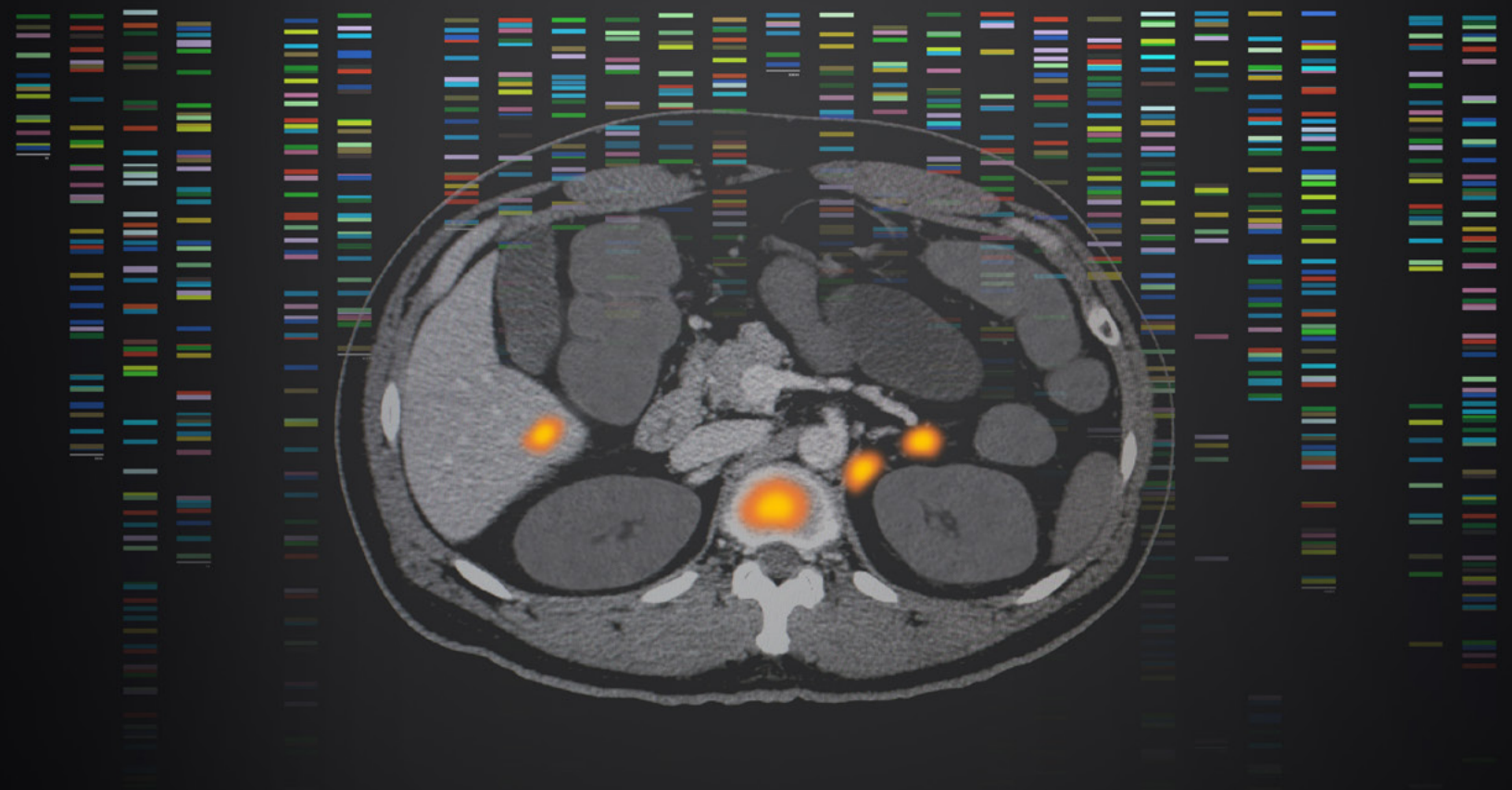
PHENOTYPIC PRECISION MEDICINE IN PROSTATE CANCER: **A PATH FORWARD**



Advanced Accelerator Applications

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Objectives

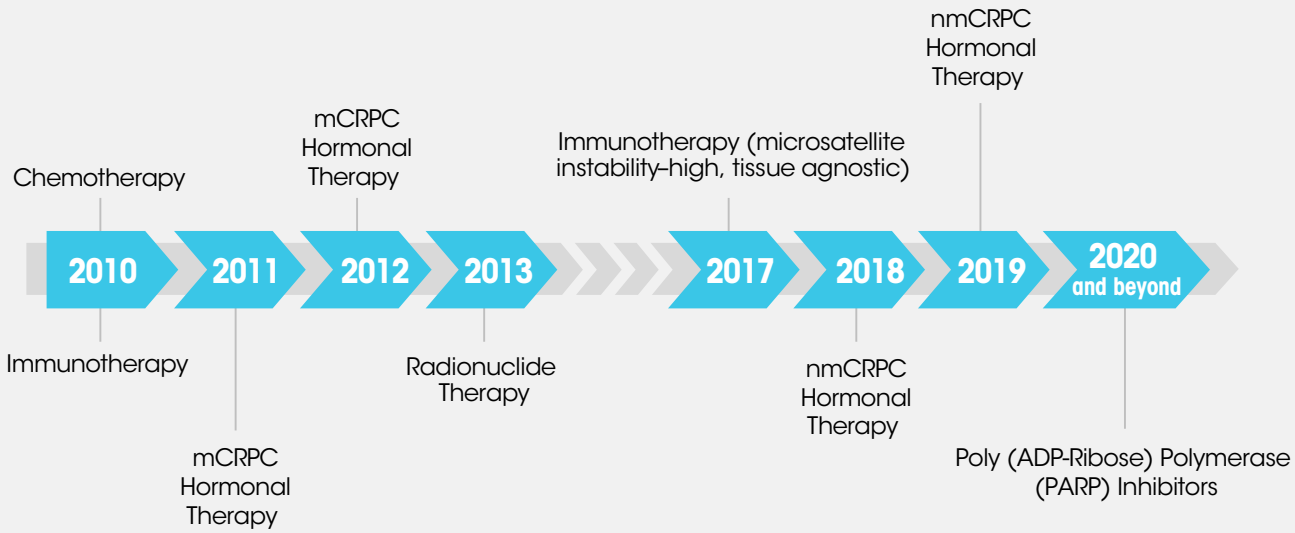
1. Examine the clinical significance of precision medicine and the use of biomarkers in managing patients with advanced prostate cancer.
2. Review the complexities of genotypic precision medicine and evaluate novel approaches in advanced prostate cancer.
3. Discuss the value of prostate-specific membrane 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 past decade, with the approval of several life-prolonging hormonal and nonhormonal treatment options (**Figure 1**).[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%.[3,4]

Selecting and sequencing the available therapeutic options can be a challenge for medical oncologists, radiation oncologists, and urologists.[2] Despite improvements with expanding treatment options, better diagnostic tools to select and sequence treatment may help improve patient outcomes.[5-8] The use of a precision medicine approach may facilitate patient selection and guide treatment decision making.[7]

Figure 1. Timeline of Drug Approvals and New Indications in APC[2,9-18]



ADP, adenosine diphosphate; nmCRPC, non-metastatic castration-resistant prostate cancer.

Precision Medicine in APC

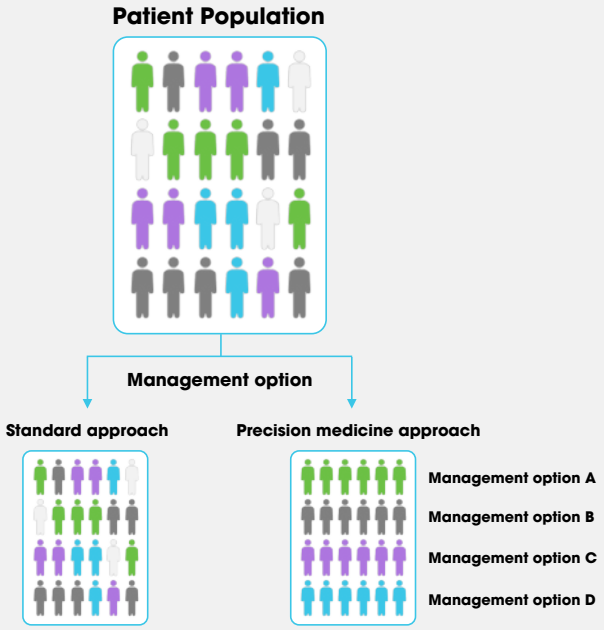
What Is Precision Medicine?

Precision medicine is an approach that utilizes diagnostic tools to select therapies for appropriate patients to optimize outcomes and minimize adverse events.[19] Ultimately, the goal of precision medicine is to efficiently and accurately decide on the most effective treatment approach for an individual patient (**Figure 2**).[20] Precision medicine is carried out using a 2-pronged methodology: 1) characterize 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 characterize those features.[21,22]

In oncology, a biomarker is a disease- or host-related indicator that is objectively evaluated to characterize normal biologic processes, pathogenic processes, or responses to medical interventions.[23] Biomarkers provide clinicians important disease information to inform evidence-based discussions with patients.[24] The 3 primary types of biomarkers in oncology are diagnostic, prognostic, and predictive (**Figure 3**).[23,25]

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.[26]

Figure 2. Precision Medicine Approach to Cancer Management[27]



This is what is known as genotypic precision medicine.[21] 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*),[28] and up to 54% of patients have genetic mutations that are targetable with pharmacotherapy.[29] Several studies have shown that patients with NSCLC and actionable genetic mutations may have better survival outcomes when they are treated with targeted therapies.[29-31]

Figure 3. Types of Biomarkers in Oncology[23,25]

