# *Current recommendations for prostate cancer genetic testing: NCCN prostate guideline*

James L. Mohler, MD,[1] Celestia S. Higano, MD,[2] Edward M. Schaeffer, MD, PhD,[3] Heather H. Cheng MD, PhD[2]

[1]Departments of Urology and Pharmacology and Therapeutics, Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA

[2]Division of Medical Oncology, University of Washington, and Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

[3]Department of Urology, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, Illinois, USA

MOHLER JL, HIGANO CS, SCHAEFFER EM, CHENG HH. Current recommendations for prostate cancer genetic testing: NCCN prostate guideline. *Can J Urol* 2019;26(Suppl 2):34-37.

*DNA sequencing has become less expensive and patients are requesting sequence information more often. The clinical utility of identifying genomic and/or somatic mutations remains uncertain in most cancers and especially in prostate cancer. However, clinical guidelines must offer guidance. The rapidly expanding knowledge base requires that guideline panels pay vigilant attention to the literature, advocate for clinical trials and correlative science, and provide frequent guideline updates.*

**Key Words:** prostate cancer, genomic and somatic sequencing, genetic counseling

## Process used to develop the genetic testing sections of the NCCN guidelines for prostate cancer

The rapid evolution of knowledge about genomic and somatic mutations in prostate cancer necessitated that the Prostate Panel procure additional expertise to improve the 2019 guideline. Additions to the algorithms and principles caused a posting delay until March 2019 (normally posted in November; the 2019 guideline is in version 4 already.[1] The changes made were explained in greater detail in a manuscript first authored by our expert[2] and in the manuscript section of the guideline. Presentations of new data at the panel in-person meeting June 27, 2019 will improve the 2020 guideline.

## Key features of the genetic testing sections of the NCCN guidelines for prostate cancer

In clinically localized prostate cancer, PROS-1[1] describes the elements of a proper family history for known germline variants (footnote c) and the family history

Address correspondence to Dr. James L. Mohler, Department of Urology, Roswell Park Comprehensive Cancer Center, Elm and Carlton Streets, Buffalo NY 14263 USA

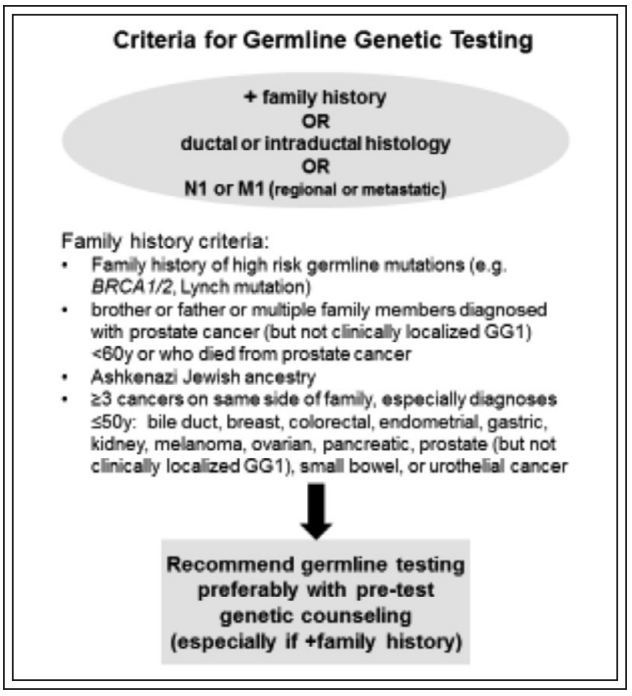


**Figure 1.** Criteria for germline genetic testing.

criteria to prompt germline testing (footnote d). Only high or very high-risk groups warrant consideration of germline testing in the absence of a positive family history (footnote k). PROS-9 recommends germline testing for all men who present with regional or metastatic prostate cancer (footnote k) and consideration of somatic testing to uncover germline mutations (footnote l) and to uncover mutations that may impact future therapy (footnotes dd and ee).

