

Supplementary Appendix

Biography details of 12 specialists/authors

Author Name	Specialization	Years in Practice	Scope of Practice
A/Prof. Ravindran Kanesvaran	Medical oncology Sub-Specialties: GU oncology and geriatric oncology.	15+	<p>Dr Ravindran Kanesvaran is Deputy Head and Senior Consultant in the Division of Medical Oncology of the National Cancer Centre Singapore, an Associate Professor at Duke-NUS Medical School and clinical senior lecturer at the Yong Loo Lin School of Medicine, National University of Singapore. He is actively involved in graduate medical education and is the Program Director of the Medical Oncology Senior Residency Program.</p> <p>After completion of his medical oncology specialty training he followed up with a fellowship in genitourinary oncology (GU) and geriatric oncology in Duke Cancer Institute in North Carolina, USA on a Healthcare Manpower Development Program (HMDP) scholarship awarded by the Ministry of Health Singapore. His research interests include GU oncology and geriatric oncology.</p>
Dr. Puey Ling Chia	Medical oncology Sub-Specialties: Genitourinary Oncology	10+	<p>Dr Puey Ling Chia is a consultant Medical Oncologist at the Tan Tock Seng Hospital with special interest in treating Genitourinary, Gastrointestinal and Thoracic Cancers</p>

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A/Prof. Edmund Chiong	<p>Surgical Oncology, Urologist</p> <p>Sub-Specialties: Reconstructive Urology, Surgical Oncology (Urology)</p>	15+	<p>A/Prof. Edmund Chiong is the Head & Senior Consultant, Department of Urology, National University Hospital, Senior Consultant, Division of Surgical Oncology, National University Cancer Institute, Singapore; Associate Professor, Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore.</p> <p>His speciality is Surgical Oncology, Urology and sub-Specialties are: Reconstructive Urology, Surgical Oncology (Urology), Urologic Oncology</p> <p>His key special Interests are: Uro-oncology (Especially Prostate Cancer, Kidney Cancer and Bladder Cancer), Prostate Cancer High-Dose Rate Brachytherapy, Robotic surgery</p>
A/Prof. Melvin Lee Kiang Chua	<p>Radiation Oncology</p> <p>Sub-specialties: Uro-Oncology, Genitourinary, Nasopharynx, Thyroid Head & Neck oncology</p>	15+	<p>Assoc Prof Chua Lee Kiang Melvin is a senior consultant at the National Cancer Centre Singapore and specializes in radiation oncology. His sub-specialty interests are in: Genitourinary, Uro-Oncology, Head & Neck, Nasopharynx and Thyroid Cancers</p>
Dr. Nye Thane Ngo	Pathology	15+	<p>Dr Ngo Nye-Thane is a Consultant with the Department of Pathology at the Singapore General Hospital. Her specialty interests are in gastrointestinal pathology and uropathology.</p>

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Dr. Samuel Ow	Medical Oncology Sub-Specialties: Cancer Genetics	15+	Dr Samuel Ow is a Consultant Medical Oncologist in the Department of Haematology-Oncology, National University Cancer Institute, Singapore (NCIS). Dr Samuel Ow's clinical and research interests are in Breast Cancer and Clinical Cancer Genetics. He received a Master of Public Health with concentration in Epidemiology and Biostatistics from the Johns Hopkins Bloomberg School of Public Health
Dr. Hong Gee Sim	Surgical Oncology, Urologist	15+	Dr Sim Hong Gee is a urologist practising in Gleneagles Hospital, Singapore. His research interests are in genitourinary cancer, especially in prostate cancer biomarkers and cancer epigenetics. He completed his subspecialty training under the Society of Urologic Oncology fellowship at the University of Washington and Fred Hutchinson Cancer Research Center in USA. Prior to private practice, Dr Sim was the director of urologic oncology at SGH and the chairman for Chapter of Urologists, College of Surgeons in Singapore.
Dr. Min-Han Tan	Medical Oncology Sub-Specialties: Clinical cancer genetics and precision oncology	15+	Dr Tan Min-Han specializes in clinical cancer genetics and precision oncology. As a cancer specialist trained in both clinical cancer genetics and medical oncology, he advises physicians and patients on integrating genetics with cancer management. He also provides specialist genetic counselling at his clinic, for either risk assessment or drug selection.
A/Prof. Kiang Hiong Tay	Vascular and Interventional Radiology,	20+	Dr Tay is currently the Head of the Vascular and Interventional Radiology Department and Assistant Chairman of the Division of Radiological Sciences at Singapore General Hospital. He is Associate Professor at the Duke NUS Graduate Medical School Singapore as well as at the Yong Loo

