Phenotypic Precision Medicine in Advanced Prostate Cancer: A Path Forward
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Precision Medicine in Advanced Prostate Cancer
Precision Medicine Is an Approach That Utilizes Diagnostic Tools to Select Therapies for Appropriate Patients to Optimize Outcomes and Minimize Adverse Events

- The concept of **precision medicine** is based on the detailed evaluation of an individual patient’s disease in order to...²
  - Characterize a genetic or molecular target
  - Tailor a treatment approach to the target

- The **goal** of precision medicine is to efficiently and accurately guide clinical management by³-⁵:
  - Assisting in patient selection
  - Simplifying treatment decision making

**Successful** use of precision medicine is dependent upon having a detailed understanding of the **molecular characteristics** of the patient’s disease²,⁶

Precision Medicine Requires Several Key Components for Successful Translation to Clinical Practice\textsuperscript{1-3}

- Key components for a successful translation of precision medicine to clinical practice:
  1. Detection of widespread driver mutations across a disease population\textsuperscript{1}
  2. Identification of biomarkers that correlate with response or function\textsuperscript{2}
  3. Correlation of mutations and biomarkers with therapeutic targets\textsuperscript{3}

Cancer morphology in non-small cell lung cancer (NSCLC) can be classified based on the presence of genomic alterations, allowing for improved precision and potential targeted treatment selection\textsuperscript{4}

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Classification of Cancer Morphology in NSCLC Based on Genomic Alterations

Precision Medicine Is Complicated in Advanced Prostate Cancer

- Treatment options for prostate cancer have dramatically expanded over the last decade\textsuperscript{2-12}
  - 10 approvals since 2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Immunotherapy</td>
</tr>
<tr>
<td>2011</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>2012</td>
<td>mCRPC Hormonal Therapy</td>
</tr>
<tr>
<td>2013</td>
<td>Radionuclide Therapy</td>
</tr>
<tr>
<td>2017</td>
<td>Immunotherapy (microsatellite instability–high, tissue agnostic)</td>
</tr>
<tr>
<td>2018</td>
<td>nmCRPC Hormonal Therapy</td>
</tr>
<tr>
<td>2019</td>
<td>2020 and beyond</td>
</tr>
<tr>
<td>2020</td>
<td>Poly (ADP-Ribose) Polymerase (PARP) Inhibitors</td>
</tr>
</tbody>
</table>

Selecting and sequencing among the available treatment options is challenging\textsuperscript{2}

References:
Precision Medicine in APC Is Not as Well Utilized Due to the Lack of Biomarkers, Which Is a Critical Component\textsuperscript{1,2}

- 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\textsuperscript{3}
- Biomarkers provide clinicians with important disease information to inform evidence-based discussions with patients\textsuperscript{4}

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Diagnostic</td>
<td>Primarily to assist diagnosis; most commonly in immunohistochemistry (IHC) on tissue sections but may also be a liquid test</td>
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<tr>
<td>Prognostic</td>
<td>Primarily as a guide to characterize the course and prognosis of disease (therapy unspecified)</td>
</tr>
<tr>
<td>Predictive</td>
<td>Specifically for classification of responders and nonresponders for a defined therapy; assay and threshold developed jointly</td>
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Challenges With Biomarkers in Prostate Cancer
PSA Is the Most Commonly Used Biomarker but Is Not Ideal for Precision Medicine¹,²

• Clinical applications for prostate-specific antigen (PSA)¹,²:
  - **Diagnosing** early disease
  - **Risk-stratifying** localized disease
  - **Monitoring** treatment response and biochemical recurrence

• PSA is not a predictive biomarker and **does not** provide guidance for selecting and sequencing treatments in APC¹

Identifying Actionable Biomarkers in APC Through Traditional Genetic Sequencing Modalities Has Been Challenging\(^1,2\)

There are **various challenges** in implementing precision medicine using genotypic biomarkers

### Clinical Challenges
- Difficulty obtaining bone biopsies\(^3\)
- Complexity of analyzing and interpreting liquid biopsies\(^1\)

### Operational Challenges
- Determining timing of molecular testing\(^4,5\)
- Appropriately counseling patients and families\(^4,5\)

### Biologic Challenges
- Disease heterogeneity\(^6-9\)
- Treatment-induced genetic alterations\(^10,11\)
- Lack of a dominant or prevalent driver mutation\(^2,12\)