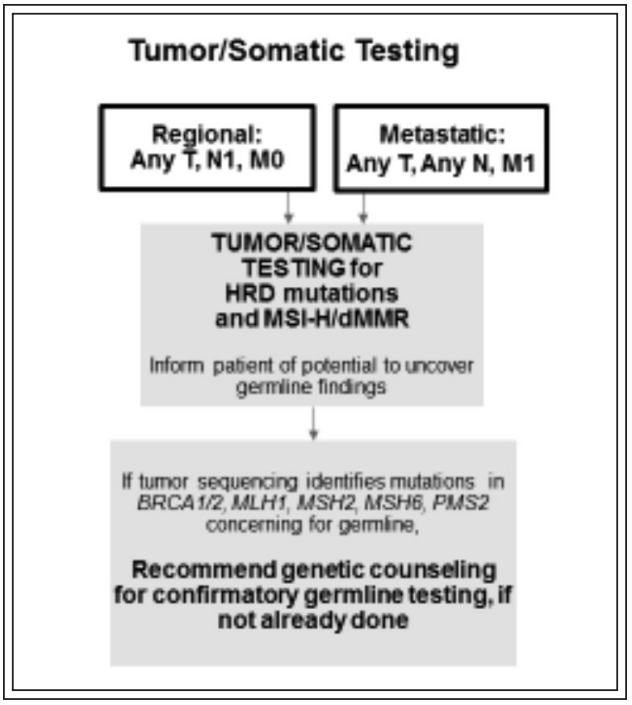


**Figure 2.** Tumor and somatic testing.

## Genetic testing algorithms for use in the clinic

An extensive family history of cancer, Figure 1, should prompt recommendation for germline testing. While family history is a necessary component of history gathering, it is not sufficient for identifying many men carrying germline genetic variants/mutations associated with cancer risk. Regional or metastatic prostate cancer[3,4] and intraductal[5] or ductal[5,6] histology has a higher association with germline cancer risk mutations.

Somatic (tumor) testing has greatest relevance in the metastatic setting, but may be important in the regional setting, Figure 2. Clinical trials are testing targeted therapies in earlier disease states (www.clinicaltrials.gov). Pembrolizumab is a treatment option for advanced prostate cancer with evidence of microsatellite instability (MSI-H) and mismatch repair deficiency (dMMR) and after failure of prior approved agents in the metastatic (m) castration-resistant prostate cancer (CRPC) setting. Earlier use of platinum-based chemotherapy[7,8] or enrollment on clinical trials testing PARP inhibitors[9] (phase II and

