic NGS testing is necessary to support such an ideal algorithmic approach to comprehensive genetic assessment of patients. Education should be provided to physicians on the requirements for and implications of both germline and somatic testing (Supplementary Figure 2; available at *cuaj.ca*). Although 95% of the PIs responded to this survey, the overall response rates of these results are limited by 35% sub-I response rates. The respondents primarily practice in academic, urban, and/or major tertiary centers. Although the number and practice setting of respondents may limit generalizability towards more academic settings, these results reflect a national, cross-sectional sample of physicians treating PCa in multiple jurisdictions within the Canadian healthcare system. Furthermore, the topic of genomics in the context of PCa treatment is becoming increasingly complex and more subspecialized in scope of practice and would potentially be beyond the scope of many general oncology or urology practitioners across the nation.

CONCLUSIONS

The results of this survey provide important insights on genetic testing practices among Canadian physicians treating PCa. Largely, Canadian physicians recognized the benefits of both germline and somatic testing, yet there is difficulty accessing testing, with variability between practices and specialties. We propose an algorithm to guide testing and biomarker-directed treatment with PARP inhibitors for patients with clinically relevant HRR genetic alterations.

COMPETING INTERESTS. Dr. Yip reports consultancy or advisory role for and honoraria from Amgen, Astellas, AstraZeneca, Merck, Bayer, Bristol Myers Squibb, Novartis, Pfizer, Hoffman-La Roche, Ipsen, Janssen, and Oncohelix.Dr. Morash hasattended advisory board meetings and given talks for honoraria for AbbVie, Amgen, Astellas, Bayer, Ferring, Janssen, Knight, Sanofi, TerSera, Tolmar, and Verity. Dr. Kolinsky has received grants/honoraria from Astellas, AstraZeneca, Bayer, BMS, Eisai, EMD Serono, Ipsen, Janssen, and Merck; and has participated in clinical trials supported by Astellas, AstraZeneca, Bayer, BMS, Eisai, EMD Serono, Ipsen, Janssen, Merck, and Seattle Genetics. Dr. Ong is a member of the GU Research Consortium Scientific Committee supported by Janssen; has received honoraria for consultancy meetings from AstraZeneca, Bayer, BMS, EMD-Serono, Janssen, Merck, Pfizer, Sanofi, and Sun Pharma; and has received research grants from AstraZeneca and BMS. Dr. Selvarajah has received grants/honoraria from AstraZeneca, Incyte Biosciences, Janssen, and Pfizer. Dr. Nuk has received

speaker/consulting/ad board honoraria from AstraZeneca, Janssen, Merck, and Pfizer. Dr. Pouliot has been an advisory board member for Amgen, Astellas, Astra Zeneca, Bayer, Janssen Novartis, Tersera, and Tolmar; and has received honoraria and/or research grants from Astellas and Merck. Dr. Lavallée has been an advisory board member for Knight; and has received an unrestricted research grant (to institution) from Tomlar. Dr. Hamilton has been an advisory board member for Astellas, Bayer, Janssen, Knight, Pfizer, TerSera, and Tolmar; and has participated in clinical trials supported by Bayer and Janssen (SPARTAN, ARASENS). Dr. Gotto has been an advisory board member for Astellas, AstraZeneca, Bayer, Ferring, Janssen, Merck, Pfizer, and Tolmar; has received honoraria and/or research grants from Astellas, Astra Zeneca, Bayer, Ferring, Janssen, Merck, Pfizer, and Tolmar; and has participated in clinical trials supported by Astellas, AstraZeneca, Bayer, Janssen, Merck, and Pfizer. Dr. Rendon has been an advisory board and speakers' bureau member for and has received honoraria from AbbVie, Amgen, Astellas, Astra Zeneca, Bayer, Ferring, Jansen, Pfizer, Roche, Sanofi, and Tolmar; has received honoraria/grants from AbbVie, Astellas, Bayer, Ferring, Janssen, Sanofi, TerSera, and Tolmar; holds investments in Myovant; and has participated in clinical trials supported by AbbVie, Astellas, Bavarian Nordic, Bayer, Ferring, Janssen, Myovant, and Sanofi. Dr. Hotte has been an advisory board member for AAA/Novartis, Astellas, Bayer, BMS, Eisai, Ipsen, Janssen, Merck, Pfizer, and Seagen; has received honoraria and/or research grants from Astellas, Bayer, BMS, and Janssen; and has participated in clinical trials supported by AAA/Novartis, Astellas, BMS, CCTG, Eisai, Merck, Pfizer, SeaGen, and SignalChem. Dr. Chi has received honoraria from Astellas, AstraZeneca, Daiichi Sanyko, Janssen, Merck, Novartis, Pfizer, Point Biopharma, Roche, and Sanofi; and has participated in clinical trials supported by Astellas, AstraZeneca, Daiichi Sankyo, Janssen, Merck, Novartis, Pfizer, Point Biopharma, Roche, and Sanofi. Dr. Saad has been an advisory board member for and has received payment/honoraria from Amgen, Astellas, AstraZeneca, Bayer, Janssen, Knight, Myovant, Novartis, Pfizer, Sanofi, and Tolmar; and has participated in clinical trials supported by Amgen, Astellas, AstraZeneca, Bayer, Janssen, Novartis, Pfizer, and Sanofi. Dr. Ko has been an advisory board member for Astellas, AstraZeneca, Bayer, BMS, Janssen, Merck, Novartis, Pfizer, and Takeda; has received honoraria from Astellas, AstraZeneca, Bayer, BMS, CADTH, Crystal Gala Foundation Janssen, Merck, Michael Smith Foundation, Novartis, Pfizer, and Takeda; and has participated in clinical trials supported by AstraZeneca, BMS, Merck, and Michael Smith Foundation. Dr. Shayegan has been an advisory board member for AbbVie, Astellas, Bayer, Ferring, Janssen, Knight, Merck, Pfizer, and TerSera; and has participated in clinical trials supported by Ipsen, Janssen, Merck, Myovant, and Pfizer. Dr. Parimi has received honoraria and/or research grants from Astellas, AstraZeneca, Bayer, BMS, Ipsen, Janssen, Merck, Novartis, Pfizer, and Taiho Details Speaking; and has participated in clinical trials supported by Astellas, Janssen, and Merck. Dr. So has been an advisory board member for AbbVie and Janssen. Dr. Feifer has been an advisory board member for Astellas, Bayer, Knight, Janssen, and Tolmar; and has received honoraria from Astella, Bayer, Janssen, and Tolmar. Dr. Finch has been an advisory board member for and received honoraria from Astellas, AstraZeneca, Bayer, BMS, Janssen, Merck, and Pfizer; has been a speakers' bureau member for Pfizer; and has participated in clinical trials supported by Astellas, Astra Zeneca, BMS, and Janssen. Dr. Ho has been a statistical consultant for Janssen. Anousheh Zardan is an employee of Janssen Inc. Canada. Dr. Niazi has been an advisory board member for GURC and Janssen; has received grants and/or honoraria from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Jansen, Knight, Sanofi, and TerSera; and has participated in clinical trials supported by Astellas, AstraZeneca, Bayer, Janssen, Sanofi, and TerSera. The remaining authors do not report any competing personal or financial interests related to this work.

ACKNOWLEDGEMENTS: The authors would like to acknowledge the invaluable contributions made by the late Dr. Anil Kapoor, who passed February 28, 2023. His loss is felt and shared by his patients and the genitourinary oncology community. The authors acknowledge Anshika Singhal, Saurabh Trikha, and Lidija Latifovic of IQVIA for medical writing support.

This paper has been peer-reviewed.

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