Precision Medicine in Advanced Prostate Cancer

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Precision Medicine Is an Approach That Utilises Diagnostic Tools to Select Therapies for Appropriate Patients to Optimise Outcomes and Minimise Adverse Events\textsuperscript{1-10}

- The concept of \textit{precision medicine} is based on the detailed evaluation of an individual patient’s disease in order to\textsuperscript{1-6}:
  - Gain insight into the disease diagnosis
  - Tailor a treatment approach to the patient
- The \textbf{goal} of precision medicine is to efficiently and accurately guide clinical management\textsuperscript{6-10}:
  - Assisting in predicting the most appropriate course of action
  - Simplifying management of complex diseases

\textbf{Application} of precision medicine is underpinned by a detailed understanding of the \textbf{molecular characteristics} of the patient’s disease\textsuperscript{1,3,4,6-10}

\textbf{Strategy for Developing Personalised Medicine}\textsuperscript{8-10}

Detection of driver mutations across a disease population

Identification of biomarkers that correlate with response or function

Association of mutations and biomarkers with therapeutic targets

**Breast Cancer as a Model for Precision Medicine in Oncology**

- Management of breast cancer includes:
  - Surgery: local management of primary; regional management of axilla\(^1\)
  - Radiation: postlumpectomy, postmastectomy, palliative radiation for metastatic disease\(^1\)
  - Medical: chemotherapy, HER2-targeted therapy, endocrine therapy, other targeted therapies (eg, PARP inhibitors, PI3K inhibitors, CDK4/6 inhibitors)\(^1,2,4-8\)

**Actionable Mutations Identified in Breast Metastases Inform Targeted Therapies**

<table>
<thead>
<tr>
<th>Detected genes</th>
<th>Drug/s</th>
<th>Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD274 (PD-L1), TP53, MDM2, MAP2K1 (MEK1), MAP2K2 (MEK2)</td>
<td>Atezolizumab, Cobimetinib, Idasanutlin</td>
<td>NCT0356648</td>
</tr>
<tr>
<td>PTEN, AKT1, MTO1, RHEB, PIK3CA</td>
<td>Gedatolisib</td>
<td>NCT01920061</td>
</tr>
<tr>
<td>PTEN, PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD50, RAD51C, RAD51D, MRE11, ATR, FANCA, FANCC</td>
<td>Talazoparib</td>
<td>NCT02401347</td>
</tr>
<tr>
<td>TP53, ESR1, PIK3CA, AKT1, GATA3, PTEN, TBX3</td>
<td>Ipatasertib</td>
<td>NCT04253561</td>
</tr>
<tr>
<td>CDK2, CDK4, CDK6</td>
<td>PF-06873600</td>
<td>NCT03519178</td>
</tr>
</tbody>
</table>

CDK, cyclin-dependent kinases; HER2, human epidermal growth factor receptor 2; PARP, poly (ADP-ribose) polymerase; PI3K, phosphatidylinositol 3-kinase.

Precision Medicine in Prostate Cancer Is Not Widely Used Due to the Lack of Actionable Biomarkers, Which Are a Critical Component of Precision Medicine\(^1\)-\(^{17}\)

- **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\(^{11}\)-\(^{13}\)

- Biomarkers provide clinicians with important disease information to inform evidence-based decision making\(^{5,13-16}\)

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**Examples of Biomarker Types\(^{17}\)**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic</td>
<td>Primarily to assist diagnosis; most commonly using immunohistochemistry (IHC) on tissue sections but may also be a liquid test (using serum)</td>
</tr>
<tr>
<td>Prognostic</td>
<td>Primarily as a guide to characterise the course and prognosis of disease (therapy unspecified)</td>
</tr>
<tr>
<td>Predictive</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>
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Precision Medicine in Advanced Prostate Cancer Is Not Yet Widely Used: PARP Inhibitors Approved Into an Already Complex Treatment Landscape

- Treatment options for prostate cancer have expanded over the last decade

Timeline of New Drug Approvals in Advanced Prostate Cancer

• Selecting and sequencing among the available treatment options is challenging

References:

ADP: adenosine diphosphate.
Challenges With Traditional Biomarkers in Advanced Prostate Cancer
**PSA Is the Most Commonly Used Biomarker but Is Not Ideal for Precision Medicine**

