Recommendations for the implementation of genetic testing for metastatic prostate cancer patients in Canada

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Funding: *Funding for the working group meeting and environmental scan was provided by AstraZeneca Canada and Merck Canada. All specialists involved were selected and the output was developed independent of the funding sponsors. AstraZeneca Canada and Merck Canada also provided funding for medical writing support through Precision Rx-Dx Inc. in accordance with the version 3 of the Good Publication Practice guidelines (https://www.ismpp.org/gpp3).*

Acknowledgements: *The authors would like to thank Precision Rx-Dx Inc. for supporting the work of the steering committee and working group. The authors acknowledge Philippa Bridge-Cook, PhD, and Andrew Seto, PhD, of Precision Rx-Dx Inc. for medical writing support.*

Cite as: Selvarajah S, Schrader KA, Kolinsky MP, et al. Recommendations for the implementation of genetic testing for metastatic prostate cancer patients in Canada. *Can Urol Assoc J* 2022 June 7; Epub ahead of print. http://dx.doi.org/10.5489/cuaj.7954

Published online June 7, 2022

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Abstract

Introduction: Genetic testing in advanced prostate cancer is rapidly moving to become standard of care. Testing for genetic alterations in genes involved in DNA repair pathways, particularly those implicated in the homologous recombination repair (HRR) pathway, in patients with metastatic prostate cancer (mPCa) can inform selection of optimal therapies, as well as provide information about familial cancer risks. However, there are currently no consistent Canadian guidelines in place for genetic testing in mPCa.
Methods: A multidisciplinary steering committee guided the process of an environmental scan to define the current landscape, as well as the perceived challenges, through interviews with specialists from 14 sites across Canada. The challenges most commonly identified include limited testing guidelines and protocols, inadequate education and awareness, and insufficient resources. Following the environmental scan, an expert multidisciplinary working group with pan-Canadian representation from medical oncologists, urologists, medical geneticists, genetic counsellors, pathologists, and clinical laboratory scientists convened in virtual meetings to discuss the challenges in implementation of genetic testing in mPCa across Canada.
Results: Key recommendations from the working group include implementation of germline and tumour HRR testing for all metastatic patients, with a mainstreaming model in which non-geneticist clinicians can initiate germline testing. The working group defined the roles and responsibilities of the various health care providers (HCPs) involved in the genetic testing pathway for mPCa patients. In addition, the educational needs for all HCPs involved in the genetic testing pathway for mPCa were defined.
Conclusions: As genetic testing for mPCa becomes standard of care, additional resources and investments will be required to implement the changes that will be needed to support the necessary volume of genetic testing, to ensure equitable access, and to provide education to all stakeholders.

Introduction

Over the last decade, characterization of the mutational landscape of prostate cancer tumours has created opportunities for cancer risk assessment and precision oncology[1]. Approximately 20 to 30% of patients with mPCa have pathogenic variants (PVs) in genes associated with the homologous recombination repair (HRR) pathway [2-5], with *BRCA2* gene alterations being the most prevalent [6]. In up to half of these, the PVs are of germline origin [4]. Germline refers to inherited PVs that people are born with, are present in every cell in the body, and have a chance to be passed on to children. Thus, prostate cancer can be a heritable disease, but it should be

noted that the absence of a family history in mPCa patients does not rule out the presence of a germline mutation[7]. The other half of PVs are somatic in origin and are acquired in tumour cells during tumorigenesis. Identification of clinically relevant variants that are germline in origin is critical since these variants have implications not only for the patient themselves but also hereditary cancer risks for family members. Somatic and germline variants in HRR genes also have prognostic and treatment implications for affected individuals. The presence of HRR deficiency may predict response to poly (ADP-ribose) polymerase (PARP) inhibitors as well as to other DNA-damaging chemotherapy agents (platinum chemotherapy) [8-10].

Given the implications for treatment and familial risk mitigation, genetic testing in mPCa patients is moving rapidly to becoming standard of care [11,12]. Patient samples for germline testing can be obtained from peripheral blood or saliva. Somatic testing (also called tumour testing) is typically performed using archived formalin-fixed paraffin-embedded tumour tissue from biopsies from the prostate or metastases, or radical prostatectomy specimens, but can also be performed on fresh frozen specimens. While bone-predominant metastatic spread is seen in mPCa, these lesions are associated with a high biopsy failure rate and present challenges for molecular analysis if the bone specimens are decalcified prior to histology processing [13,14]. Tumour DNA for somatic testing can also be obtained via "liquid biopsy" approaches from peripheral blood, by isolating cell free DNA (cfDNA) that has been shed by cells undergoing apoptosis, a proportion of which is tumour derived and termed circulating tumour DNA (ctDNA) [15,16]. Tumour testing is required to identify patients eligible for PARP inhibitor therapy, since germline testing alone would miss about half of the eligible patients. Conversely, tumour testing does not necessarily distinguish whether a variant is present in the germline or was acquired in the tumour; however, depending on the methodology used, some cfDNA assays that analyze both ctDNA and genomic DNA from leukocytes can provide both tumour and germline testing results from a single assay. Tumour and germline testing in mPCa are both typically performed by next-generation sequencing (NGS), as this method can assess multiple genes concurrently and can evaluate different types of variants such as single nucleotide variants (SNVs), small insertions and deletions, and copy number variants (CNVs).

Currently there are no Canadian guidelines for germline or tumour testing in mPCa, although international clinical practice guidelines provide some recommendations on tumour and germline testing [11,17,18]. Based on the paucity of data in the Canadian context, we performed an environmental scan to gain insight into the current Canadian landscape of genetic testing for mPCa patients, and the barriers to ensuring that appropriate patients have timely access to testing. We then convened an expert multidisciplinary working group to discuss the findings of the environmental scan and develop recommendations to support implementation of testing in Canada.

