



**QUEEN'S
UNIVERSITY
BELFAST**

Practical guidance on establishing a molecular testing pathway for alterations in homologous recombination repair genes in clinical practice for patients with metastatic prostate cancer

Schostak, M., Bradbury, A., Briganti, A., Gonzalez, D., Gomella, L., Mateo, J., Penault-Llorca, F., Stenzinger, A., Wyatt, A. W., & Bjartell, A. (2024). Practical guidance on establishing a molecular testing pathway for alterations in homologous recombination repair genes in clinical practice for patients with metastatic prostate cancer. *European Urology Oncology*, 7(3), 344-354. <https://doi.org/10.1016/j.euo.2023.08.004>

Published in:
European Urology Oncology

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights

Copyright 2023 the authors.
This is an open access article published under a Creative Commons Attribution-NonCommercial-NoDerivs License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits distribution and reproduction for non-commercial purposes, provided the author and source are cited

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Open Access

This research has been made openly available by Queen's academics and its Open Research team. We would love to hear how access to this research benefits you. – Share your feedback with us: <http://go.qub.ac.uk/oa-feedback>



European Association of Urology

Practical Guidance on Establishing a Molecular Testing Pathway for Alterations in Homologous Recombination Repair Genes in Clinical Practice for Patients with Metastatic Prostate Cancer

Martin Schostak^{a,*}, Angela Bradbury^b, Alberto Briganti^c, David Gonzalez^d, Leonard Gomella^e, Joaquin Mateo^f, Frédérique Penault-Llorca^g, Albrecht Stenzinger^h, Alexander W. Wyattⁱ, Anders Bjartell^{j,k}

^aDepartment of Urology, Urooncology, Robot-assisted and Focal Treatment, University Hospital Magdeburg, Magdeburg, Germany; ^bPerelman Center for Advanced Medicine, Philadelphia, PA, USA; ^cVita-Salute San Raffaele University, Milan, Italy; ^dPatrick G. Johnston Centre for Cancer Research, Queen's University, Belfast, UK; ^eDepartment of Urology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA; ^fVall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; ^gUniversity Clermont Auvergne, Centre Jean Perrin, Clermont-Ferrand, France; ^hInstitute of Pathology, University Hospital Heidelberg, Heidelberg, Germany; ⁱVancouver Prostate Centre, University of British Columbia, Vancouver, Canada; ^jDepartment of Urology, Skåne University Hospital, Malmö, Sweden; ^kDepartment of Translational Medicine, Lund University, Lund, Sweden

Article info

Article history:

Received 11 October 2022

Received in Revised form

1 August 2023

Accepted 14 August 2023

Available online 14 September 2023

Associate Editor: Morgan Rouprêt

Keywords:

Circulating tumour DNA
Metastatic castration-resistant prostate cancer
Molecular diagnostics
Multidisciplinary team
PARP inhibitors
Tumour testing

Abstract

Context: Prostate cancer is a molecularly heterogeneous disease that is amenable to diagnostic testing to identify patients potentially eligible for personalised treatments inform familial risk and provide relevant information about potential prognosis. Several guidelines support the integration of genomic testing in a shared decision-making framework so that both health care professionals (HCPs) and patients are involved in determining the best treatment approach.

Objective: To review current guidelines on molecular diagnostic testing for homologous recombination repair (HRR) gene alterations in patients with metastatic prostate cancer, with the aim of providing practical considerations for effective guideline implementation and establishment of an appropriate pathway for molecular diagnostic testing.

Evidence acquisition: We undertook a nonsystematic narrative review of the literature using PubMed to identify current guidelines and recommendations on molecular diagnostic testing for *BRCA* and/or homologous recombination repair gene alterations (HRRm) in patients with prostate cancer. In addition, selected articles that included *BRCA*/HRRm testing in clinical trials in metastatic castration-resistant prostate cancer and real-world evidence were also evaluated. Websites for relevant societies were reviewed for molecular diagnostic guidelines not published on PubMed.

Evidence synthesis: Our review of guidelines published by several international societies that include molecular testing in prostate cancer identified variations in molecular testing approaches. The review of testing approaches used in clinical trials and real-world settings also highlighted several aspects that require improvement. Therefore, we compiled practical guidance for establishing an appropriate *BRCA*/HRR mutation testing pathway.

Conclusions: While there are several challenges to molecular testing and interpretation of test results that require enhancement, a multidisciplinary team approach will

* Corresponding author. Department of Urology, Urooncology, Robot-assisted and Focal Treatment, University Hospital Magdeburg, Leipziger Street 44, 39120 Magdeburg, Germany. Tel. +49 391 6715036.

E-mail address: martin.schostak@med.ovgu.de (M. Schostak).

empower HCPs and their institutions to improve on or initiate their own molecular testing pathways. This in turn will lead to improvements in management strategies for patients with metastatic prostate cancer, for whom better treatment outcomes is a significant unmet need.

Patient summary: Establishing a molecular testing pathway in clinical practice for patients with metastatic castration-resistant prostate cancer will lead to fairer and more equal access to personalised treatments. This should lead to better outcomes, particularly for patients whose disease has spread to other areas of the body.

© 2023 The Authors. Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Prostate cancer is the most prevalent noncutaneous cancer among men worldwide [1]. If diagnosed early, patients have good prognosis; however, despite early detection, 20–30% of patients who receive treatment for nonmetastatic disease will experience relapse to advanced disease, of whom 70–80% will have bone metastases [2]. At the metastatic stage, prognosis is poorer, with current 5-yr survival rates of approximately 30% [3]. To improve outcomes, precision medicines are increasingly being used as a standard of care in the management and treatment of prostate cancer. Central to the initial development of precision medicines in the monotherapy setting are molecular diagnostic testing techniques that can identify, for example, alterations in a specific gene known to be directly or indirectly involved in the DNA homologous recombination repair (HRR) pathway. Exploitation of deficiencies in this repair pathway has led to the development of precision treatments for a variety of solid tumour cancers, including prostate cancer [4]. Molecular testing can also be used to provide information about the likely prognosis and relevant information for benefit/risk discussions for patients with prostate cancer receiving combination treatment approaches that include precision medicine.

1.1. Genomic status of prostate cancer

The molecularly heterogeneous nature of prostate cancer makes it amenable to treatment with personalised medicines. The prevalence of genomic (germline and somatic) alterations in DNA repair genes, including those with an involvement in HRR, ranges from approximately 5% in localised disease to approximately 25% in metastatic prostate cancer, with *BRCA2* alterations the most common [5–7]. Evidence also suggests an association of germline HRR alterations with more aggressive disease characteristics that lead to earlier progression to lethal metastatic disease than for cases without such alterations [8]. In addition, somatic HRR alterations drive prostate carcinogenesis, with loss of *BRCA2* the most commonly reported [9]. Although there are clinical guidelines on the use of molecular diagnostic testing to drive treatment decision-making, they are not widely implemented; however, it is hoped that such testing will become routine practice for patients with advanced and metastatic prostate cancer in the coming years. Identification of HRR gene alterations in patients with prostate cancer

will become increasingly important in the search for prognostic markers for aggressive disease and in optimising outcomes to standard-of-care therapies and informing the use of targeted therapies such as poly(ADP-ribose) polymerase (PARP) inhibitors and other novel treatments.

