

An approach to genetic testing in patients with metastatic castration-resistant prostate cancer in Singapore

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ABSTRACT

Introduction: There has been a rapid evolution in the treatment strategies for metastatic castration-resistant prostate cancer (mCRPC) following the identification of targetable mutations, making genetic testing essential for patient selection. Although several international guidelines recommend genetic testing for patients with mCRPC, there is a lack of locally endorsed clinical practice guidelines in Singapore.

Method: A multidisciplinary specialist panel with representation from medical and radiation oncology, urology, pathology, interventional radiology, and medical genetics discussed the challenges associated with patient selection, genetic counselling and sample processing in mCRPC.

Results: A clinical model for incorporating genetic testing into routine clinical practice in Singapore was formulated. Tumour testing with an assay that is able to detect both somatic and germline mutations should be utilised. The panel also recommended the “mainstreaming” approach for genetic counselling in which pre-test counselling is conducted by the managing clinician and post-test discussion with a genetic counsellor, to alleviate the bottlenecks at genetic counselling stage in Singapore. The need for training of clinicians to provide pre-test genetic counselling and educating the laboratory personnel for appropriate sample processing that facilitates downstream genetic testing was recognised. Molecular tumour boards and multidisciplinary discussions are recommended to guide therapeutic decisions in mCRPC. The panel also highlighted the issue of reimbursement for genetic testing to reduce patient-borne costs and increase the reach of genetic testing among this patient population.

Conclusion: This article aims to provide strategic and implementable recommendations to overcome the challenges in genetic testing for patients with mCRPC in Singapore.

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CLINICAL IMPACT

What is New

- Genetic testing should be incorporated into routine practice for prostate cancer, given its prognostic and predictive values.
- A clinical model providing real-time guidance to clinicians who treat prostate cancer patients is proposed.

Clinical Implications

- Pre-test counselling by clinicians and post-test discussion by genetic counsellors (hybrid approach) are recommended.
- Clinicians managing prostate cancer should be trained to provide pre-test genetic counselling for implementing the hybrid approach.
- Pathologists play a crucial role in the testing journey and should be included in the multidisciplinary team and molecular tumour board meetings for managing mCRPC.

INTRODUCTION

Prostate cancer is the fifth most common cancer in Asian men, and with its rising incidence, is emerging as a health priority in Asia.¹ Across Asian countries, age-standardised incidence rates (ASIRs) of prostate cancer range from 0.9 to 56.1 per 100,000 population, with the second highest ASIR reported in Singapore (30.7 per 100,000 population) in 2020.² More than 80% of patients with an indolent, low-grade castration-sensitive prostate cancer eventually progress and develop high-grade metastatic castration-resistant prostate cancer (mCRPC) despite optimal disease control with androgen deprivation therapy.^{3,4}

Several studies have extensively investigated the heritable component of prostate cancer.⁵⁻⁷ In a genome-wide association study of patients with prostate cancer, 269 risk variants (86 new and 183 previously reported loci)—which represented 33.6% of the estimated familial relative risks in men of East Asian ancestry—were identified.⁶ Mutations in homologous recombination repair (HRR) genes, specifically the breast cancer genes 1 (*BRCA1*) and 2 (*BRCA2*), are implicated in the development of prostate cancer and are associated with aggressive disease and poor prognosis, with a higher likelihood of nodal involvement and distant metastasis.^{8,9} A genomic sequencing study in 150

patients with advanced prostate cancer identified HRR mutations in 22.7% of cases, the most frequent being *BRCA2* mutations (in 12.7% of cases).¹⁰ The frequency of somatic and germline HRR mutations in patients with mCRPC were found to be between 28% and 33%.^{11,12} In studies where only germline mutations were analysed, approximately 11.8–17.2% of patients were reported to possess HRR mutations.¹³⁻¹⁵ Although the rate of HRR mutations in patients with prostate cancer has not been extensively studied in patients of Asian descent, limited published data suggest rates similar to those reported in Western populations (9.8–11.8%).^{16,17}

Olaparib, the first polyadenosine diphosphate-ribose polymerase (PARP) inhibitor, was approved in Singapore by the regulatory agency in March 2021 for the treatment of mCRPC in patients harbouring *BRCA1*, *BRCA2* and/or ataxia-telangiectasia mutated (*ATM*) mutations (germline, somatic or both) who have progressed following a prior new hormonal agent.¹⁸ Given that PARP inhibitors have shown clinically meaningful efficacy in patients with mCRPC,^{12,19} genetic testing for HRR mutations has become paramount. Although genetic testing for patients with mCRPC is recommended by international guidelines, challenges associated with patient selection, genetic counselling processes, and sample storage and processing hinder its routine implementation in real-world clinical practice. In the Asia-Pacific region, including Singapore, clinical practice guidelines for genetic testing in patients with mCRPC are currently yet to be routinely adopted.²⁰ Hence, a multidisciplinary panel of medical oncologists, radiation oncologists, urologists, interventional radiologists, pathologists and cancer geneticists involved in the management of prostate cancer from both public and private institutions across Singapore was formed to address this issue. A meeting was held to formulate a reasonable approach to incorporate genetic testing into the management of patients with mCRPC in Singapore.