- Clinical applications for prostate-specific antigen (PSA):
  - **Initial diagnosis** of prostate cancer
  - **Risk-stratifying** disease
  - **Monitoring** biochemical recurrence

- PSA is not a predictive biomarker and **does not** provide guidance for selecting treatments in advanced prostate cancer due to a disconnect between change in PSA levels and survival outcomes

References:
Identifying Optimal Biomarkers in Advanced Prostate Cancer Through Traditional Genetic Sequencing Modalities Is Challenging

There are various challenges in implementing precision medicine using genotypic biomarkers. Examples include:

<table>
<thead>
<tr>
<th>Biologic Challenges</th>
<th>Clinical Challenges</th>
<th>Operational Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease heterogeneity</td>
<td>Biopsies are technically difficult and associated with morbidity</td>
<td>Determining timing and type of molecular testing and interpretation of test results</td>
</tr>
<tr>
<td>Treatment-induced genetic alterations</td>
<td>Complexity of interpreting biopsies due to tumour heterogeneity</td>
<td>Appropriately counselling patients and families</td>
</tr>
<tr>
<td>Few widespread mutations identified</td>
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</tr>
</tbody>
</table>

Heterogeneity in Advanced Prostate Cancer Makes the Use of Precision Medicine Challenging\textsuperscript{1-4}

- Heterogeneity in prostate cancer is attributed to\textsuperscript{1,5-7}:
  1. Genomic instability of advancing disease\textsuperscript{1,5,7}
  2. Treatment-induced selective pressures\textsuperscript{1,5,6}

- Together, these factors lead to the development of the genetic complexity that is characteristic of advanced prostate cancer\textsuperscript{1-4}

Few Widespread Mutations Have Been Identified Due To Heterogeneity of Prostate Cancer, Further Complicating Use of Targeted Therapies\textsuperscript{1,2}

- The genomic heterogeneity of mutations in prostate cancer is characterised by a long tail of driver mutations\textsuperscript{1,2}
- Traditional cancer gene screening panels may not be effective for identifying actionable driver mutations\textsuperscript{3,4}
- Next-generation sequencing (NGS) modalities, which can potentially capture individualised genomic data, may be complex and expensive to perform\textsuperscript{5-8}

\textsuperscript{a}In an exome sequencing analysis study, data from 1013 prostate cancers (primary, n=680; metastatic, n=333) were aggregated and uniformly analysed to identify recurrently mutated genes that occur at lower frequencies.\textsuperscript{1}

## Genetic Biomarkers Can Be Clinically Challenging to Obtain and Measure in Prostate Cancer Due to Biopsy Limitations

### Comparison of Liquid and Tissue Biopsies

<table>
<thead>
<tr>
<th>Biopsy Type</th>
<th>Definition</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Tissue      | Direct sampling and evaluation of tumour tissue\(^1\) | • Pathologic gold standard\(^2\)  
• Histology and phenotypic changes easily assessed\(^2\) | • Morbidity associated with biopsy of primary and metastatic lesions\(^2-8\)  
• Difficult to biopsy bone metastases (technically challenging, lesions frequently sclerotic)\(^2,9-12\)  
• Primary tumour biopsy results may not be representative of metastatic tumour genetic profile and may not capture disease heterogeneity\(^2,9,13-15\) |
| Liquid      | Measuring tumour cells or circulating tumour DNA in the blood; may also apply to other measurements in the blood, urine, or saliva\(^16\) | • Noninvasive and less morbid\(^2,17\)  
• May provide a better reflection of the heterogeneity of disease\(^2\) | • Challenging to establish a prognosis, especially in the metastatic setting; modest clinical utility\(^2\) |

### References:
Operational Challenges Associated With Genotypic Biomarker-Based Precision Medicine

Implementing precision medicine with genomic sequencing tools presents various operational challenges to oncologic and urologic practices\textsuperscript{1-5}

- Determining timing of molecular testing\textsuperscript{1-4}
- Selecting optimal tests\textsuperscript{1-4}
- Obtaining the optimal biopsy\textsuperscript{1}
- Interpreting genetic test results with large volumes of information\textsuperscript{1,2}
- Appropriately counselling patients and families\textsuperscript{1,3}
- Navigating, recording, and storing data\textsuperscript{1,2}
- Accessing/obtaining reimbursement for testing (eg, NGS)\textsuperscript{1,2,5}

Challenges Associated With the Use of Genotypic Biomarkers in Advanced Prostate Cancer Underscore the Need for a Novel Approach¹⁻⁹

Optimal biomarkers should be⁶,¹⁰

- Clinically significant
- Noninvasive
- Highly sensitive and specific

Understanding the Role of Phenotypes in Precision Medicine
Imaging Phenotypes May Provide a Novel Biomarker Approach

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).