1.2. HRR gene alterations and PARP inhibition in prostate cancer

In prostate cancer and various other solid tumours, HRR gene alterations are associated with sensitivity to PARP inhibition [10–13]. Two PARP inhibitors, olaparib and rucaparib, are currently approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in patients with qualifying HRR alterations. Details of PARP inhibitor studies and the variety of HRR gene alterations being investigated in trials that include patients with mCRPC are shown in Table 1 [14–23]. Research has shown that not all HRR gene alterations in metastatic prostate cancer achieve a similar efficacy benefit from PARP inhibition. It has been reported that patients with homozygous *BRCA2* deletions and biallelic loss of *PALB2* derive the greatest benefit [5].

Identification of patients with eligible HRR gene alterations via molecular testing to inform clinical decisions is of major importance because of the significant unmet need for better treatments for patients with mCRPC. Here, we provide practical guidance to empower physicians and their institutions to initiate a molecular diagnostic testing pathway and to help in improving the efficiency of pathways already in place, given that the current guidelines are limited. The aim of this practical guidance is to support the identification of more patients with mCRPC and HRR alterations who may benefit from personalised treatment. The [Supplementary material](#) provides further information on PARP inhibitor modes of action and approvals for prostate cancer, a discussion of the future landscape for *BRCA*/HRR mutation (HRRm) testing in prostate cancer, and an infographic that visually summarises the key points we raise.

2. Evidence acquisition

A nonsystematic narrative literature search was performed in PubMed to identify guidelines on molecular diagnostic testing in prostate cancer published up to December 2022. In addition, selected manuscripts that included *BRCA*/HRRm testing in clinical trials and as real-world evidence in the mCRPC setting were evaluated. As some guidelines on

Table 1 – Altered HRR genes most frequently investigated in PARP inhibitor clinical trials in patients with mCRPC

Treatment arm(s)	Clinical trial	Study type	Patient population	Molecular test	Genes investigated	GS/PS
Olaparib	TOPARP-A (NCT01682772) [14]	Phase 2 single-arm, open-label	mCRPC with disease progression on 1 or 2 taxane chemotherapies and a qualifying HRR mutation	Whole-exome (and targeted as needed) sequencing of 113-gene panel (GeneRead) in tissue (and saliva for germline testing)	No predefined list	RGS
Olaparib	TOPARP-B (NCT01682772) [15]	Phase 2 randomised, open-label	mCRPC with disease progression on ≥ 1 but not > 2 taxane chemotherapies and a qualifying HRR mutation	Targeted sequencing of a 113-gene panel (GeneRead) in tissue	ARID1A, ATM, ATRX, BRCA1, BRCA2, CDK12, CHEK1, CHEK2, FANCA, FANCF, FANCG, FANCI, FANCM, MSH2, PALB2, NBN, RAD50, WRN	PGS
Olaparib Physician's choice of Abi or enzalutamide + prednisone	PROfound (NCT02987543) [5,16]	Phase 3 randomised, open-label	mCRPC with disease progression on an NHA and a qualifying HRR mutation	Investigational clinical trial assay (based on the FoundationOne CDx using a prespecified 15-gene panel) in tissue	ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, ^a RAD51B, RAD51C, RAD51D, RAD54L	PGS
Olaparib + Abi Placebo + Abi	PROpel (NCT03732820) [17] ^b	Phase 3 randomised, double-blind, placebo-controlled	First-line mCRPC independent of HRR mutation status	FoundationOne CDx in tissue using a prespecified 14-gene panel ^a	ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L	RGS
Rucaparib	TRITON 2 (NCT02952534) [11]	Phase 2 single-arm, open-label	mCRPC with disease progression on 1 or 2 NHAs and 1 taxane chemotherapy and a qualifying HRR mutation	FoundationOne CDx in tissue	ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54	PGS
Rucaparib Physician's choice of Abi, enzalutamide, or docetaxel	TRITON 3 (NCT02975934) [18]	Phase 3 open-label, randomised	mCRPC with disease progression on an NHA and a qualifying HRR mutation	FoundationOne CDx in tissue	ATM, BRCA1, BRCA2	PGS
Rucaparib + enzalutamide Placebo + enzalutamide	CASPAR (NCT04455750) [19] ^b	Phase 3	First-line mCRPC independent of HRR mutation status	Not stated	BRCA1, BRCA2, PALB2	PGS
Talazoparib	TALAPRO-1 (NCT03148795) [20]	Phase 2 single-arm, open-label	mCRPC with disease progression on an NHA and 1 or 2 chemotherapy regimens (including at least 1 taxane) and a qualifying HRR mutation	FoundationOne CDx (prespecified 11-gene panel) in tissue	ATM, ATR, BRCA1, BRCA2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C	PGS
Talazoparib + enzalutamide Placebo + enzalutamide	TALAPRO-2 (NCT03395197) [21] ^b	Phase 3 double-blind, randomised, placebo-controlled	First-line mCRPC independent of HRR mutation status	FoundationOne CDx or FoundationOne Liquid CDx test	BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12	PGS
Niraparib	GALAHAD (NCT02854436) [22]	Phase 2 single-arm, open-label	mCRPC with disease progression on an NHA and at least 1 taxane and a qualifying HRR mutation	FoundationOne (T7 bait-set) or FoundationOne CDx in tissue	ATM, BRCA1, BRCA2, BRIP1, HDAC2, CHEK2, FANCA, PALB2	PGS
Niraparib + AbiP Placebo + AbiP	MAGNITUDE (NCT03748641) [23] ^b	Phase 3 double-blind, randomised, placebo-controlled	First-line mCRPC independent of HRR mutation status	Not stated	ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2	PGS
Fuzuloparib ^c + AbiP Placebo + AbiP	NCT04691804 (ongoing) ^b	Phase 3	First-line mCRPC independent of HRR mutation status	Not stated	N/S	PGS

Abi = abiraterone; AbiP = abiraterone with prednisone; HRR = homologous recombination repair; mCRPC = metastatic castration-resistant prostate cancer; NHA = next-generation hormonal agent; GeneRead = GeneRead DNaseq Mix-n-Match Panel V2 from Qiagen; GS/PS = gene selection relative to patient selection; RGS = retrospective gene selection; PGS = prospective gene selection.

^a PPP2R2A was evaluated in the PROfound study but was not included in the olaparib label and so was not included in the PROpel study.

^b These studies included patients independent of their HRR mutation status, but secondary analyses by HRR status are planned.

^c Fuzuloparib was formerly known as fluzoparib.

molecular diagnostic testing may not be published in journals, we also searched the websites of relevant societies, including the National Comprehensive Cancer Network (NCCN), American Society of Oncology (ASCO), European Society of Medical Oncology (ESMO), American Urological Association (UAU), and European Association of Urology (EAU).

