Objectives

1. Highlight why biomarkers are important in prostate cancer management
2. Identify key clinical scenarios where biomarkers offer the most relevance
3. Highlight some of the new tissue, blood, urine and image-based biomarkers
4. Describe the future of the next generation biomarkers
The role of PSA in prostate cancer management

- The Randomised Study of Screening for Prostate Cancer (ERSPC)
- The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)

Definitions

- Prognostic biomarker – provides information on the likely course of the disease in an untreated individual
- Predictive biomarker – can be used to identify subpopulations of patients who are most likely to respond to a given therapy


Brunner N. Connections 2009.
Key clinical scenarios for biomarkers in prostate cancer

- How do we distinguish aggressive disease from indolent disease in patients on active surveillance (AS)?
- How do we identify patients with localized prostate cancer who will benefit from radiation therapy post-radical prostatectomy?
- How do we select and sequence drugs for patients with castration-resistant prostate cancer (CRPC) in the context of several recently approved new agents?

Tissue-based gene signatures

- Myriad Genetics Prolaris Score™
- Genome Health OncotypeDx™ Genomic Prostate Score (GPS)
- GenomeDx Biosciences Decipher™
- NF-kB–activated recurrence predictor 21 (NARP21)
Myriad Genetics Prolaris Score™

- 31 to 46-gene RNA expression signature in formalin-fixed paraffin-embedded (FFPE) biopsy specimens
- Clinical Evidence
  - Predictor of biochemical relapse (BCR) after radical prostatectomy (RP) in 3 cohorts of CaP patients (n=582).
  - Predictor of BCR after external beam radiation therapy (EBRT) in 141 CaP patients.
  - Predictor of overall survival (OS) especially when combined CAPRA-S* score in 413 CaP patients.


Myriad Genetics Prolaris Score™

- Kaplan-Meier plots of biochemical progression-free probability by cell-cycle progression (CCP) scores (Prolaris Score™) grouped the subset of patients who were intermediate or high risk by clinical criteria defined by CAPRA-S score ≥ 3.
- With or without adjustment for clinical variables, increasing CCP score (Prolaris Score™), both as a continuous and categorized variable, was associated with markedly higher hazard ratios for progression (continuous HR 2.1, 95% CI 1.6-2.9, P<0.001).

CCP=cell-cycle progression score
Cooperberg MR. J Clin Oncol 2013.
Genome Health OncotypeDx™ Genomic Prostate Score (GPS)

- 17-gene RNA expression signature in FFPE biopsy specimens
- Clinical Evidence
  - Predictor of suitability for active surveillance in 441 RP and 562 biopsy specimens from men with low and intermediate risk.
  - In the same population the addition of GPS was shown to reclassify many men stratified to high risk based on CAPRA-S ≥6 alone. Patients with both high GPS and high CAPRA-S risk scores were at markedly elevated post-RP risk for lethal CaP.


Genome Health OncotypeDx™ Genomic Prostate Score (GPS)

- Cumulative incidence of prostate cancer–specific mortality (CSM) for the CAPRA-S high-risk stratified by genomic classifier (GPS).
- For patients with both high CAPRA-S and high genomic classifier (GPS) scores, the cumulative incidence of CSM was 45% at 10 yrs.

Cooperberg MR. Eur Urol 2014.
GenomeDx Biosciences Decipher™

- 22-gene RNA expression signature in FFPE RP specimens
- Clinical Evidence
  - Predictor of early metastasis in 545 high-risk RP patients.
  - Predictor of metastasis in 1010 high-risk RP patients.


GenomeDx Biosciences Decipher™

GenomeDx Biosciences Decipher™

• Clinical Evidence
  – Predictor of BCR and metastasis in 139 high-risk RP patients post-adjuvant radiation.
  – Predictor of early metastasis in 219 high-risk RP patients, especially when combined with CAPRA-S score.
  – Predictor of early metastasis in 85 men with BCR after RP.


GenomeDx Biosciences Decipher™

• Clinical Evidence
  – Decipher™ results affect decision making with respect to post-RP adjuvant radiation clinical utility testing.

Badani KK. BJU Int 2014.
NF-kB–activated recurrence predictor 21

- 21-gene signature in RP specimens
- Clinical Evidence
  - Predictor of metastasis-free and disease specific survival in previously publically archived dataset of 596 RP samples.