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	Interventional Radiology Sub-specialties: Vascular and Interventional Radiology		Lin School of Medicine in National University of Singapore. Dr Tay is also the Academic Vice Chair for Clinical Service Transformation of the Singhealth Duke NUS Radiological Sciences Academic Clinical Programme.
Dr. Alvin Seng Cheong Wong	Medical Oncology Special Interests: Genitourinary cancers (kidney, prostate, bladder and germ cell cancers)	15+	<p>Dr Alvin Wong is a Senior Consultant, Department of Haematology-Oncology, National University Cancer Institute, Singapore and also a Senior Consultant at Department of Oncology - Medical & Radiation, Ng Teng Fong General Hospital.</p> <p>He sub-specialises in genitourinary malignancies (kidney, prostate, bladder and germ cell cancers). His research collaborations include the investigation of Tumour Associated Macrophages in Renal Cell Carcinoma (Singapore Immunology Network) and the epidemiology of prostate cancer (NUS Epidemiology & Public Health). He has published on a range of topics in local and international journals and enjoys a ‘seamless’ approach to GU cancers with his trainees and colleagues.</p>
Dr. Siew Wei Wong	Medical Oncology Special Interests: prostate, kidney, bladder, upper	15+	<p>Dr Wong Siew Wei is a Senior Consultant, Medical Oncologist at Parkway Cancer Centre. Dr Wong’s areas of expertise and interest are in prostate, kidney, bladder, upper gastrointestinal and lung cancers.</p> <p>Prior to private practice, Dr Wong Siew Wei was a Consultant, Medical Oncologist with Johns Hopkins Singapore International Medical Centre (JHSIMC) and Tan Tock Seng Hospital (TTSH). He was involved in</p>

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	gastrointestinal and lung cancers.		<p>multidisciplinary tumour boards for gastrointestinal, thoracic and genitourinary malignancies during his appointment at JHSIMC / TTSH and led a number of clinical trials in his previous institution. He moved into private practice in 2018.</p> <p>Dr Wong Siew Wei was a clinical teacher at the Lee Kong Chian School of Medicine at Nanyang Technological University. He has lectured at various oncology meetings at both national and regional levels, especially on the topic of genitourinary cancers, and given numerous public talks on cancer awareness.</p>
Prof. Puay Hoon Tan	Pathology Special Interests: Breast, urologic and renal pathology	20+	<p>Professor Tan Puay Hoon, was the Senior Consultant Histopathologist and Chairman, Division of Pathology, Singapore General Hospital, Singapore. She has active interests in breast, urologic and renal pathology. Apart from a busy service largely focused on subspecialty surgical signouts, she and her collaborators are recipients of several research grants related to translational studies of breast and prostate cancer. She is author of more than 400 publications, and participates regularly in regional and international meetings.</p> <p>Research Interests:</p> <p>Breast pathology, focusing on the classification of breast fibroepithelial lesions and their molecular pathogenesis, triple negative breast cancer, and ductal carcinoma in situ. In urologic pathology, she collaborates on research in kidney and prostate cancers</p>

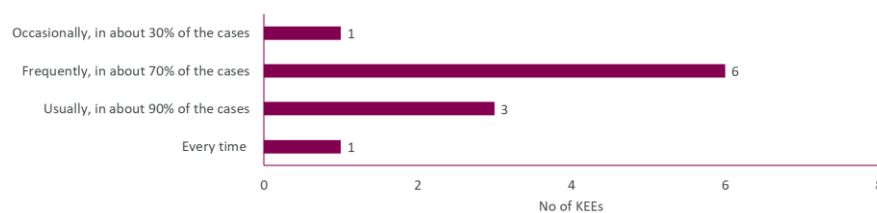
Summary of Pre-Meeting Survey Questionnaire and Responses

- What is the patient selection criteria for genetic testing in prostate cancer?

