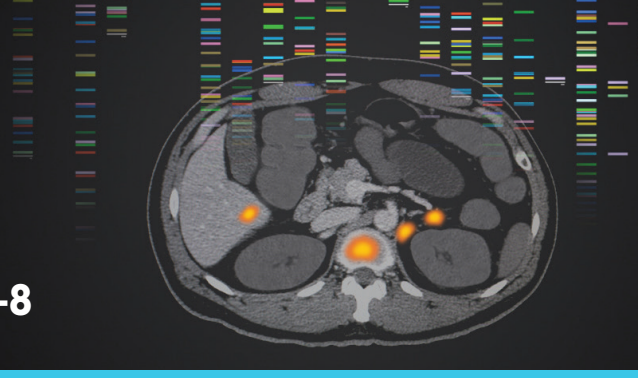
PHENOTYPIC BIOMARKERS MAY FACILITATE THE USE OF PRECISION MEDICINE IN ADVANCED PROSTATE CANCER[1-8]



pre·ci·sion med·i·cine
[/prəˈsiZHən/ \ˈme-di-sən]
An approach that utilises diagnostic tools to select therapies for appropriate patients to **optimise outcomes** and **minimise adverse events**.[9-11]

The complexity of advanced prostate cancer (APC) makes the implementation of genotypic precision medicine challenging in various ways[12-15]:

1 CLINICAL	Biopsies are often technically difficult, associated with morbidity, and challenging to interpret due to tumour heterogeneity.[13-27]
2 OPERATIONAL	Optimising test selection, biopsy technique, and test result interpretation is a challenge for genotypic precision medicine.[28-30]
3 BIOLOGIC	Few widespread mutations have been identified, further complicating the use of genotypic precision medicine.[31,32]

Taken together, these features of APC underlie the need for novel precision medicine approaches, including the use of **phenotypic biomarkers** that can be detected through noninvasive diagnostics such as prostate-specific membrane antigen positron emission tomography (PSMA PET) imaging.[3-6,11,33-38]

PSMA PET leverages radiotracers to visualise **PSMA expression** in prostate cancer tissue at a high sensitivity and specificity.[36,39-43] PET imaging with radiotracers offers a phenotypic approach that may facilitate the use of precision medicine in APC.[3-8]

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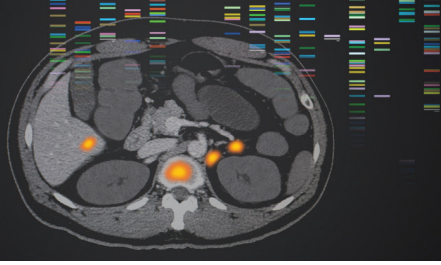
PSMA IS A DIAGNOSTIC BIOMARKER THAT MAY IMPACT TREATMENT DECISIONS IN ADVANCED PROSTATE CANCER[1-6]



PSMA expression is an example of a **phenotypic trait**, which is defined as an observable characteristic that is produced through the interaction of a genotype and environment.[1,3,6-9] Phenotypes can be assessed through noninvasive diagnostics, such as PSMA PET imaging.[1,3,6,9-12]

PSMA has been shown to have potential utility at multiple points within the prostate cancer care spectrum[1,2,4,5]:

Diagnosis

Compared with conventional imaging, PSMA PET/CT (computed tomography) was 27% (95% CI 23-31) more accurate (92% [88-95] vs 65% [60-69]; *P*<0.0001) for identifying pelvic nodal or distant metastatic disease.[1,*]

Prognosis

PSMA expression level was negatively associated with 5-year prostate-specific antigen (PSA) recurrence-free survival (88.2% for no expression vs 26.8% for high expression).[2,†]

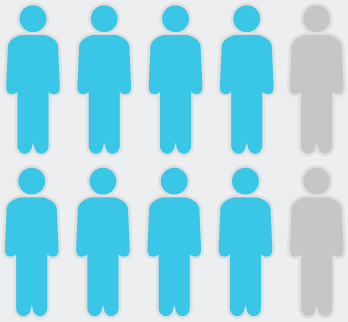
Clinical Management

PSMA PET/CT results after conventional imaging may have led to management changes in up to 60% of patients.[4,5,‡]

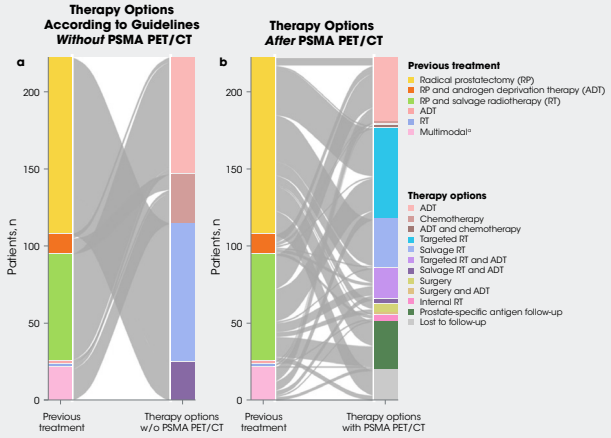
PSMA is highly expressed in the tumour tissue of

>80%

of men with prostate cancer[2,13-16]



PSMA PET/CT may help guide clinical management with a tailored approach[4,‡]



[a]Multimodal included surgery, salvage RT, ADT, and/or chemotherapy combined.[4]
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PSMA is a diagnostic and potential therapeutic target that may enable a phenotypic precision medicine approach to managing APC.[1-6]

* The ProPSMA study was a prospective, multicenter, randomised, controlled trial of men with high-risk, apparently localised prostate cancer. A total of 302 men were randomly assigned to receive either CT and bone scan (conventional imaging) or PSMA PET/CT. First-line imaging was done within 21 days of randomisation. The primary end point was accuracy of first-line imaging for identifying either pelvic nodal or distant-metastatic disease defined by the receiver-operating curve using a predefined reference-standard including histopathology, imaging, and biochemistry at 6-month follow-up. Results for subgroups of patients with pelvic nodal (area under the curve [AUC] 91% vs 59% [32% absolute difference; 28–35]) and distant (95% vs 74% [22% absolute difference; 18–26]) metastases also showed superiority of PSMA PET/CT.[1]

† PSMA expression was assessed in a retrospective study by immunohistochemistry (IHC) in 294 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 recurrence-free survival was used as the primary end point for survival analysis.[2]

‡ The aim of the retrospective, real-world, single-institution 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.[4]

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