Methods

An expert multidisciplinary steering committee was formed to guide the process of assessing the current Canadian landscape for genetic testing in mPCa and the challenges in implementing equitable and timely access to testing for all patients who would benefit. Members of the steering committee were selected from four provinces based on their expertise and experience working with genetic testing in mPCa patients, and familiarity with the barriers and challenges in this area. In addition, this committee was formed to provide a national perspective, and to cover key multidisciplinary specialties involved in genetic testing in mPCa: medical oncology, urology, clinical genetics, and laboratory medicine.

The steering committee developed an environmental scan questionnaire to use in semi-structured virtual interviews with specialists involved in genetic testing or downstream users of genetic testing for mPCa. Genetic testing in mPCa was not widely implemented across Canada at the time of the environmental scan; therefore, sites were chosen based on their involvement in genetic testing in mPCa, and specialists interviewed had to be familiar with the requirement for genetic testing in mPCa patients. Interviews were conducted in July and August 2021in 14 different testing centres in six provinces to provide a pan-Canadian perspective. Twenty-six in depth interviews were conducted with multidisciplinary specialists, with representation from pathology/laboratory medicine (n=8), medical oncology (n=4), urology (n=6), clinical genetics (n=3), and genetic counselling (n=5). The questionnaire was designed to probe key aspects of the current genetic testing landscape for mPCa including what type of testing is being done, how and where testing is done, and at what disease stage. Interviewees were also asked about what they perceived as current and near-term future challenges for genetic testing in mPCa. Following the interviews, the information on the testing landscape at the different sites was summarized, and challenges identified by interviewees were grouped into common themes. The frequency of the types/ themes of challenges identified by the interviewees was used to rank the challenges by order of most commonly listed to least commonly listed .

Following the environmental scan, an expert multidisciplinary working group was formed to develop recommendations and commentary on process improvements to address the challenges that had been identified in genetic testing across Canada. Members of the working group were identified by the steering committee based on their involvement in genetic testing in mPCa, and familiarity with the requirement for genetic testing in mPCa. The group had pan-Canadian representation and included the steering committee members as well as additional medical oncologists, urologists, medical geneticists, genetic counsellors, pathologists, and clinical molecular geneticists. The expert working group convened in two virtual meetings to review the findings of the environmental scan and discuss potential approaches to address the challenges in testing. Topics discussed included at which disease stage tumour and germline testing should be done, what biomarkers should be tested, specimen types, how to integrate tumour and germline testing, and which testing models/workflows would be most efficient. The

working group also discussed the roles and responsibilities of health care providers (HCPs) along the testing pathway, and the education that would be required to implement genetic testing in mPCa. After the meetings, recommendations and commentary were developed by the steering committee based on the meeting discussions and circulated to the working group members for their review and additional input. Final recommendations were approved by all of the working group members.

Results

Environmental scan

From the twenty-six interviews conducted from 14 testing sites, it was the general opinion of most that very small percentages of mPCa patients are currently receiving genetic testing, although there are no formal tracking systems in place at any site.

Responses from interviewees about germline testing for mPCa across Canada are summarized in Table 1. Among the sites, 65% currently have defined eligibility criteria in place for germline testing in mPCa patients. However, since one of the selection criteria for the sites was involvement in genetic testing in mPCa patients, this is not likely representative of sites across Canada, and the percentage of all sites that would have eligibility criteria for germline testing in mPCa patients is likely lower. Criteria vary by site and by province. The interviewed specialists stated that germline testing for prostate cancer is typically done in metastatic or metastatic castration-resistant patients, as well as high risk patients with family histories of BRCA-related cancers. Out of province or out of country (OOP/ OOC) testing was being carried out by 71% of the sites, with only 36% of sites testing in house; however, 36% of sites carrying out OOP/OOC testing are in the process of bringing testing in-house. Most laboratories in Canada require blood samples and do not have an option for saliva testing, although testing of saliva samples is available through out-of-country laboratories. Mainstreaming models, in which clinicians such as oncologists, urologists, or oncology surgeons consent patients for germline testing and order the tests themselves, are in use at some sites. Currently, 36% of sites have the option for clinicians to use a mainstreaming model, and an additional 29%are planning to implement this.. The turnaround time (TAT) for mainstreamed or urgent/expedited testing ranges from three to six weeks for Canadian laboratories. Upon special request, test results can sometimes be expedited to be returned in 2 weeks. In addition, OOC laboratories may have faster TATs than Canadian laboratories. For patients who do not have testing initiated by their non-geneticist physicians, the wait for germline genetic testing through referral to genetics services varies widely across the country, from two weeks to 18 months.

Currently, funding for tumour testing is limited in Canada outside of research studies, although most sites are in the process of developing such testing (Table 1). While at the time of the interviews, only 14% of sites had defined eligibility criteria for tumour testing, three provinces have since defined provincial eligibility criteria, which increases the percentage of

sites with defined eligibility criteria to 64%. Tumour testing is typically being done in metastatic patients who are progressing on novel hormonal agents (NHAs, i.e. abiraterone acetate, apalutamide, darolutamide, enzalutamide), primarily to determine PARP inhibitor eligibility. Archived paraffin-embedded tissue specimens are the most commonly used sample type, although there is also some access to testing of liquid biopsy specimens through clinical trials and studies. Public funding for tumour testing in mPCa is currently provided in only three provinces.

A shared opinion among the specialists was that the most common barrier to genetic testing in mPCa was limited and/or varying testing guidelines and protocols (Figure 1). The insufficient guidelines and protocols were perceived to be a barrier for both germline and tumour testing. Few sites have a formal protocol or algorithm for genetic testing in mPCa, or a clear process linking germline and tumour testing. Only three provinces have defined eligibility criteria for germline testing, and three provinces have eligibility criteria for tumour testing. Interviewees also stated that processes for requisitioning testing are not clear, and harmonization of clinical reporting is needed.