METHOD

In pursuance of developing recommendations for genetic testing in patients with mCRPC in Singapore, a 4-step survey-based process was implemented (online Supplementary Fig. S1). A pre-meeting survey was distributed to and completed by 12 specialists (online Supplementary Appendix). In the meeting that followed, key aspects of genetic testing, counselling and the sample journey were discussed. The specialists provided insights based on their clinical experience regarding common practices and challenges in genetic testing in Singapore and provided strategic and implementable recommendations to overcome the challenges. An

evidence-based literature search, including a review of relevant international and regional guidelines, was conducted to support the recommendations from the panel. A clinical model was formulated for incorporating genetic testing and counselling into routine practice. The recommendations and clinical algorithm were reviewed and approved by all authors. This position paper provides an overview of the burden of prostate cancer in Singapore and elucidates the challenges and recommendations for genetic testing in patients with mCRPC.

Burden of prostate cancer in Singapore

The ASIR of prostate cancer is comparatively higher in Singapore than in other Asian countries like China (34.3 versus 10.2) and India (34.3 vs 5.5).² According to the Singapore Cancer Registry Annual Report 2019, prostate cancer was the second most frequent cancer in males, with an incidence of 15.4%, and was the fourth leading cause of cancer-related mortality in males, with 989 deaths during 2015–2019 in Singapore.²¹ During the period, the number of cases of prostate cancer reported was highest in elderly individuals (22.0% of cases in individuals aged 70–79 years and 18.3% in those aged 60–69 years).²¹ Comprehensive data on the incidence of mCRPC in Singapore are lacking. According to the United in Fight against prostate cancer (UFO) study, 73.2% of patients with metastatic prostate cancer in Singapore present with de novo metastases.²² Despite the increased ASIR of prostate cancer from 4.0 per 100,000 population in 1968–1972 to 34.6 per 100,000 population in 2015–2019, the age-standardised relative survival almost doubled from approximately 47.3% to 87.8% in Singapore.²¹ The increased incidence and survival of prostate cancer could be due to the extensive use of prostate-specific antigen testing in Singapore.²³ With targeted therapies available for patients harbouring genetic mutations, it is critical to test patients for genetic mutations with the aim to increase overall survival and quality of life.

Genetic testing in mCRPC

Patient selection and time for testing

Selecting eligible patients and determining the optimal time for genetic testing are critical in the management of mCRPC. HRR mutations, especially in *BRCA1* and *BRCA2*, have been established as negative prognostic factors and are associated with early-onset disease, high Gleason score, nodal involvement, metastatic disease at diagnosis, shorter metastatic-free survival and shorter overall survival in patients with mCRPC.⁸

However, HRR mutations act as positive predictive markers with respect to treatment outcomes, as several HRR-mutated tumours have shown response to PARP inhibitors as well as platinum chemotherapy.^{11,24} Several international guidelines, such as those from the National Comprehensive Cancer Network, American Urological Association, American Society for Radiation Oncology, Society of Urologic Oncology, European Society for Medical Oncology and Philadelphia Prostate Cancer Consensus, have recommended testing for HRR mutations in all patients with mCRPC (Table 1).^{25–28}

It is now known that the risk of prostate cancer doubles in individuals with first-degree relatives with prostate cancer.^{15,29} Although germline testing is important in identifying familial risk, solely performing germline testing may miss approximately 59% of patients with prostate cancer who have somatic mutations. Pritchard et al. reported germline HRR mutations in 11.8% of patients with metastatic prostate cancer.¹³ In the PROREPAIR-B study of unselected patients with mCRPC, 16.2% of patients had germline mutations.¹⁴ In a cross-sectional study of 3,607 men with a history of prostate cancer who underwent germline genetic testing between 2013 and 2018, 17.2% had germline mutations, 30.7% of which were *BRCA1/2* mutations.¹⁵ Of note, genetic (somatic plus germline) mutations were reported in 33% of patients in the TOPARP-A study.¹¹ In the PROfound study, HRR mutations were reported in 27.9% of patients.¹² Therefore, somatic testing should be considered in patients with mCRPC since it has the ability to detect patients with HRR mutations. As recommended in international guidelines (Table 1), all patients with mCRPC should undergo testing for HRR mutations. Interestingly, studies have shown that approximately 30–40% of HRR mutation carriers may not report a family history of cancer.^{13–15} Thus, family history should not be the sole factor for determining the need for testing. Table 2 describes the recommendations of international guidelines on patient selection and optimal time for genetic testing.

Genetic counselling of patients with mCRPC

Although the main aim of genetic testing in patients with mCRPC is to identify targetable mutations, the results of genetic testing may uncover unanticipated hereditary mutations.³⁰ A suspicion of genetic predisposition mandates extensive genetic counselling prior to and after germline testing to help patients understand the familial implications.³¹ Genetic counselling has been shown to improve patient outcomes with positive downstream effects as patients are more equipped with sharing the results of genetic tests with extended families.³² Genetic counselling has now become a critical aspect of disease

Table 1. Recommendations from international guidelines for genetic testing in patients with castration-resistant prostate cancer (mCRPC).