	All men with mPca	All men with high-risk locally-advanced Pca	Men with family h/o cancer and mPca	Men with family h/o cancer and high risk locally-advanced PCa	Other
Medical oncologist	✓	✓	✓	✓	
Medical oncologist	✓		✓	✓	
Medical oncologist	✓		✓		
Medical oncologist	✓	✓	✓	✓	
Medical oncologist	✓	✓			
Medical oncologist	✓		✓		
Pathologist			✓	✓	
Radiation oncologist	✓	✓			
Urologist			✓	✓	✓
Urologist			✓	✓	

- All the key external experts (KEEs) agreed that men with metastatic prostate cancer and a family history of cancer should be screened for genetic aberrations. Four KEEs indicated genetic screening of men with high-risk locally advanced prostate cancer as well.

- Are relevant guidelines applied in all cases during testing and management of prostate cancer?



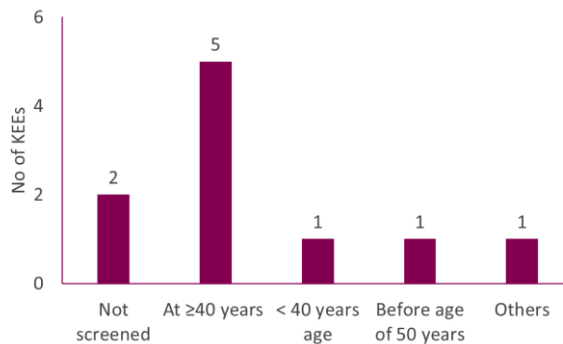
- Of 11 KEEs, 10 responded that relevant National Comprehensive Cancer Network (NCCN) and/or local guidelines were applied in more than 70% of the cases.

- Was the family history of cancers enquired?

	Breast cancer	Ovarian cancer	Prostate cancer	Colorectal cancer	Lung cancer	Other cancer
Medical oncologist	✓	✓	✓	✓	✓	
Medical oncologist	✓	✓	✓	✓	✓	
Medical oncologist	✓	✓	✓			✓
Medical oncologist	✓	✓		✓	✓	
Medical oncologist	✓	✓	✓	✓	✓	✓
Medical oncologist	✓	✓	✓			
Pathologist			✓			
Radiation oncologist	✓	✓	✓	✓		✓
Urologist	✓	✓	✓			
Urologist			✓			

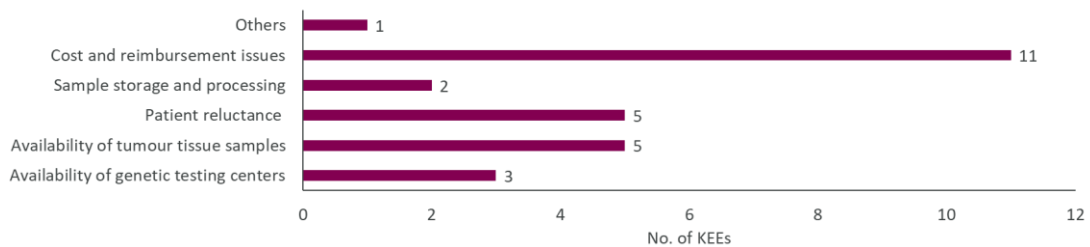
- Eight out of 11 KEEs confirmed that they enquire about the family history of breast and ovarian cancers apart from prostate cancer. A few KEEs also enquire about colorectal cancer, lung cancer and nasopharyngeal cancer.

➤ What are the criteria for screening for prostate cancer in men with *BRCA* carrier mutation?



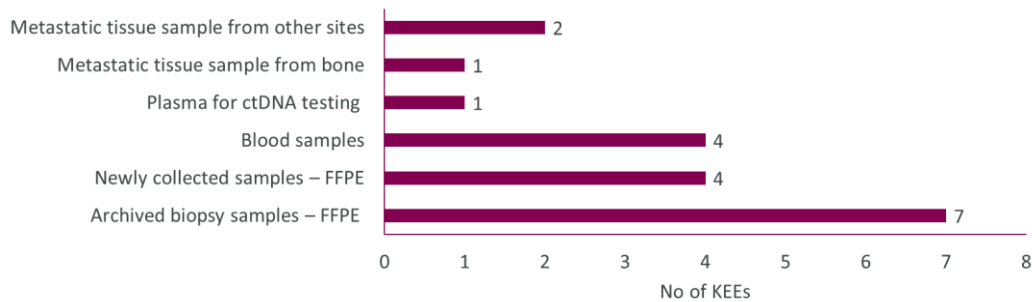
- Fifty percent of the KEEs recommend regular screening after the age of 40 years for men with *BRCA* carrier mutations.