Having sufficient budgetary resources to provide the testing that will be required for mPCa patients was also perceived to be a significant barrier (Figure 1). Laboratories need more funding in order to provide complex testing services. Test delivery is dependent upon capital equipment (high throughput sequencing instruments) and test validation costs, as well as personnel such as medical laboratory technologists, bioinformaticians and clinical laboratory scientists/molecular pathologists. Furthermore, there is currently very limited public funding for tumour testing in mPCa. In addition, germline testing processes were thought to be insufficient to manage the expected volume, particularly by medical geneticists and genetic counsellors. Both the volume of referrals and the urgency of referrals for germline testing are expected to increase because of new treatment options, and few centres have either a formal priority process to help manage the volume, or formal referral criteria.

Inadequate education, competencies, and awareness among both HCPs and patients was also identified by interviewees as a challenge for implementing genetic testing in mPCa (Figure 1). The interviewed specialists identified the following general educational needs: the specificities of tumour and germline testing and the utility of each type of testing, how to access testing, and how the results should be interpreted and used. Education outside of academic centres may be particularly important for clinicians who do not specialize in treating mPCa. Given that the level of familiarity with hereditary cancer was noted to be low in men, it is critically important for HCPs to update their competency in this area so that they can fill in the knowledge gap for this patient population. Uncertain roles and responsibilities for HCPs involved in genetic testing in mPCa were also perceived to be a barrier. Urologists, genetic counsellors, and medical geneticists were most likely to mention uncertain roles and responsibilities as a barrier for testing implementation (Figure 1).

Specimen challenges were also cited as a barrier, particularly by pathologists, clinical molecular geneticists and urologists (Figure 1). There are multiple potential challenges with older archived tissue specimens such as nucleic acid integrity as well as logistical issues such as coordination of shipping blocks to testing centers and retrieving older specimens from offsite storage facilities. The failure rate for NGS testing of tissue specimens may be high: in the PROFOUND trial, 30% of archival or recent tissue specimens were not successfully sequenced due to low DNA input from small biopsy specimens or sample decalcification by acid solutions [8]. However, alternative NGS techniques using amplicon-based library preparation typically yield an improved success rate even with minimal DNA material extracted from small biopsy or cytology specimens, and non-acid decalcification solutions (i.e. ethylenediaminetetraaceticacid (EDTA) preservative) should always be considered for bone specimen pre-processing. Liquid biopsy testing was also thought to have a number of challenges such as false positive (due to non-actionable clonal hematopoiesis-associated variants) or false negative results due to both technical (sample processing, limited sensitivity), and biological (non- or low-shedding tumors) factors. In addition, the interpretation of a cfDNA test result is dependent on the ctDNA to total cfDNA fraction, which is impacted by tumour burden, disease aggressiveness and response to treatment. The impact of these factors may not be necessarily understood by the clinician ordering the test.

Discussion and recommendations from the expert multidisciplinary working group

The expert multidisciplinary working group considered the challenges and barriers to genetic testing of mPCa that were identified by the environmental scan and developed commentary and recommendations to address them, as well as commentary on the gaps in evidence that is needed to inform additional recommendations. The recommendations from the working group are summarized in Table 2.

Discussion: Clinical flow

Patients with mPCa need genetic testing both to inform familial cancer risks and to inform treatment selection. The working group recommends that all mPCa patients receive germline and tumour testing to identify pathogenic variants in genes associated with HRR. This aligns with current guidelines from European Society for Molecular Oncology (EMSO) and National Comprehensive Cancer Network (NCCN) [11,18]. Some sites may also integrate genetic testing of prostate cancers with adverse histologies earlier in the disease course, dependant on availability of funding, particularly as intraductal or cribriform pattern on biopsy has been associated with bi-allelic *BRCA2* mutations [11,19]. If tumour testing is done first, positive results should be followed up with germline test after appropriate counselling to determine whether a particular variant is of germline or tumour origin. However, if tumour testing is performed with a limited gene panel such as *BRCA1*, *BRCA2*, and *ATM*, then germline testing should still be performed even when the tumour testing results are negative—this is key to identifying potential germline

variants in other HRR associated genes and other genes associated with hereditary prostate cancer. In addition, if tumour testing results are negative, but the family history is suggestive of hereditary cancer as described in Supplementary Materials 1 (SM1), the patient should be referred to a cancer genetics clinic for appropriate follow-up.

The optimal testing algorithm has not yet been defined. A harmonized algorithm for tumour and germline testing needs to be developed and implemented consistently to ensure equitable access across Canada. Issues such as cost effectiveness, practicalities, logistics of testing, provincial funding and test availabilities should be considered in the development of the testing algorithm. Timing of genetic testing relative to the disease stage and how the results will be used in terms of cascade genetic testing of at-risk biological relatives and eligibility for PARP inhibitor therapy will also need to be considered. The working group recommends health technology assessment of the cost-effectiveness of the various testing algorithms/clinical workflows in order to inform the optimal algorithm. In addition to the development of a harmonized testing algorithm, there is a need for development of regional or provincial protocols for testing workflows as well as where specimens should be sent. Although there are challenges in Canada with wait times for access to genetics services and faster TAT may be possible through out-of-country testing, it is important to keep testing within Canada as much as possible unless raw data can be shared and stored in provincial systems. This will ensure the development of Canadian expertise and understanding of local population genetic variation for variant classification. As protocols are developed, it is critical to create a multidisciplinary process between HCPs involved in the testing process to ensure that all patients have equitable access to testing. This is particularly true for community sites without local genetics resources.

Ordering germline testing through mainstreaming models

Due to the prevalence of the disease, the volume of mPCa patients requiring genetic testing will require the use of alternative models of care for germline testing as opposed to the traditional model, in which the patient is referred to a genetics service to manage the pre-test counselling, order the genetic testing, disclose the results, and manage the post-test counselling (Figure 2). Mainstreaming is an alternate model that allows access to genetic testing for mPCa patients with less burden on genetics services. In a mainstreaming model, germline testing is initiated by a non-genetics clinician, who does the pre-test counselling and orders the test (Figure 2) [20]. When the pre-test counselling is performed by clinicians in patients who have already been diagnosed with cancer, there are several key points to cover (Table 3). These points can generally be covered in a reasonably short amount of time; however, referral of a patient to a genetics clinic is suggested if pre-test counselling is found to take an increased amount of the clinician's time. Readily available patient education materials such as pamphlets, videos for pretest genetic education, telehealth, or digital communication tools can enhance or aid in the patient's education, informed consent and decision-making process.

