APPENDIX

How to identify hereditary cancer through family history

Cancer that runs in families creates certain patterns that can be identified by health care providers. Signs of hereditary cancer in family histories include:

- The **same type(s) of cancer** in **two or more close relatives** on the same side of the family, often over **multiple generations** on the same side of the family
- cancer **diagnoses at younger ages** than expected
- **multiple primary** tumors
- **rare cancers**
- **pattern** of cancer history suggestive of a known hereditary cancer syndrome, such as breast, ovarian, pancreatic and prostate cancer, or colorectal and endometrial cancer

Specific signs of hereditary prostate cancer in addition to the above include:

- Personal history of prostate cancer with ≥1 close relatives[1] with prostate cancer.
    - One relative must have evidence of high risk or metastatic disease.
- Personal history of prostate cancer with ≥2 close relatives with prostate, pancreatic, and/or breast cancer regardless of age or stage

[1]Note that close relatives typically refer to first degree (parents, siblings, children) and second degree (uncles, aunts, nephews, nieces, grandparents, and grandchildren) relatives on the same side of the family.

When taking a cancer family history, it is important to:

- Consider at least 3 generations, on both maternal and paternal sides of family, in first and second degree relatives
- Consider ethnic background
- R all types of cancer, and age at diagnosis when possible
- When histories of common metastatic sites are given, encourage further inquiry about the primary site
- Ask for updates to cancer family history over time

Supplementary Table 1. Advantages and disadvantages of tissue and liquid biopsy for somatic genetic testing in metastatic prostate cancer[1-5]

	Advantages	**Disadvantages**
Tissue biopsy specimen	• Provides direct sampling of tumor tissue • High clinical and analytical sensitivity • Archival tissue may be available for testing • Well-established method for use in clinical settings (i.e., easily integrated into the diagnostic workflow) • Can detect all mutations relevant for treatment decisions (germline and somatic) • Does not require upfront consent for germline genetic testing (although does require general education of the referring clinician or pathologist around the chance of finding something that may require germline confirmation) • Does not require germline confirmation of variants of uncertain significance (independent of patient eligibility of provincially funded germline testing)	• Specialty expertise required for tissue acquisition • Biopsy procedure is invasive and with risk of procedural complications • Difficult to repeat biopsy if necessary • May not reflect tumor heterogeneity • Diagnostic biopsy may not reflect tumor evolution (subclones that expand in the metastatic phase may non-uniformly represented) • Serial biopsy not feasible for some populations/impractical for periodic monitoring of treatment response • Obtaining samples from metastases may be challenging due to the invasive nature of the procedure or location of metastatic lesions • Both archival tissue and fresh biopsies can have a significant failure rate if hybrid capture technique is used for NGS

	• If the same gene panel is used for somatic testing and germline testing, a tumor-first testing approach can allow for triaging of patients reflexively, which reduces the burden on the clinical genetics service	• May not distinguish between germline and somatic mutations, thus may need to be followed by germline testing to inform familial and personal risk
Liquid biopsy specimen	• Minimally invasive procedure to obtain sample (advantageous in patients who have comorbidities) • Faster turnaround time than tissue biopsy • Can detect all mutations relevant for treatment decisions (germline and somatic) but results require confirmatory germline testing if not performed concurrently • Convenient for serial sampling/ real-time monitoring for drug response and resistance • Potential to reveal spatial and temporal tumor heterogeneity • Less resource intensive (e.g., does not require digital imaging as performing tissue biopsies usually do)	• Can be expensive to validate and offer routinely, depending on the biomarker (hotspot vs. multi-gene panel) • Can lead to false negatives if there is not enough ctDNA being shed • Can miss homozygous somatic deletions • Not typically offered to all patients earlier in the disease course due to insufficient disease burden (ctDNA shedding may be insufficient for detection) • More complex requirements for specimen collection and transportation with significant preservation failure rates (special collection tubes are needed to prevent hemolysis during transportation)

References

1. Cheng H, Powers J, Schaffer K, et al. Practical methods for integrating genetic testing into clinical practice for advanced prostate cancer. *Am Soc Clin Oncol Educ Book* 2018; 38:372-81. https://doi.org/10.1200/EDBK_205441
2. Cheng H.H, Sokolova AO, Schaeffer EM, et al. Germline and somatic mutations in prostate cncer for the clinician. *J Natl Compr Canc Netw* 2019;17:515-21. https://doi.org/10.6004/jnccn.2019.7307

3. Di Capua D, Bracken-Clarke D, Ronan K, et al. The liquid biopsy for lung cancer: State of the art, limitations, and future developments. *Cancers (Basel)* 2021;13:3923. https://doi.org/10.3390/cancers13163923
4. Gonzalez-Billalabeitia E, Conteduca V, Wetterskog D, et al. Circulating tumor DNA in advanced prostate cancer: Transitioning from discovery to a clinically implemented test. *Prostate Cancer Prostatic Dis* 2019;22:195-205. https://doi.org/10.1038/s41391-018-0098-x
5. Ossandon MR, Agrawal L, Bernhard EJ, et al. Circulating tumor DNA assays in clinical cancer research. *J Natl Cancer Inst* 2018;110;929-34. https://doi.org/10.1093/jnci/djy105