Guidelines	Germline testing	Tumour testing
NCCN (v1.2023) ²⁵	In patients with metastatic, regional (node-positive), very high- or high-risk localised prostate cancer. Any patient with prostate cancer who has Ashkenazi Jewish ancestry, strong family history of cancer ^a or breast cancer. Intraductal/criform histology.	In patients with metastatic prostate cancer for HRR mutations such as <i>BRCA1</i> , <i>BRCA2</i> , <i>ATM</i> , <i>PALB2</i> , <i>FANCA</i> , <i>RAD51D</i> , <i>CHEK2</i> , <i>CDK12</i> . In patients with mCRPC that is MSI-H or dMMR.
ESMO (2020) ²⁶	Testing for <i>BRCA2</i> and other DDR genes associated with cancer predisposition syndromes is recommended in patients with a family history of cancer and should be considered in all patients with metastatic prostate cancer.	Testing for homologous recombination genes and dMMR (or MSI) in patients with mCRPC.
AUA/ ASTRO/ SUO (2020) ²⁸	In patients with mHSPC, regardless of age and family history, clinicians should offer genetic counselling and germline testing. In patients with mCRPC, clinicians should offer germline genetic testing to identify DNA repair deficiency mutations and MSI status that may inform prognosis and counselling regarding family risk as well as potential targeted therapies.	In patients with mCRPC, clinicians should offer somatic tumour genetic testing to identify DNA repair deficiency mutations and MSI status that may inform prognosis and counselling regarding family risk as well as potential targeted therapies.
Philadelphia Prostate Cancer Consensus Conference (2019) ²⁷	In patients with metastatic prostate cancer (either castration-resistant or castration-sensitive). Men with 1 brother or father or 2 or more male relatives diagnosed with prostate cancer at age <60 years, died of prostate cancer or had metastatic prostate cancer. Patients should undergo genetic testing for the following genes: • Comprehensive (large) panel testing for therapy/clinical trial eligibility • Priority germline testing (metastatic prostate cancer): ◦ <i>BRCA2/BRCA1</i> ◦ DNA MMR genes ◦ Test additional genes on the basis of personal or family history	Next-generation sequencing for all men with metastatic prostate cancer, followed by confirmatory germline testing.

ASTRO: American Society for Radiation Oncology; AUA: American Urological Association; DDR: DNA damage response and repair; dMMR: deficient mismatch repair; DNA: deoxyribonucleic acid; ESMO: European Society for Medical Oncology; HRR: homologous recombination repair; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; MMR: mismatch repair; MSI: microsatellite instability; MSI-H: microsatellite instability - high; NCCN: National Comprehensive Cancer Network; SUO: Society of Urologic Oncology

^a Family history and/or ancestry with ≥1 first-, second- or third-degree relative with breast, colorectal or endometrial cancer at age ≤50 years, male breast cancer or ovarian cancer or exocrine pancreatic cancer or metastatic, regional, very high-risk or high-risk prostate cancer at any age; ≥1 first-degree relative with prostate cancer at age ≤60 years; ≥2 first-, second- or third-degree relatives with breast cancer or prostate cancer at any age; ≥3 first- or second-degree relatives with Lynch syndrome-related cancers, especially if diagnosed at age <50 years; a known family history of familial cancer risk mutations, especially in *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*.

management particularly in diverse multiethnic countries like Singapore, where the likelihood of encountering variants of unknown significance (VUS) presents challenges for clinicians and patients.^{33,34} Although genetic counselling services for patients with ovarian and breast cancer are well established, such services are underutilised in patients with prostate cancer, with less than 3% of patients undergoing genetic testing from 2014 to 2019, according to the cancer genetics service of a major institution in Singapore.^{32,35}

In the traditional model, patients are referred to a genetic counsellor once a decision for germline testing is made.³⁶ Genetic counselling is conducted in 2 phases: pre-test and post-test counselling. An in-depth genetic counselling session involves taking a detailed

3-generation family and disease history, including that of both maternal and paternal relatives, prior to genetic testing.^{37,38} The components of the pre-test and post-test sessions are described in Table 3.^{27,36-42} Genetic counsellors advise on the need for testing after considering patients' understanding and concerns, in addition to the ethical, legal and social implications of germline testing.⁴³ In post-genetic testing, patients will be counselled on the implications of the test results before they are referred to their primary oncologist for further management of mCRPC.

This conventional route, although ideal, is marked by several challenges. Particularly in Singapore, there is an acute shortage of genetic counsellors, with only approximately 10 genetic counsellors for a population

of 5.7 million being reported in 2019.⁴⁴⁻⁴⁶ Patients are currently referred to 1 of the 3 major centres for genetic counselling: National University Cancer Institute, Singapore; National Cancer Centre Singapore (NCCS); and Tan Tock Seng Hospital. More than 9,000 new patients with cancer visit NCCS each year for cancer treatment, approximately 5% (450 patients) of which might harbour germline mutations.³² The waiting time for genetic counselling at this institution was reported to be between 2 and 3 months, resulting in patients being lost to follow-up.³² Thus, genetic counselling prior to germline testing has created a bottleneck because of the overwhelming demand for cancer genetics services. Other key barriers to germline testing include little or no reimbursement for genetic testing and counselling, lack of definitive guidelines, and clinical time and space constraints.⁴⁷⁻⁴⁹

Henceforth, we recommend a hybrid method involving a brief pre-test counselling conducted by the managing clinician prior to somatic testing and a post-test discussion by a genetic counsellor (post-somatic testing, but prior

to germline testing, for patients with mutations) be adopted in Singapore (Fig. 1).^{27,50} A brief pre-test counselling followed by somatic molecular testing can reduce the delays and bottlenecks (Fig. 1). This method is known as the “mainstreaming” of genetic counselling and has been established for ovarian and breast cancer in several countries, with a positive impact on disease management.⁵¹⁻⁵³ In Malaysia, the mainstreaming approach led to increased patient satisfaction and a reduction in the decisional conflict in patients with ovarian cancer.⁵⁴ An Australian prospective study pioneered this mainstreaming approach in men with metastatic prostate cancer and demonstrated that it was feasible and highly accepted, as well as ensured timely and equitable access to genetic testing.⁵³ In this article, the specialist panel formulated a model for incorporating genetic counselling into the mainstream management of mCRPC in Singapore. The recommendations for genetic testing and counselling are summarised in Table 2 and the model is outlined in Fig. 1. Although mainstreaming of genetic counselling may increase the consultation

Table 2. Recommendations for medical/radiation oncologists and urologists for genetic testing and counselling of patients with prostate cancer.