➤ What are the main hurdles in conducting HRR genetic testing in patients with prostate cancer?



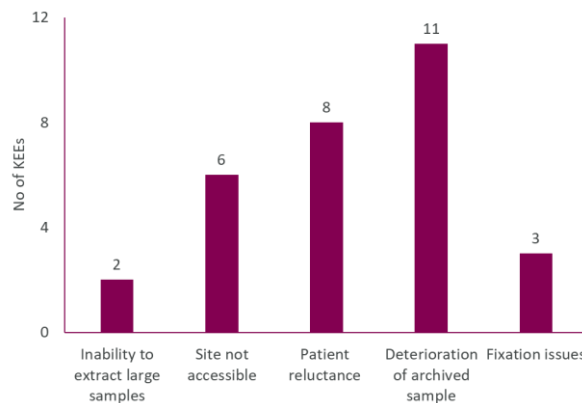
- All KEEs agreed that the cost associated with HRR testing is a major hurdle. Sample storage, the age of the archived sample, difficulties in processing the archived sample and small DNA yield are some challenges associated with the processing of samples.

➤ What are samples preferred for genetic testing?



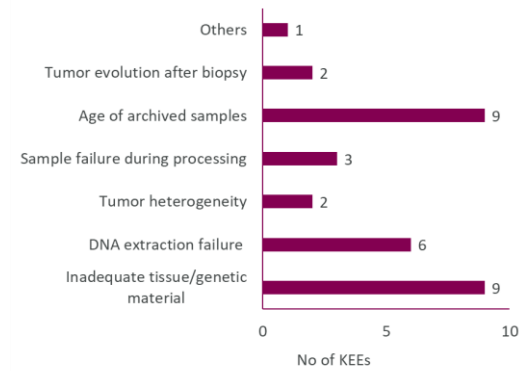
The majority of the experts answered that archived samples are mostly preferred/available for genetic testing.

➤ What are the major challenges in obtaining samples for genetic testing?



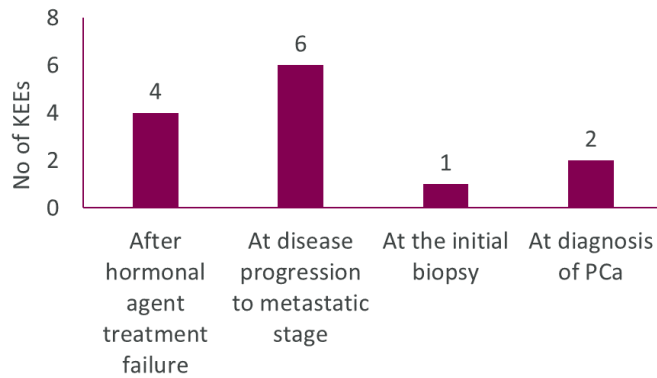
- All the KEEs pointed at the deterioration of archived samples as the major challenge in genetic testing.

➤ What are the common reasons for the failure of genetic testing?



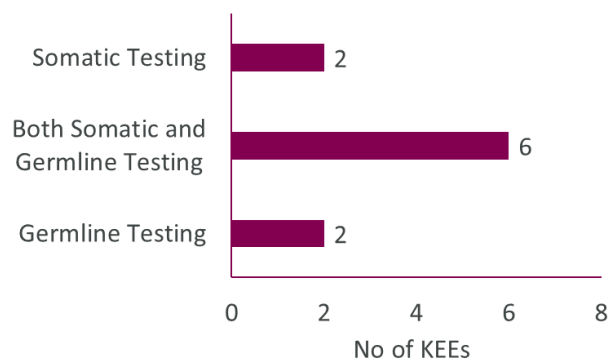
- The age of the archived sample and inadequate tissue or genetic material remains the prime reasons for the failure of genetic testing.