Diagnostic	Prognostic	Predictive
Primarily to assist diagnosis; most commonly in immunohistochemistry (IHC) on tissue sections but may also be a liquid test	Primarily as a guide to characterize the course and prognosis of disease (therapy unspecified)	Specifically for classification of responders and nonresponders for a defined therapy; assay and threshold developed jointly

Implementation of Precision Medicine Is Complicated in APC

In contrast with NSCLC and certain other tumor types, APC is a disease in which precision medicine is not as prevalent, in part due to a lack of adequate biomarkers (**Box 1**).[32] To successfully utilize precision medicine in a specific cancer type, several key clinical and scientific features should be met. Shared successes in tumor 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.[33,34] Once biomarkers have been identified and validated, the correlation of mutations and biomarkers with therapeutic targets is another critical step to implementing precision medicine.[35] Optimal biomarkers for precision medicine should be clinically significant, noninvasive in characterizing, and highly sensitive and specific.[25,36]

The characteristics of prostate cancer have thus far limited the identification of optimal biomarkers due to a combination of different types of challenges:

- Clinical
- Operational
- Biological

Clinical Challenges of Genotypic 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.[37,38] Due to the intra- and intertumoral heterogeneity of prostate cancer, a single tissue biopsy may not be representative of the tumor from which it was obtained, let alone the tumor burden of the patient. Even within the same patient, different metastases can display genetic heterogeneity, making the interpretation of genotypic tissue biopsy results challenging.[38,39]

In some tumor types, liquid biopsies have emerged as noninvasive alternatives to tissue biopsies, further assisting in the implementation of genotypic precision medicine.[38,40]

Operational Challenges of Genotypic 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[41-43]:

- Obtaining the optimal biopsy
- Selecting optimal tests
- Determining timing of molecular testing
- Interpreting genetic test results, which often have large volumes of information
- Appropriately counseling 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.[7] PSA is useful for a multitude of clinical decisions, particularly in early-stage and biochemically recurrent prostate cancer. A few examples of the utility of PSA include risk-stratifying localized disease and monitoring treatment response and biochemical recurrence.[7,32] 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.[32]

Biological Challenges of Genotypic Precision Medicine

Heterogeneity exists at nearly every level in prostate cancer, from the patient level (eg, geographic and ethnic diversity) to the molecular level (eg, androgen receptor [AR] expression differences).[44-47] Specifically, intra- and intertumoral heterogeneity have had the greatest impact on the ability to use precision medicine.[37,39] The differences between tumors (eg, multifocal primary tumors, metastatic tumors) and within tumors have been linked to 2 different concepts in APC, outlined in **Figure 4**[46,48-50]:

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.[51,52] In an exome sequencing analysis study, the authors described a long tail of driver mutations in APC in which a few mutations were present in about 5% to 20% of tumors (**Figure 5**); however, the majority of identified driver mutations were present in only a small subset (<5%) of prostate cancer tumors.[51]

Figure 4. Increasing Tumor Heterogeneity in APC[46,48-50,53]

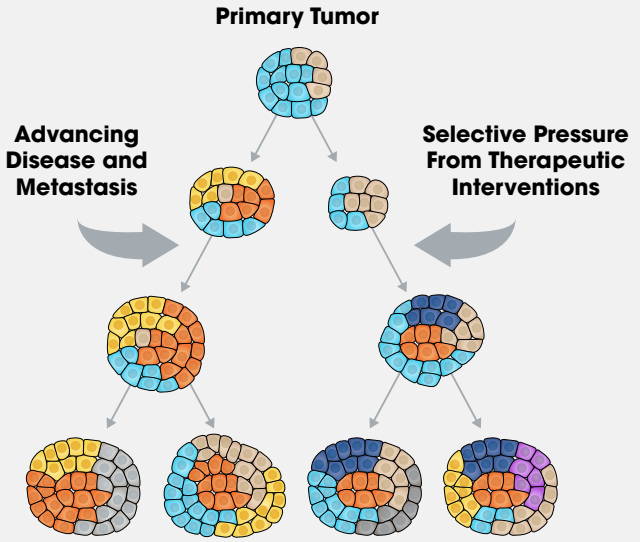
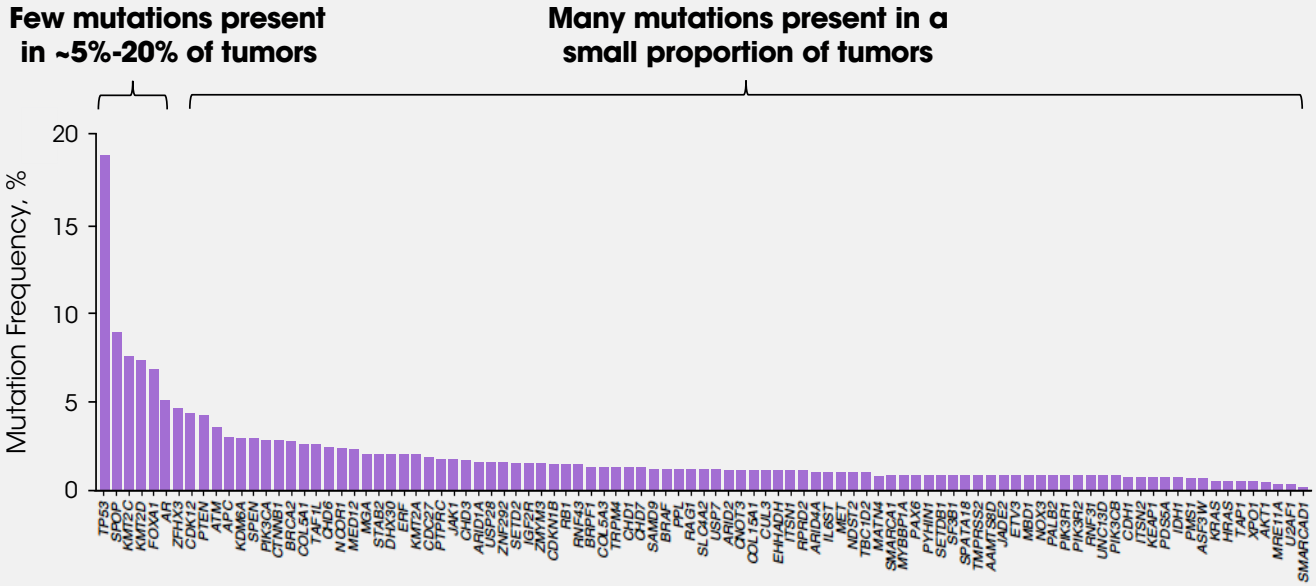


