PHENOTYPIC PRECISION MEDICINE IN PROSTATE CANCER: A PATH FORWARD
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Objectives

1. Examine the clinical significance of precision medicine and the use of biomarkers in managing patients with advanced prostate cancer.

2. Review the complexities of genotypic precision medicine and evaluate novel approaches in advanced prostate cancer.

3. Discuss the value of prostate-specific membrane antigen (PSMA) as a phenotypic biomarker and its relevance in clinical management of advanced prostate cancer.
Introduction: Complexity of Clinical Management in Advanced Prostate Cancer

Management of advanced prostate cancer (APC) has evolved substantially over the last decade, with the approval of several life-prolonging hormonal and nonhormonal treatment options (Figure 1).\textsuperscript{1,2} With current treatment options, the median overall survival for patients with metastatic castration-resistant prostate cancer (mCRPC) ranges from 1.8 to 2.8 years, and the 3-year overall survival rate is 46%.\textsuperscript{3,4}

Selecting and sequencing the available therapeutic options can be a challenge for medical oncologists, radiation oncologists, and urologists.\textsuperscript{2} Despite improvements with expanding treatment options, better diagnostic tools to select and sequence treatment may help to improve patient outcomes.\textsuperscript{2,5-15} The use of a precision medicine approach may facilitate patient selection and guide treatment decision making.\textsuperscript{6,16-18}

Figure 1. Timeline of Drug Approvals and New Indications in APC\textsuperscript{2,8-15}

ADP, adenosine diphosphate; APC, advanced prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer.
Precision Medicine in APC

What Is Precision Medicine?

Precision medicine is an approach that utilises diagnostic tools to select therapies for appropriate patients to optimise outcomes and minimise adverse events. Ultimately, the goal of precision medicine is to efficiently and accurately decide on the most effective treatment approach for an individual patient (Figure 2). Precision medicine is carried out using a 2-pronged methodology: 1) characterise a molecular or genetic target, and 2) tailor a treatment approach to the target. The success of precision medicine is predicated on a detailed understanding of the molecular characteristics of a patient’s disease as well as the ability to accurately characterise those features.

A biomarker is a disease- or host-related indicator that is objectively evaluated to characterise normal biologic processes, pathogenic processes, or responses to medical interventions. Biomarkers provide clinicians with important disease information to inform evidence-based decision making. The 3 primary types of biomarkers in oncology are diagnostic, prognostic, and predictive (Figure 3).

Cancer type can be classified based on the presence of genomic alterations along with other molecular changes, allowing for precise and potential targeted treatment selection.

This is what is known as genotypic precision medicine. A classic example of the successful use of precision medicine in oncology can be found in the management of non-small cell lung cancer (NSCLC). An estimated 64% of patients with NSCLC have oncogenic driver mutations (ie, KRAS, EGFR, ALK, ERBB2, BRAF, PIK3CA, NRAS, MEK1, or MET), and up to 54% of patients have genetic mutations that are targetable with pharmacotherapy. Several studies have shown that patients with NSCLC and actionable genetic mutations may have better survival outcomes when they are treated with targeted therapies.

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**Figure 3. Common Biomarkers in Oncology**

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Prognostic</th>
<th>Predictive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primarily to assist diagnosis; most commonly using immunohistochemistry (IHC) on tissue sections but may also be a liquid test using serum</td>
<td>Primarily as a guide to characterise the course and prognosis of disease (therapy unspecified)</td>
<td>Specifically, for classification of responders vs nonresponders for a defined therapy; assay and threshold developed jointly in clinical trial with the specified drug</td>
</tr>
</tbody>
</table>
Implementation of Precision Medicine Is Complicated in APC

APC is a disease in which precision medicine is not as prevalent, in part due to a lack of adequate biomarkers (Box 1).\textsuperscript{35} To successfully utilise precision medicine in a specific cancer type, several key clinical and scientific features should be met. Shared successes in tumour types in which precision medicine is prevalent have depended upon detection of widespread driver mutations across a disease population and identification of biomarkers that correlate with response or function.\textsuperscript{23,30,36,37} Once biomarkers have been identified and validated, the correlation of mutations and other biomarkers with therapeutic targets is another critical step to implementing precision medicine.\textsuperscript{38} Optimal biomarkers for precision medicine should be clinically significant, noninvasive in their characterisation, and highly sensitive and specific.\textsuperscript{26,39}

Implementation of precision medicine using genotypic biomarkers has thus far been limited due to a combination of different types of challenges:

- Clinical\textsuperscript{40,41}
- Operational\textsuperscript{42-44}
- Biological\textsuperscript{45-51}

Clinical Challenges of Genotypic Biomarker-Based Precision Medicine

Genetic biomarkers can be clinically challenging to evaluate in APC due to inherent limitations of obtaining bone biopsies from prostate cancer metastases. Bone biopsies are painful, technically difficult, and challenging to interpret.\textsuperscript{38,50} Due to the intra- and intertumoural heterogeneity of prostate cancer, a single tissue biopsy may not be representative of the tumour from which it was obtained, let alone the tumour burden of the patient. Even within the same patient, different metastases can display genetic heterogeneity, making the interpretation of genotypic tissue biopsy results challenging.\textsuperscript{41,52}

In some tumour types, liquid biopsies have emerged as noninvasive alternatives to tissue biopsies, further assisting in the implementation of genotypic precision medicine.\textsuperscript{40,53}

Operational Challenges of Genotypic Biomarker-Based Precision Medicine

Although precision medicine is a promising field in oncology, the practicalities of implementing a precision medicine approach in APC using genomic sequencing tools presents a variety of operational challenges to oncologic and urologic practices\textsuperscript{42-44}:

- Obtaining the optimal biopsy
- Selecting optimal tests
- Determining timing of molecular testing
- Interpreting genetic test results, which often have large volumes of information
- Appropriately counselling patients and families
- Navigating, recording, and storing data

Box 1. Prostate-Specific Antigen: A Validated Biomarker, but Not Used for Precision Medicine

Prostate-specific antigen (PSA) is the most commonly used biomarker in prostate cancer.\textsuperscript{6} PSA is useful in making clinical decisions, particularly in early-stage and biochemically recurrent prostate cancer. A few examples of the utility of PSA include risk-stratifying localised disease and monitoring treatment response and biochemical recurrence.\textsuperscript{6,54} However, PSA is not a predictive biomarker (ie, it cannot predict responders and nonresponders for certain therapies) and therefore does not provide guidance for selecting and sequencing treatments in APC.\textsuperscript{35,55-58}
Biological Challenges of Genotypic Biomarker-Based Precision Medicine

Heterogeneity exists at nearly every level in prostate cancer, from the patient level (e.g., geographic and ethnic diversity) to the molecular level (e.g., androgen receptor [AR] expression differences). Current methods in precision medicine do not fully address tumour heterogeneity in prostate cancer. The differences between tumours (e.g., multifocal primary tumours, metastatic tumours) and within tumours have been linked to 2 concepts in APC, outlined in Figure 4:

1. Genomic instability of advancing disease
2. Treatment-induced selective pressures, which can lead to genetic mutations and resistance

Furthermore, a lack of widespread driver mutations can make targeted interventions challenging. In an exome sequencing analysis study, the authors described a long tail of driver mutations in APC, in which there were a few mutations that were present in about 5% to 20% of tumours (Figure 5); however, the majority of identified driver mutations were present in only a small subset (<5%) of prostate cancer tumours.
Harnessing Phenotypes in Precision Medicine

The genetic heterogeneity of APC and the challenges of genotyping these tumors underlie the need for novel techniques for the characterization and targeting of prostate cancer.\(^5,6^2\) Therapy for patients with prostate cancer is selected according to individual patient characteristics, including risk profile and volume of disease.\(^5^4,6^3\) Expression of biomarkers such as prostate-specific membrane antigen, or PSMA, represents additional phenotypic information that can be harnessed to help individualize patient management.\(^6^4\) The use of imaging phenotypes has emerged as a novel biomarker approach.\(^6^5\)

A phenotypic trait is an observable characteristic that is produced through the interaction of genotype and environment (eg, the physical expression of genes, such as protein expression levels).\(^6^6\) Genotypes and phenotypes are distinct, albeit biologically related ways to characterize a single disease.\(^6^5\)

Phenotypes can be detected through noninvasive imaging, such as PSMA-based positron emission tomography (PET).\(^6^4,6^7,6^8\) The uses of PET are rapidly evolving and have led to an improved ability to characterize prostate cancer with enhanced sensitivity and specificity using radiotracers.\(^5^4,6^9-7^1\)

The radiotracers target molecules that are highly expressed in prostatic cancer cells (Table 1).\(^5^4,7^2-7^4\)