Recommendations
- Genetic testing considerations should be part of routine practice as it can inform on personal and familial risk, and provides predictive and prognostic value - Family history and informed consent should form part of routine clinical practice - During patient selection for somatic/germline testing, the following factors should be considered: - Somatic testing - Patients with metastatic prostate cancer^a - Germline testing - Age <55 years - Strong positive family history^b - High-risk or very high-risk localised prostate cancer or metastatic prostate cancer regardless of family history - Intraductal histology - Patients who test positive on somatic testing for homologous recombination repair mutations - Ashkenazi Jewish ancestry - Germline testing should be undertaken in patients with somatic mutations to evaluate whether the mutation is of germline origin and subsequent familial risk for patients and relatives - In the context of available targeted therapies, somatic testing should be conducted at disease progression to metastatic castration-resistant prostate cancer, followed by germline testing to evaluate familial risk if mutations are detected - Genetic counselling should be performed with an overall perspective on optimal disease management and potential downstream effects - A hybrid method involving pre-test counselling prior to somatic testing conducted by the treating urologist or medical oncologist and post-test counselling (after somatic testing but prior to germline testing in indicated patients) by the genetic counsellor should be adopted in Singapore - Urologists and medical oncologists should be appropriately trained in genetic counselling - The distress of unexpected results should be taken into account during the counselling session
Educational points
- Genetic testing and counselling should be discussed with the patients early in the course of the disease as patients with genetic aberrations are likely to have aggressive disease leading to an early metastatic stage that needs extensive management - Somatic testing in particular tissue testing is considered the gold standard as it is well-established and can identify more patients with HRR mutations - An algorithm that combines testing modalities (e.g. Fig. 1) should ensure that all meaningful pathogenic variants are identified - Relying solely on family history of prostate cancer for conducting genetic tests may lead to missing the detection of patients, as it has been shown that 30–40% of HRR mutation carriers may not report a family history of cancer

^a In patients with low- and favourable intermediate-risk localised prostate cancer and life expectancy of ≥ 10 years, somatic testing should be considered on a case-to-case basis according to the discretion of the healthcare professionals and patient decision.

^b Family history includes high-risk germline mutations (e.g. *BRCA1/2*); brother or father or multiple family members diagnosed with prostate cancer (but not clinically localised grade group 1) at <60 years or who died from prostate cancer; ≥ 3 cancers on the same side of the family, especially diagnosed at age ≤ 50 years, bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localised, grade group 1), small bowel or urothelial cancer

time for physicians, it should be encouraged with the consideration of availability of resources and funds.⁵⁵ In order to incorporate the mainstreaming approach in Singapore, every effort should be made to establish effective clinical workflows for genetic testing, enhance genetic counselling training programmes for clinicians, and provide sufficient educational materials to support them in the pre-test counselling sessions. In addition, the cost-effectiveness of genetic testing is related to cascade testing in relatives of patients identified with germline mutations. However, several studies in patients with ovarian and breast cancer indicate that only a third of at-risk relatives undergo cascade testing. Moreover, male relatives show higher reluctance towards cascade testing than their female counterparts.⁵⁶⁻⁵⁹ This lack of cascade testing is a concern in view of the missing opportunity to detect and prevent hereditary cancers. Easier access to genetic testing and counselling and increased awareness of disclosing genetic test results to relatives are vital to improve cascade testing.

Sample journey in mCRPC

Selecting an appropriate tissue sample is essential for the success of genetic testing. Of the available testing options (e.g. tissue, blood, circulating tumour DNA [ctDNA]), tissue testing remains the gold standard as it is well established and can identify both germline and somatic mutations; however, it cannot differentiate between germline and somatic mutations based on

the tumour test result alone. A confirmatory blood test is required to determine the germline status of the mutation.^{12,60} An algorithm that combines testing modalities (e.g. Fig. 1) is important to ensure that all meaningful pathogenic variants are identified. In the PROfound study, most samples (83%) were obtained from tumour tissue and only 16.6% from the metastatic site. The success rate of tumour tissue testing was higher with metastatic tumours than with primary tumours (63.9% vs 56.2%).⁶¹ Metastatic sites are associated with aggressive cancers and are rich in mutated tumour cells, thus having higher DNA yield, and are biopsied relatively later than are archived primary tumour samples (online Supplementary Fig. S2).^{10,12,61} Despite higher test success rates with metastatic sites, repeat biopsy is challenging in mCRPC, with metastatic sites being bone-predominant with potential low yields and sample processing interference (e.g. decalcification).⁶² Obtaining samples from metastatic sites is an invasive process that is associated with high costs, morbidity and patient reluctance.^{63,64} In addition, challenges with tumour tissue heterogeneity limit sampling, which may only partially reflect tumour biology.⁶²

Circulating cell-free DNA testing is an emerging, minimally invasive technique for obtaining genetic material.⁵⁹ Circulating cell-free DNA is shed into the bloodstream by cancerous and non-cancerous cells. ctDNA is obtained from the cell fragments of the tumour including the metastatic tissue. One of the

Table 3. Components of genetic counselling.