Figure 5. Long Tail of Driver Mutations in APC[51,a]



[a]In an exome sequencing analysis study, data from 1013 prostate cancers (primary, n=680; metastatic, n=333) were aggregated and uniformly analyzed to identify recurrently mutated genes that occur at lower frequencies.

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] The use of phenotypic biomarkers has emerged as a novel approach.[54] 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).[55] Genotypes and phenotypes are distinct, albeit biologically related, ways to characterize a single disease.[54]

Phenotypes can be detected through noninvasive diagnostics, such as prostate-specific membrane antigen positron emission tomography (PSMA PET) imaging.[56-58] 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.[32,59-61] The radiotracers target molecules that have been overexpressed in prostatic cancer cells (**Table 1**).[32,62-64]

Early iterations of PET imaging biomarkers were suboptimal relative to sensitivity and specificity in prostate cancer. For example, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is a glucose analog 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 in early stages, which has limited the effectiveness of ^{18}F-FDG for initial diagnosis.[65] Furthermore, androgen ablation has been shown to decrease FDG accumulation in primary and metastatic prostate cancer lesions.[66] More recent iterations of radiotracers in prostate cancer have improved upon specificity and sensitivity for diagnostic purposes, but radiotracers such as ^{11}C-choline and ^{18}F-fluciclovine, which are markers for cell membrane synthesis and amino acid transport, respectively, may have limited utility as prognostic and predictive biomarkers.[67,68]

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

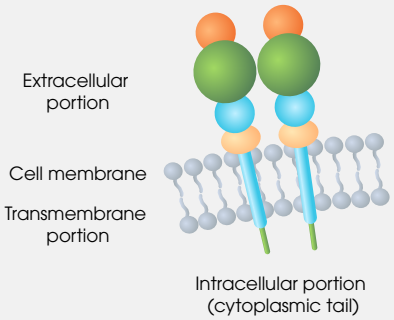
Radiotracer (Date of FDA Approval, if Applicable)	Physiologic Target	Characteristics
^{18}F-FDG (2005[69])	Glucose metabolism[69]	• Widely available[65] • Prognostic indicator in APC[70] • Prostate cancer has low glucose metabolism in early stages, resulting in low sensitivity[65]
^{11}C-choline (2012[71])	Cell membrane synthesis[71]	• Higher diagnostic sensitivity than FDG-PET/CT[67,68,a] • Variable sensitivity and specificity for biochemical recurrence, especially at low PSA levels[72] • Short half-life of 20.4 minutes requires an on-site cyclotron[71]
^{18}F-fluciclovine (2016[73])	Amino acid transport[73]	• Used in restaging, particularly for patients with higher PSA values[67] • Lesion detection rate higher than choline[74,b] • Potential variability in sensitivity and specificity related to location of metastases[75]
PSMA-based radiotracers	Targets PSMA[67]	• High specificity and sensitivity, even at low PSA levels[67] • May provide better biochemical recurrence detection than ^{18}F-fluciclovine[61,c] • Currently considered investigational by NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[32]

CT, computed tomography; FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network.
[a]In a meta-analysis of the diagnostic performance of ^{11}C-choline carried out on 8 selected studies including 276 patients.[68]
[b]In a head-to-head comparison performed in 50 patients radically treated for prostate cancer and presenting with rising PSA levels.[74]
[c]In a prospective, single-center, open-label comparative study, 50 adults with biochemical recurrence after radical prostatectomy and PSA levels <2 ng/mL.[61]

