

Challenges with mainstreaming genetic testing for metastatic prostate cancer treatment in Singapore

Jianbang Chiang^{1,2}*FAMS*, Joanne Yuen Yie Ngeow^{1,2,3}*FAMS*

Compared with other solid tumours, patients with metastatic prostate cancer typically have better survival in the range of years.¹ The long survival translates to a high prevalence, and thus, a large number of men living with prostate cancer. Singapore has one of the highest age-standardised incidence rates of prostate cancer in Asia, at 35 per 100,000 population.² Yet, after androgen deprivation therapy, existing data suggest that 4 in 5 men with prostate cancer will develop castrate-resistant prostate cancer,³ with median survival of 20 months in the chemotherapy-naïve group.⁴ In recent years, the agents available to men with metastatic castration-resistant prostate cancer (mCRPC) has expanded beyond traditional chemotherapy agents (e.g. docetaxel and cabazitaxel) to include novel hormonal therapies (e.g. abiraterone and enzalutamide), and other targeted therapies.

One of the newest classes of agents is the polyadenosine diphosphate-ribose polymerase (PARP) inhibitors. Based on the results of the PROFOUND trial, mCRPC patients with *BRCA1*, *BRCA2* and ataxia-telangiectasia mutated (*ATM*) pathogenic variants have an improved overall survival of 18.5 months with olaparib (PARP inhibitor), compared to an alternative hormonal agent.⁵

Treatment-indicated germline genetic testing in breast cancer, ovarian cancer and pancreatic cancer has boosted demand for genetic counselling services, resulting in prolonged wait times in most cancer genetics clinics.⁶ This is due to the importance of pre-test counselling for genetic testing. A pre-test genetics consult entails explanation of possible germline genetic results and its implication on both patient and his/her family, as well as possible ethical, legal and social ramifications of genetic testing.⁷ Care must be taken to differentiate somatic from germline pathogenic variants—the former may be important in selecting targeted therapies, but only the latter has hereditary implications.

Published in this issue of the *Annals*, Kanesvaran et al.⁸ proposed for pre-test counselling to be provided by the managing clinician, prior to testing all mCRPC

patients for somatic variants in the homologous recombination repair (HRR) pathway. The authors suggest a “mainstreaming” approach where the managing clinician (i.e. treating urologist or medical oncologist) taking care of the patient first broach the subject of somatic testing with the patient, and if agreeable, to proceed with tumour testing that is able to detect somatic and possibly germline pathogenic variants. If tumour testing identifies somatic pathogenic variants, patients are then to be referred for a post-test discussion with a dedicated genetics counsellor, prior to germline evaluation. This clinical model serves to incorporate somatic genetic testing into routine clinical practice for the management of patients with mCRPC, and taps on existing personnel and infrastructure available in tertiary cancer centres in Singapore.

Similar mainstreaming has been trialled in other countries,^{9,10} typically in cancers such as epithelial ovarian cancer, where approximately one quarter of patients have an underlying hereditary cancer syndrome.¹¹ A Malaysian study showed no significant differences between mainstreaming and formal genetics consultation in terms of satisfaction and psychosocial impact, with 80% of clinicians keen to integrate genetic testing into their practice.⁹ Adopting such an approach requires education and training of clinicians on genetics knowledge and counselling skills, as well as development of new guidelines and improving current clinical resources. This proposed hybrid approach involving both specialists and genetic counsellors (GCs) is a popular idea in the research setting. However, it has been shown to be difficult to implement as most specialists are unwilling to perform the required pre-test counselling.¹² Mainstreaming relies on busy clinicians who are more costly on a unit-time basis compared to a genetics clinic run by GCs.¹³ GC-led pre-test counselling, either through telegenetics and/or in person, remains the most cost-effective mode of delivery; also, there are increasing numbers of genetic counselling training programmes and GCs in Asia to

¹ Cancer Genetics Service, Division of Medical Oncology, National Cancer Centre Singapore, Singapore

² Duke-NUS Medical School, Singapore

³ Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Correspondence: Prof Joanne Yuen Yie Ngeow, Lee Kong Chian School of Medicine, Nanyang Technological University, 11 Mandalay Road, Singapore 308232.
Email: joanne.ngeow@ntu.edu.sg

address current clinical gaps.¹⁴ Extensive efforts have been made to train more GCs and geneticists to meet current and future demand. Mainstreaming will further help to reduce pressure on genetics services, and allow dedicated genetics-trained clinicians to focus their efforts on patients and families with hereditary cancer syndromes, rather than screen the general cancer population. Despite the increasing supply of GCs, it remains challenging for genetic services to justify headcount increase and adequate remuneration for GCs as frontline clinicians to hospitals and health systems in Asia, where a doctor-led system is common.

As Singapore moves towards Healthier SG (an initiative by the Singapore government to help the population take steps to better health) and as we aim to move from specialist-led care to care in the community, we will need to increasingly expand the roles GCs to serve in routine clinical care. A key component of clinical genetic testing is cascade testing—the downstream flow of genetic information to the family members of an individual with a pathogenic variant.¹⁵ This allows at-risk individuals to be identified early for gene-directed surveillance and cancer risk-reducing surgery. For family members not at risk, a negative test can help to avoid further unnecessary screening and tests. It remains unclear if mainstreaming will affect the uptake of cascade testing and would warrant monitoring.