Elements	Description
Purpose of testing	Precision therapy, early detection strategies and/or to identify hereditary cancer syndrome/risk
Possibility of uncovering hereditary cancer syndrome	Depending on the test, it might uncover a hereditary cancer syndrome, such as HBOC and Lynch syndrome
Types of test results	Mutation (pathogenic/ likely pathogenic variants), variants of uncertain (unknown) significance and negative
Potential to uncover additional cancer risks	Multiple gene-specific risks may be identified beyond prostate cancer risk that affects men and their families
Potential out-of-pocket cost	Not all insurance plans cover genetic testing; some mandate referral to a genetic counsellor
GINA and other laws that address genetic discrimination	Protects patients from genetic discrimination from health insurance companies and employers, with specific limitations on the type of employer and size of the company
Cascade testing/ additional familial testing	Testing blood relatives for pathogenic variants or additional genetic testing by family history; worry and anxiety that may result from hereditary cancer testing; effect on family relationships
Data-sharing/ data-selling policies of genetic laboratories	Each genetic testing laboratory may have unique data-sharing and data-selling policies that patients must be aware of
Privacy of genetic tests	Protection of genetic data from a data breach or access by third party

GINA: Genetic Information Non-discrimination Act; HBOC: hereditary breast and ovarian cancer

main limitations is dependence on the quality and quantity of the shredded DNA as the ctDNA fraction in the blood varies with tumour size, location, clinical disease state, tumour vascularity and metastatic location.⁶⁵ A low concentration of ctDNA is present during the early stage of the disease, making ctDNA-based testing in patients difficult.⁶⁶ In the later stages, patients with progressive mCRPC have demonstrated higher ctDNA fraction than those with metastatic hormone-sensitive prostate cancer receiving androgen deprivation therapy. Recent studies described below demonstrate the utility of ctDNA assays in identifying patients who may benefit from targeted therapies.^{64,67}

In the TRITON2/3 trial, ctDNA was used for assessing genetic mutations in 3,334 patients with 75% concordance between ctDNA and tissue testing. When the authors assessed samples containing more than 20% of ctDNA, the concordance with tissue testing increased to more than 85%.¹⁹ In the PROfound study, the high concordance between ctDNA-based testing and tissue testing was observed in patients with *BRCA1*, *BRCA2* or *ATM* mutations, with a positive percentage agreement of 81% and a negative percentage agreement of 92%, making ctDNA-based testing a viable option for patients with mCRPC.⁶⁸

The multidisciplinary panel recommends ctDNA testing as an option for the diagnostic pathway,

with sample collection preferably done at biochemical or radiological progression to mCRPC to optimise yield (Fig. 1).

A comparative chart of ctDNA-based testing with tumour and blood testing is provided in the online Supplementary Table S1.

Optimising sample processing

The role of pathologists has evolved immensely in the rapidly advancing field of oncology, with many treatment decisions guided by tumour biomarker analyses. Pathologists play a critical role in the sample journey as they are involved in every step of tissue testing, from obtaining an adequate amount of diagnostic material to appropriate storage of the remaining samples for further testing, including genetic analysis.⁶⁹ In the PROfound study, test failure occurred in 31% out of 4,047 samples. The reasons for test failure are described in the online Supplementary Fig. S3.^{12,70} The journey of tumour samples from the clinic to the laboratory has 3 milestones regarding genetic testing: the pre-analytical phase that includes biopsy, sample collection, fixation, storage during transit and pre-processing; the analytical phase of procuring adequate genetic material from the sample for testing; and the post-analytical phase of presentation and interpretation of results, including preparation of the report for dissemination of information to the treating clinician.