While genotypes require biologic samples for genetic sequencing, phenotypes can be characterised by **noninvasive diagnostics**:

- **Conventional imaging**—i.e., computed tomography (CT) or bone scan.
- **Next-generation imaging**—i.e., positron emission tomography (PET)/CT.

References:
Next-Generation Imaging Can Detect Phenotypic Biomarkers

- Phenotypic assessment through next-generation imaging is improving the ability to detect prostate cancer by enhancing the sensitivity and specificity compared to other available options.

- PET imaging leverages radiotracers to detect molecules that may be highly expressed in prostatic cancer cells.

- Examples of radiotracers used in prostate cancer imaging:
  - $^{18}$F-fluciclovine: amino acid transport
  - $^{11}$C-choline: cell membrane synthesis
  - $^{68}$Ga-PSMA, $^{18}$F-DCFBC, $^{18}$F-DCFPyL: targets prostate-specific membrane antigen (PSMA)
  - $^{18}$F-NaF: bone matrix

Genotyping vs Phenotyping in Advanced Prostate Cancer\textsuperscript{1,2}

- PET imaging with radiotracers offers a phenotypic approach that may facilitate decision making and the use of precision medicine in advanced prostate cancer\textsuperscript{2-7}

Phenotypic Biomarkers May Facilitate the Use of Precision Medicine in Advanced Prostate Cancer

- 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 while minimising adverse events.

- Prostate-specific membrane antigen (PSMA) is an example of a phenotypic biomarker whose detection by positron emission tomography (PET) represents a potential phenotypic precision medicine approach.

References:
Most Recently, PSMA PET Has Emerged as an Example of a Sensitive and Specific Imaging Technique in Prostate Cancer

Radiotracers Used in Prostate Cancer Imaging (EU)

<table>
<thead>
<tr>
<th>Radiotracer</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>18F-FDG</strong></td>
<td>Widely available(^5)</td>
</tr>
</tbody>
</table>

**PSMA-targeting radiotracers**

<table>
<thead>
<tr>
<th>Radiotracer</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>68Ga-PSMA</strong></td>
<td>High specificity and sensitivity, even at low PSA levels(^2, 32, 33, d)</td>
</tr>
</tbody>
</table>

**References:**

PSMA as a Diagnostic, Prognostic, and Clinically Relevant Biomarker in Prostate Cancer
The Role of PSMA in Prostate Cancer
**PSMA Is a Transmembrane Protein That Is Highly Expressed in Prostate Cancer**

- PSMA is a transmembrane protein that is anchored in the cell membrane of prostate cells
- Despite the name, PSMA is not specific to the prostate gland and is found in:
  - Normal tissues: renal tubules, prostate epithelium, duodenum, and colon
  - Tumour-associated neovasculature: eg, renal, bladder, and colon
  - Prostatic tumour tissues: primary prostate, and lymph node and bone metastases
- However, PSMA is expressed at much higher levels in prostate cancer cells

**References:**
PSMA Is Highly Expressed in >80% of Men With Prostate Cancer\textsuperscript{1-5}

- PSMA is a transmembrane protein that is anchored in the cell membrane of prostate cells\textsuperscript{6,7}
- Ligand binding to the extracellular portion of PSMA enables detection or targeting of tumour cells\textsuperscript{8-14}
- Expression is significantly higher in tumour tissue compared to benign tissue\textsuperscript{1,4}
- Expression is associated with:
  - Higher tumour stage and positive nodal status\textsuperscript{1,4}
  - Metastatic disease\textsuperscript{1}
  - Disease progression\textsuperscript{15}
  - Disease recurrence\textsuperscript{1,4,16}

PSMA Is an Imaging Target in Prostate Cancer Due to Its High Expression in Malignant Tissues$^1$-$^7$

PSMA is highly expressed in prostate cancer cells, suggesting a large potential patient population that could be appropriate for PSMA imaging$^5$-$^12$

PSMA, prostate-specific membrane antigen.