NF-kB–activated recurrence predictor 21

- Kaplan–Meier plot for the systemic metastasis-free survival of patients with prostate cancer who had lymph node metastasis at the time of RRP surgery.
- Survival analyses showed that the NF-kB signature predicts significant differences in the distant metastasis-free survival of the patients that had lymph node metastasis at the time of surgery (HR = 2.1; 95% CI, 1.0–4.3; P = 0.0324).

Tissue-based gene signatures

- The Prolaris Score™ and the OncotypeDx™ can be used in prostate biopsy tissue to identify adverse pathologic features that predict those patients who may benefit from active intervention rather than active surveillance. Prognostic.

- Decipher™, the Prolaris Score™ and the NF-kB signature have been designed to predict clinical outcome after radical prostatectomy. Prognostic.

- Decipher™ has been validated in multiple cohorts and has demonstrated potential to influence the clinical decision to recommend radiation post-radical prostatectomy.

Tissue-based gene signatures

- A critical consideration for tissue markers in prostate cancer is under sampling of the prostate with the risk of missing a more threatening tumour.

- All of these markers have been developed in retrospective studies. Optimal clinical validation to prove clinical utility will require prospective clinical trials.

- Cost may be a factor in decision making.
Tissue-based gene signatures

<table>
<thead>
<tr>
<th>Tissue-based gene Signature</th>
<th>Prolaris Score™</th>
<th>Oncotype Dx™ GPS</th>
<th>GenomeDx Decipher™</th>
<th>NF-kB gene signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per patient (US)</td>
<td>$3400</td>
<td>$3800</td>
<td>$4250*</td>
<td>-</td>
</tr>
</tbody>
</table>

Blood-based biomarkers

- microRNA
- cell-free DNA
- Circulating tumour cells
microRNA

- Small noncoding RNAs found in tissue and serum samples that are involved in post-transcriptional regulation of a large number of biological processes.


microRNA

Disease progression

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Active Surveillance</th>
<th>Localized Prostate Cancer</th>
<th>CRPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum miR-141 is associated with higher GS in 170 patients undergoing prostate biopsy.</td>
<td>A serum signature of 2-3 differentially expressed miRs had a high positive predictive value for biochemical failure in 105 CaP patients at time of RP.</td>
<td>Serum miR-375, miR-141 are significantly overexpressed in 30 high risk localized CaP patients and 26 metastatic CRPC patients.</td>
<td>Higher serum miRNA signature is associated with worse outcome on docetaxel chemotherapy in 97 CRPC patients.</td>
</tr>
<tr>
<td>Serum miR-16 levels is useful in discriminating CaP from BPH in 47 patients undergoing biopsy.</td>
<td>Serum miR-182 expression is associated with biochemical and clinical progression free survival in various samples (60 RP, 273 biopsies, and 92 urine) from CaP patients.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In serum higher miR levels are correlated with CaP diagnosis in a series of patients (78 with CaP and 28 without CaP).</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cell-free DNA

- Small amounts of cell-free DNA in plasma, which likely originates from cancer cells and, therefore, might constitute source of genetic material for the identification of tumour-associated molecular alterations.

Sample
dying tumour cells release small pieces of their DNA into the bloodstream known as cell-free DNA

screening cell-free DNA for somatic mutations can be used to detect and follow the progression of a patient's tumour


Cell-free DNA

Disease progression

<table>
<thead>
<tr>
<th>Diagnosis</th>
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</tr>
</thead>
<tbody>
<tr>
<td>- There was a significant differences in cell-free DNA levels in CaP versus BPH patients.</td>
<td>- A significantly shorter biochemical recurrence free survival is associated with at least one value above 140ng/mL of cell-free DNA in 133 patients with CaP as compared to 33 controls.</td>
<td>- The presence of the androgen receptor (AR) gene aberration in cell-free DNA is correlated with radiographic and clinical disease progression on enzalutamide (AR directed therapy).</td>
<td>- The detection of AR gain and AR L702H mutation in cell-free DNA is associated with resistance to abiraterone.</td>
</tr>
<tr>
<td>- Higher cell-free DNA levels are significantly correlated with tumour stage and category in 81 CaP patients.</td>
<td></td>
<td>- A mutation in F876L detected in cell-free DNA was associated with resistance to novel drug ARN-509.</td>
<td></td>
</tr>
</tbody>
</table>

Circulating tumour cells (CTCs)

- Rare circulating cancer cells in the peripheral blood that may have an important role in tumour dissemination and progression.