Early iterations of PET imaging biomarkers were suboptimal relative to sensitivity and specificity in prostate cancer.\(^7^5,7^6\) For example, \(^1^8\)F-fluorodeoxyglucose (\(^1^8\)F-FDG) is a glucose analogue, and its cellular uptake can be suggestive of increased cell metabolism in rapidly proliferating cells in many cancer types. However, prostate cancer cells have low glucose metabolism levels, which has limited the effectiveness of \(^1^8\)F-FDG for initial diagnosis.\(^7^5\) Furthermore, androgen ablation has been shown to decrease FDG accumulation in primary and metastatic prostate cancer lesions.\(^7^7\)

More recent iterations of radiotracers in prostate cancer have improved upon specificity and sensitivity for diagnostic purposes, but radiotracers such as \(^1^1\)C-choline and \(^1^8\)F-fluciclovine, which are markers for cell membrane synthesis and amino acid transport, respectively, may have limited utility as prognostic and predictive biomarkers.\(^7^0,7^1,7^6,7^8-8^0\)

Table 1. Comparison of Select Radiotracers Used in Prostate Cancer Imaging

<table>
<thead>
<tr>
<th>Radiotracer (Date of EMA or FDA approval, if applicable)</th>
<th>Physiologic Target</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(^1^8)F-FDG</strong> (EMA: 2012; FDA: 2005)(^1^0^4-1^0^5)</td>
<td>Glucose metabolism(^5^1,5^2)</td>
<td>Widely available(^5^5)</td>
</tr>
<tr>
<td><strong>(^1^8)C-choline</strong> (FDA: 2012)(^6^4)</td>
<td>Cell membrane synthesis(^6^4)</td>
<td>Higher diagnostic sensitivity than FDG-PET/CT(^7^4,7^9)</td>
</tr>
<tr>
<td><strong>(^1^8)F-choline</strong>(^8^5,8^6)</td>
<td>Cell membrane synthesis(^8^5)</td>
<td>High diagnostic performance for accurate staging and restaging in patients with prostate cancer(^1^0^2)</td>
</tr>
<tr>
<td><strong>(^1^8)F-fluciclovine</strong> (EMA: 2017; FDA: 2016)(^1^0^8,1^0^9)</td>
<td>Amino acid transport(^1^0^0,1^0^1)</td>
<td>Useful for restaging, particularly for patients with higher PSA values(^7^8,1^0^3)</td>
</tr>
<tr>
<td><strong>PSMA-based radiotracers</strong></td>
<td>Targets PSMA</td>
<td>High specificity and sensitivity, even at low PSA levels(^7^0,7^1,7^6,8^0,1^0^6)</td>
</tr>
</tbody>
</table>

APC, advanced prostate cancer; CT, computed tomography; EMA, European Medicines Agency; \(^1^8\)F-FDG, \(^1^8\)F-fluorodeoxyglucose; FDA, US Food and Drug Administration; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

1In a meta-analysis of the diagnostic performance of \(^1^3\)C-choline carried out on 8 selected studies including 276 patients.\(^7^9\)
2In a meta-analysis of the staging/restaging performance of \(^1^3\)C-choline carried out on 16 patient-based and 4 lesion-based studies in 2122 patients and 1039 lesions, respectively.\(^7^9\)
3In a head-to-head comparison performed in 50 patients radically treated for prostate cancer and presenting with rising PSA levels.\(^1^0^3\)
4In a prospective, single-center, open-label comparative study, 50 adults with biochemical recurrence after radical prostatectomy and PSA levels <2 ng/mL.\(^7^1\)
5In a meta-analysis of the predictive performance of \(^1^8\)Ga-PSMA in 16 studies involving 1309 patients.\(^7^0\)
6In a single-arm prospective trial of 635 patients with biochemically recurrent prostate cancer who underwent \(^1^8\)Ga-PSMA-11 PET.\(^1^2^5\)
Prostate-Specific Membrane Antigen: A Diagnostic, Prognostic, and Clinically Relevant Biomarker

PSMA is a key phenotypic biomarker in APC due to its combination of sensitivity and potential utility across the clinical spectrum.\textsuperscript{16,17,69,107-109} PSMA is a transmembrane protein that is anchored in the cell membrane of prostate cancer epithelial cells (Figure 6).\textsuperscript{110,111}

Despite its name, PSMA is not specific to the prostate gland but is found in tumour-associated blood vessels across a wide range of tumour types as well as healthy prostatic and nonprostatic tissues.\textsuperscript{112-114} Compared to benign prostate tissue, however, malignant prostate cells may express PSMA at a substantially higher level.\textsuperscript{107}