3. Evidence synthesis

3.1. Molecular testing guidelines for prostate cancer

3.1.1. Current guidelines

Guidelines on management and treatment pathways for patients with metastatic prostate cancer that incorporate molecular testing to identify germline and somatic alterations in patients with prostate cancer vary between professional associations, although there are some consistencies, such as the recommendation to test tumour tissue from patients with mCRPC. Details of the guidelines on molecular testing to assist medical professionals in management of the disease are summarised in Table 2. Germline testing of blood or saliva from patients with a prostate cancer diagnosis to identify inherited alterations that predispose to cancer can be important for informing family members of their potential disease risk (referred to as cascade testing) and subsequent enrolment in screening programmes where appropriate. Testing of tumour tissue can be highly useful in informing treatment decisions regarding eligibility for personalised medicines and clinical trial participation, as it identifies both germline and somatic alterations. Furthermore, guidelines advise that patients should be informed that tumour testing has the potential to uncover germline findings that may warrant further investigation, and that patients with pathogenic or likely pathogenic alterations identified via tumour testing should be referred for genetic

counselling and germline testing. Despite the availability of regional guidelines, there is considerable variation in the amount of molecular testing conducted among institutions, varying from little or no testing in community practice to higher rates in academic settings [24]. Reasons for this variation include access to testing facilities, availability of tumour samples, and the cost of testing, as well as a lack of local or national approval for drugs or testing reimbursement. Therefore, it would be beneficial to patients if the guidelines currently available were more widely implemented and followed in a more consistent manner to ensure equality in the management of patients' disease.

3.1.2. How can implementation of current guidelines be improved?

The guidelines for molecular testing from the various organisations highlighted in Table 2 [25–28] are clear to understand; however, we believe that there are areas for which further information would be useful to practitioners regarding patient treatment in the metastatic prostate cancer setting. There are ongoing discussions on the optimal way to perform testing, the time point for testing, and the test design itself. Therefore, we suggest that the type of questions to be addressed to facilitate better use of these guidelines include, for example, the time point during a patient's disease course at which to conduct the test (ie, should it be at first diagnosis of prostate cancer [any stage] or at diagnosis of metastatic disease?), and which test to undertake first (germline or tumour tissue?). Germline testing appears to be more widely used, whereas tumour tissue testing was primarily implemented in clinical trials and is now being adopted in clinical routine to identify patients who may be suitable for targeted treatment. Additional queries include which tumour sample type is best (ie prostatectomy vs prostate biopsy), whether metastatic tissue needs to be collected or if archival primary samples are adequate and,

Table 2 – Examples of international guidelines with current recommendations on molecular testing for alterations in HRR genes in mCRPC

National Comprehensive Cancer Network [25]
Germline testing is recommended for patients with: <ul style="list-style-type: none"> – Prostate cancer (high-risk, very-high-risk, regional, or metastatic) or a history of breast cancer – Family history of other cancers, including Lynch syndrome-related cancers – Family history of risk mutations, especially in <i>BRCA1</i>, <i>BRCA2</i>, <i>ATM</i>, <i>PALB2</i>, <i>CHEK2</i>, <i>MLH1</i>, <i>MSH2</i>, <i>MSH6</i>, <i>PMS2</i>, and <i>EPCAM</i> – Ashkenazi Jewish ancestry
Germline testing may be considered in patients with: <ul style="list-style-type: none"> – Prostate cancer and specific tumour characteristics (intermediate-risk prostate cancer with intraductal histology) – Prostate cancer and a personal history of other qualifying cancers
Tumour testing for treatment decision-making in metastatic prostate cancer is recommended for the HRR genes <i>BRCA1</i> , <i>BRCA2</i> , <i>ATM</i> , <i>PALB2</i> , <i>FANCA</i> , <i>RAD51D</i> , <i>CHEK2</i> , and <i>CDK12</i> .
European Society for Medical Oncology [26]
Germline testing is recommended for <i>BRCA2</i> and other DNA damage repair genes associated with cancer predisposition in patients with a family history of cancer and all patients with metastatic prostate cancer.
Tumour testing is recommended for treatment decision-making for HRR genes in patients with mCRPC.
European Association of Urology [27]
Germline testing should be considered for: <ul style="list-style-type: none"> – Men with metastatic prostate cancer and men with high-risk prostate cancer and a family member diagnosed with prostate cancer at age <60 years – Men with multiple family members diagnosed with castration-sensitive prostate cancer at age <60 years or a family member who died from prostate cancer – Men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family. Genes for which testing is recommended in metastatic or high-risk prostate cancer are <i>BRCA1</i>, <i>BRCA2</i>, and <i>ATM</i>, and other mismatch repair defects.
Tumour testing recommended for patients with mCRPC (and/or germline molecular testing, and testing for mismatch repair deficiencies or microsatellite instability). ctDNA may be tested in place of tumour tissue.
American Urological Association [28]
Germline and tumour tissue testing is recommended for patients with mCRPC to inform prognosis.
ctDNA = circulating tumour DNA; mCRPC = metastatic castration-resistant prostate cancer; HRR = homologous recombination repair.

if so, if there is a limit on sample age? Real-world data on the testing of prostate tumour samples are limited, but results from clinical trials have revealed that tumour testing provides results from 60–70% of samples, meaning that 30–40% failed to produce a test result. The main reasons for test failure are limited biopsy tissue (potentially also because of exhaustion of diagnostic material during histological diagnosis), insufficient tumour content for analysis, and suboptimal DNA yield/quality because of DNA degradation [5,9,29,30]. Therefore, in some settings, germline testing is undertaken first. However, this may not be the most cost-effective option, as this test only identifies germline mutations and while it may be useful in informing familial risk, it is not sufficient to identify all patients who may benefit from targeted treatment. An alternative option when tumour testing has failed is testing of circulating tumour DNA (ctDNA) to identify both germline and somatic alterations, which is required if the objective of testing is treatment stratification. In addition to the sample and test types, knowing which genes to test and the regions and types of alterations (eg, mutations, deletions, etc) is an important consideration. In agreement with guidelines, we recommend collection of a metastatic tumour biopsy and, if unfeasible (eg, in patients without access to tumour testing, without available tissue, or those for whom tissue testing has failed), a plasma sample for analysis of circulating cell-free DNA (cfDNA), preferably collected at biochemical or radiographic progression to maximise the ctDNA yield. Further details on the potential for ctDNA testing are discussed below.

The timing for when to conduct molecular testing is currently unclear because of regional differences in diagnostic policies and testing capabilities. For example, germline screening for genes predisposing to cancer in patients with a strong family history of cancer may be requested even when only local/regional disease is present. Conversely, tissue-based molecular diagnostic testing (that identifies alterations that could be of somatic or germline origin) is most likely to be requested for patients with mCRPC, as this is when targeted treatment may be required. Our preference would be for an earlier time point at the metastatic hormone-sensitive prostate cancer (mHSPC) stage, which is likely to happen in the future as trials investigate PARP inhibitors in this setting, and even in high-risk patients before metastases have been detected. Collection of primary tumour samples at prostate cancer diagnosis with storage under optimal conditions for later use is appropriate to inform HRR status even after disease progression to mCRPC. This is because the majority of HRR alterations in prostate cancer are either germline alterations or appear to occur early in the disease course and before metastatic spread [31]. As practitioners tend to be less familiar with tumour testing than with germline testing, extra guidance would be useful on the different gene panels and next-generation sequencing (NGS) platforms that are available, as well as interpretation of the official guidance on which patients are eligible for tumour testing. Guidance on the optimal biopsy and sample processing conditions to ensure sufficient high-quality material is obtained for tumour sequencing is also valuable [32]. In addition, a better understanding

of how tumour testing is conducted, and how germline and somatic results are interpreted regarding alteration classification and variant interpretation/curation, would enable practitioners to correctly select patients who should be referred for hereditary genetics counselling and/or who may benefit from PARP inhibitor therapy. While guidelines on which patients should be referred for germline testing as a secondary test after somatic testing (referred to as reflex testing) are available [33], we would like to underline that both somatic and genomic testing are important and one should not replace the other. Although there was no consensus on the timing of testing at the 2021 Advanced Prostate Cancer Consensus Conference (APCCC), 96% of the 86 panellists (international prostate cancer experts) recommended that testing should be undertaken in mCRPC and mHSPC settings, and there was consensus among those voting for tumour genomic testing that it should be performed after progression on a next-generation hormonal agent [34]. To help in alleviating some of the shortfalls in the various molecular testing guidelines, we have drawn on our clinical experience and propose a comprehensive testing process covering the stages from sample acquisition to clinical decision-making, including DNA extraction, quality control, library preparation, genetic sequencing, data analysis and filtering, and reporting (Fig. 1). Figure 1 also highlights specific recommendations for reporting, which should provide clear and simple guidance in relation to mutations of likely pathogenicity and variants of unknown significance.