$^1$PSMA expression was assessed by immunohistochemistry 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, and 52 benign prostatic samples from patients who underwent surgery for prostate cancer in the Hospital of Goeppingen, Germany between 2002 and 2014. An additional 78 distant metastases of patients who were treated at the University Hospital Schleswig-Holstein, Campus Luebeck, Germany, were included in the study. PSMA expression was categorised as no expression (score of 0), low expression (1), medium expression (2), or high expression (3).$^8$


Figure modified from Hupe MC et al. Front Oncol. 2018;8:623.
PSMA as a Diagnostic Biomarker in Prostate Cancer
PSMA Is a Sensitive and Specific Diagnostic Biomarker for Primary and Recurrent Prostate Cancer\textsuperscript{1,2}

**Meta-analysis\textsuperscript{1,a}**

PSMA PET trials assessing prediction of primary and recurrent prostate cancer

Per-patient sensitivity 86%

Per-patient specificity 86%

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**Head-to-head trial\textsuperscript{2,b}**

PET/CT with PSMA-based radiolabeled ligands or \textsuperscript{18}F-fluciclovine for localisation of biochemically recurrent disease after RP

Per-patient sensitivity

\textsuperscript{18}F-fluciclovine 33%

PSMA PET/CT 66% vs

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CT, computed tomography; PET, positron emission tomography; FACBC, fluciclovine; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy.

\textsuperscript{a}In a meta-analysis of 16 articles including 1309 patients, the sensitivity and specificity values were calculated for patients who underwent \textsuperscript{68}Ga-PSMA PET. Studies evaluating the utility of \textsuperscript{68}Ga-PSMA PET in detecting metastatic disease in advanced prostate cancer were included in the overall meta-analysis.\textsuperscript{1}

\textsuperscript{b}In a prospective, single-center, open-label comparative study, 50 adults with biochemical recurrence after radical prostatectomy and PSA levels 0.2 to 2.0 ng/mL received \textsuperscript{18}F-fluciclovine or PSMA-based PET/CT. The primary end point was identification of tumour locations, at the patient level and by anatomical region. Per-patient sensitivity was 33% (95\% CI, 15–58; five true positives and ten false negatives) for \textsuperscript{18}F-fluciclovine and 66\% (42–85; ten true positive and five false negative) for PSMA PET-CT (odds ratio, 3.6 [95\% CI, 0.67–34.5]; \textit{P}=0.18).\textsuperscript{2}

In the ProPSMA Study, PSMA PET/CT Was Superior to Conventional Imaging for Diagnosis of Metastases

- The ProPSMA study was a multicenter randomised controlled trial of men with high-risk apparently localised prostate cancer
- Three hundred two men were randomly assigned to receive either CT and bone scan (conventional imaging) or $^{68}$Ga PSMA-11 PET/CT
- PSMA PET/CT had 27% absolute greater area under the curve (AUC) for accuracy compared to 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 (AUC 91% vs 59% and 95% vs 74%, respectively)

Comparison of PSMA PET/CT and Conventional Imaging in 2 Men With Normal Conventional Imaging Results

Figure modified from Hofman MS et al. Lancet. 2020;395(10231):1208-1216.

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 (at baseline) and (B) multiple sub-cm pelvic and distant nodal metastasis. Six-month follow-up imaging is shown in (B) after systemic treatment and disease regression.

PSMA as a Prognostic Biomarker in Prostate Cancer
PSMA PET/CT Shows Utility As a Prognostic Biomarker

- PSMA PET/CT results have been associated with freedom from progression after salvage radiotherapy

PSMA PET Positivity Was More Independently Predictive of Freedom From Progression Than Established Clinical Factors

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95.0% CI for Exp(B)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>PSMA</td>
<td>2.73</td>
<td>1.45</td>
<td>5.14</td>
</tr>
<tr>
<td>PSA</td>
<td>1.17</td>
<td>0.82</td>
<td>1.68</td>
</tr>
<tr>
<td>T stage at RP</td>
<td>0.71</td>
<td>0.11</td>
<td>4.45</td>
</tr>
<tr>
<td>Gleason score</td>
<td>0.69</td>
<td>0.23</td>
<td>2.06</td>
</tr>
</tbody>
</table>

CT, computed tomography; Exp(B), exponentation of the B coefficient; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatatectomy; T, testosterone.

