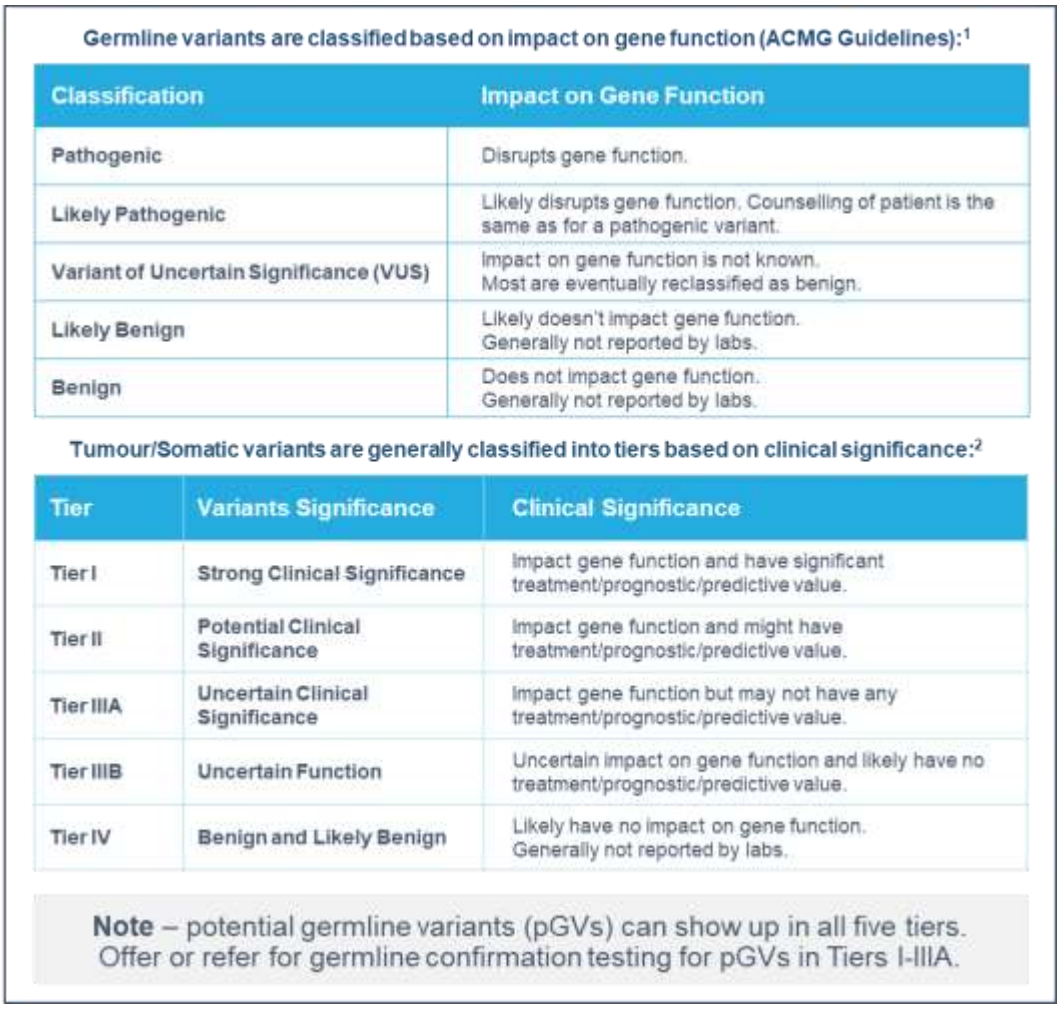
APPENDIX

Supplementary Figure 1. Germline and somatic variant classification.



Germline variants are classified based on impact on gene function (ACMG Guidelines):[1]

Classification	Impact on Gene Function
Pathogenic	Disrupts gene function.
Likely Pathogenic	Likely disrupts gene function. Counselling of patient is the same as for a pathogenic variant.
Variant of Uncertain Significance (VUS)	Impact on gene function is not known. Most are eventually reclassified as benign.
Likely Benign	Likely doesn't impact gene function. Generally not reported by labs.
Benign	Does not impact gene function. Generally not reported by labs.