Although other alternate models of care for germline testing may be adopted, such as group genetic counselling, mainstreaming is the most frequently adopted model because it results in a faster TAT and also can decrease the burden on genetics services, depending on the degree to which genetics clinics remain involved in the results disclosure on the backend [21]. There are different permutations of mainstreaming, and each centre may adopt a different model. Next-generation models where the clinician orders the test, is responsible for communicating the result, and prioritizes only patients with pathogenic/likely pathogenic variants, relevant variants of uncertain significance, or those with a significant family history for referral to the genetics service for post-test genetic counselling will have the most impact on decreasing the burden on the genetics service [22]. When mainstreaming is implemented at a centre, it is important to ensure that appropriate referrals for genetic counselling take place. Some examples of how to ensure this include having the genetics service acting as a hub for all patients who receive testing and identifying patients for cascade testing, and/or having a genetic counsellor affiliated with the laboratory. In addition, laboratories that accept germline testing requests from non-genetics clinicians through mainstreaming, such as oncologists, radiation oncologists, urologists, or urologic oncologists, should recommend referral of patients with pathogenic/likely pathogenic variants for genetic counselling; a standard operating protocol should be developed to ensure that appropriate referral takes place.

Mainstreaming models have successfully been introduced for breast and ovarian cancer in many large academic centres. However, implementation of a mainstreaming model in mPCa requires adaptations, given the relatively recent understanding of the significant burden of hereditary cancer risk in patients with mPCa. This contrasts with the original introduction of mainstreaming for breast and ovarian cancer indications that followed a 20-year history of genetic testing for *BRCA1* and *BRCA2*; when mainstreaming was introduced in these indications, many clinicians treating gynecologic and breast cancers would have been familiar with the need for genetic testing. Additionally, general urologists and even more specialized clinicians may not have the same familiarity with genetics or baseline level of comfort, knowledge, awareness, or ability to participate in a mainstreaming model of genetic testing. The sheer volume of mPCa patients requires a large number of health care professionals, primarily urologists, who may have diverse practices, making knowledge dissemination challenging. At present, genetic testing is recommended in the NCCN guidelines for patients with mPCa, patients with node-positive, high-risk, or very high–risk localized prostate cancer, or patients with a significant family history [11]; therefore, providers must be aware of the patient's changing disease course and remember to initiate genetic testing when appropriate. Furthermore, the diversity of providers who care for mPCa patients, including general practitioners, urologists, radiation oncologists, and medical oncologists, will require multidisciplinary communication to ensure each provider knows their individual responsibilities regarding genetic testing. Although the working group recommends mainstreaming as an ideal model, there also should be flexibility to ensure that when

mainstreaming is not possible, germline testing is still accessible in a timely manner for patients through other pathways.

Selection of the optimal specimen for testing

Tumour testing can be performed using traditional tissue testing with fresh or archived tissue specimens, or with plasma derived cfDNA obtained from peripheral blood specimens (Figure 2). A detailed discussion of the advantages and disadvantages of tissue versus liquid biopsy is beyond the scope of this manuscript; however, a brief summary can be found in the Supplementary Materials (SM1, Table 1). Liquid biopsy for prostate cancer and its technical constraints have also been recently reviewed by Herberts and Wyatt [23]. The algorithm for selection of the optimal specimen for tumour testing in various clinical scenarios needs to be established. Due to the limitations in each method, access to both ctDNA and tissue-based testing will allow successful testing in the greatest number of patients. In patients with a high burden of actively progressing disease, levels of ctDNA are typically higher and liquid biopsy assays are more likely to give successful sequencing and interpretable test results [24]. In addition, ctDNA testing may be ideal for patients with a clinical diagnosis of mPCa who have never had a tissue biopsy. If ctDNA results are inconclusive, tissue testing should be performed if tissue is available. It is important for ctDNA assays to assess germline variants concurrently to distinguish mutations arising from clonal hematopoiesis of indeterminate potential and also to identify mutations with a germline origin. Laboratories should clearly define and communicate specimen requirements as well as test limitations to ordering physicians.

Access to genetic testing

Equity of access to genetic testing for mPCa patients is critical. Although there are limited Canadian data to provide insight on demographics among patients receiving genetic testing versus those not receiving testing, data from the United States suggest that there are disparities in testing and that Black, Hispanic, and Asian Pacific Islanders are underrepresented in testing [25,26]. In Canada, racial and ethnic minorities are also underrepresented in testing both for cancer patients themselves, and for their family members, especially Indigenous peoples [27,28]. In addition, patients who were older than 65 years of age or not proficient in English were less likely to receive genetic testing [29]. Patients in rural, remote and Northern communities in Canada may also have less access to testing. Therefore, the working group recommends that centres should develop a process to identify gaps in equity for patients in access to genetic testing. Unless there is a systematic process to ensure equitable access to genetic assessment for all patients with mPCa, there should be a quality control system in place to evaluate which patient subgroups are being referred and receiving testing, and which subgroups are being under-tested.

Gene panels for germline and tumour testing

The working group recommends a germline testing gene panel that can both inform both familial cancer risk, as well as provide information that may impact treatment and clinical trial options. The minimum set of genes for germline testing in mPCa should include *ATM, BRCA1, BRCA2, CHEK2,* large deletions in *EPCAM, HOXB13, MLH1, MSH2, MSH6, PALB2,* and *PMS2.* This gene panel aligns with current recommendations from international guidelines such as NCCN, ESMO, and the Philadelphia Prostate Cancer Consensus Conference [11,12,18]. Additional genes may be important depending on the clinical context taking into account the patient's personal and family history. In addition to single nucleotide variants (SNVs) and small deletions and insertions (indels), germline testing should also be able to identify copy number variants (CNVs), at exon-level resolution if possible. It should be noted that use of a larger gene panel for germline testing will lead to more patients who receive results with variants of uncertain significance (VUS), which may cause anxiety for patients. Most variants of uncertain significance are later downgraded to benign or likely benign variants [30].