In a prospective multicenter study of 260 men with rising PSA following radical prostatectomy who were considered for salvage radiotherapy were enrolled. Median PSA was 0.26 ng/mL. Of the 90 men with negative PSMA PET, 32% did not receive treatment. Freedom from progression was defined as serum PSA remaining ≤0.2 ng/mL above the post salvage radiotherapy nadir, without either the initiation of androgen deprivation therapy or additional radiation therapy after completion of salvage radiotherapy.

Higher PSMA expression level, as detected by IHC on preoperative biopsy, was associated with shorter 5-year PSA recurrence-free survival. The 5-year PSA recurrence-free survival rates are 88.2%, 74.2%, 67.7%, and 26.8% for patients exhibiting no, low, medium or high PSMA expression on preoperative biopsy, respectively.

**PSMA as a Prognostic Biomarker Is Also Demonstrated by a Negative Association With 5-Year PSA Recurrence-Free Survival**

- Higher PSMA expression level, as detected by IHC on preoperative biopsy, was associated with shorter 5-year PSA recurrence-free survival

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

*PSMA expression was assessed in a retrospective study by 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). Disease recurrence was defined as biochemical recurrence (prostate-specific antigen increase above the postoperative nadir following radical prostatectomy) and used as the end point for survival analysis. Log rank P<0.001 by univariate analysis for PSMA negative vs PSMA high expression.

**Reference:** Hupe MC et al. *Front Oncol.* 2018;8:623.
PSMA as a Clinically Relevant Biomarker in Prostate Cancer
PSMA PET/CT Provides Clinically Relevant Insights to Guide Treatment Plans With a Tailored Approach\textsuperscript{1,2}

- In real-world studies and clinical trials of PSMA PET/CT, changes in management plans have been made after PSMA PET/CT\textsuperscript{1,2}
  - PSMA PET/CT contributed to management changes in up to 60% of patients\textsuperscript{1-3}
  - PSMA PET/CT results were used for metastasis-targeted treatment, and radiotherapy with or without systemic treatment was the most frequently selected option\textsuperscript{1}
  - Use of systemic therapy with or without local treatment was less frequent after PSMA PET/CT than it would have been according to guidelines (before PSMA PET/CT)\textsuperscript{1}

Change in Therapy Options With and Without PSMA PET/CT\textsuperscript{1,a}

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.

\textsuperscript{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 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 valued of at least 50% from baseline at the time of the scan representing a partial response.\textsuperscript{1}

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

PSMA Upregulates Several Key Oncogenic Pathways* and Is a Potential Therapeutic Target in Prostate Cancer

- PSMA has emerged as an attractive potential therapeutic target due to its role in several oncogenic signalling pathways
- PSMA has been linked with a number of pathways that promote oncogenic cell growth and tumour progression
- Expression of PSMA in the vasculature of some tumour types has been reported to be linked with worse survival

### References:

*In in vitro and animal studies.
Staging and risk-assessment

- Technetium bone scan and thoraco-abdominal CT scan or whole-body magnetic resonance imaging (MRI) or PSMA PET/CT
- Men with intermediate- or high-risk disease should have imaging for nodal or metastatic disease
- Whole-body MRI, choline PET/CT and PSMA PET/CT have better sensitivity and specificity than CT or bone scan
  - However, they have not been shown to improve clinical outcomes
  - Evidence regarding PET and whole-body MRI in this setting is not adequate to make a recommendation concerning their use

Treatment of relapse after radical local treatment

- Re-staging: for patients with biochemically recurrent prostate cancer, PSMA PET imaging is replacing conventional imaging, based on its superior sensitivity and specificity
  - Nevertheless, there are no trials indicating that the earlier detection of recurrence and subsequent change in management improves outcomes
  - The study of modern imaging methods has focused on their diagnostic performance, not their effect on care pathways

PSMA Is a Key Phenotypic Biomarker That May Facilitate the Use of Precision Medicine in Advanced Prostate Cancer

- PSMA is a diagnostic biomarker and potential therapeutic target, enabling a phenotypic precision medicine approach to help guide patient selection for therapy in advanced prostate cancer
  - Detection of a clinically relevant biomarker using a noninvasive imaging tool
  - Optimisation of patient selection to help inform management decisions
  - Utilisation of phenotypic precision medicine with the goal of improving outcomes