➤ What is the optimal time for genetic testing?



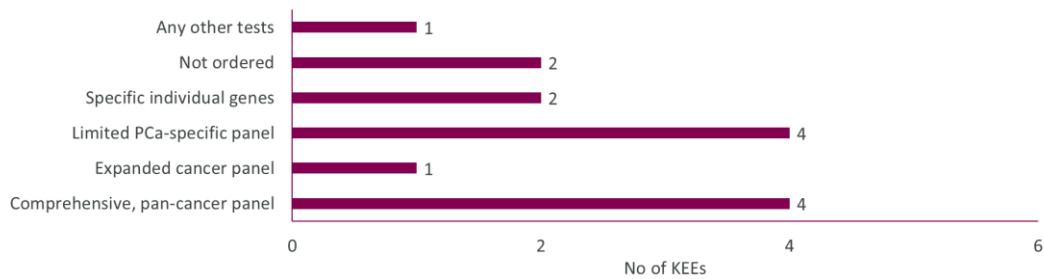
- Most KEEs agreed that genetic testing should be performed at disease progression. Some KEEs also mentioned that genetic testing could be conducted if the hormonal treatment fails.

➤ Which type of genetic testing is most preferred?



- Most KEEs (6 out of 10) agreed that both somatic and germline testing should be conducted.

➤ What are the genetic tests to be conducted in metastatic prostate cancer? What is the turnaround time?



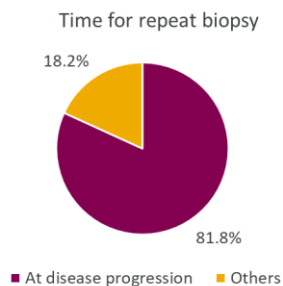
- Most KEEs preferred comprehensive panel tests or at least a PCa-specific panel of tests. The mean turnaround time for receiving the report of tests is 2.9 weeks with a minimum of 2 weeks (n=4) and a maximum of 4 weeks (n=3).

➤ What percentage of patients with metastatic prostate cancer are presented at multi-disciplinary team meetings?

No. of respondents (n = 9)	Patients with metastatic Pca (%)
1	5
2	10
4	20
1	50
1	75

- KEEs replied that patients with PCa are not routinely presented at multi-disciplinary team (MDT) meetings with 6 KEEs presenting less than 20% of cases.

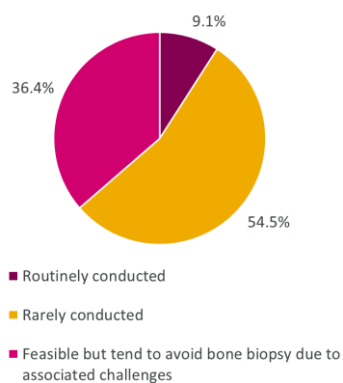
➤ When and where is repeat biopsy done?



- Most KEEs (more than 80%) preferred repeat biopsy at disease progression. The site preferred for repeat biopsy was a metastatic site apart from bone.

➤ Is repeat biopsy feasible and routinely taken from the bone in metastatic disease?

	Prostate	Bone	Other metastatic site apart from bone	Liquid biopsy
Medical oncologist				✓
Medical oncologist			✓	
Medical oncologist			✓	✓
Medical oncologist				✓
Medical oncologist		✓	✓	
Pathologist			✓	✓
Pathologist	✓	✓	✓	
Radiation oncologist		✓	✓	
Urologist			✓	
Urologist	✓			✓



- Bone biopsy was not preferred by the majority of KEEs (n=6) due to challenges associated with the biopsy.

Supplementary Tables

Supplementary Table S1. Advantages and Limitations of Tissue, ctDNA and Blood-based Germline Testing¹⁻⁵