Tumour testing in mPCa patients can provide information about the responsiveness of a patient's cancer to various treatment options, inform prognosis, and assist in selection of clinical trials. Positive tumour testing results also indicate the possibility of hereditary cancer risks that should be investigated through germline confirmatory testing. The working group recommends that the minimum set of genes for tumour testing in mPCa should include *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2,* and *CDK12.* In addition, tumour testing for microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) is clinically indicated in mCRPC [11], and thus testing of *MLH1, MSH2, MSH6, PMS2* and *EPCAM* (large deletions) is also warranted. Additional genes may also be included for research purposes or inclusion of patients in clinical trials. Despite the importance of CNVs, it can be difficult to detect these alterations in the tumour genome due to low tumour cellularity as well as intra-tumour heterogeneity and sampling bias which can make calling CNV segments complicated. Furthermore, formalin fixed, paraffin-embedded tissue specimens on which the tumour tests are usually performed can yield poor quality DNA, which adds another layer of challenge for CNV detection. Therefore, these limits should be considered in the design of the NGS panel and computational methods used for estimation of CNVs in tumour testing.

Since understanding a patient's hereditary cancer risk requires screening with the minimum set of genes recommended for germline testing, the working group recommends that as much as possible, tumour testing gene panels should be aligned with germline testing gene panels for efficiency in combining treatment-focused and hereditary cancer assessments.

Reporting

To improve awareness of genetic testing for mPCa patients, pathology reports should incorporate a statement commenting on the availability of genetic testing for mPCa patients that is in alignment with provincial guidelines and funding. Furthermore, laboratories reporting the results

of genetic testing in mPCa should ensure that the communication of these results can be understood by clinicians ordering the testing. Clear, top line, actionable information should be highlighted at the beginning of the report. Variants reported from tumour testing may have treatment implications and/or germline implications, both of which should be summarized in the report. However, since analysis is limited to tumour tissue, testing of a peripheral blood sample should be performed whenever a variant is identified, in order to determine whether it is somatic or germline in origin. Thus, reports should include a recommendation for germline genetic testing. Reports should be clear about how variants of uncertain significance are defined, and the guidelines used for variant interpretation: there may be differences in the interpretation of the same variant in the germline versus tumour setting. For example, in the context of tumour testing and reporting using the the Association for Molecular Pathology, College of American Pathologists, and American Society of Clinical Oncology (AMP/ASCO/CAP) guidelines, a variant that is defined as Tier 3 (variants of uncertain clinical significance) because of uncertain therapeutic, diagnostic, or prognostic clinical implications for the patient's cancer [31] may be pathogenic or likely pathogenic in the context of hereditary cancer genetic testing. Thus, reports should clearly indicate any Tier 1 or 2 variants with treatment implications, as well as pathogenic or likely pathogenic variants in cancer susceptibility genes that are a concern for hereditary cancer risk. Patients with VUS results may also be offered the option of a referral to a genetics service for a more thorough explanation and counselling about what a VUS is, and the importance of keeping in touch with the genetics service over time. In addition, when tumor testing gene panels are not aligned with the recommended germline testing gene panels, there should be a statement on the report indicating that the patient may have germline variants in other genes not tested in tumour testing, and that germline testing is recommended. Limitations of the test should also be clear on the report, whether the test is a germline test, a tissue-based tumour test, or a cfDNA-based test.

Roles and responsibilities of health care providers involved in genetic testing

The uncertainty and variability of roles and responsibilities of HCPs involved in genetic testing for mPCa patients, as well as limited coordination on the testing process within centres, create challenges in ensuring that all eligible patients receive the appropriate genetic testing. The roles of all the HCPs involved need to be well defined to ensure that the necessary testing is consistently and appropriately performed. The addition of a mainstreaming model as an option for germline testing is a key change in practice that will affect oncologists, urologists, pathologists, cancer genetics programs, and primary care providers.

The working group considered the optimal roles of all of the HCPs involved in the testing pathway. Tumour testing will likely be ordered by clinicians to assist in selection of appropriate therapies. However, once the results of tumour testing are received, clinicians will also need to order germline testing for patients with relevant pathogenic/likely pathogenic variant results in genes that have relevance for hereditary cancer predisposition, after appropriate consent is

obtained. If the gene panel for the tumour test is limited, clinicians will need to order germline testing regardless of the results of the tumour test, since the tumour testing may miss variants in other genes that could inform on hereditary cancer risks for patients and their families. Tumour boards may have utility in helping clinicians interpret results, but not all clinicians will have access to that type of resource. It should be clear who is responsible for disclosure of genetic test results to patients, even for patients with negative results. Patients should ideally receive a copy of any germline genetic test results so that they can share them with their family members. The role of pathologist-initiated reflex testing will be limited in mPCa unless specific issues are addressed. Since most patients do not have metastatic disease at the time of their diagnostic biopsy and only a portion develop metastatic disease years later, pathologists may not have access to clinical data to suggest the patient has metastatic disease, or imaging studies may be performed only after the biopsy is performed. Allied HCPs can be a resource and help facilitate the testing process with clinicians; for example, nurses, nurse navigators, and nurse practitioners can facilitate ordering the tests, with sign off on test orders by the physician, according to regional guidelines and practices. Primary care physicians should support decision-making around testing, take appropriate actions related to prevention and early detection in affected individuals and families, and support and encourage access to testing.