3.2. Plasma ctDNA testing in the mCRPC setting and implementation in clinical practice

Tumour tissue testing is currently the gold standard for identifying patients with mCRPC who harbour HRR gene alterations, although not all have sufficient and/or good-quality tumour tissue available in a timely manner for molecular testing. Therefore, ctDNA testing can be implemented as an alternative or complementary minimally invasive (collection of blood samples is easier than collection of tissue samples) and highly feasible approach, as the majority of patients with clinically progressing mCRPC have high levels of ctDNA in their blood. Thus, ctDNA testing is becoming an established molecular technology for use in precision medicine, with US Food and Drug Administration (FDA)-approved liquid biopsy assays now available for use. ctDNA testing may become routine for patients when tissue testing fails to provide a result or when the sample quality is poor. This approach has generated interest among health care professionals (HCPs), but its implementation is not yet routine. Factors that currently limit routine implementation include a lack of standardised procedures and assays, a potential lack of sensitivity in comparison to tumour tissue testing, and differences in hospital capabilities and funding. There may also be difficulties in maximizing the ctDNA yield because effective treatment can rapidly reduce the ctDNA fraction, potentially leading to inconclusive test results. This highlights the importance of correct timing for blood collection and the short window of time available to clinicians to order ctDNA testing. However, not all patients with mCRPC have high ctDNA levels and thus may not be amenable to ctDNA testing (particularly

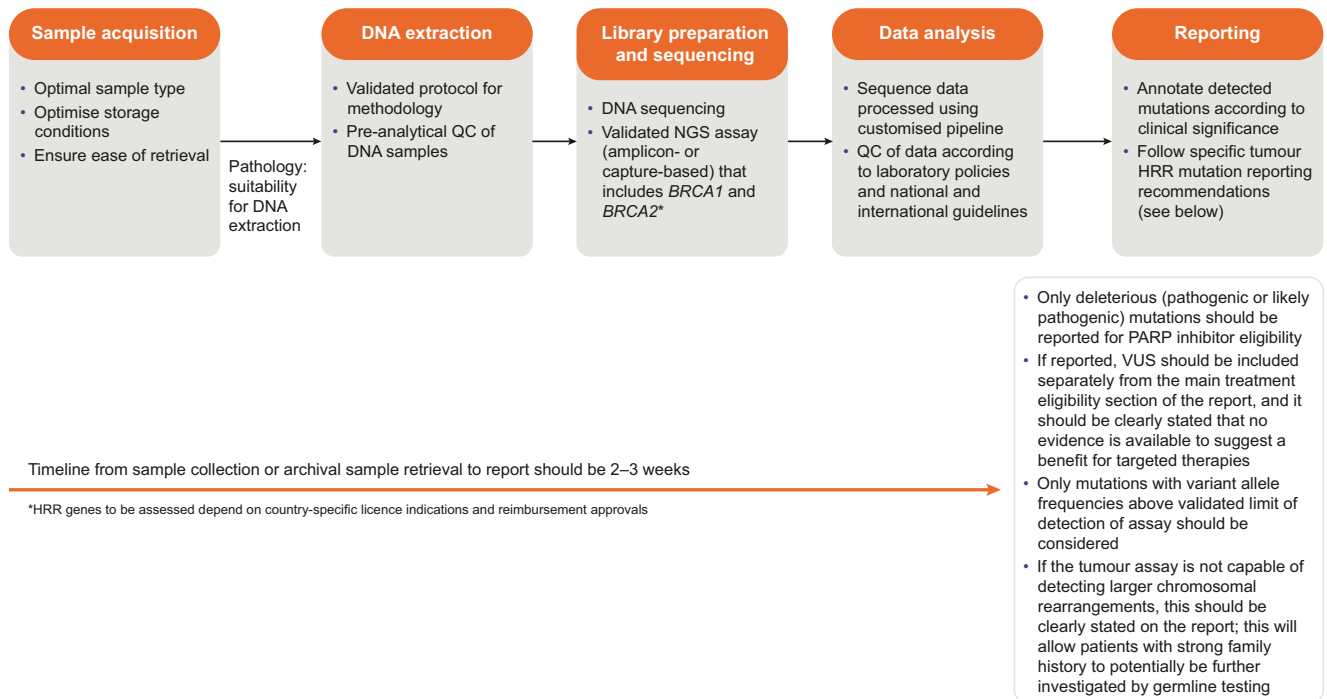


Fig. 1 – Molecular diagnostic testing process for HRR gene alterations from sample collection to clinical decision [32]. HRR = homologous recombination repair; HRRm = HRR gene mutation; NGS = next-generation sequencing; QC = quality control; VUS = variant of unknown significance.

those with a lower tumour burden); unfortunately, it is not yet clear how to identify patients with a high ctDNA level. Of note, an evaluation of matched tumour tissue and ctDNA samples from patients with mCRPC screened in the PROfound study showed 81% positivity agreement for *BRCA1*, *BRCA2*, and *ATM* alterations between tumour tissue and ctDNA (using tissue as the reference material) [35]. Among the patients with positive findings for *BRCA* or *ATM* alterations in tumour tissue but negative findings in ctDNA, low levels of or nonshedding ctDNA were the main reason for the difference affecting assay sensitivity. Furthermore, the ability of the ctDNA test to detect structural variation alterations, including homozygous *BRCA* deletions, was limited, especially at low ctDNA fractions. While there are limitations to its use that need to be addressed and a need to further understand the place of ctDNA testing within the diagnostics pathway and best practices for implementation, an increasing number of clinical studies, including PROfound and PROpel, have shown favourable concordance between tumour- and ctDNA-based testing [35–37]. In PROpel, an 85% overall percentage agreement for HRRm status was observed between tumour tissue and ctDNA testing with tumour tissue as the reference [36]. Interestingly, the PROfound and PROpel studies also had low false-negative rates of 4–6% with ctDNA testing using tumour tissue as the reference [35,36]. Real-life concordance studies of genomic findings from ctDNA and tumour tissue testing would help in validation of ctDNA testing and guiding improvements. A better understanding of the technical and clinical relevance of clonal haematopoiesis of indeterminate potential (CHIP) alterations in prostate cancer is also needed, as mistaken identification of CHIP mutations as originating

from tumour cells may result in incorrect treatment decisions. In the future, practitioners should be aware of whether their chosen test can filter candidate CHIP mutations.