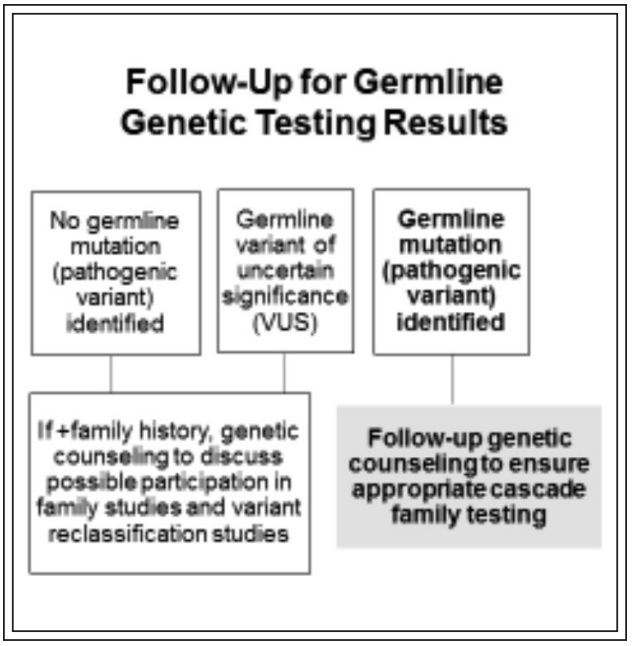


**Figure 3.** Follow up for germline genetic testing results.

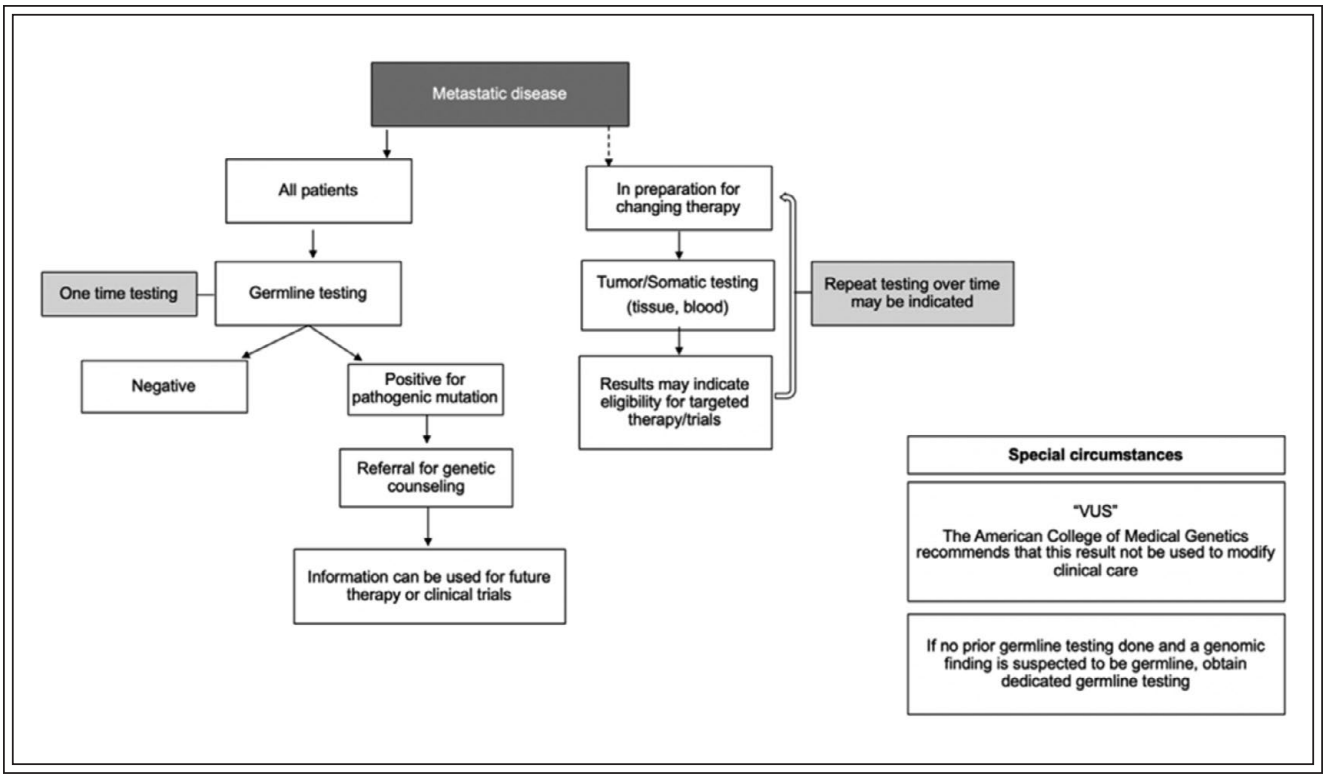


**Figure 4.** Algorithm.

III studies are in process that include the phase III PROFOUND study of olaparib in mCRPC) may be warranted in prostate cancer patients with homologous recombination DNA repair alterations.

Tumor/somatic testing may reveal a gene mutation that is potentially germline. Identifying somatic mutations in genes associated with cancer predisposition may suggest need for reflex genetic counseling for confirmatory germline testing, if not already done.

Understanding the potential outcomes of germline testing and responsibilities of the ordering provider for follow up is critical since workflows vary across practices, Figure 3. For example, if a germline pathogenic variant or likely pathogenic variant (i.e. mutation) is identified in a gene associated with cancer risk, follow up genetic counseling, if not already done, is essential to ensure appropriate patient understanding and appropriate cascade family testing (testing of at-risk relatives). In addition, patients with very strong family histories of cancer (high pre-test suspicion) and/or who are found to carry variants of uncertain significance (VUS) may have opportunities for research studies, in which new genes or variants are identified, or VUS may be reclassified.

## Integration of genetic testing in to clinical practice

Most practices have focused on better history taking and, in cases of increased risk of genomic mutations, proceeding with (i) genetic testing and, if positive, referral for genetic counseling, (ii) genetic counseling educational videos with possible testing or (iii) genetic counseling followed by possible testing. Somatic mutations may be sought in metastatic prostate cancer, especially CRPC, and especially when considering change in therapy, Figure 4.

Genomic testing may use targeted (about $250 self-pay to $2500 for full *BRCA* analysis) or next generation sequencing (NGS; about $3500) but NGS tests are neither designed nor validated for germline assessment. The utility of germline variant identification remains uncertain. For example, identifying a *BRCA1* or *BRCA2* mutation is not sufficient, since many lack known function.[10]

Genetic counselors are highly trained medical professionals with expertise in counseling, addressing questions and anxiety about testing, and facilitating intra-family communication and appropriate follow up. They play essential roles in the processes described

above, but are in high demand and limited supply, so that close partnership to optimize and triage their resources is necessary and will require more providers to become familiar with basic information about genetics and to take on certain aspects of pre-test counseling.

The Prostate Panel continues to deal with the explosion of genetic information, interacts with the Prostate Cancer Early Detection Panel, and hopes to provide congruency with the Breast, Ovarian and Colorectal guideline genetic recommendations. Best practice recommendations will emerge with more data and experience.

## Disclosures

The authors have no disclosures. □

References


1. Mohler JL, Antonarakis ES, Armstrong AJ et al. NCCN clinical practice guidelines in oncology, prostate cancer. J Natl Compr Canc Netw: 2019; Version 4.2019. Accessed August 23, 2019.
2. Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and somatic mutations in prostate cancer for the clinician. *J Natl Compr Canc Netw* 2019;17(5):515-521.
3. Nicolosi P, Ledet E, Yang S et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. *JAMA Oncol* 2019;5(4):523-528.
4. Pritchard CC, Mateo J, Walsh MF et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016;375(5):443-453.
5. Bottcher R, Kweldam CF, Livingstone J et al. Cribriform and intraductal prostate cancer are associated with increased genomic instability and distinct genomic alterations. *BMC Cancer* 2018;18(1):8.
6. Isaacsson Velho P, Silberstein JL, Markowski MC et al. Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. *Prostate* 2018;78(5):401-407.
7. Cheng HH, Pritchard CC, Boyd T, Nelson PS and Montgomery B. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. *Eur Urol* 2016;69(6):992-995.
8. Pomerantz MM, Spisak S, Jia L et al. The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. *Cancer* 2017;123(18):3532-3539.
9. Mateo J, Carreira S, Sandhu S et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med* 2015;373(18):1697-1708.
10. Cline MS, Liao RG, Parsons MT et al. BRCA challenge: BRCA exchange as a global resource for variants in BRCA1 and BRCA2. PLoS Genet 2018;14(12):e1007752.