Education

Insufficient education and awareness in both HCPs and patients were identified as a barrier to the implementation of genetic testing in mPCa. Many clinicians in genitourinary oncology have limited experience with genetic testing and the mainstreaming model of delivery of germline testing. Therefore, the working group recommends that education should be provided to all stakeholders involved in genetic testing in mPCa. Testing champions within centres can be critical to assist in knowledge dissemination and help facilitate HCP involvement in testing. Because of the multidisciplinary nature of the clinical flow for genetic testing in mPCa, there should be a formal multidisciplinary process or forum for communication, decision-making, and education within a centre. In addition, patient education materials should be available to improve both awareness around tumour and/or germline testing, and the quality of discussion between patients and their healthcare providers.

Medical oncologists, urologists, radiation oncologists and any other clinicians treating mPCa patients will require education on the difference between germline and tumour testing and when and why each type of testing is used. In addition, the practicalities of testing will need to be clearly outlined for clinicians so that they understand the following: the process to access testing, the process of obtaining patient consent for germline testing, the appropriate specimen type and collection solutions, and the eligibility criteria for germline and tumour testing. Clinicians will also need to understand the advantages and problems associated with the use of fresh versus archival tissue and from various sites; for example, bone biopsies present additional complexity for genetic testing and may have a higher failure rate [13,14]. In addition, testing cfDNA in liquid

biopsy specimens is associated with challenges and idiosyncrasies as described above. Finally, interpretation of the results and next steps for the clinician will require education. For example, it is important that if cfDNA testing returns an inconclusive result due to insufficient tumour fraction, tissue testing should be performed if there is tissue available. Management of VUS results will be new to many clinicians and will thus need explanation.

Education for pathologists involved in genetic testing for mPCa patients should include the rationale for and importance of the test, which histologic features to highlight for clinicians, and how to identify the best biopsy core for testing. In addition, education should include tissue considerations specific to mPCa such as the potential for failure of genetic testing if bone biopsies are decalcified using acidic solution [14].

As health care professionals with strong patient relationships, primary care providers are an important source of support for the patients and their families in their decision-making regarding germline genetic testing. Primary care providers need to be aware of the increasing importance of hereditary cancer, appropriate testing strategies and availability, referral and testing criteria, and appropriate actions around prevention and early detection in affected individuals. Primary care providers should also have an understanding of the Genetic Non-Discrimination Act (GNDA) so that they can provide reassurance to patients who have fears about how their test results might be used [32]. The GNDA prevents companies like insurance providers from requiring the results of genetic testing when providing services or goods, or when entering contractual agreements, and also prevents companies from denying services based on the results of genetic tests.

Since genetic testing for mPCa patients is relatively new, genetic counsellors may require an overview of prostate cancer as a disease, including staging and management. Furthermore, genetic counsellors may benefit from information about how to create alternative models of care in their centres such as telephone, video, or group genetic counselling. These alternative models have been shown to be acceptable alternatives to the traditional model in terms of knowledge, patient satisfaction, psychosocial measures, and the uptake of genetic testing [33,34].

Resources

To ensure timely access to both tumour and germline testing for mPCa patients, additional resources and investments for genetic testing will be needed. The lack of resources to manage the capacity and workload required for tumour and germline testing are currently a significant barrier. This includes resources across the testing pathway, such as the following: (1) the time required from all stakeholders for onboarding to the genetic testing process; (2) extra time required from clinicians and pathologists for the testing itself; (3) the laboratory capacity required to support testing; (4) the genetics service capacity. Public funding needs to include infrastructure for testing to support the expected capacity, aspects of the testing process that are currently not funded such as test validation and capital equipment, and funding for additional genetic counselling services. Lack of sufficient resources to support testing limits the timely

availability of testing results, which can affect patients' access to treatment options and informed decision-making about cancer risks for their family members.

Future directions

As genetic testing in mPCa becomes implemented more widely across Canada, additional studies are needed to inform the optimization of testing pathways, including health technology assessment evaluation of various testing algorithms, information about patient demographics receiving testing, and better understanding of the prevalence of HRR variants in non-metastatic disease. In addition, tools must be developed for all involved stakeholders, patients, and patient organizations that focus on the main areas of educational need. Patient education materials, including information for consent, and FAQs will need to be developed and translated to different languages to provide support necessary to ensure equitable testing.

Conflicts of interest: S.S. reports an institutional grant from AstraZeneca and consulting fees from AstraZeneca Canada, Janssen Canada and Incyte Biosciences Canada. K.A.S. reports honoraria from Pfizer, AstraZeneca, and an insitutional research grant from CIHR. M.P.K. reports consulting fees from Astellas, AstraZeneca, Bayer, BMS, Eisai, Ipsen, Janssen, and Merck. R.A.R. reports a leadership/fiduciary role in the Canadian Urological Association. S.E-H. reports an institutional grant from AstraZeneca Canada. N.F. reports grants from Janssen, Astellas, Bayer, Sanofi, Nucleix, and Progenix, consulting fees from Amgen, Janssen, Astellas, Bayer, Sanofi, Abbvie and Ferring, honoraria from Ferring and CUA, and support for meetings and travel from UCLA Department of Urology, University San Raffaele, Bayer, Jo-Events, Tecnofarma Prostate Forum, and Jannsen.N.A.F. reports a leadership/fiduciary role in Verity Pharmaceuticals and POINT Biopharma, and stock/stock options in Verity Pharmaceuticals and POINT Biopharma. S.J.H. reports research grants from BMS, Bayer, Janssen, and Astellas. J.L. reports honoraria from TerSera and has a leadership/fiduciary role in the PROMISE registry. R.P. reports honoraria from AstraZeneca Canada for lectures. F.P. reports consulting fees from Astellas, AstraZeneca, Merck, Tolmar, TerSera, Janssen, and Novartis. A.S. reports consulting fees from AstraZeneca, BMS, Amgen, Janssen, Pfizer, AbbVie, Roche, Lilly, and Merck. S.Y. reports participation in data safety monitoring boards/advisory boards from Amgen, AstraZeneca, Bayer, Incyte, Novartis, and Roche. K.N.C. reports institutional grants from AstraZeneca, Janssen, Merck, Novartis, Point Biopharma, and Roche, consulting fees from Astellas, AstraZeneca, Daiichi Sankyo, Janssen, Merck, Novartis, and Macrogenics, honoraria from Janssen, and payment for expert testimony from AstraZeneca, Janssen, and Novartis. S.S., K.A.S., M.P.K., R.A.R., S.E-H., N.F., S.J.H., J.L., K.P., R.P., F.P., A.S., S.Y., and K.N.C. report honoraria from AstraZeneca Merck Canada for participation in the environmental scan and working group meetings related to this project.