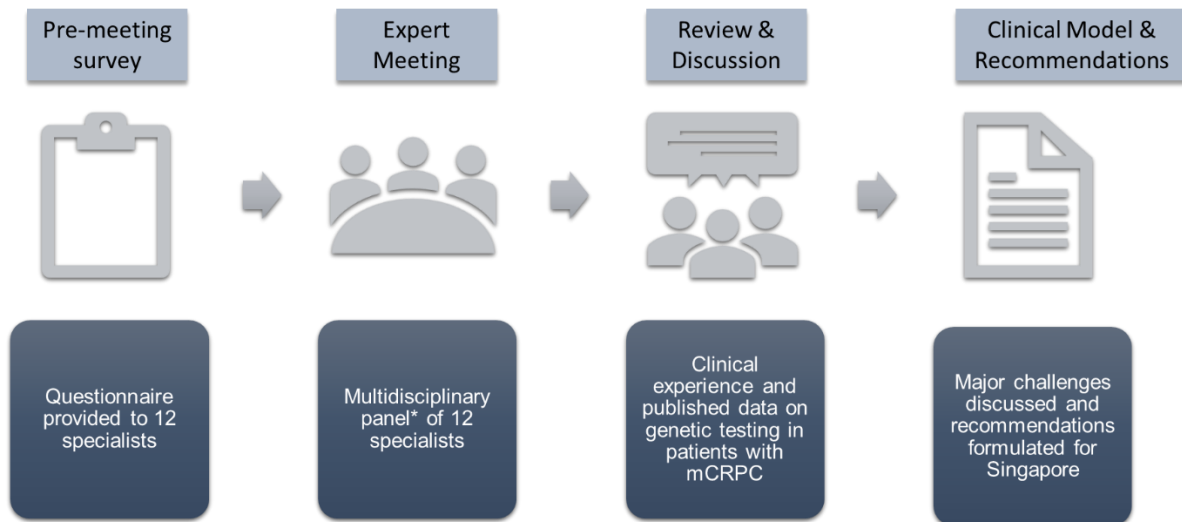
	Tissue	ctDNA	Blood
Type of mutation detected	Somatic and germline		Germline only
Turnaround time	~ 2–8 weeks	~ 1–2 weeks	~ 2–4 weeks
Genetic counselling	Extensive counselling is not required for somatic testing		Requires counselling
Testing benefits	<ul style="list-style-type: none"> • The gold standard for tumour analysis • High clinical sensitivity • Archival tissue for tumour histology (Gleason scoring and grading may already be available and provides an option for testing) 	<ul style="list-style-type: none"> • Better representative of tumour heterogeneity and metastatic deposits than primary biopsy • Minimally invasive and easily repeatable • Real-time detection of comprehensive cancer profile 	<ul style="list-style-type: none"> • Analysis feasible in 100% of cases • Minimally invasive and easily repeatable • Real-time detection of comprehensive cancer profile • Blood testing is currently used to detect significant genomic rearrangements
Testing limitations	<ul style="list-style-type: none"> • Invasive and difficult to repeat • May miss within-tumour genetic heterogeneity • Single snapshot over time and space 	<ul style="list-style-type: none"> • Lower clinical sensitivity for somatic variants compared to tissue • Low coverage and sequencing artefact can lead to missed mutations. • Highly sensitive tests are required 	<ul style="list-style-type: none"> • Does not identify patients with mutations of somatic origin or capture the potentially changing genetic profile of disease progression • Lack of standardisation

Tissue	ctDNA	Blood
<ul style="list-style-type: none">• Low coverage and sequencing artefact can lead to missed mutations.	<ul style="list-style-type: none">• May result in false positives• Testing is limited by the availability of an adequate amount of ctDNA, particularly at the early stages• Lack of standardisation• Novel technologies, not used in routine clinical practice	