**References:**
Biopsy Limitations Make Genetic Biomarkers Clinically Challenging to Characterize in APC

Comparison of Liquid and Tissue Biopsies

<table>
<thead>
<tr>
<th>Biopsy Type</th>
<th>Definition</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td>Direct sampling and evaluation of tumor tissue¹</td>
<td>• Pathologic gold standard²</td>
<td>• Invasive with inherent risks of biopsy³</td>
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<tr>
<td></td>
<td></td>
<td>• Histology and phenotypic changes easily assessed²</td>
<td>• Difficult to biopsy bone metastases (painful, technically challenging, lesions frequently sclerotic)³</td>
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<td></td>
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<td></td>
<td>• Primary tumor biopsy results may not be representative of metastatic tumor genetic profile⁴</td>
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<td></td>
<td></td>
<td></td>
<td>• May not capture disease heterogeneity²</td>
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<tr>
<td>Liquid</td>
<td>Measuring tumor cells or circulating tumor DNA in the blood; may also apply to other measurements in the blood, urine, or saliva⁵</td>
<td>• Minimally invasive and ease of sample collection²,⁶</td>
<td>• Challenging to establish a prognosis, especially in the metastatic setting; modest clinical utility²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May provide a better reflection of the heterogeneity of disease²</td>
<td></td>
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Operational Challenges of Genotypic-Based Precision Medicine\textsuperscript{1-3}

Implementing precision medicine with genomic sequencing tools presents various operational challenges to oncologic and urologic practices\textsuperscript{1-3}

- Obtaining the optimal biopsy\textsuperscript{1}
- Selecting optimal tests\textsuperscript{1-3}
- Determining timing of molecular testing\textsuperscript{1}
- Interpreting genetic test results with large volumes of information\textsuperscript{2}
- Appropriately counseling patients and families\textsuperscript{1}
- Navigating, recording, and storing data\textsuperscript{1,2}

Heterogeneity in APC Makes the Use of Precision Medicine Challenging

• Heterogeneity in prostate cancer is attributed to 2-5:
  1. Genomic instability of advancing disease
  2. Treatment-induced selective pressures

• Together, these factors lead to the development of the genetic complexity that is characteristic of APC

Heterogeneity Also Contributes to Fewer Widespread Driver Mutations, Making Use of Targeted Therapies Challenging

- The genomic heterogeneity of mutations in prostate cancer is characterized by a long tail of driver mutations\(^1\)
- Traditional cancer gene screening panels may not be effective for identifying actionable driver mutations\(^2\)
- Next-generation sequencing (NGS) modalities, which can potentially capture individualized genomic data, may be complex and expensive to perform\(^3,4\)

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.\(^1\)

Genotypic Biomarkers Are Challenging to Characterize in APC, Creating a Need for a Novel Approach\textsuperscript{1-2}


Optimal biomarkers should be\textsuperscript{3,4}

- Clinically significant
- Noninvasive
- Highly sensitive and specific
A **phenotypic trait** is defined as an observable characteristic that is produced through the interaction of genotype and environment (e.g., the physical expression of genes, such as protein expression levels)\(^4\)

While genotypes require biologic samples for genetic sequencing, phenotypes can be characterized by **noninvasive imaging** such as positron emission tomography (PET) / computed tomography (CT)\(^1-3\)

**References:**
Genotyping vs Phenotyping in APC

**Genotyping in APC**

Prostate-specific membrane antigen (PSMA) PET imaging is emerging as a noninvasive diagnostic to characterize phenotypes.

**Phenotyping in APC**

Harnessing Phenotypes in Precision Medicine
Noninvasive Diagnostic Imaging Can Detect Phenotypic Biomarkers Such as PSMA$^{1-7}$

- Phenotypic assessment through noninvasive diagnostic imaging is improving the ability to characterize prostate cancer by enhancing the sensitivity and specificity compared with other approved options$^{1-7}$.
- PET imaging leverages radiotracers to target molecules that may be overexpressed in prostatic cancer cells$^{8-11}$.
- Examples of radiotracers used in prostate cancer imaging$^8$:
  - $^{18}$F-fluciclovine: amino acid transport
  - $^{11}$C-choline, $^{11}$C-acetate: cell membrane synthesis
  - $^{68}$Ga–PSMA*, $^{18}$F-DCFBC, $^{18}$F-DCFPyL: prostate cancer–specific proteins and receptor molecules
  - $^{18}$F-NaF: bone matrix adjacent to metastases

$^*$Currently in development.