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.[59,76-80] PSMA is a transmembrane protein that is anchored in the cell membrane of prostate cancer epithelial cells (**Figure 6**).[81]

Figure 6. Structure of PSMA, a Transmembrane Protein[82]



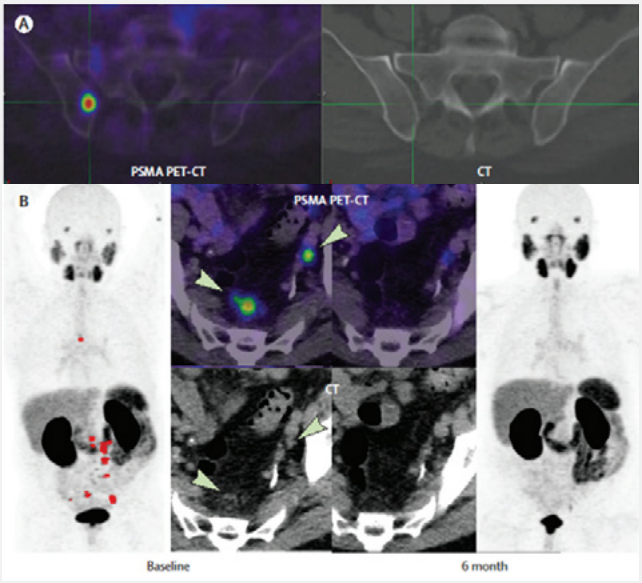
Used with permission. Chang SS. Overview of prostate-specific membrane antigen. *Rev Urol*. 2004;6(suppl 10):S13-S18.

Despite its name, PSMA is not specific to the prostate gland but is found in tumor-associated blood vessels across a wide range of tumor types as well as healthy prostatic and nonprostatic tissues.[82,83] Compared to benign prostate tissue, however, malignant prostate cells may express PSMA at a substantially higher level.[76]

PSMA as a Diagnostic Biomarker Used in PET Scanning

PSMA has been shown to be a useful biomarker for the diagnosis of localized and advanced disease.[59,61] In ProPSMA, a prospective, multicenter, randomized, controlled trial, 302 men with high-risk localized 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.[59]

Figure 7. Comparison of PSMA PET/CT and Conventional Imaging in 2 Men With Normal Conventional Imaging Results[59,a]



[a]Images show PSMA PET/CT and conventional imaging results for 2 patients: 1 with A) a right iliac bone metastasis and 1 with B) multiple sub-cm pelvic and distant nodal metastasis. Six-month follow-up imaging is shown after systemic treatment and disease regression.

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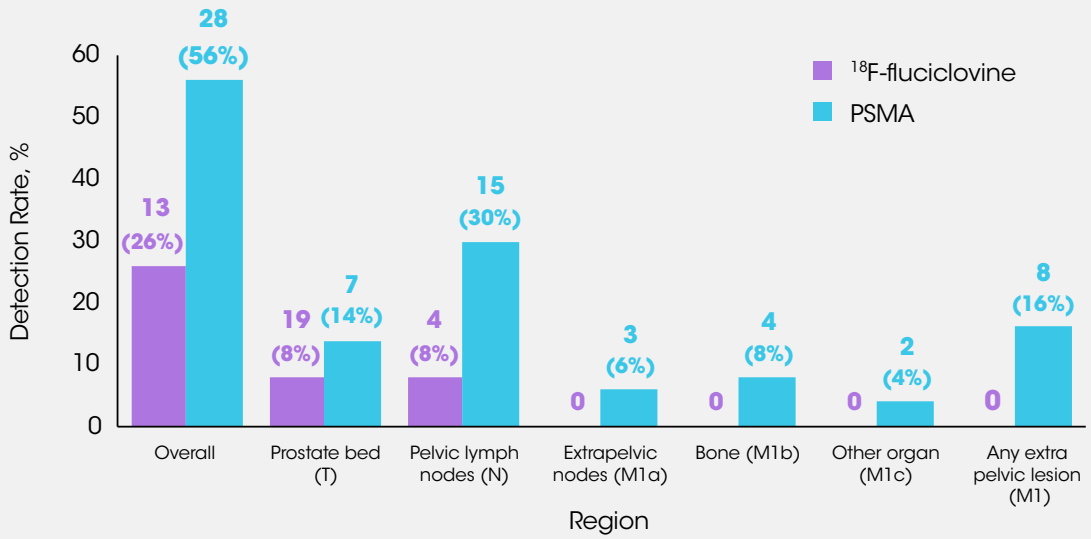
PSMA-based imaging has also shown utility in advanced disease. A separate prospective, single-center, open-label, single-arm comparative imaging study of ^{18}F-fluciclovine and PSMA PET/CT evaluated 50 adults with biochemical recurrence after prostatectomy and PSA levels <2 ng/mL. In this study, PSMA PET/CT was shown to have a 4.8-fold higher rate of disease detection than ^{18}F-fluciclovine (95% CI, 1.6-19.2; *P*=0.0026) (**Figure 8**).[61]

Figure 8. PSMA-Based Imaging Detects Prostate Cancer Metastases at a Higher Rate Than ^{18}F-fluciclovine[61,a]



M, metastasis; N, node; T, tumor.