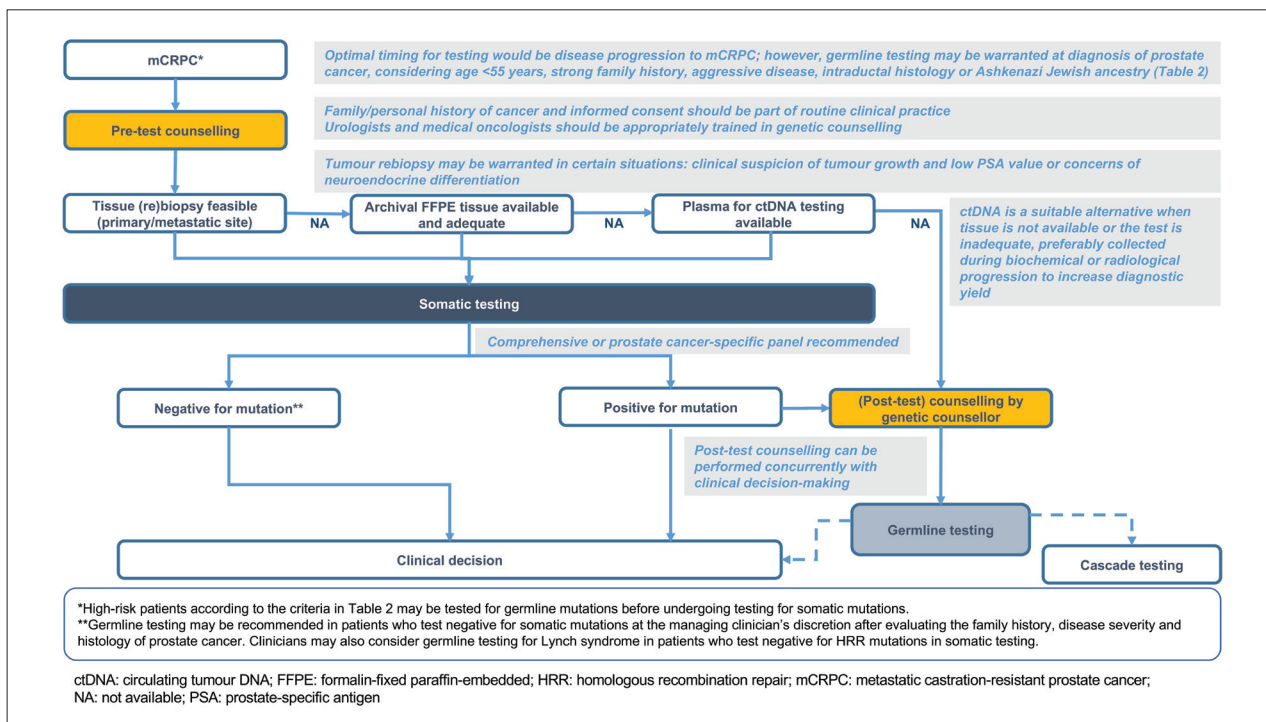


Fig. 1. Clinical model: Genetic testing for patients with metastatic castration-resistant prostate cancer (mCRPC)

Pre-analytical and analytical phases

During the pre-analytical and analytical phases, multiple challenges such as an insufficient tumour or biopsy sample, unsatisfactory DNA yield or quality and consequently the need for repeat tests are often faced. These challenges are frequently related to tissue sampling and processing issues, difficulties with bone biopsy, archived tissue age (more than 5 years), improper storage, and low tumour yield, quality or both.⁷¹⁻⁷⁶ The sample yield and quality may be affected by the route and technique of the biopsy. Polito et al. reported high sensitivity (98.2%) and specificity (98.1%) with transrectal fine-needle aspiration with a low false-negative rate (6.6%).⁷⁷ However, a prospective study showed that core biopsy was more accurate than fine-needle aspiration biopsy in biopsy sampling to determine cancer diagnosis (45.6% vs 33.3%).⁷⁸ In the PROfound study, core needle biopsy was the most common collection method (65.8%), followed by radical prostatectomy (12.4%), excisional biopsy (8.2%) and transurethral resection of the prostate (7.6%) of the specimens used. Among these, testing success rates were highest with radical prostatectomy (74%), which may be attributed to the availability of larger tumour quantum in radical prostatectomy.¹² When needle biopsy is used for obtaining tissue, tumour heterogeneity should be factored in and at least 12 core samples should be collected.^{79,80} The accuracy of core needle biopsies can be improved by using imaging technology for guiding the needle.⁸¹

In the PROfound study, a higher testing success rate was observed for biopsy from metastatic sites than from the prostate tissue (63.7% vs 56.3%). The highest success rate was observed for lymph nodes (74.7%) and the lowest for bone (42.6%). Procuring a metastatic tissue sample from the bone is difficult because of low accessibility and amenability.⁷³ Computed tomography-guided bone biopsy is commonly used for sample collection in case of metastases to the bone.⁷² The yield of bone samples and success rates can be improved by standardising the process for DNA isolation. The use of ethylenediaminetetraacetic acid for decalcification of bone instead of formic acid results in better yield as formic acid decalcification tends to degrade DNA.⁷³ The separation of softer portions of the submitted specimen from hard bony parts—which require decalcification for routine processing and subsequent genetic analysis has also resulted in increased yield and higher DNA quality for testing.⁸²

Although fresh paraffinised samples are preferred for genetic analysis, their utilisation is limited by the feasibility of rebiopsy and patient reluctance. Formalin-

fixed paraffin-embedded (FFPE) samples are most commonly used for molecular testing as they can be stored for several years without hampering the cellular and molecular integrity and can be retrieved retrospectively for this purpose.^{63,74,75} In the case of inadequate tumour content, it is advisable to obtain micro-dissected target tissue to enrich the tumour content.⁸³ Tissue fixation should be performed with 10% neutral buffered formalin, with a fixation time of 1 day (3 to 6 hours for core biopsies), and the heat treatment of tissue lysates at 95°C for 30 minutes may be done to ensure good-quality FFPE samples.^{76,84} An individual section should be 5-10µm thick, containing a minimum of more than 5,000 total nucleated cells with more than 10–20% neoplastic content.⁸⁴ The panel recommends pre-analytical quality control of DNA samples as an imperative step to ensure that the sample reaches the minimum threshold for testing.

The sample age is often a challenge when using stored FFPE samples. In the PROfound study, the highest success rate (68.1%) was obtained in samples that were less than 1 year old (n=923), but most samples were 5–10 years old (n=1,275; success rate 50.4%).⁶¹ This result may be attributed to the deterioration of samples over time and the different storage environments.⁶³ FFPE samples are usually collected at the initial prostate cancer diagnosis; hence, the time lapse from prostate cancer diagnosis to genetic testing may be more than 5 years.^{85,86} A potential hurdle could be laboratory accreditation policies for sample storage. The storage period for tissues is usually 8–10 years in several legislations;⁸⁷⁻⁹⁰ thus, patients with late disease progression may need to undergo rebiopsy, with challenges already addressed in this article. These challenges can be resolved with minimally invasive ctDNA-based “liquid biopsy”. The collected plasma should be stored in Streck tubes for further processing within 1 week of collection.