In addition, negative somatic testing cannot rule out germline pathogenic variants. Clinicians should be cognisant of false negative results—where patients with significant personal medical history or strong family history of cancer, and negative somatic testing should still be evaluated for an underlying hereditary cancer syndrome. This is because patients with a strong family history of cancer can have a sixfold increased risk of carrying a germline pathogenic variant.¹⁶ These patients may benefit from early direct referral to the cancer genetics clinic rather than detour to perform somatic testing first, to minimise delays and unnecessary cost of the more expensive somatic test.

With the rising indications for genetic testing, many questions remain for all health systems, especially in Asia. Mainstreaming as proposed by Kanesvaran et al.⁸ for metastatic prostate cancer is a well-considered one given that only 17.2% of prostate cancer patients with 43.8% of HRR will require germline testing.¹⁷

Presently, industry sponsors mainstreaming approaches to help identify patients for gene-directed treatments. While this addresses the short-term concerns for access to genetic testing for patients with metastatic prostate cancer, collectively, the community

will need to address reimbursement and affordability of genetic testing. Addressing these issues on a broad scale can ensure that access to testing is equitable across the health system and not limited only to those who can afford testing and/or only for patients eligible for therapy. Current industry-influenced clinical pathways preclude access to subsidised genetic testing for a 40-year-old patient with non-metastatic prostate cancer and with a family history of hereditary breast and ovarian cancer syndrome, as an example. It is important to remember that at the health system level, it is the early cancer detection of at-risk family members that drives cost-effectiveness.

We should ensure that all (and not only metastatic) prostate cancer patients who meet clinical criteria for clinical genetic testing receives support for testing and are receptive to the mainstreaming of genetic testing by GC-led consults in the near future.

Disclosure

Prof Joanne Yuen Yie Ngeow receives research funding from AstraZeneca.

REFERENCES

1. Zhang AC, Rasul R, Golden A, et al. Incidence and mortality trends of metastatic prostate cancer: Surveillance, Epidemiology, and End Results database analysis. *Can Urol Assoc J* 2021;15:E637-43.
2. National Registry of Diseases Office. Singapore Cancer Registry Annual Report 2020. <https://www.nrdo.gov.sg/publications/cancer>. Accessed 28 March 2023.
3. Teo MY, Rathkopf DE, Kantoff P. Treatment of Advanced Prostate Cancer. *Annu Rev Med* 2019;70:479-99.
4. Chan J, Yap SY, Fong YC, et al. Real-world outcome with abiraterone acetate plus prednisone in Asian men with metastatic castrate-resistant prostate cancer: The Singapore experience. *Asia Pac J Clin Oncol* 2020;16:75-9.
5. de Bono J, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med* 2020;382:2091-02.
6. Shaw T, Metras J, Ting ZAL, et al. Impact of Appointment Waiting Time on Attendance Rates at a Clinical Cancer Genetics Service. *J Genet Couns* 2018;27:1473-81.
7. Chiang J, Ngeow J. The management of BRCA1 and BRCA2 carriers in Singapore. *Chin Clin Oncol* 2020;9:62.
8. Kanesvaran R, Chia PL, Chua MLK, et al. An approach to genetic testing in patients with metastatic castration-resistant prostate cancer in Singapore. *Ann Acad Med Singap* 2023;52:135-48.
9. Yoon SYY, Wong SW, Ahmad NS, et al. Mainstreaming genetic counselling for genetic testing of BRCA1/2 in ovarian cancer patients in Malaysia (MaGIC study). *Ann Oncol* 2019;30:IX192.
10. Ip E, Young AL, Scheinberg T, et al. Evaluation of a mainstream genetic testing program for women with ovarian or breast cancer. *Asia Pac J Clin Oncol* 2022;18:e414-9.
11. Konstantinopoulos PA, Norquist B, Lacchetti C, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. *J Clin Oncol* 2020;38:1222-45.

12. Bokkers K, Vlamming M, Engelhardt EG, et al. The Feasibility of Implementing Mainstream Germline Genetic Testing in Routine Cancer Care—A Systematic Review. *Cancers (Basel)* 2022;14:1059.
 13. Tan RYC, Met-Domestici M, Zhou K, et al. Using Quality Improvement Methods and Time-Driven Activity-Based Costing to Improve Value-Based Cancer Care Delivery at a Cancer Genetics Clinic. *J Oncol Pract* 2016;12:e320-31.
 14. Haidle JL, Stern DL, Dickerson JA, et al. Genetic counselors save costs across the genetic testing spectrum. *Am J Manag Care* 2017;23:SP428-30.
 15. Courtney E, Chok AK, Ang ZLT, et al. Impact of free cancer predisposition cascade genetic testing on uptake in Singapore. *NPJ Genom Med* 2019;4:1-7.
 16. Bylstra Y, Lim WK, Kam S, et al. Family history assessment significantly enhances delivery of precision medicine in the genomics era. *Genome Med* 2021;13:3.
 17. 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;5:523-8.
-