3.3. Key elements of a successful *BRCA*/HRRm testing pathway

Molecular testing in prostate cancer comes with some unique challenges, such as a potentially low DNA yield because of the small tumour sample size achieved with some biopsy techniques (ie, core needle biopsies). In addition, the bone-predominant metastatic spread of prostate cancer can result in poor-quality samples for testing because the strong acids used for decalcification may degrade nucleic acids [38]. Furthermore, and unique to mCRPC in comparison to other faster-growing solid tumours, the logistics of retrieving archival tissue and the potential for degradation of archival tissue need to be resolved. Improvements in sampling techniques can maximise the success rate for tissue testing [32], although differences in molecular testing pathways for mCRPC remain that prevent the adoption of pathways established for other tumour types. Figure 2 provides a summary of what we consider to be the key elements of a successful *BRCA*/HRRm testing pathway for patients with mCRPC.

3.4. Role and core membership of the multidisciplinary team

One factor that is common to molecular testing pathways for prostate cancer and other tumour types is the need for a multidisciplinary team (MDT) approach. Figure 3 illustrates the typical involvement and roles of members within

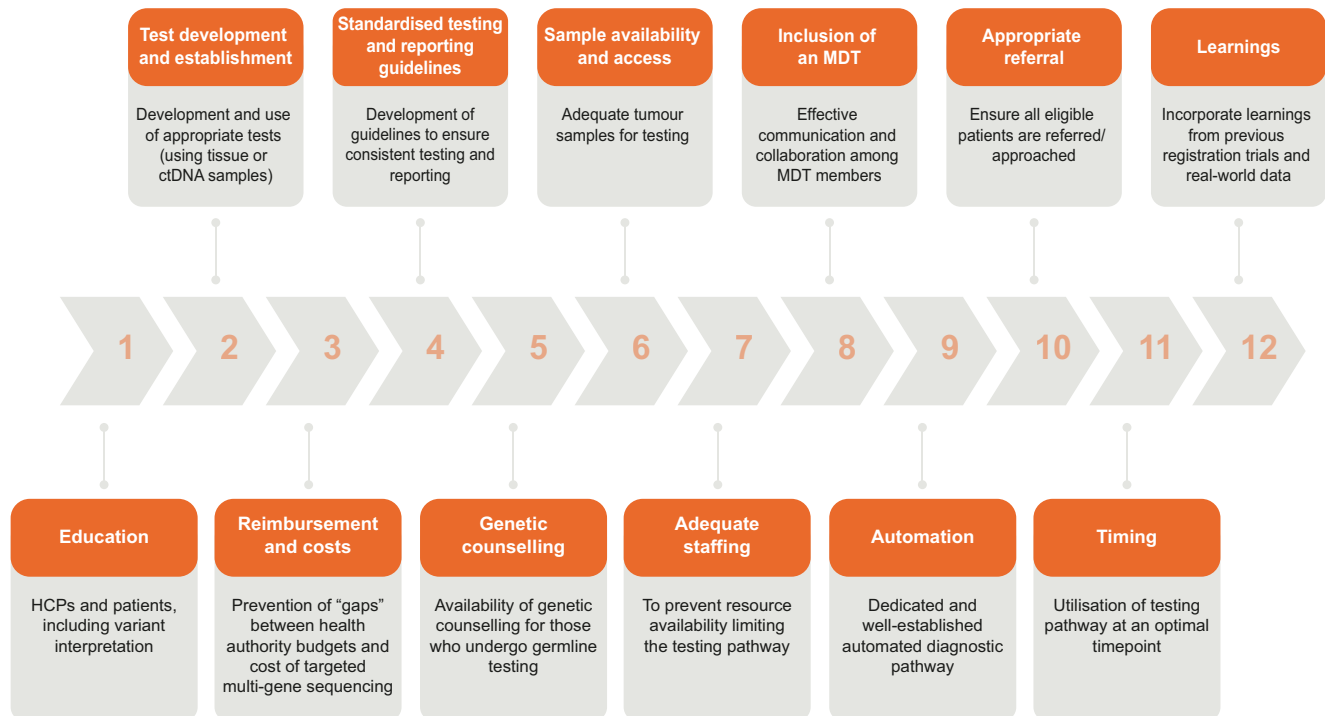


Fig. 2 – The key elements for establishing a successful BRCA/HRRm testing pathway. ctDNA = circulating tumour DNA; HCP = health care professional; HRRm = homologous recombination repair gene mutation; MDT = multidisciplinary team.

an MDT. A systematic review of MDT meetings for four tumour types revealed that MDTs have a significant impact on management plans [39]. In the prostate cancer setting, MDT meetings lead to changes in management plans in 27% of cases on average, with higher rates reported for cases with metastatic disease (33% and 38%) than for cases with localised disease (~23%) [40,41]. However, these findings were only from a few studies and there was no information regarding the impact of these management changes on diagnostic or treatment outcomes, suggesting that further research is needed. If an institution already has an MDT in place for the management of other tumour types, we suggest that efforts should focus on how to integrate genomics results for patients with mCRPC into everyday MDT discussions of the appropriate treatment and how the MDT membership can be reshaped to facilitate new discussions with patients about the implications of their genomic results and therefore the best management plan. For institutions with no MDT in place, we suggest that an MDT should be established with an overall role, once notification of molecular test results has been received, of assessing the significance of genetic alterations identified via testing and discussing subsequent management options. The MDT should also, if necessary, refer a patient for germline testing.

The roles of a typical MDT vary between academic centres and community practices, and between countries. A recent review highlighted the challenges for rural areas and community practices, including the greater difficulty in accessing MDT specialists in comparison with academic centres and urban areas; community MDTs may need to consult academic MDTs for certain complicated cases, and access to clinical trials or novel therapeutics may be limited

in community practices [42]. In addition, there may be more internal barriers to setting up and maintaining community MDTs. Two approaches that can overcome challenges in the community setting are the use of virtual molecular tumour boards and academic-community partnerships [42,43]. Regarding country differences, medical oncologists and urologists are typically at a similar decision-making level in the treatment of prostate cancer in countries such as the USA and Sweden, whereas urologists in other countries may be less involved in decision-making. To implement tumour tissue testing as part of the diagnostic process, we believe that all professionals involved in patient care should be educated in genomic testing (ie, when to request a molecular diagnostic test, how to obtain the best sample type, and obtaining consent from the patient to undertake the test). Clinicians from all specialties (urologists, pathologists, and oncologists), as well as medical geneticists, should be involved in clinical interpretation of the test results. Furthermore, other specialists beyond the MDT may need to be involved in the process at certain institutions. For example, organ-specific urology boards may discuss whether a BRCA/HRRm test should be initiated for a patient, while clinical interdisciplinary tumour boards may discuss whether PARP inhibition therapy may be a viable treatment option and, therefore, if BRCA/HRRm testing should be carried out. In addition, specific molecular tumour boards may discuss complicated and/or interesting NGS reports at the request of the oncologist. Limited data are currently available on the costs for molecular-guided therapy; however, the MOSCATO study in a French cancer centre noted that molecular diagnosis accounts for only 6% of the cost of molecular-guided therapy per patient