Post-analytical phase

The post-analytical phase includes all the processes after the completion of laboratory analysis until the receipt of results by the treating physician. The steps involved examination and validation of results, and reporting. Commonly reported errors in this phase include erroneous data validation, delayed reporting or misreporting, and manual errors, and account for 12.5–20% of total testing errors.⁹¹

The interpretation of test results in accordance with the geneticist's professional judgement should also be encouraged, enabling oncologists to make an informed decision.⁴¹ Also, the variants should be classified as

“pathogenic”, “likely pathogenic”, “VUS”, “likely benign” and “benign”, with VUS preferably reported separately, to direct disease management.⁹²⁻⁹⁴ Since the reports of genetic tests are integrated into patient medical records, they should be concise and easy to interpret.⁹² Other recommendations for decreasing manual errors during the post-analytical phase include effective quality control processes and training of laboratory staff personnel to mitigate manual errors. The recommendations for the sample journey are mentioned in Fig. 2.

Recommended genetic testing clinical model for mCRPC in Singapore

In clinical practice, the treating physician is often challenged with coming up with a suitable action plan regarding testing for genetic mutations. This plan includes the choice of an appropriate sample, a suitable time for testing, genetic counselling and commencement of the appropriate therapy. A model (Fig. 1) was generated by the specialists to overcome these challenges and provide real-time guidance to the multidisciplinary teams (MDTs) and, in particular, the treating oncologists and urologists in Singapore.

Tumour testing is preferred, considering the prognostic and predictive value of identifying mutations in patients with mCRPC. Somatic testing is advocated to be performed at disease progression owing to the limitation of resources and time lag between the development of

mCRPC from the castration-sensitive prostate cancer stage. However, in high-risk patients (according to the criteria defined in Table 2), germline testing may be considered before somatic testing. For somatic testing, primary biopsy material or rebiopsy of metastatic tissue is preferred. However, if the rebiopsy sample is not available, testing of archived tissue followed by a plasma sample for ctDNA testing is favoured. For archived samples, FFPE samples are used, while for rebiopsy samples, freshly paraffinised tissue samples are also suitable in Singapore.

The mainstreaming approach for genetic counselling can be adopted in Singapore to reduce the bottlenecks often observed at cancer genetics services. Although not mandated by local regulations, informed consent and pre-test counselling should be conducted at the time of somatic testing. Pre-test counselling includes providing information about the genetic tests, the type of testing and significance of genetic testing on disease management, and will enable urologists or medical oncologists to obtain the necessary family history and informed consent for somatic testing. From a diagnostic perspective, somatic molecular testing does not require extensive genetic counselling; hence, a brief pre-test counselling can suffice. In the event that the somatic testing result is positive, it is important to evaluate the hereditary nature of the disease for which germline testing is recommended. Post-somatic and pre-germline test counselling can then be conducted by genetic counsellors

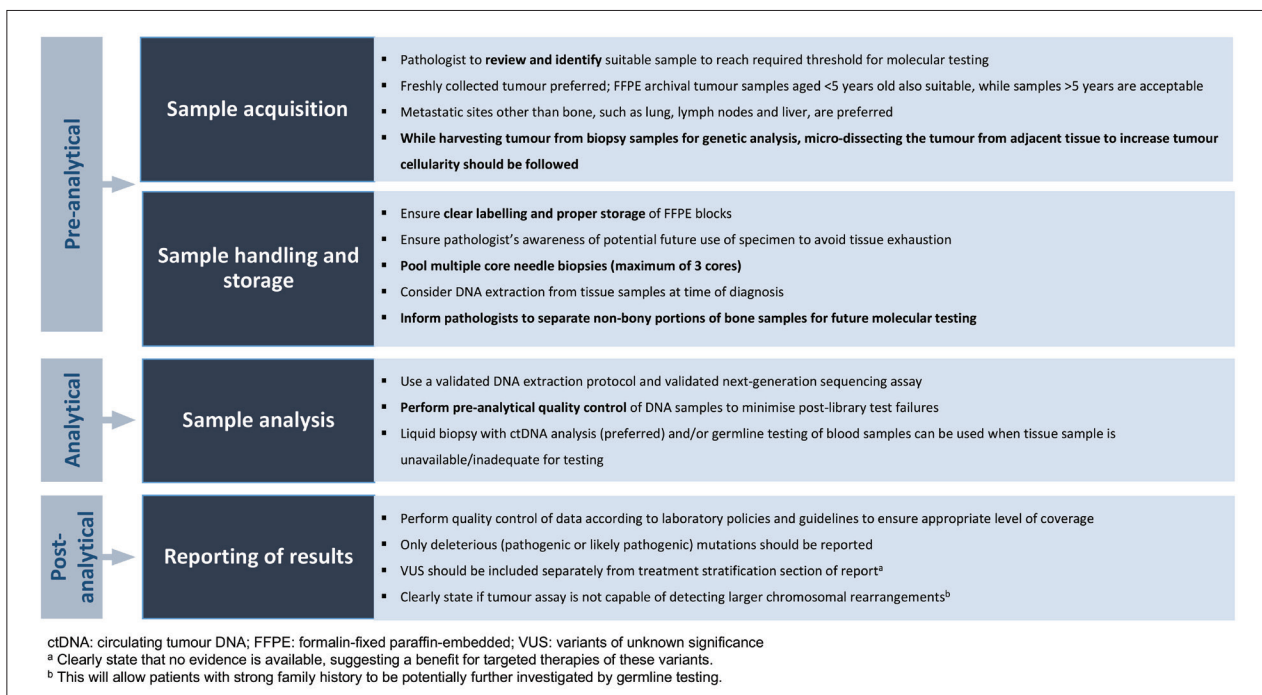


Fig. 2. Key challenges and recommendations for sample journey in patients with metastatic castration-resistant prostate cancer in Singapore.

