Considerations of germline testing in prostate cancer screening

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POLASCIK TJ, ORABI H, on behalf of the Duke Cancer Institute Prostate Cancer Screening Collaborative. *Can J Urol* 2019;26(Suppl 2):46-47.

Prostate cancer screening remains controversial in the medical field. While screening men above 50 years can impose overdiagnosis and overtreatment, targeted screening of males with pathologic variants of genetic mutations is evolving and viewed as sensible. Identifying such patients requires genetic testing in males having family history of prostate cancer or certain ethnicity. Such strategies will likely occur as routine practice once favorable results of ongoing studies assessing genetic predisposition are released.

Key Words: germline mutations, prostate cancer, prostate cancer screening, *BRCA1*, *BRCA2*, genetic testing

Hereditary prostate cancer (HPC), with approximately 10% incidence among prostate cancer patients, is defined by having ≥ 3 first-degree relatives within the same family or three successive generations or two first-degree relatives < 65 years with prostate cancer.[1] Familial prostate cancer, with incidence of 25%, is considered with a history of prostate cancer in the family but not meeting the criteria of HPC.[2] Both groups presage more aggressive disease and higher cancer-specific mortality than those without family history. The principal difference between those groups is the presence of inherited genetic mutations such as *BRCA1/2* among HPC. As such, HPC has increased risk of secondary primary malignancies such as male breast, pancreatic and colon cancers. When prostate cancer was detected in patients with prostate cancer family history, nearly half in the early PROFILE study had normal PSA < 3 ng/mL.[3]

In prostate cancer, the percentage of patients with germline mutations differ according to disease stage, ranging from 4.6% (localized) upwards of 11.8% to 16.2% (metastatic).[4,5] Mutations include *BRCA1/2*, *FANC*, *ATM*, *PALB2*, *NBN*, *MRE11*, *BLM*, and *ATR*. *BRCA1/2* are the most commonly tested and identified associated with prostate cancer. *BRCA2* and *BRCA1* mutations are identified in 5.3% and 0.9 % with metastatic prostate cancer, respectively.[4]

Clinical trials are investigating the genetic predisposition to prostate cancer in individuals with family history and certain ethnicity, such as IMPACT, PROFILE and BARCODE 1. In the IMPACT study (ClinicalTrials.gov NCT00261456), prostate cancer detection rates during the initial year of screening were 2.3% for *BRCA1* carriers and 3.3% for *BRCA2* carriers.[6] The low cancer detection rate was attributed to the limited number of men who had biopsies performed before the widespread adoption of mpMRI and fusion biopsies. The pilot PROFILE study (ClinicalTrials.gov NCT02543905) that included 100 males with family history of prostate cancer, showed a 25% cancer detection rate,[3] a higher rate than IMPACT since all subjects underwent prostate biopsy irrespective of PSA level. Another PROFILE study (NCT02543905) is recruiting 700 individuals with family history of prostate cancer. The BARCODE 1 study (ClinicalTrials.gov NCT03158922) will evaluate the genetic profile using 170 prostate cancer risk single-nucleotide polymorphisms (SNPs) in men with genetic susceptibility. Men in the top 10% risk score will undergo prostate biopsy.

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Genetic testing incorporated into routine prostate cancer screening can have a plethora of benefits for the patient and family. Detectable mutations of *BRCA1/2* will facilitate targeted screening with early diagnosis and treatment before cancer advances. It may impact treatment options for patients requiring platinum-based chemotherapy or PARP-1 inhibitors. Moreover, it encourages screening for other primary cancers such as colon and pancreas, possibly initiating preventive strategies for yet unaffected organs. It will alert other family members to screen for breast and ovarian cancer and potentially offer early treatment with better prognosis and quality of life.

Current NCCN guidelines recommend genetic testing for all patients with metastatic, regional, very high-risk disease, or high-risk prostate cancer regardless of family history. Those genes include *BRCA1*, *BRCA2*, *ATM*, *PALB2*, and *FANCA*.[7] There is no consensus yet regarding prostate cancer screening for carriers of pathogenic germline mutations as we await ongoing studies. However, it is recommended that prostate cancer screening in carriers commence at age 40-45 with annual PSA and DRE, utilizing age-adjusted PSA cut-points. If PSA is above the upper limit, PSA is retested in 6-12 months; if increased, mpMRI/TRUS-biopsy is advised.

Although genetic testing has appeal, there are recognized limitations. Genetic testing is offered to those with strong family histories of prostate, breast or ovarian cancer according to contemporary guidelines. However, germline mutations such as *BRCA1/2* have been detected in individuals lacking family history. Most genetic studies focus on detection of *BRCA1/2* while less prevalent mutations such as *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PMS2* are ignored. Lack of ample genetic counsellors, insurance coverage and defined follow up plans also remain challenges.

Several predictive instruments have been developed to better identify individuals with higher probability of germline *BRCA1/2* mutations. The Manchester scoring system is a mathematical model that is more sensitive to *BRCA2* mutations, taking into consideration cancer type and age at diagnosis. Additional optimization and refinements are required to identify people eligible for genetic testing. PSA and PSA velocity may not be sufficient for cancer screening in high-risk patients having genetic mutations as seen in IMPACT and PROFILE. mpMRI and novel prostate cancer markers could be an additional screening tool to detect high-risk prostate cancer at early stages.

At Duke University, we developed and implemented an EHR-embedded, risk-stratified prostate cancer screening algorithm as a clinical decision support tool in a primary care network, screening 49,980 in the first year. We implemented system-wide screening, incorporating, age, race, family history and genetic risk in a single health care system. Future efforts will incorporate more robust genetic testing in high-risk men as evidence becomes available.

Disclosures

The authors have no disclosures. □

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