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Circulating tumour cells

**Disease progression**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Active Surveillance</th>
<th>Localized Prostate Cancer</th>
<th>CRPC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CTC detection is rare in 12 patients with localized CaP.</td>
<td>Unfavorable pretreatment CTC counts are predictive of shorter overall survival in 231 patients with progressive CRPC patients.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CTC CD117 levels decrease after radical prostatectomy and increase again in patients who have biochemical recurrence.</td>
<td>Baseline CTC counts are well correlated with overall survival in 100 patients with CRPC.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Higher CTC counts are associated with overall survival in 57 patients treated with docetaxel.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High CTC counts are associated with high risk of death in 276 patients with metastatic CaP (IMMC38 trial).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Higher CTC counts were observed in patients with bone metastasis relative to those with soft tissue disease (n=120 patients with CRPC).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CTC with AR-V7 positivity are associated with lower PSA response rates, shorter PSA progression free survival and shorter overall survival in 31 CRPC enzalutamide-treated patients and 31 CRPC abiraterone-treated patients.</td>
</tr>
</tbody>
</table>

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CTCs - limitations

- The major limitation impacting the clinical utility of CTCs is not having sufficient DNA capture due to low CTC numbers in biological samples.
- Current platforms can also be limited by their selectivity and ability to extract the separated cells.
- New technologies are being validated to overcome this shortcoming.

Platforms for the capture of CTCs

<table>
<thead>
<tr>
<th>EpCAM-affinity based</th>
<th>CellSearch® system</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdnaTest BreastCancerDetect</td>
<td></td>
</tr>
<tr>
<td>CTC-Chip</td>
<td></td>
</tr>
<tr>
<td>Dynal®</td>
<td></td>
</tr>
<tr>
<td>MACS®</td>
<td></td>
</tr>
<tr>
<td>MagSweeper</td>
<td></td>
</tr>
<tr>
<td>On-Q®-ity</td>
<td></td>
</tr>
<tr>
<td>CTC-ETI</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical properties-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISET</td>
</tr>
<tr>
<td>ScreenCell®</td>
</tr>
<tr>
<td>ApoStream™</td>
</tr>
<tr>
<td>Density Gradient Centrifugation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAST</td>
</tr>
<tr>
<td>EPISPOT</td>
</tr>
<tr>
<td>Flow cytometry (FACS)</td>
</tr>
<tr>
<td>PRO Onc Assay</td>
</tr>
</tbody>
</table>

Blood-based biomarkers

- microRNA can be used to predict outcome in patients on docetaxel chemotherapy. **Prognostic and Predictive.**

- cell-free DNA can be used to predict resistance to enzalutamide, abiraterone and ARN-509. **Predictive.**

- CTCs can be used to prognosticate disease and predict response to enzalutamide and abiraterone. **Prognostic and Predictive.**
Blood-based biomarkers

- Blood-based biomarkers have the potential to overcome the inherent heterogeneity of CaP and capture the tumour characteristics in their entirety.

- Blood-based biomarkers fulfill the goal of a “liquid biopsy”, enabling non-invasive, real-time monitoring of disease status and response to therapy, especially in the context of metastatic CRPC.

- Using blood-based biomarkers we are able to monitor molecular changes in response to therapy. Thus we are able to monitor drug targets and guide corresponding alterations in therapy; the essence of precision oncology.

Urine-based biomarkers

- PCA3
- TMPRSS2-ERG
- Metabolin Prostarix™
PCA3

• CaP-specific gene located on chromosome 9q21-22 that can be detected in urine samples.

• Clinical Evidence
  – The urine PCA3 assay demonstrated a sensitivity of 69% and specificity of 79% for predicting CaP diagnosis in 143 men undergoing biopsy.


PCA3

• Clinical Evidence
  – Urine PCA3 levels were predictive of those patients who need a repeat biopsy in men who have elevated PSA and a prior negative biopsy.

  – For biopsy-naïve patients, a high PCA3 level increases the probability that an initial prostate biopsy will identify cancer.

  – Higher urine PCA3 levels are associated with higher volume CaP and high-grade disease in 387 men on an active surveillance protocol.

TMPRSS2-ERG

• Gene fusion involving the 5’ untranslated region of the androgen-regulated gene TMPRSS2 with ERG or ETV1 that can be detected in urine samples.