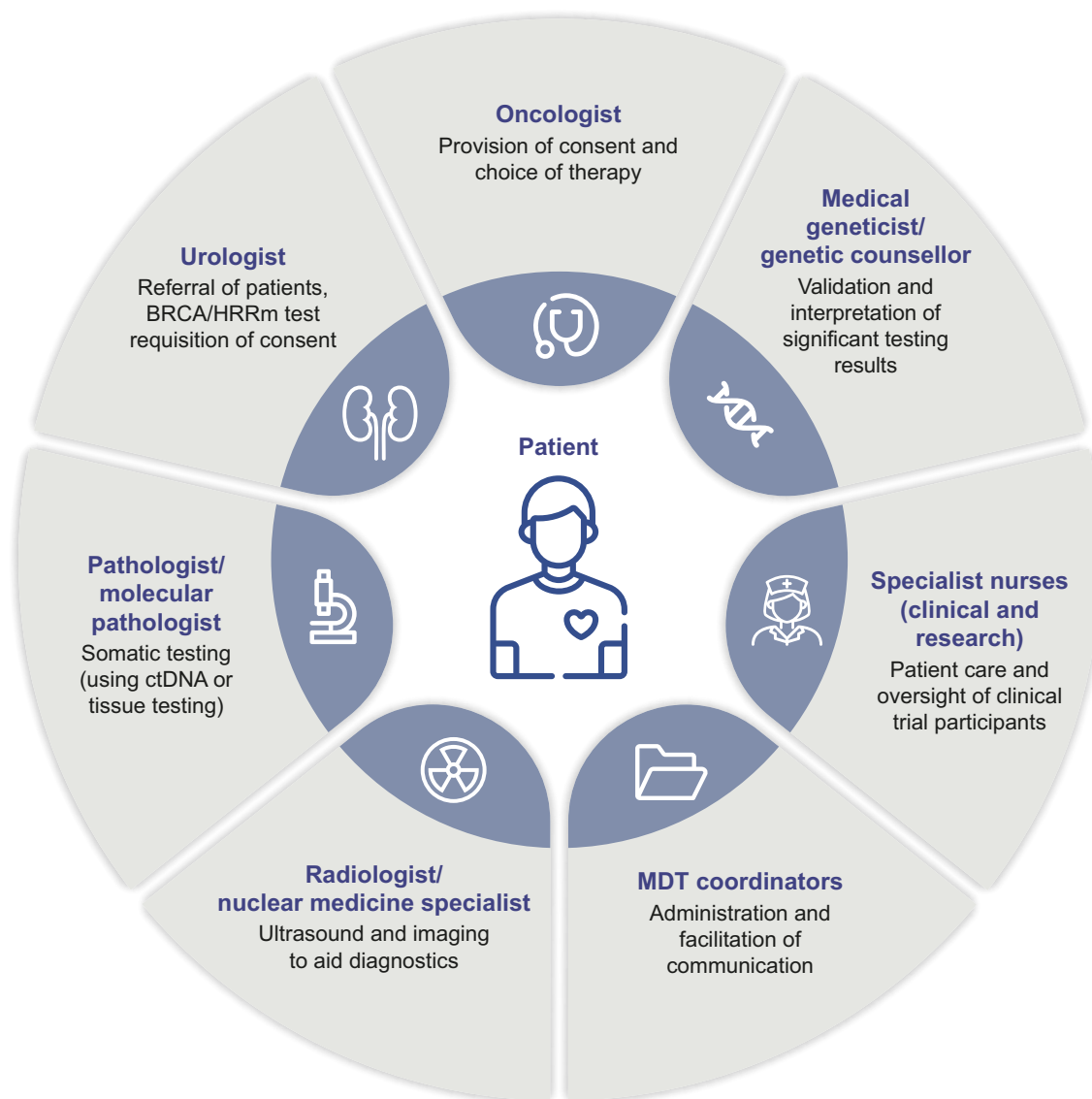


Fig. 3 – Suggested core membership disciplines for the multidisciplinary team. ctDNA = circulating tumour DNA; HRRm = homologous recombination repair gene mutation; MDT = multidisciplinary team.

and that drugs and hospitalisations were the main cost drivers [44]. This costing does not account for clinician time spent in MDTs, which needs to be considered and will differ between settings and according to reimbursement approaches.

3.5. Challenges and solutions in establishing a molecular diagnostic testing pathway

One of the main challenges in setting up a molecular diagnostic testing pathway is the need to improve HCP understanding of the testing approach, including genomic alterations and their expected frequency, the terminology used, the testing process itself, and what it all means from a patient's treatment perspective. To build up knowledge and HCP confidence, the use of educational programmes, e-health digital tools, and electronic medical report (EMR) alerts (automated messages that notify the physician of

important information) could play a primary role. For example, US real-world studies evaluating EMRs have provided useful information about testing rates and genomic alteration rates. One such study evaluating EMRs from 5213 patients with mCRPC from 2013 to March 2019 (before PARP inhibitor approvals) found that the rate of documented genomic testing for alterations in *ATM*, *BRCA1*, *BRCA2*, *CDK12*, *FANCA*, and/or *PALB2* was low (13%), although there was a modest increase after the 2017 NCCN recommendations were updated to include testing [45]. The Adelphi Prostate Cancer Disease Specific Programme, which collected data from EMRs for 348 patients and from physician surveys between January and August 2020, showed that only 38% of patients underwent HRRm testing, despite physicians having access to testing. However, the proportion of patients positive for HRRm was higher than expected (39%), suggesting that testing was prioritised for high-risk cases [46]. Triggering of EMR alerts on the basis of testing

Table 3 – Challenges and potential solutions for molecular diagnostic testing pathways

Challenge	Potential solution
HCP education (especially nonacademic urologists and genitourinary pathologists)	
<ul style="list-style-type: none"> – Technical limitations of different tests (tissue vs ctDNA vs germline) – Limited genomic literacy and confidence about testing – Novelty of ctDNA testing – Unknown frequency of molecular aberrations – Lack of referral of and reporting for all patients eligible for testing – Limitations/challenges of testing (eg, biopsy tissue insufficiency) – Lack of standardization of informed consent requirements – Complicated process to obtain genomic data – Interpretation of variants – Understanding of specific terminology – Appropriate role of different HCPs in testing pathway 	<ul style="list-style-type: none"> – Educational programmes (eg, webinars, tutorials, e-health) to increase genomic literacy – Use of e-health digital tools such as Helix [49] – Use of electronic medical report alerts – Standardisation of informed consent requirements – Incorporation of genomics modules in residence or fellowship programmes
Patient awareness	
Limited knowledge of molecular testing and implications of test findings	Improve patient education through: <ul style="list-style-type: none"> – Patient advocacy groups – Early involvement of genetic counsellors – Use of video or web-based interventions (in-person counselling may be challenging to achieve for all patients undergoing germline testing)
Tumour tissue testing	
Type of tissue sample and timing of collection	<ul style="list-style-type: none"> – Samples should be collected in parallel with patient referral – Obtain permission to use prostate biopsy and RP specimens collected for histology instead of collecting additional new samples
Use and storage of archival tissue blocks	<ul style="list-style-type: none"> – Use a common, centralised administrative unit and biobank to request tissue blocks from other hospitals in the region to improve ease of access to samples – Optimise storage conditions to minimise sample degradation
Germline testing	
Higher rates of patient referral for germline testing adversely affect staffing and the provision of molecular testing services	Secondary germline testing after identification of a genomic alteration via tumour testing may be considered for any variants suspected to be of germline origin (the chance of detecting a germline BRCA and/or ATM alteration is believed to be >50%, making the whole process “efficient”)
Genetic counselling	
Lack of genetic counsellors	<ul style="list-style-type: none"> – Long-term investment in the recruitment and training of genetic counsellors – Increase the expertise of primary care providers and other HCPs
Poor attendance at genetic counselling sessions before germline testing	Introduce POC videos and independent, self-directed web interventions for counselling before testing and receipt of results
Requirement for provision and documentation of consent, especially outside of clinical trials and large academic centres	Use therapeutic assays that do not require genetic counselling or upfront consent (based on existing pathways for ovarian cancer and Lynch syndrome)
Standardisation	
No standard testing procedures or reporting instructions	<ul style="list-style-type: none"> – Standardise procedures and reporting to make it easier for all physicians to understand results and make decisions – Include information on what to report in cases with negative results with low cellularity, regions, and screening depth, variants to report, and drugs authorised in cases with a genetic alteration

ctDNA = circulating tumour DNA; HCP = health care professional; RP = radical prostatectomy; POC = point of care.