ctDNA, circulating tumour DNA

Supplementary Figures

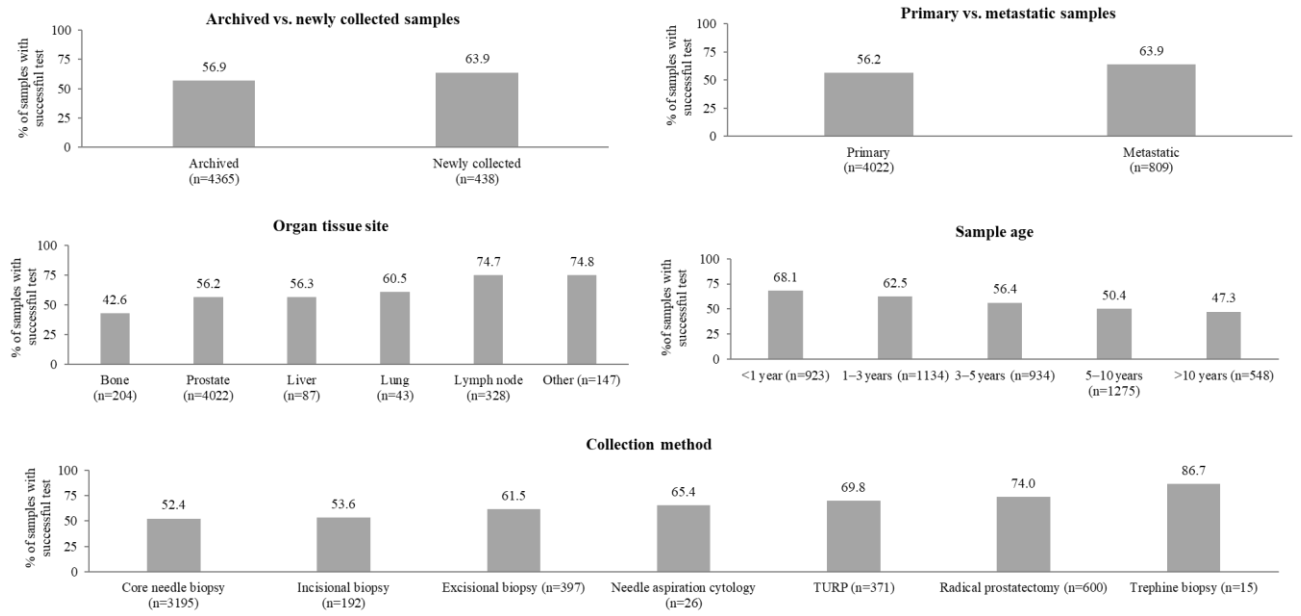
Supplementary Figure S1. Methodology for Development of Position Paper



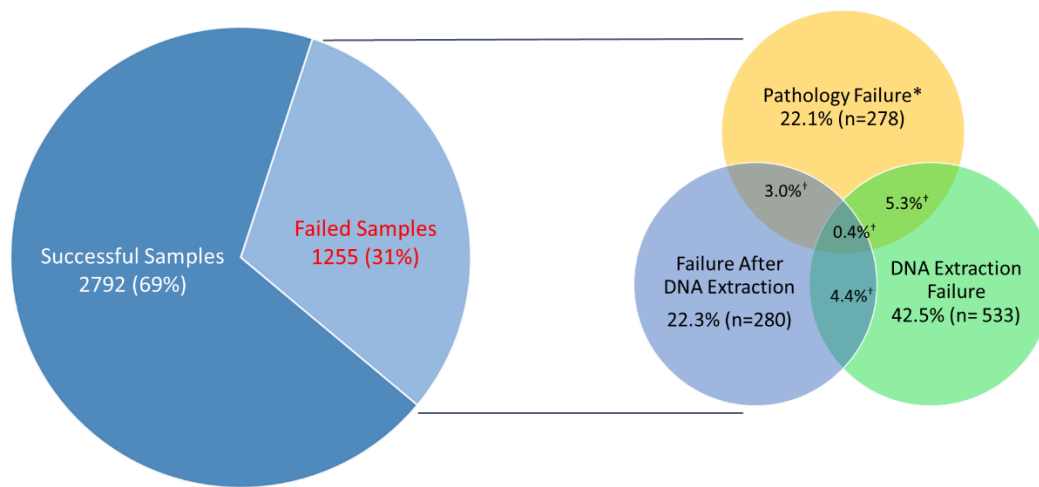
*Panel = medical oncologists (6) [including cancer geneticist], pathologists (2), urologists (2), radiation oncologist (1) and interventional radiologist (1)

mCRPC, metastatic castration-resistant prostate cancer

Supplementary Figure S2. Testing Success Rates in PROfound Study⁶



Supplementary Figure S3. Reasons for Sample Failure in PROfound Study^{7,8}



Note: Patients could have more than one tissue sample tested and samples may have failed at different stages of the next-generation sequencing testing process.

*Sample does not meet pathology requirements for the test if there is $\leq 20\%$ tumour content or $< 5-7.5 \text{ mm}^2$ viable nucleated tissue. †165 (13.1%) patients failed in more than 1 category.

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