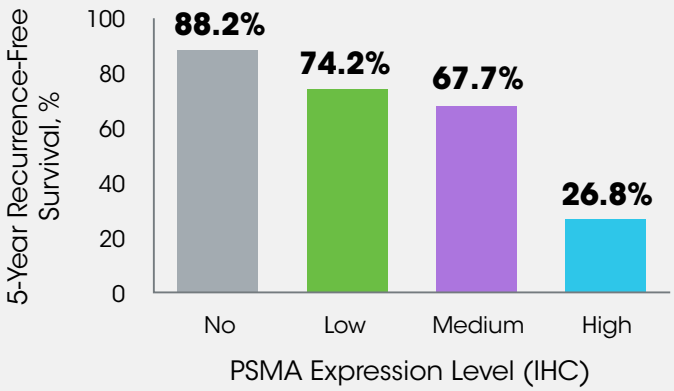
[a]In a prospective, single-center, open-label, single-arm comparative imaging study of ^{18}F-fluciclovine and PSMA PET/CT, 50 adults with biochemical recurrence after prostatectomy and PSA levels <2 ng/mL were evaluated. The detection rates of biochemical recurrence per patient were significantly lower with ^{18}F-fluciclovine (13 [26%; 95% CI, 15-40] of 50) than with PSMA PET/CT (28 [56%; 95% CI, 41-70] of 50), with an overall response of 4.8 (95% CI, 1.6-19.2; *P*=0.0026).

The sensitivity and specificity of PSMA as a diagnostic biomarker have 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%.[60] In the previously described comparative imaging study, the per-patient sensitivity was 66% for PSMA PET/CT vs 33% for ^{18}F-fluciclovine (95% CI, 0.67–34.5; *P*=0.18).[61]

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 tumors, 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**).[76]

Figure 9. 5-Year Recurrence-Free Survival According to PSMA Level at Diagnosis[76,a,b]



[a]PSMA expression was assessed in a retrospective study by IHC in 294 preoperative biopsies, 621 primary tumor foci from 242 radical prostatectomies, 43 locally advanced or recurrent tumors 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 categorized as no expression (score of 0), low expression (1), medium expression (2), or high expression (3). Expression was correlated with recurrence-free survival as the primary end point measure.

[b]Disease recurrence was defined as biochemical recurrence (PSA increase above the postoperative nadir following radical prostatectomy) and used as the end point for survival analysis.