Tumour/Somatic variants are generally classified into tiers based on clinical significance:[2]

Tier	Variants Significance	Clinical Significance
Tier I	Strong Clinical Significance	Impact gene function and have significant treatment/prognostic/predictive value.
Tier II	Potential Clinical Significance	Impact gene function and might have treatment/prognostic/predictive value.
Tier IIIA	Uncertain Clinical Significance	Impact gene function but may not have any treatment/prognostic/predictive value.
Tier IIIB	Uncertain Function	Uncertain impact on gene function and likely have no treatment/prognostic/predictive value.
Tier IV	Benign and Likely Benign	Likely have no impact on gene function. Generally not reported by labs.

Note – potential germline variants (pGVs) can show up in all five tiers. Offer or refer for germline confirmation testing for pGVs in Tiers I-IIIA.

[1]Adapted from Richards et al.[1]

[2]Adapted from Li et al.[2]

1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetic Med* 2015;17:405-23. https://doi.org/10.1038/gim.2015.30
2. Li MM, Datto M, Duncavage EJ, et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer: A joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. *J Molec Diag* 2017;19:4-23. https://doi.org/10.1016/j.jmoldx.2016.10.002

Supplementary Figure 2. Molecular genetic analysis for patients with PCa: Points to consider.

1. Pre-Test:
    1.1. Know what is covered/what your patient is eligible for in your province or territory, what you can order, and what has to be ordered by a genetics specialist:
        1.1.1. Tumour Testing
        1.1.2. ctDNA
        1.1.3. Germline Testing
    1.2. If you are ordering the testing:
        1.2.1. Know what genes are included in the test.
        1.2.2. Keep in mind that tissue/ctDNA testing is generally **not** equivalent to a germline test.
            1.2.2.1. Referral to genetics should be considered for patients who have a negative test, particularly in the context of a strong family history of cancer.
        1.2.3. Counsel patient on purpose and possible outcomes of genetic testing.
            1.2.3.1. The possible results (including VUS).
            1.2.3.2. The potential implications for themselves and their relatives.
            1.2.3.3. That tumour testing may identify a potential germline variant.
                1.2.3.3.1. Consider discussing implications of a positive result with patient prior to ordering the test.
            1.2.3.4. A referral to genetics/further genetic testing (e.g., germline confirmation) may be needed after you disclose the results.
        1.2.4. Consider providing an information sheet so the patient can review the main discussion points.
        1.2.5. Document your discussion and the patient's consent in their chart.
2. Post-Test:
    2.1. Know when to refer to genetics and/or offer germline confirmation.
        2.1.1. All patients with a LP/P germline variant should be referred to discuss screening recommendations and testing for family members.
        2.1.2. Genetics may see some or all patients with a VUS.
        2.1.3. Are you able to order germline confirmation testing for variants detected on tumour tests, or do you need to refer to Genetics?
    2.2. Disclose the results to the patient.
    2.3. For patients with LP/P variants, discuss implications for family members and how they can access testing.
    2.4. Do NOT alter cancer screening or management based on a VUS.
    2.5. Let the patient know what the next steps are (e.g., appointment with Genetics) and where they can get more information.
    2.6. Consider providing an information sheet to the patient about their results.

2.7. Document your discussion with the patient in their chart.

3. When in doubt, contact Genetics!

ctDNA: circulating tumour DNA; LP/P: likely pathogenic/pathogenic variants; PCa: prostate cancer; VUS: variant of unknown significance.

PLAIN LANGUAGE SUMMARY: LAY ABSTRACT

What was the study about?