who may also discuss the implications for cascade testing. This mainstreaming of genetic testing will lead to a decrease in the time lag between disease progression and somatic testing for patients with mCRPC and relieve overall congestion of the cancer genetics service.

Nevertheless, increased consultation time for clinicians and the lack of funds and resources should be considered prior to implementation of the mainstreaming model in clinical practice. In addition, strategies for increasing cascade testing should be implemented to increase screening and detection, and provide risk-reduction strategies for at-risk individuals.

Role of MDT and molecular tumour boards in mCRPC

With the arrival of precision medicine, MDT meetings have become crucial in managing patients with advanced prostate cancer. In the Asia-Pacific region, there has been a rise in molecular tumour boards (MTBs) that are specifically designed to assist clinicians in understanding the molecular biology of tumours and direct patients with these tumours to the appropriate targeted treatment where possible.^{95,96} Typically, MDTs and MTBs for prostate cancer include medical oncologists, radiation oncologists, surgical oncologists, urologists, pathologists, genetic counsellors, nurses and other related specialists for a discussion on the treatment course. Given that patients with mCRPC are likely to harbour genetic mutations, molecular pathologists play a significant role in MDT discussions. Molecular pathologists can provide expertise in assessing the tissue sample, the need for rebiopsy in case of sample failure, and deciphering the results, especially in the case of VUS identification. These meetings aim to have a holistic discussion after taking into account the patient's overall status, disease characteristics and treatment history before formulating an action plan.⁹⁶

In a prospective analysis, significant management decision changes were made for more than 40% of patients with prostate cancer, with most patients having a Gleason score of 7.⁹⁷ mCRPC cases managed by the MDT had a longer survival than those not managed by the team (39.7 vs 27.0 months, hazard ratio 0.549, $P=0.001$).⁹⁸ MDT meetings were also associated with increased patient satisfaction and adherence to treatment guidelines.⁹⁹⁻¹⁰¹ Although international guidelines recommend MDT meetings for shared decision-making,^{26,102} a limited number of cases with prostate cancer are discussed in MDT meetings. In a retrospective review of 7,500 patients from a single tertiary care centre in Australia, 100% of cases with lung cancer and upper gastrointestinal cancer were discussed at MDT

meetings, while almost 28% of cases with prostate cancer were discussed.¹⁰³

Despite the increased awareness and occurrence of regular MDT meetings, adherence to the MDT recommendations has not been uniformly recorded or followed.¹⁰⁴ Irregularities in MDT record keeping or lack of follow-up may be some reasons for the low adherence. Introducing standardised recording of the MDT recommendations in the patients' medical records might increase adherence to the treatment plan.¹⁰⁴ However, the time lag between case presentation to the specialists and its discussion in MDT meetings can delay treatment initiation. Logistic challenges and costs may further exacerbate this delay. This issue may be resolved to some extent by the provision of virtual meetings to increase the frequency of MDT meetings.¹⁰⁵ For countries planning to implement such meetings, recommendations include emphasising the value of partnerships and interventions to reduce infrastructure costs while accelerating genetic-guided treatment.^{96,104}

CONCLUSION

The arena of genetic testing for patients with mCRPC has undergone a radical change in the last 5 years. With the approval of PARP inhibitors, somatic testing in patients for identifying actionable HRR mutations is of prime importance. The incorporation of somatic testing in routine clinical practice will ensure that most patients with mCRPC are tested and, when appropriate, prescribed PARP inhibitors, which have shown improved survival outcomes. Along with the challenges discussed above, another hindrance to incorporating genetic testing in clinical practice is the associated costs. In Singapore, genetic testing and counselling costs have to be borne by the patients as they are currently not reimbursed or subsidised by the government. The reimbursement of testing, treatment and out-of-pocket costs as well as subsidies for patients may increase the reach of genetic testing to a larger population. The formation of a registry for patients with prostate cancer and the generation of real-world data on genetic testing and related treatment options such as PARP inhibitors in Singapore may help provide the impetus to convince the government to extend more financial assistance for this purpose.

This article discusses an approach for incorporating genetic testing in routine clinical practice in Singapore. We have proposed a hybrid model for genetic counselling in which pre-test counselling prior to somatic testing can be conducted by managing clinicians, while patients with HRR mutations can then be referred to genetic

counsellors for post-test counselling prior to germline testing to reduce the burden at the counselling stage. However, it is important to train managing clinicians about the fundamentals of genetic counselling. Challenges in the sample journey can be overcome with the recommended steps for sample processing and storage. Laboratory personnel engagement for appropriate handling and processing of samples is imperative for the success of genetic tests. Finally, an MDT approach with the involvement of the MTB is recommended for the effective and optimal management of patients with mCRPC in Singapore.

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