**PSMA as a Diagnostic Biomarker Used in PET Scanning**

PSMA has been shown to be a useful biomarker for the diagnosis of localised and advanced disease.\textsuperscript{69,71} In ProPSMA, a prospective, multicenter, randomised, controlled trial, 302 men with high-risk localised prostate cancer were randomly assigned to receive conventional imaging (ie, computed tomography [CT] and bone scan) or PSMA PET/CT. PSMA PET/CT had a 27% (95% CI 23-31) absolute greater area under the curve for accuracy than conventional imaging for the diagnosis of metastases in this population (92% [88-95] vs 65% [60-69]; \(P<0.0001\)). In addition, based on post-hoc analysis, PSMA PET/CT was shown to be 32% more accurate for pelvic nodal metastases and 22% more accurate for distant metastases. Figure 7 shows an example of a comparison between PSMA PET/CT and conventional imaging in 2 men with normal results from baseline conventional imaging.\textsuperscript{69}

PSMA-based imaging has also shown utility in advanced disease. A separate prospective, single-center, open-label, single-arm comparative imaging study of \(^{18}\text{F}\)-fluciclovine and PSMA PET/CT evaluated 50 adults with biochemical recurrence after prostatectomy and PSA levels <2 ng/mL. In this study, PSMA PET/CT was shown to have a 4.8-fold higher rate of disease detection than \(^{18}\text{F}\)-fluciclovine (95% CI 1.6-19.2; \(P=0.0026\)) (Figure 8).\textsuperscript{71}
The sensitivity and specificity of PSMA as a diagnostic biomarker has been shown in a meta-analysis of PSMA PET trials, in which prediction of primary and recurrent prostate cancer had a per-patient sensitivity of 86% and a per-patient specificity also of 86%. In the previously described comparative imaging study, the per-patient sensitivity was 66% for PSMA PET/CT vs 33% for 18F-fluciclovine (95% CI 0.67-34.5; P=0.18).

PSMA as a Prognostic Biomarker

In addition to its utility in diagnosis, PSMA has also been shown to be a prognostic biomarker. In a retrospective evaluation of prostate cancer biopsies from primary and metastatic tumours, PSMA expression level at diagnosis was negatively correlated with 5-year recurrence-free survival rates. The 5-year recurrence-free survival rates were 88.2%, 74.2%, 67.7%, and 26.8% for patients exhibiting no, low, medium or high PSMA expression on preoperative biopsy, respectively (Figure 9).

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**Figure 8. PSMA-Based Imaging Detects Prostate Cancer Metastases at a Higher Rate Than 18F-fluciclovine**

<table>
<thead>
<tr>
<th>Region</th>
<th>18F-fluciclovine</th>
<th>PSMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic lymph nodes (N)</td>
<td>4 (8%)</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>Prostate bed (T)</td>
<td>19 (14%)</td>
<td>28 (56%)</td>
</tr>
<tr>
<td>Extrapelvic (M1a)</td>
<td>0 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Bone (M1b)</td>
<td>3 (8%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Other organ (M1c)</td>
<td>2 (4%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Any extra pelvic lesion (M1)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

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**Figure 9. 5-Year Recurrence-Free Survival According to PSMA Level at Diagnosis**

- IHC, immunohistochemistry; PSA, prostate-specific membrane antigen; PSMA, prostate-specific membrane antigen.
- PSMA expression was assessed in a retrospective study by IHC in 924 preoperative biopsies, 621 primary tumour foci from 242 radical prostatectomies, 43 locally advanced or recurrent tumours obtained from transurethral prostate resection, 34 lymph node metastases, 78 distant metastases, and 52 benign prostatic samples from patients who underwent surgery. PSMA expression was categorised as no expression (score of 0), low expression (1), medium expression (2), or high expression (3). Expression was correlated to recurrence-free survival as the primary end point measure.
- Disease recurrence was defined as biochemical recurrence (PSA increase above the postoperative nadir following radical prostatectomy) and used as end point for survival analysis.
- By univariate analysis for PSMA negative vs PSMA high expression.
**PSMA as a Clinically Relevant Biomarker**

PSMA-based PET/CT has also been used to guide treatment decisions in patients with prostate cancer. As mentioned previously, in the ProPSMA study, first-line conventional imaging resulted in less frequent management change than PSMA PET/CT imaging (15% vs 28%). Furthermore, an additional 27% of men who underwent second-line PSMA PET/CT imaging also had management changes compared with 5% of patients who had management changes after second-line conventional imaging.69