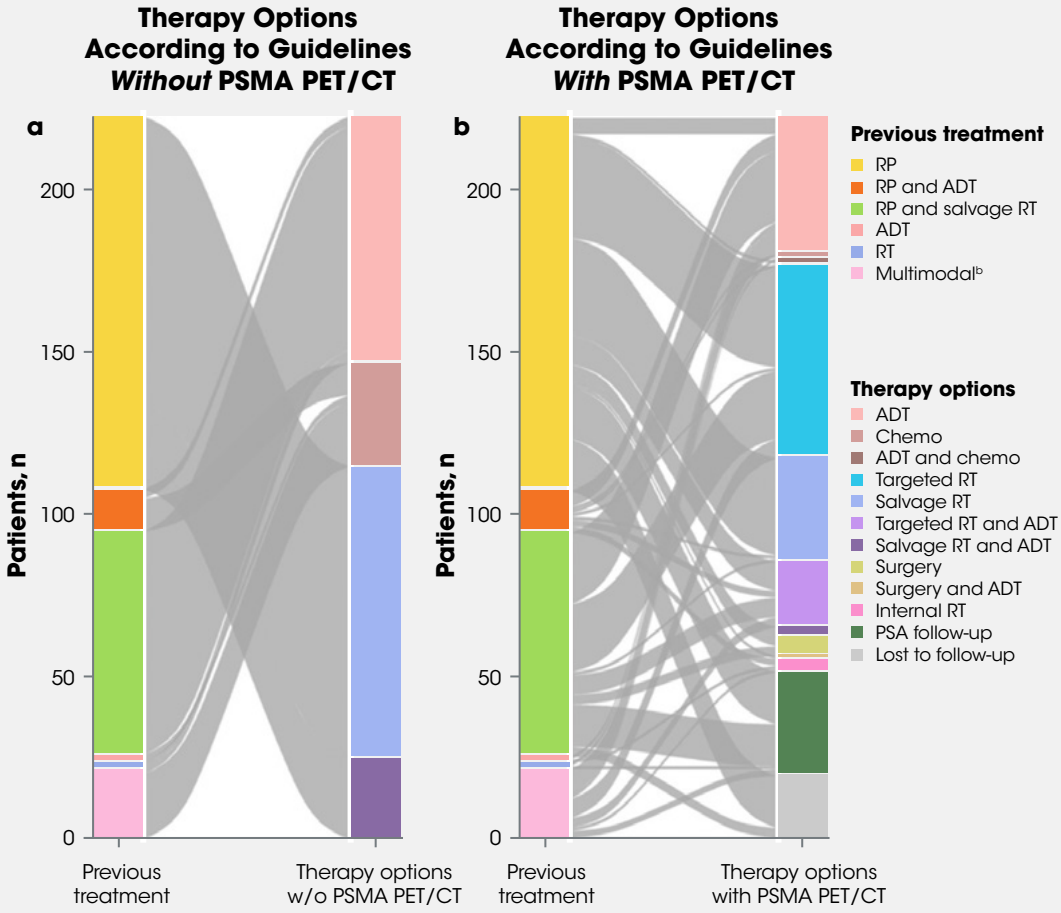
PSMA as a Clinically Relevant Biomarker

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 changes 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.[59]

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 analyzed.[78] Among the 203 patients with 6-month follow-up results, a change in management was recorded in up to 60% of patients.[78,84] As shown in **Figure 10**, therapy options may have been tailored with the addition of PSMA PET/CT imaging.[78] These results have been replicated in another real-world study.[85] Although there is currently no clinical data available that link expanded clinical options with

Figure 10. Change in Therapy Options (a) Without PSMA PET/CT and (b) With PSMA PET/CT[78,a]

PSMA PET/CT may help guide clinical management with a tailored approach.



ADT, androgen deprivation therapy; chemo, chemotherapy; RP, radical prostatectomy; RT, radiotherapy.

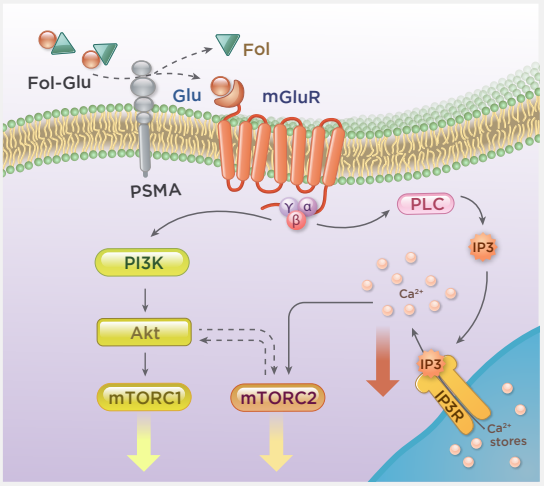
[a]The aim of the retrospective study from Switzerland was to assess the effect of PSMA PET/CT on management and outcome in all patients imaged during the first year after its introduction into clinical routine. The rate of detection of recurrence was based on clinical reports. In the 203 patients with 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 <0.2 ng/mL representing a complete response and a decrease in PSA value of at least 50% from baseline representing a partial response.
[b]Multimodal included surgery, salvage RT, ADT, and/or chemo combined.

Box 2. PSMA and Oncogenic Signaling Pathways

Preliminary data have shown that PSMA may play a role in signaling pathways related to phosphatidylinositol-3-kinase (PI3K), rat sarcoma virus (RAS)/rapidly accelerated fibrosarcoma (RAF)/mitogen-activated protein kinase (MAPK), nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB), and p21-activated kinase (PAK 1).[86-89] These pathways modulate the following cellular properties:

- Cell proliferation and survival[86-88,90]
- Cell migration[90]
- Angiogenesis[89,91]

Figure 11. Cascade Signaling Effect of PSMA-Binding Ligands[86]



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improved outcomes, real-world studies showed an increased rate of systemic treatments for patients with metastases,[85] suggesting clinically matched interventions. Future studies should investigate the correlation between PSMA PET imaging and individualizing treatments with the goal of optimizing outcomes.[92]

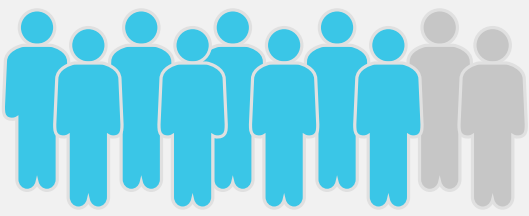
In addition to its utility for PET/CT, PSMA has emerged as an attractive potential therapeutic target due to its role in several oncogenic signaling pathways.[86-89] Although no natural ligand for PSMA has been identified to date, PSMA has been convincingly linked with a number of kinase pathways that promote oncogenic cell growth and tumor progression (**Box 2**).[86-91] This is particularly relevant for patients with APC, who may develop resistance mutations to AR-directed therapies (**Figure 11**).[93] Evidence exists from various tumor types that PSMA expression in the vasculature is associated with worse survival outcomes.[94,95]

PSMA is overexpressed in >80% of men with prostate cancer, making it an attractive therapeutic target (**Figure 12**).[76,96,97] Another feature includes the accessibility of the molecule due to its location on the cell surface. PSMA-binding ligands also undergo cell internalization by PSMA, which allows the delivery of both small molecules and larger biologics inside the cell.[81]

