Urology perspective on the expanding world of germline testing for prostate cancer

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The management of high-risk prostate cancer is evolving. Currently, most decisions are based on traditional factors such as tumor grade and stage. However, we are in a state of evolution. A new understanding of the value of both genetic and somatic germline testing is upon us. Perhaps even more exciting is the recognition that genomic testing can and should be moved up in certain high-risk patients so more effective and targeted therapy can be applied earlier in the disease state.

Key Words: prostatic neoplasm, genetic testing, germline mutations

The management of men with prostate cancer that includes high-risk localized, regional, metastatic castration sensitive prostate cancer (mCSPC) and castration resistant prostate cancer (CRPC) is evolving. Currently, most decisions are based on traditional factors such as tumor grade (Gleason), stage, volume and location of metastatic burden, response to therapy and performance status. Studies in mCSPC have reported additional survival benefit with treatment added to traditional ADT.[1,2] However, even in the CRPC state clinical factors such as prior treatments, degree of symptomology, performance status, staging and location of tumor predominantly drive treatment recommendations.[3] Along the way, we have begun to appreciate the predictive and potentially prognostic value of both genetic and somatic germline testing. The hope, and in some instances the reality, is that analyzing genetic alterations may help to select therapy that is more effective as first line or in the salvage setting. Perhaps even more exciting is the recognition that genomic testing can and should be moved up in certain high-risk localized disease to guide those at risk for disease progression so that more effective therapy can be applied earlier in the disease state.

As urologists and urologic oncologists, we have been aware of a hereditary basis for prostate cancer in men with newly diagnosed prostate cancer and those presenting for screening.[4] We were taught to assess family history of prostate cancer, and routinely queried our patients for first and second-degree relatives with prostate cancer. Those men with a strong family history of prostate cancer were encouraged to seek genetic counseling and testing. However, we often failed to recognize the importance of asking about other malignancies and familial syndromes in prostate cancer inheritance. Now, with an increasing understanding of the genomic profile of metastatic prostate cancer, prostate cancer is increasingly being recognized as a part of other inherited syndromes including hereditary breast and ovarian syndrome (HBOS), Lynch syndrome and hereditary prostate (HPC).[5] With this increasing awareness of inherited germline mutations, we have broadened our questioning to include breast, ovarian, endometrial, pancreatic, bile duct, colorectal, and urothelial cancers. We now know that 20%-25% of patients with mCRPC will harbor either homologous recombination (HR) mutations or DNA mismatch repair (MMR) gene mutations.[6,7] So, now there is an even greater emphasis on obtaining genomic testing on tissue in men with mCRPC.

What are the goals of genetic testing in men with prostate cancer? When should testing be considered? The answer is not a "one size fits all" approach. For men contemplating prostate cancer screening, the goal could be to assess an individual's increased risk or probability above the general population for developing the disease. Patient and family members at increased risk may also elect for earlier or more aggressive screening. Further, they may also seek to modify behavior or environmental exposures in hopes of delaying or preventing the disease. Genetic and germline testing may also have an impact on prognosis. This could affect treatment selection in situations where certain therapeutics may be more or less effective in the setting of specific mutations. Recently, it was reported that intraductal carcinoma (IDCP) and invasive adenocarcinoma are *BRCA2*-mutant tumors

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that can arise from the same ancestral clone, implying that a temporal evolutionary trajectory exists.[8] Functional studies have shown that *BRCA2*-mutant tumors may contain a subpopulation of cancer cells that can tolerate castration de novo, enabling the tumor to evade ADT therapy. So, for localized patients with this variant they might be better served with surgery as compared to radiation therapy that would normally be combined with ADT. Thus, this molecular profiling may alter treatment recommendations in the case of IDC and other subtypes.

Targeted therapy may be suitable for some men with identified pathogenic variants in specific genes. Examples of this are already being seen in some men with mCRPC who have failed first line therapy. A recent study found that patients with mCRPC with DNA repair abnormalities in the tumor have better response and an overall survival (OS) benefit when treated with poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibition with olaparib.[9] Preliminary results of the TRITON-2 study in men with mCRPC who have failed at least one line of androgen receptor–directed therapy and one prior line of taxane-based chemotherapy reported patients with the *BRCA1* or 2 mutation responded to rucaparib, whereas other patients, including those with other gene mutations like *ATM* and *CDK12*, did not respond.[10] In another study, mCRPC patients who are *BRCA2* carriers also demonstrate a 75% PSA response to carboplatin versus 17% in noncarriers.[11] These examples demonstrate how genomic information can help identify patients for treatment and hold promise for more effective personalized medicine.

Currently, guidelines for genetic testing in patients at high risk for developing prostate cancer as well as those with an established diagnosis are evolving. Recently, the updated 2019 National Comprehensive Cancer Network (NCCN) guidelines on prostate cancer reflect the growing importance of "genetic testing and genomically-informed disease management into clinically practice" in the management of men with prostate cancer.[12,13] They recommend consideration of tumor testing for HR mutations and microsatellite instability or deficient MMR (dMMR) among patients with either regional spread or metastatic prostate cancer. The NCCN also recommends testing for germline mutations in all newly diagnosed men with NCCN high-risk, very high-risk, regional or metastatic prostate cancer, as these men may harbor germline mutations at a higher rate than the general population. Currently, within the Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline (2017), it states, "Clinicians may consider referral for genetic counseling for patients (and their families) with high-risk localized prostate cancer and a strong family history of specific cancers (e.g., breast, ovarian, pancreatic, other gastrointestinal tumors, lymphoma).[14] In addition, it is highly anticipated that a position statement or Guideline by either the American Urologic Association or the Society of Urologic Oncology addressing the role of genetic testing in prostate cancer will be forthcoming in the near future.

Disclosures

Dr Michael S. Cookson is a consultant for Myovant Sciences and Astellas Pharma US.
He is on the advisory board for Janssen Scientific Affairs, Bayer Healthcare and Ferring Pharmaceuticals. □

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