results could facilitate acceleration of the management pathway. We also believe that patient education could be improved, primarily via the involvement of genetic counsellors and video- or web-based interventions. There is currently a general shortage of genetic counsellors [47], which can lead to substantial delays in genetic testing determination and can negatively impact treatment or management decisions. However, the future may be brighter, as genetic counselling seems to be growing globally as a profession, with international collaboration and reciprocal agreements facilitating improvements in training, regulation, and scopes of practice [48]. Table 3 highlights additional challenges when setting up a molecular diagnostic testing pathway and proposes solutions to these challenges.

4. Conclusions

Molecular diagnostic testing to inform familial risk, prognosis, and clinical decision-making is an important aspect of

the management of patients with mCRPC. Although regional molecular testing guidelines are available to assist HCPs in the management of mCRPC, these guidelines could be expanded. Providing institutions with the knowledge to improve current molecular testing pathways or initiate such a pathway will lead to the availability of prognostic information for HCPs that may support treatment decisions for patients with mCRPC. This in turn will lead to better outcomes, particularly for patients whose disease has progressed to the metastatic stage, for whom prognosis is poor and a personalised treatment may be indicated.

Author contributions: Martin Schostak had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Schostak, Bjartell.

Acquisition of data: All authors.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: None.

Obtaining funding: Schostak, Bjartell.

Administrative, technical, or material support: None.

Supervision: None.

Other: None.

Financial disclosures: Martin Schostak certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Martin Schostak has received consultancy and advisory board fees from Astellas, AstraZeneca, Bayer, Merck BMS, MSD Novartis, and Pfizer, and institutional research funding from AstraZeneca, BMS, MSD, and Pfizer Oncology. Angela Bradbury and Alberto Briganti have nothing to disclose. David Gonzalez has served on advisory boards and participated in speaker bureaus for AstraZeneca, Novartis, Roche, Pfizer, and Illumina, and has received research funding from AstraZeneca, Roche, and Novartis. Leonard Gomella has received consultancy and advisory board fees from Astellas, Abbvie, AstraZeneca, Bayer, Clovis, Merck, and MDx Health. Joaquin Mateo has served on advisory boards for Amgen, AstraZeneca, Clovis Oncology, Janssen, Merck/MSD, and Roche, has participated in speaker bureaus for AstraZeneca, Pfizer, Janssen, Sanofi, and Astellas Pharma, and has received institutional research funding from AstraZeneca and Pfizer Oncology. Frédérique Penault-Llorca has received consultancy fees from AbbVie, Agendia, AstraZeneca, Bayer, BMS, Eisai, Genomic Health, GSK, Janssen, Lilly, Merck Lifa, MSD, Myriad, Nanostring, Novartis, Pfizer, Pierre-Fabre, Roche, Sanofi, and Tesaro; institutional fees from AstraZeneca, Bayer, BMS, Genomic Health, MSD, Myriad, Nanostring, and Roche; and fees for congress attendance from AbbVie, AstraZeneca, Bayer, BMS, MSD, Novartis, Roche, and Lilly. Albrecht Stenzinger has served on advisory boards and participated in speaker bureaus for AstraZeneca, Bayer, BMS, Eli Lilly, Illumina, MSD, Novartis, Roche, Seattle Genetics, Takeda, and Thermo Fisher, and has received grants from Bayer, BMS, and Chugai. Alexander W. Wyatt has received honoraria from AstraZeneca, Bayer and Janssen, and has a contract research agreement with Janssen. Anders Bjartell has received honoraria, consulting fees, speaker fees, and travel support from Janssen, Sandoz, and Ipsen; grant support, honoraria, consulting fees, speaker fees, and travel support from Astellas Pharma and Bayer; consulting fees and travel support from Incyte; grant support, honoraria, speakers fees, and travel support from Ferring Pharmaceuticals; consulting fees from Merck Sharp & Dohme Corp and AstraZeneca, board member fees, travel support, and stock options from LIDDs Pharma; grant support, board member fees, travel support, and stock options from Glactone Pharma, of which he is co-founder; and stock options from WntResearch and Noviga Research.

Funding/Support and role of the sponsor: Medical writing assistance was provided by Martin Goulding of Mudskipper Business and was funded by AstraZeneca.

Disclaimer: This work includes contributions from, and was reviewed by, individuals who are employed by AstraZeneca and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. The content is solely the responsibility of the authors and does not necessarily represent the official views of AstraZeneca or Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euo.2023.08.004>.

References

- [1] International Agency for Cancer Research. Cancer today: estimated number of prevalent cases in 2020, worldwide, males, all ages. Lyon, France: IARC; 2020.
- [2] Manna FL, Karkampouna S, Zoni E, et al. Metastases in prostate cancer. *Cold Spring Harb Perspect Med* 2019;9:a033688.
- [3] American Cancer Society. Cancer facts & figures 2020. Atlanta, GA: ACS; 2020.
- [4] Li LY, Guan YD, Chen XS, Yang JM, Cheng Y. DNA repair pathways in cancer therapy and resistance. *Front Pharmacol* 2020;11:629266.
- [5] de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med* 2020;382:2091–102.
- [6] Abida W, Campbell D, Patnaik A, et al. Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 study. *Clin Cancer Res* 2020;26:2487–96.
- [7] Castro E, Romero-Laorden N, Del Pozo A, et al. PROREPAIR-B: a prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 2019;37:490–503.
- [8] Antonarakis ES, Velho PI, Agarwal N, et al. CDK12-altered prostate cancer: Clinical features and therapeutic outcomes to standard systemic therapies, PARP inhibitors, and PD1 inhibitors. *Ann Oncol* 2019;30:v325–55.
- [9] Abida W, Armenia J, Gopalan A, et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. *JCO Precis Oncol* 2017;2017:PO.17.00029.
- [10] Smith MR, Sandhu SK, Kelly WK, et al. Pre-specified interim analysis of GALAHAD: a phase 2 study of niraparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD). *Ann Oncol* 2019;30 (Suppl 5):v884–5.
- [11] Abida W, Patnaik A, Campbell D, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. *J Clin Oncol* 2020;38:3763–72.
- [12] Mateo J, Bianchini D, McGovern UB, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol* 2020;21:162–74.
- [13] Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med* 2019;381:317–27.
- [14] Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med* 2015;373:1697–708.
- [15] Mateo J, Porta N, Bianchini D, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, Phase 2 trial. *Lancet Oncol* 2020;21:162–74.
- [16] Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. *N Engl J Med* 2020;383:2345–57.
- [17] Saad F, Armstrong AJ, Thiery-Vuillemin A, et al. PROpel: phase III trial of olaparib (ola) and abiraterone (abi) versus placebo (pbo) and abi as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 2022;40 (6 Suppl):11.
- [18] Ryan CJ, Abida W, Bryce AH, et al. TRITON3: an international, randomized, open-label, phase III study of the PARP inhibitor rucaparib vs. physician's choice of therapy for patients with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination deficiency (HRD). *J Clin Oncol* 2018;36(6 Suppl):TPS389.
- [19] Rao A, Heller G, Ryan CJ, et al. Alliance A031902 (CASPAR): a randomized, phase (ph) 3 trial of enzalutamide with rucaparib/placebo as novel therapy in first-line metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 2022;40(6 Suppl):TPS194.

