Germline Testing

By Kalli Spencer

Germline testing is done on cells that do not have cancer. It is done to see if a person has a gene mutation that is known to increase the risk of developing cancers and other health problems. Approximately 4% of men less than 75years of age present with metastatic prostate cancer. Several research reports have found high rates of germline mutations among these patients, mostly in DNA repair genes such as *BRCA1, BRCA2*, and *ATM*. DNA repair genes usually repair any errors that may occur during cell division and growth preventing excessive cell growth, particularly of cancer cells. If there is a mutation of this gene then the repair process can't take place and cancerous cells may be allowed to grow unchecked. This mutated germline DNA can be passed on from parents to children and therefore genetic testing is advisable. The other advantage is that some patients with these mutations may be able to have their cancer treated with immunotherapy such as PARP inhibitors or pembrolizumab.

Factors that may prompt germline testing include a family history of cancer, particularly breast cancer, ovarian, pancreatic cancer or melanoma. Having one or more family member with a cancer related to Lynch syndrome is associated with having a high risk of a germline mutation. In those patients whose prostate biopsy pathology shows ductal/intraductal histology also have higher rates of germline mutations.

Those diagnosed with prostate cancer and a *BRCA2* mutation are recommended to undergo a clinical breast examination, starting at the age of 35 years of age, owing to their higher risk of male breast cancer. Given the increase in pancreatic cancer risk, these men may be referred to a gastroenterologist to discuss pancreatic cancer screening. Since melanoma risk is elevated, male *BRCA2* carriers are also recommended to undergo detailed skin examinations. Cascade testing is important to identify *BRCA* carriers and address cancer risks and screening in male and female blood relatives. A similar screening process is recommended for those with Lynch Syndrome under the advice of genetic counsellors. Genetic counsellors provide pre-test information that allows patients to make an informed decision on genetic testing, order genetic testing, discuss results and recommendations based off test results and coordinate cascade testing. Genetic testing is a specialised area which has several implications that needs to be discussed with the patient: purpose of testing; impact on treatment or management; identification of additional cancer risks; hereditary cancer implications and legal protections for mutation carriers.

There are multiple therapeutic implications of germline mutations in men with metastatic prostate cancer. Currently those with germline mutations may be offered immunotherapy after progressing on initial lines of therapy (such as docetaxel and abiraterone or enzalutamide). While germline testing does not currently impact the initial treatment of men with metastatic prostate cancer, Dr Stacy Loeb a urologist at New York University, believes "there may be a shift to the use of targeted therapy, particularly PARP inhibitors, earlier in the treatment paradigm pending further study results."[1]

In a recent review article by Loeb, it is reported there may be a role for treatment in early-stage prostate cancer where mutation rates may be as high as 5-7%[1]. Not only does this impact treatment options but it influences cancer risk, screening, and management across the cancer stage spectrum for men and their families. Instead of placing a patient with the potential for more aggressive disease on active surveillance it may be prudent to opt for more radical treatments such as radiation or a prostatectomy upfront. There may be a role for early immunotherapy in those with localised prostate cancer with a germline mutation in the future.

Since there is an increased demand for germline testing based on new research findings, healthcare providers need to update their practice to ensure testing where appropriate. A few studies have examined the use of germline testing by different prostate cancer service providers. In a 2017–2018 survey of medical oncologists in the Prostate Cancer Clinical Trials Consortium, 62% of respondents reported taking personal responsibility for some/all genetic education and testing, and the remainder referred to a separate department[2]. At that time, only 62% considered testing for all patients with metastatic disease, while others also considered family history and/or clinical trial eligibility. In addition, 54% considered germline testing for some patients with high-risk localized disease. Reported barriers to widespread use included delayed or limited access to genetic counselling, insurance coverage, workflow issues, time constraints, and insufficient educational materials.

Loeb et al found in their study that overall, 10% of urologist respondents in the US perform germline testing in their practice, 47% referred to a genetic counsellor, and 11% do both[3]. Conversely, 33% do not refer to a counsellor or perform testing. While most respondents ask patients about a family history of prostate cancer, 28% do not ask about cancer history in female relatives. Virtually none of the respondents had formal education in genetics, and one-third do not feel confident with their genetic knowledge.

In a recent Australian study “mainstreaming” men with metastatic prostate cancer is a feasible, resource efficient method which is both satisfactory to both clinicians and patients[4]. Mainstreaming is the process whereby “oncology staff (rather than a genetic specialist—ie, a genetic counsellor/clinical geneticist) are responsible for counselling, consenting, and ordering genetic testing. Mainstreaming has been investigated in ovarian and breast cancer but has not been evaluated in an older male population with breast cancer. The researchers believe this model will help relieve the workload for already constrained genetic counsellors as genetic testing becomes more prevalent.

There are clearly several advantages to germ line testing and as highlighted they may not be exclusively limited to advanced stages of cancer. Health care practitioners in all specialities should be aware of the important role of germline testing. Loeb suggests that “further research into the barriers to and facilitators of germline genetic evaluation is needed to ensure guideline-concordant care and optimal management strategies for patients with germline mutations across the spectrum of disease.”

References

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About the Author

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Kalli is an internationally renowned Urological Surgeon, specialising in oncology and robotic surgery. He trained and worked in South Africa, before relocating to Australia where he has worked at Macquarie University Hospital and Westmead Hospital. His passion for what he does extends beyond the operating room, through public health advocacy, education and community awareness of men's health, cancer and sexuality.

Kalli has been involved with the Prostate Cancer Foundation of Australia for many years, advocating for improved cancer care and facilitating community prostate cancer support groups.