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Figures and Tables

Figure 1. Summary of challenges for germline and tumour testing for metastatic prostate cancer in Canada.

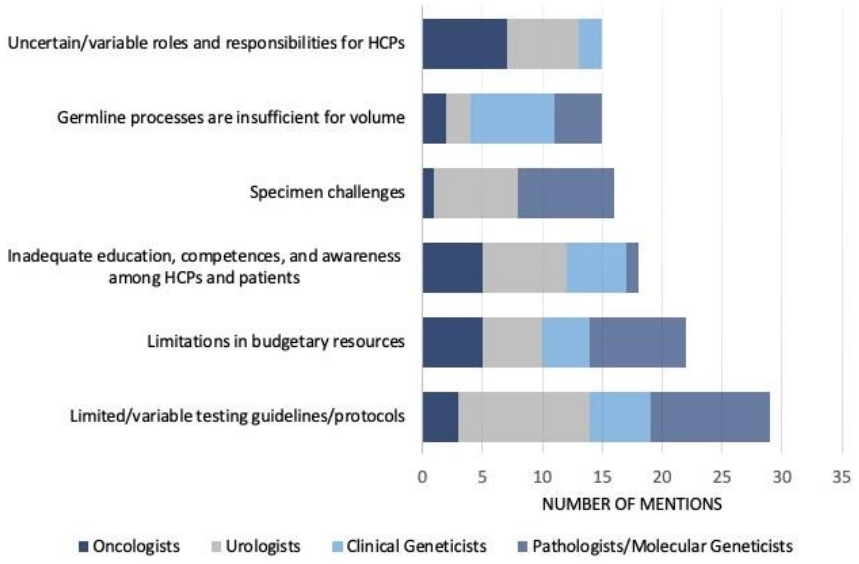

Figure 2. Clinical flow options for genetic testing in metastatic prostate cancer. **(A)** Germline testing through a traditional model or a mainstreaming model. **(B)** Somatic (tumor) testing using tissue or liquid biopsy specimens.