• Clinical Evidence
  – TMPRSS2-ERG detection has yielded a specificity of 93% and a positive predictive value of 94% for the diagnosis of CaP in 78 men with PSA >3ng/mL and/or abnormal DRE.


TMPRSS2-ERG

• Clinical Evidence
  – TMPRSS2-ERG detection independently predicted Gleason score and clinical tumour stage in 497 men undergoing biopsy.
  – TMPRSS2-ERG score is associated with higher volume CaP and high-grade disease in 387 men on an active surveillance protocol.

Metabolin Prostarix™

• Four metabolite signature detected in urine by liquid chromatography mass spectrometry.

**Disease progression**

<table>
<thead>
<tr>
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<th>CRPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>−Biopsy Prostarix™ score was associated with increased risk of CaP in 1122 patients.</td>
<td></td>
<td>−RP Prostarix™ score was associated with disease free survival rates in 148 CaP patients.</td>
<td>−Urine Prostarix™ score was associated with metastases in patients with CaP (bone metastases n=20, normal bone n=14, malignant prostate tissue n=13, benign prostate tissue n=17 and plasma samples n=15).</td>
</tr>
</tbody>
</table>


Urine-based biomarkers

• The PCA3 assay can be used to predict need for repeat biopsy in men who have elevated PSA and a prior negative biopsy. **Prognostic.**

• The Prostarix™ score can be used to stratify the risk of a patient with previous negative biopsy for occult cancer. **Prognostic.**

• The Prostarix™ score can be used to predict for disease free survival and metastasis. **Prognostic.**
Urine-based biomarkers

• Urine-based biomarkers are available in large quantities and can be collected non-invasively.
• Urine-based biomarkers are particularly attractive when the prostate is intact, especially in the setting of screening and early stage disease.

Image-based biomarkers

• MRI
• PET/CT
### MRI

#### Disease progression

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Active Surveillance</th>
<th>Localized Prostate Cancer</th>
<th>CRPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI can help guide repeat biopsy in patients with previously negative biopsy and elevated PSA.</td>
<td>MRI is important in staging with reduction in the risk of missing occult higher-risk disease.</td>
<td>MRI is used to assess for extraprostatic extension prior to radical prostatectomy.</td>
<td>MRI predicted biochemical relapse after radical prostatectomy and metastatic disease progression.</td>
</tr>
</tbody>
</table>


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### MRI

MRI images of a 76M with four negative biopsies and a PSA of 329.

## PET/CT

**Disease progression**

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<th>Localized Prostate Cancer</th>
<th>CRPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET has not proven useful in differentiating biopsy-proven CaP from BPH.</td>
<td></td>
<td></td>
<td>–(11)C-choline PET/CT before salvage radiation therapy during the early phase of biochemical relapse helps select patients who may benefit from this aggressive treatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>–18F-fluorocholine PET/CT may be utilized in biochemical relapse of prostate cancer after radical treatment, with an overall disease detection rate close to 50%.</td>
</tr>
</tbody>
</table>


#### Image-based biomarkers

- MRI provides clinical utility in diagnosis, active surveillance, localized prostate cancer and CRPC settings in conjunction with other biomarkers.

- PET may provide clinical utility in the CRPC setting.
Image-based biomarkers

• Utilization of MRI for quantitative image analysis is a novel concept that is in the early stages of development:

• Quantitative image analysis can also be used to measure tumour response to therapy, which in turn can guide clinical decision-making.

Key clinical scenarios for biomarkers in prostate cancer

• How do we distinguish aggressive disease from indolent disease in patients on active surveillance (AS)?

• How do we identify patients with localized prostate cancer who will benefit from radiation therapy post-radical prostatectomy?