PSMA Has Emerged as a Sensitive and Specific Phenotypic Biomarker in Prostate Cancer¹,²

Radiotracer (Date of FDA Approval, if Applicable) | Advantages | Disadvantages |
---|---|---|
¹⁸F-FDG (2005³) | • Widely available² | • Prostate cancer has low glucose metabolism in early stages, resulting in low sensitivity² |
 | • Meaningful prognostic indicator in APC³ | | |
¹¹C-choline (2012⁴) | • Higher diagnostic sensitivity than FDG-PET/CT⁵,⁶,⁸ | • Variable sensitivity and specificity for biochemical recurrence, especially at low PSA levels⁷ |
 | | • Short half-life of 20.4 minutes requires an on-site cyclotron⁴ | | |
¹⁸F-fluciclovine (2016⁸) | • Useful for restaging, particularly for patients with higher PSA values⁵ | • Potential variability in sensitivity and specificity related to location of metastases¹⁰ |
 | • Lesion detection rate superior to choline⁹,b | | |
PSMA-based radiotracers | • High specificity and sensitivity, even at low PSA levels⁵ | • ⁶⁸Ga agents must be produced on-site with a generator¹² |
 | • May provide better biochemical recurrence detection than ¹⁸F-fluciclovine¹¹,¹²,c | • Currently investigational in the United States¹² | | | |

APC, advanced prostate cancer; CT, computed tomography; FDG, fludeoxyglucose; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

¹ In a meta-analysis of the diagnostic performance of ¹¹C-choline carried out on 8 selected studies including 276 patients.⁶
² In a head-to-head comparison performed in 50 patients radically treated for prostate cancer and presenting with rising PSA levels.⁹
³ In a prospective, single-center, open-label comparative study, 50 adults with biochemical recurrence after radical prostatectomy and PSA levels <2 ng/mL.¹¹
PSMA as a Diagnostic, Prognostic, and Clinically Relevant Biomarker in Prostate Cancer
PSMA Is a Transmembrane Protein Highly Expressed in Prostate Cancer and Other Epithelial Cancers\textsuperscript{1-4}

- PSMA is a transmembrane protein that is anchored in the cell membrane of prostate cancer epithelial cells\textsuperscript{1}.
- Despite the name, PSMA is not specific to the prostate gland and is found in tumor-associated neovasculature as well as some healthy prostatic and nonprostatic tissues\textsuperscript{2,3}.
- However, PSMA is expressed at much higher levels in prostate cancer cells\textsuperscript{4}.

>80% of Men With Prostate Cancer Overexpress PSMA\(^{1-3}\)

- PSMA is a membrane protein and is highly accessible to ligand binding\(^{4}\)
- PSMA-binding ligands undergo cell internalization by PSMA, making it an appealing molecular target\(^{4}\)
- Expression is independently correlated with...\(^{1,5}\)
  - Tumor stage
  - Metastatic disease
  - Risk of recurrence
  - Poor prognosis

PSMA Is an Imaging Target in Prostate Cancer Due to its Overexpression in Malignant Tissues

PSMA is overexpressed in prostate cancer cells, suggesting a large potential patient population that could benefit from PSMA imaging.

PSMA Is a Sensitive and Specific Diagnostic Biomarker for Localized and Advanced Disease¹,²

Meta-analysis¹,a

PSMA PET trials assessing prediction of primary and recurrent prostate cancer

Per-patient sensitivity  Per-patient specificity

86%  86%

Head-to-head trial²,b

PSMA PET/CT vs ¹⁸F-FACBC for localization of biochemically recurrent disease post–radical prostatectomy (RP)

Per-patient sensitivity

PSMA PET/CT  66% vs ¹⁸F-fluciclovine  33%

¹In a meta-analysis of 16 articles including 1309 patients, the sensitivity and specificity values were calculated for patients who underwent ⁶⁸Ga-PSMA PET.¹
²In a prospective, single-center, open-label comparative study, 50 adults with biochemical recurrence after radical prostatectomy and PSA levels <2 ng/mL received ¹⁸F-FACBC or PSMA-based PET/CT. The primary end point was detection of cancer by anatomical region. Per-patient sensitivity was 33% (95% CI, 15–58; five true positives and ten false negatives) for ¹⁸F-fluciclovine and 66% (42–85; ten true positive and five false negative) for PSMA PET/CT (OR 3.5 [95% CI, 0.67–34.5], P=0.18).²