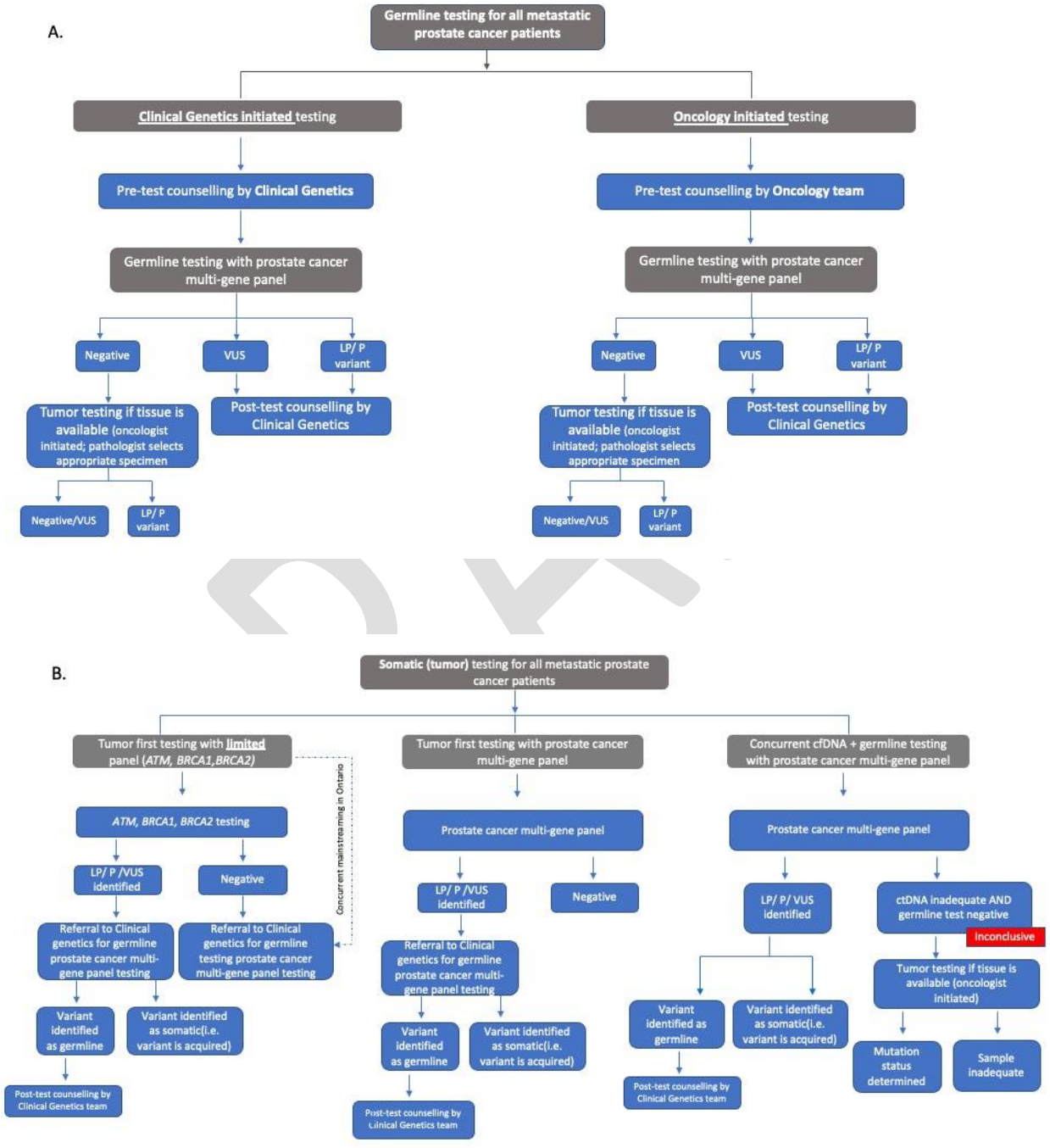

Table 1. Summary of results from 14 sites on the current landscape for germline and tumor testing in Canada		
	Germline testing	**Tumor testing**
Testing criteria	9 sites (64%) have defined criteria	2 sites (14%) have defined criteria
Stage of disease when testing is typically done	Metastatic PCa, mCRPC, high risk patients with familial PCa	Metastatic patients progressing on NHA, patients with metastatic PCa regardless of prior therapy
Where is testing done	5 sites (36%) are testing in house, and 10 sites (71%) refer to laboratories out of the country or outside their province	1 site (7%) is doing clinical testing in house, 1 site (7%) is doing research-based testing for patients at that institution, and 12 sites (86%) are in the process of bringing testing in house
Sample type used	Blood samples are typically used; one site in Canada offers saliva as an option, as well as out-of-country labs	Archived tissue specimens are the most common, although there is also some use of liquid biopsy specimens
Size of gene panel	In house panels in Canada range from 9–19 genes, whereas out-of-country panels range from 16–73 genes	72–300 genes
Turnaround time	For mainstreamed or urgent testing, TAT ranges from 3–6 weeks. Referral to genetics service can range from 2–18 months.	2–4 weeks

CRPC: castration-resistant prostate cancer; NHA: novel hormonal agent; PCa: prostate cancer; m: metastatic; TAT: turnaround time.

Table 2. Summary of recommendations from the expert multidisciplinary working group
Clinical flow 1. All metastatic prostate cancer (mPCa) patients should receive germline and tumour HRR testing. If tumour testing is done first, then positive results should be followed up with a confirmatory germline test following appropriate counselling. If the gene panel for tumour genetic testing does not encompass all the genes on a germline gene panel, then all metastatic patients should receive both germline and tumour testing. 2. The optimal testing algorithm for tumour and germline testing needs to be considered, including cost effectiveness, practicalities, and test availabilities. 3. Health technology assessment of the cost-effectiveness of various testing algorithms/clinical workflows should be done.
Ordering germline testing through mainstreaming models 4. Mainstreaming is recommended as an ideal model that lessens the burden on genetics services and supports timely initiation of germline testing. However, there should be flexibility to ensure that when mainstreaming is not possible, genetic testing for patients is accessible through other pathways in a timely manner. Also, the physicians ordering the testing should have competency to offer pre-test counselling to patients and ensure adequate follow-up with genetics services on both the tested patients and their families. 5. Any laboratory allowing providers outside of genetics services (eg. medical oncologists, urologists, oncology surgeons) to order germline testing through mainstreaming should recommend referral of patients with pathogenic/likely pathogenic variants and relevant variants of uncertain significance for genetic counselling. A standard operating protocol should be developed to ensure appropriate referral takes place.
Selection of the optimal specimen for testing 6. The algorithm for selection of the optimal specimen for tumour testing (ie. tissue vs blood) in various clinical scenarios needs to be established. However, cfDNA assays are an option for tumour testing in mPCa. cfDNA tests should assess germline variants concurrently to rule out false positive findings due to CHiP (clonal hematopoiesis of indeterminate potential) and to also concurrently identify germline variants. 7. Laboratories should clearly define and communicate specimen requirements to ordering physicians.
Access to genetic testing 8. Centres need to develop a process to identify gaps in equity for patients in access to genetic testing. 9. Unless there is a systematic process to ensure equitable access to genetic assessment for all patients with mPCa, there should be a quality control system in place to evaluate which patient subgroups are being referred and receiving testing, and which patient subgroups are being missed.

Gene panels for germline and tumour testing 1. The minimum set of genes for germline testing in mPCa should include *ATM, BRCA1, BRCA2, CHEK2, EPCAM* (large deletions), *HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2.* Additional genes may be important depending on clinical context. 2. The minimum set of genes for tumour testing in mPCa should include *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2,* and *CDK12.* In addition, tumour testing for microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) is clinically indicated in mCRPC. Additional genes may also be included for research purposes or inclusion of patients in clinical trials. 3. As much as possible, tumour testing gene panels should be aligned with germline testing gene panels for efficiency in combining treatment-focused and hereditary cancer assessments.
Reporting 4. Pathology reports should incorporate a statement commenting on the availability of genetic testing for mPCa patients that is in alignment with provincial guidelines and funding. 5. Reports should be clear about how variants of uncertain significance are defined, and the clinical implications of the reported variants. 6. Reports should be clear about the guidelines used for variant interpretation in germline versus tissue testing as there could be potential differences in the interpretation of the same variant in the germline versus tumour setting (i.e. ACMG guidelines, VICC guidelines, ASCO/AMP/CAP guidelines).
Education 7. Education needs to be provided to all stakeholders involved in genetic testing, with particular focus on areas of need identified in this document. 8. Testing champions within centres are critical to assist in knowledge dissemination and facilitate stakeholder involvement in testing. 9. There should be a formal multidisciplinary process or forum for communication, decision making and education within a centre. 10. Patient education materials should be available to improve both awareness around tumour and/or germline testing, and the quality of discussion between patients and their healthcare providers.

Table 3. Key points to cover when consenting metastatic prostate cancer patients for germline genetic testing
This is a blood test to see **if your cancer is hereditary**
The results may **guide the treatment** of this cancer
This test may determine **other cancer risks** for you
The results may have **implications for your relatives**
It is possible that the interpretation of your result **may not be clear** at this time
Genetic information is **protected** (Canadian Genetic Non-Discrimination Act (GNDA) passed into law May 2017, upheld by the Supreme Court July 2020)
In the event that you are not available to receive your genetic test results, please provide the name and contact information of a relative who the results can be shared with.