- [20] de Bono JS, Mehra N, Scagliotti GV, et al. Talazoparib monotherapy in metastatic castration-resistant prostate cancer with DNA repair alterations (TALAPRO-1): an open-label, phase 2 trial. *Lancet Oncol* 2021;22:1250–64.
- [21] Agarwal N, Azad A, Shore ND, et al. Talazoparib plus enzalutamide in metastatic castration-resistant prostate cancer: TALAPRO-2 phase III study design. *Future Oncol* 2022;18:425–36.
- [22] Smith MR, Scher HI, Sandhu S, et al. Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2022;23:362–73.
- [23] Chi KN, Rathkopf DE, Smith MR, et al. Phase 3 MAGNITUDE study: first results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations. *J Clin Oncol* 2022;40(6 Suppl):12.
- [24] Leith A, Ribbands A, Kim J, et al. Real-world homologous recombination repair mutation testing in metastatic castration-resistant prostate cancer in the USA, Europe and Japan. *Future Oncol* 2022;18:937–51.
- [25] National Comprehensive Cancer Network. Principles of genetics and molecular/biomarker analysis. NCCN clinical practice guidelines in oncology: prostate cancer version 1.2023. Plymouth Meeting, PA: NCCN; 2022.
- [26] Parker C, Castro E, Fizazi K, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020;31:1119–34.
- [27] Mottet N, Cornford P, van den Bergh RCN, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer. Arnhem, The Netherlands: European Association of Urology; 2022.
- [28] Lowrance WT, Breaux RH, Chou R, et al. Advanced prostate cancer: AUA/ASTRO/SUO guideline part II. *J Urol* 2021;205:22–9.
- [29] Hussain M, Corcoran C, Sibilla C, et al. Tumor genomic testing for >4000 men with metastatic castration-resistant prostate cancer in the phase III trial PROfound (olaparib). *Clin Cancer Res* 2022;28:1518–30.
- [30] Zhu J, Tucker M, Marin D, et al. Clinical utility of FoundationOne tissue molecular profiling in men with metastatic prostate cancer. *Urol Oncol* 2019;37:813.e1–e9.
- [31] van Dessel LF, van Riet J, Smits M, et al. The genomic landscape of metastatic castration-resistant prostate cancers reveals multiple distinct genotypes with potential clinical impact. *Nat Commun* 2019;10:5251.
- [32] Gonzalez D, Mateo J, Stenzinger A, et al. Practical considerations for optimising homologous recombination repair mutation testing in patients with metastatic prostate cancer. *J Pathol Clin Res* 2021;7:311–25.
- [33] Mandelker D, Donoghue M, Talukdar S, et al. Germline-focussed analysis of tumour-only sequencing: recommendations from the ESMO Precision Medicine Working Group. *Ann Oncol* 2019;30:1221–31.
- [34] Gillissen S, Armstrong A, Attard G, et al. Management of patients with advanced prostate cancer: report from the Advanced Prostate Cancer Consensus Conference 2021. *Eur Urol* 2022;82:115–41.
- [35] Chi KN, Barnicle A, Sibilla C, et al. Detection of BRCA1, BRCA2, and ATM alterations in matched tumor tissue and circulating tumor DNA in patients with prostate cancer screened in PROfound. *Clin Cancer Res* 2023;29:81–91.
- [36] Armstrong AJ, Saad F, Thiery-Vuillemin A, et al. 1370P Detection of mutations in homologous recombination repair (HRR) genes in tumour tissue (TT) and circulating tumour DNA (ctDNA) from patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC) in the phase III PROpel trial. *Ann Oncol* 2022;33:S1168.
- [37] Oya M, Armstrong AJ, Thiery-Vuillemin A, et al. 1570 Biomarker analysis and updated results from the phase III PROpel trial of abiraterone (abi) and olaparib (ola) vs abi and placebo (pbo) as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *Ann Oncol* 2022;33:S1495.
- [38] Goswami RS, Luthra R, Singh RR, et al. Identification of factors affecting the success of next-generation sequencing testing in solid tumors. *Am J Clin Pathol* 2016;145:222–37.
- [39] Kočo L, Weekenstroom HHA, Lambregts DMJ, et al. The effects of multidisciplinary team meetings on clinical practice for colorectal, lung, prostate and breast cancer: a systematic review. *Cancers* 2021;13:4159.
- [40] De Luca S, Fiori C, Tucci M, et al. Prostate cancer management at an Italian tertiary referral center: does multidisciplinary team meeting influence diagnostic and therapeutic decision-making process? A snapshot of the everyday clinical practice. *Minerva Urol Nefrol* 2019;71:576–82.
- [41] Rao K, Manya K, Azad A, et al. Uro-oncology multidisciplinary meetings at an Australian tertiary referral centre – impact on clinical decision-making and implications for patient inclusion. *BJU Int.* 2014;114:50–4.
- [42] Shore ND, Morgans AK, El-Haddad G, Srinivas S, Abramowitz M. Addressing challenges and controversies in the management of prostate cancer with multidisciplinary teams. *Target Oncol* 2022;17:709–25.
- [43] Pishvaian MJ, Blais EM, Bender RJ, et al. A virtual molecular tumor board to improve efficiency and scalability of delivering precision oncology to physicians and their patients. *JAMIA Open* 2019;2:505–15.
- [44] Pagès A, Foulon S, Zou Z, et al. The cost of molecular-guided therapy in oncology: a prospective cost study alongside the MOSCATO trial. *Genet Med* 2017;19:683–90.
- [45] Shore N, Ionescu-Iltu R, Yang L, et al. Real-world genetic testing patterns in metastatic castration-resistant prostate cancer. *Future Oncol* 2021;17:2907–21.
- [46] Leith A, Ribbands A, Last M, et al. Genomic/genetic testing patterns for patients with metastatic castrate-resistant prostate cancer: results from a real-world study in the United States. *J Clin Oncol* 2021;39(6 Suppl):49.
- [47] Raspa M, Moultrie R, Toth D, Haque SN. Barriers and facilitators to genetic service delivery models: scoping review. *Interact J Med Res* 2021;10:e23523.
- [48] Abacan M, Alsubaie L, Barlow-Stewart K, et al. The global state of the genetic counseling profession. *Eur J Hum Genet* 2019;27:183–97.
- [49] Giri VN, Walker A, Gross L, et al. Helix: a digital tool to address provider needs for prostate cancer genetic testing in clinical practice. *Clin Genitourin Cancer* 2021;20:e104–13.