In the ProPSMA Study, PSMA PET/CT Was More Accurate Than Conventional Imaging for Diagnosis of Metastases

• The ProPSMA study was a prospective, multicenter, randomized, controlled trial of men with high-risk, apparently localized prostate cancer

• Three hundred two men were randomly assigned to receive either CT and bone scan (conventional imaging) or PSMA PET/CT

Accuracy of PSMA PET/CT was 27% greater than that of conventional imaging (92% vs 65%; P<0.0001). PSMA PET/CT was 32% more accurate for pelvic nodal metastases and 22% more accurate for distant metastases.

1 The primary end point was accuracy of first-line imaging for identifying either pelvic nodal or distant-metastatic disease. The accuracy was assessed by the area under the curve.
2 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 better accuracy of PSMA PET/CT.

CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

*Images show PSMA PET/CT and conventional imaging results for 2 patients with (a) a right iliac bone metastasis and (b) multiple sub-cm pelvic and distant nodal metastases. Six-month follow-up imaging is shown after systemic treatment and disease regression.

PSMA as a Prognostic Biomarker Is Also Demonstrated by a Negative Correlation of 5-Year Recurrence-Free Survival

PSMA expression level as detected by IHC on initial biopsy was **negatively correlated** with 5-year recurrence-free survival\(^a,^b\)

IHC, immunohistochemistry; PSMA, prostate-specific membrane antigen.

\(^a\)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 to 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 recurrence-free survival was used as the primary end point for survival analysis.

PSMA PET/CT Provides Clinically Relevant Insights to Guide Treatment Plans With a Tailored Approach\(^1,2\)

- In a retrospective, real-world, single-institution Swiss study of PSMA PET/CT, changes in management plans have been made after PSMA PET/CT\(^1\):
  - PSMA PET/CT may have contributed to management changes in up to 60% of patients\(^1,2\)
  - PSMA PET/CT-detected local disease was more likely to be considered for local treatment, while PSMA PET/CT-detected metastatic disease was more likely to be considered for systemic or combination approaches\(^1\)

ADT, androgen deprivation therapy; CT, computed tomography; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; 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 of <0.2 ng/mL representing a complete response and a decrease in PSA value of at least 50% from baseline representing a partial response.\(^1\)

\(^b\)Multimodal included surgery, salvage radiation therapy (RT), ADT, and/or chemotherapy combined.\(^1\)


Preliminary Data Indicate PSMA Upregulates Several Key Oncogenic Pathways, Suggesting Its Clinical Relevance as a Potential Therapeutic Target in Prostate Cancer:

- PSMA has emerged as an **attractive potential therapeutic target** due to its preliminary role in several oncogenic signaling pathways.
- PSMA has been linked with a number of kinase pathways that promote oncogenic cell growth and tumor progression.
- Expression of PSMA in the vasculature of various tumor types has been linked with worse survival.

**References:**
PSMA Is a Key Phenotypic Biomarker That May Simplify the Approach to Precision Medicine in APC\textsuperscript{1-10}

- PSMA is a **diagnostic and potential therapeutic target**, enabling a phenotypic precision medicine approach to treating advanced prostate cancer in the following ways\textsuperscript{2-5}
  - Detection of a clinically relevant biomarker using a noninvasive imaging tool\textsuperscript{6,7}
  - Optimization of patient selection to help inform management decisions\textsuperscript{3,4,8,9}
  - Utilization of phenotypic precision medicine with the goal of improving outcomes\textsuperscript{4,5}

Key Takeaways

1. Precision medicine is an approach that utilizes diagnostic tools to hopefully select therapies for appropriate patients to optimize outcomes and minimize adverse events.\(^1\)

2. The use of genotypic biomarkers in APC is challenging because of the heterogeneity of the disease and lack of widespread driver mutations.\(^2\)

3. PSMA is overexpressed in >80% of men with prostate cancer and is emerging as a diagnostic, prognostic, and clinically relevant biomarker.\(^3\)-\(^9\)

Thank You

Visit the website for more information:
www.PhenotypicPrecisionMedicine.com