Clinical Relevance of PSMA-Based Imaging in APC

PSMA is a diagnostic and potential therapeutic target that may enable a phenotypic precision medicine approach to managing APC.[59,76,78] 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.[54,57-59,81,84] 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.[5,6,98]

Figure 12. >80% of Men With Prostate Cancer Overexpress PSMA[76,96,97]



Discussion Highlights

- Precision medicine is an approach that utilizes diagnostic tools to hopefully select therapies for appropriate patients with the goal of optimizing outcomes and minimizing side effects[19]
- The complexity of APC makes the implementation of genotypic precision medicine challenging in various ways[37]:
    - Clinical
    - Operational
    - Biological
- PSMA is a diagnostic and potential therapeutic target, enabling a phenotypic precision medicine approach to treating APC in the following ways[59,76,78-80]:
    - Detection of a clinically relevant biomarker using a noninvasive diagnostic tool[57,58]
    - Optimization of patient selection to help inform management decisions[54,59,78,84]
    - Utilization of phenotypic precision medicine with the goal of improving patient outcomes[78,79,85]

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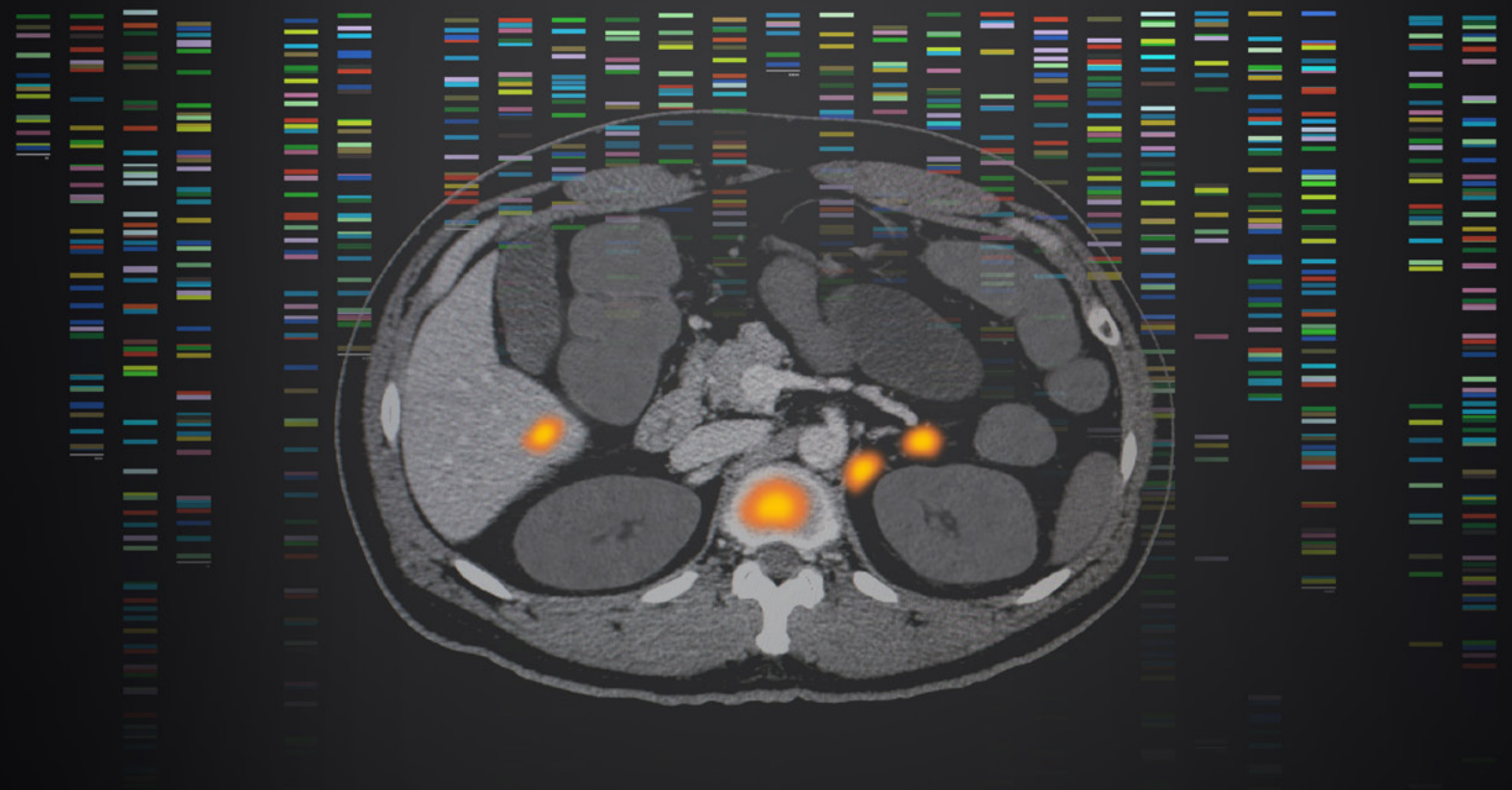

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