Similar results have been reported in a retrospective, real-world study. In a Swiss single-institution study, 223 men with biochemically recurrent prostate cancer were imaged with PSMA PET/CT, and changes in management plans were analysed.108 Among the 203 patients with 6-month follow-up results, a change in management was recorded in up to 60% of patients.108,115 As shown in Figure 10, therapy options can be tailored with the addition of PSMA PET/CT imaging.108 These results have been replicated in another real-world study.106 Although there are currently no clinical data available that link expanded clinical options with

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**Figure 10. Change in Therapy Options (a) Without PSMA PET/CT and (b) With PSMA PET/CT**

ADT, androgen deprivation therapy; chemo, chemotherapy; CT, computed tomography; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy.

*The aim of the retrospective study from Switzerland was to assess the effect of PSMA PET/CT on management and outcome in all patients imaged during the first year after its introduction into clinical practice. The rate of detection of recurrence was determined from review of patient charts. In the 203 patients with follow-up 6 months after PSMA PET/CT, the therapies effectively implemented as well as follow-up PSA levels were evaluated, with a PSA value of <0.2 ng/mL representing a complete response and a decrease in PSA value of at least 50% from baseline at the time of the scan representing a partial response.

*Multimodal included surgery, salvage radiotherapy, ADT, and/or chemotherapy combined.

Preliminary data have shown that PSMA may play a role in signalling pathways related to phosphatidylinositol-3-kinase (PI3K), RAS/RAF/mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NF-κB), and p21-activated kinase (PAK 1). These pathways modulate the following cellular properties:

- Cell proliferation and survival
- Cell migration
- Angiogenesis

PSMA is highly expressed in >80% of men with prostate cancer, making it an attractive therapeutic target. Clinical relevance of PSMA-based imaging in APC:

- PSMA is a diagnostic biomarker and potential therapeutic target that may enable a phenotypic precision medicine approach to help guide patient selection for therapy in APC.


Phenotypic precision medicine is an approach that utilises noninvasive diagnostic imaging to characterise observable traits in order to select therapies for appropriate patients with the goal of optimising outcomes and minimising adverse events.

PSMA-based imaging and potential therapeutic targets represent a novel approach to precision medicine through the identification of a target, the development of a noninvasive method for measuring that target, and then a method for tailoring treatment according to biomarker results. Ongoing studies are investigating the efficacy of small molecule and biologic agents targeting PSMA, and treatment of APC may benefit from the identification and development of additional functional biomarkers to complement the current treatment armamentarium.5,62,130

In addition to its utility for PET/CT, PSMA has emerged as an attractive potential therapeutic target due to its role in several oncogenic signalling pathways. Although no natural ligand for PSMA has been identified to date, PSMA has been convincingly linked with a number of kinase pathways that promote oncogenic cell growth and tumour progression. This is particularly relevant for patients with APC, who may develop resistance mutations to AR-directed therapies (Figure 11). Evidence exists from various tumour types that PSMA expression in the vasculature is associated with worse survival outcomes.

Clinical Relevance of PSMA-Based Imaging in APC:

PSMA is highly expressed in >80% of men with prostate cancer, making it an attractive therapeutic target (Figure 12). Another feature includes the accessibility of the molecule due to its location in the cell membrane. PSMA-binding ligands also undergo cell internalisation by PSMA, which allows the delivery of both small molecules and larger biologics inside the cell.

Figure 11. Cascade Signalling Effect of PSMA-Binding Ligands

Figure 12. PSMA Is Highly Expressed in >80% of Men With Prostate Cancer


Discussion Highlights

- Precision medicine is an approach that utilises diagnostic tools to select therapies for appropriate patients to optimise outcomes and minimise unnecessary side effects\textsuperscript{19}

- There are various types of challenges in implementing precision medicine using genotypic biomarkers.\textsuperscript{40} Examples include:
  - Clinical\textsuperscript{40,41}
  - Operational\textsuperscript{42-44}
  - Biological\textsuperscript{45-51}

- PSMA is a diagnostic and potential therapeutic target, enabling a phenotypic precision medicine approach to treating APC in the following ways\textsuperscript{17,69,107-109}:
  - Detection of a clinically relevant biomarker using a noninvasive diagnostic tool\textsuperscript{67,68}
  - Optimisation of patient selection to help inform management decisions\textsuperscript{65,69,108,115}
  - Utilisation of phenotypic precision medicine with the goal of improving patient outcomes\textsuperscript{17,106,108}
References


54. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 26, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.


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