An estimated 24,600 Canadian men were diagnosed with prostate cancer in 2022. Certain therapies that treat prostate cancer work better when patients have been identified to have specific changes to their DNA through genetic testing. These changes can either be inherited (*germline)*, which are passed down from parent to child, or acquired (*somatic)*, which instead happen during a person's lifetime.

What did we do?

We surveyed 38 Canadian academic specialist physicians, who treat prostate cancer, to understand: how they access genetic testing; what type of testing they offer; when they offer testing; and to which patients do they offer this testing.

What did we find?

Access to genetic testing is not equal across regions in Canada. Many physicians must refer patients to a genetic specialist to gain access to genetic testing, which can delay treatment. Most physicians offer genetic testing for both germline and somatic changes to patients with:

- High-risk prostate cancer,
- Prostate cancer that has spread to other parts of the body, or
- Family history of cancer,

Many physicians find it more difficult to access somatic testing than germline testing. Physicians believe testing for germline and somatic changes should occur at the same time. Knowing the results of both types of testing help physicians determine the best available treatment for patients. Germline testing also helps identify family relatives who should be offered testing, who may have higher risk of developing cancer given their risk of inheriting a change to their own genetics.

PLAIN LANGUAGE SUMMARY: INFOGRAPHIC

Yip et al. Genetic testing practices among specialist physicians who treat prostate cancer: A Canadian, cross-sectional survey

What did we find?

Current Situation

- Most physicians offer genetic testing to prostate cancer patients and recognize the need for both germline and somatic testing.
- A large proportion require referral to a genetic specialist to start germline genetic testing.

Referral Process

- Most physicians refer to a genetics specialist when high risk mutations are found (e.g., BRCA or ATM mutations).

Access

- Most physicians have access to germline testing, with fewer having access to somatic testing.
- An access gap and uncertainty around how to order genetic tests were the most common reasons for not testing.

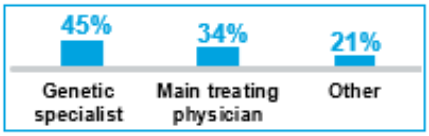
Risk Stratification

- Generally, physicians indicated that germline and somatic testing should be offered to prostate cancer patients with high-risk disease or disease that has spread to other parts of the body, especially when there is a family history of cancer.

Provincial Differences

- There are differences across regions in Canada regarding the availability of genetic testing.
- Patients are encouraged to discuss testing practices in their region with their health care provider.

Who orders the test?

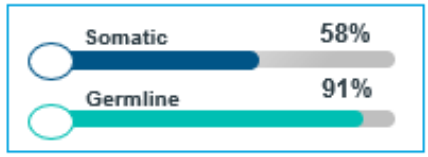


Which genetic changes are tested?

94% are referred to a genetic specialist when BRCA1, BRCA2 or ATM genetic changes are identified.

Compared to 27% when any other genetic changes are identified.

The type of testing currently available to physicians



Physicians who did not offer genetic testing, did not because of ...

Access gap	50%
Uncertainty about how to order or interpret results	33%
No impact on patient management	17%

Recommendation

Genomic Testing in Prostate Cancer

- For patients with prostate cancer that has spread to other parts of the body, both germline and somatic testing are recommended to identify targets for treatment and to inform future cancer risk in patients and their family relatives.
- Patients with specific genetic changes (e.g., BRCA1 or BRCA2) and advanced prostate cancer may be offered treatment with targeted therapies (i.e., PARP inhibitor) or platinum-based chemotherapy at some point in their course of treatment.

Note: BRCA is short for BReast CAncer gene, ATM stands for ataxia-telangiectasia mutated, and PARP stands for poly-ADP ribose polymerase.

The benefits of genetic testing for selection of optimal treatment for prostate cancer and informing future cancer risk for patients and their relatives are widely recognized among Canadian physicians. However, differences exists in accessing testing across provinces. Patients with advanced or high-risk prostate cancer should be tested for both germline and somatic genetic changes at the same time to optimize treatment.

Want to learn more or get more details?

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GURC
Genitourinary Research Consortium