• How do we select and sequence drugs for patients with CRPC in the context of several recently approved new agents?
Diagnosis

- Blood-based microRNA and cell-free DNA can be used to discriminate CaP from BPH. **Prognostic.**

- Urine PCA3 can prognosticate need for repeat biopsy in men who have elevated PSA and a prior negative biopsy. **Prognostic.**

- Urine Prostarix™ can stratify risk of occult cancer in men with previous negative biopsy. **Prognostic.**

Active Surveillance

- Tissue-based gene signatures (e.g. Prolaris Score™, OncotypeDx™) can identify patients on active surveillance who may harbor occult higher-risk disease warranting definitive intervention. **Prognostic.**

- Image-based MRI can help focus repeat biopsy on specific prostatic lesions. **Prognostic.**
Localized Prostate Cancer

- Tissue-based gene signatures (e.g. Decipher™) can predict recurrence and progression after RP and help determine if the patient may benefit from adjuvant radiation therapy. **Prognostic.**

- Blood-based microRNA can predict biochemical and clinical progression. **Prognostic.**

- Blood-based cell-free DNA can predict biochemical recurrence. **Prognostic.**

CRPC

- Blood-based microRNA can predict outcome on docetaxel chemotherapy. **Prognostic and Predictive.**

- Blood-based cell-free DNA can predict resistance to enzalutamide, abiraterone and ARN-509. **Predictive.**

- Blood-based circulating tumour cells can prognosticate disease progression and predict response to enzalutamide and abiraterone. **Prognostic and Predictive.**

- Urine Prostarix™ score can prognosticate for metastases. **Prognostic.**

- Image-based MRI, PET/CT can predict for biochemical relapse. **Prognostic.**
The Future of Biomarkers in Prostate Cancer

• Future technology must focus on improving biomarker assay robustness.

Detection of tumor cells in blood

High sensitivity + Diagnostic specificity = High potential clinical impact

Screening → Diagnosis → Prognosis → Therapeutic efficacy → Disease progression

Potential for reducing mortality 100% 0%


The Future of Biomarkers in Prostate Cancer

• With the novel agents arising in the management of CRPC disease the use of easily accessible urine and blood-based biomarkers will bloom.

• The development of microRNA, cell-free DNA and CTCs technologies for urine and blood samples will be instrumental to predicting specific therapy outcome and optimizing sequential use of these novel agents in the treatment of patients with CRPC.
The Future of Biomarkers in Prostate Cancer

• Two significant barriers:
  – the need for careful clinical validation,
  – the associated costs to the system.

• Incorporating of these biomarkers into ongoing and future clinical trials will be essential in developing and implementing them in clinic.

---

Clinical Validation

<table>
<thead>
<tr>
<th>Phases:</th>
<th>Phase 1 Preclinical Exploratory</th>
<th>Phase 2 Clinical Characterization &amp; Assay Validation</th>
<th>Phase 3 Clinical Association: Retrospective Repository studies</th>
<th>Phase 4 Clinical Association: Prospective Screening studies</th>
<th>Phase 5 Disease control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>Target Biomarker Identification, Feasibility</td>
<td>Study assay in people with &amp; without disease</td>
<td>Case-control studies using repository specimens</td>
<td>Longitudinal studies to predict disease</td>
<td>Clinical use</td>
</tr>
<tr>
<td>Site</td>
<td>Biomarker Development Lab</td>
<td>Biomarker Validation Lab</td>
<td>Clinical Epidemiologic Centers</td>
<td>Cohort Studies</td>
<td>Community</td>
</tr>
<tr>
<td>Design</td>
<td>Cross-sectional</td>
<td>Cross-sectional</td>
<td>Case-control</td>
<td>Prospective</td>
<td>RCT</td>
</tr>
<tr>
<td>Sample Size</td>
<td>Small</td>
<td>Small</td>
<td>Modest</td>
<td>Medium</td>
<td>Large</td>
</tr>
<tr>
<td>Validity</td>
<td>Content &amp; construct validity</td>
<td>Criterion validity</td>
<td>Predictive validity</td>
<td>Efficacy of strategy</td>
<td>Effectiveness</td>
</tr>
<tr>
<td>Result</td>
<td>Assay precision, reliability, sensitivity</td>
<td>Reference limits, intra-individual variation</td>
<td>Screening characteristics, true &amp; false rates</td>
<td>ROC analyses</td>
<td>No-needed to screen/treat</td>
</tr>
</tbody>
</table>

Associated Costs

- **Tissue**
  
<table>
<thead>
<tr>
<th>Tissue-based gene Signature</th>
<th>Prolaris Score™</th>
<th>OncotypeDx™ GPS</th>
<th>GenomeDx Decipher™</th>
<th>NF-κB gene signature</th>
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<tr>
<td>Cost per patient (US)</td>
<td>$3400</td>
<td>$3800</td>
<td>$4250*</td>
<td>-</td>
</tr>
</tbody>
</table>

- **Blood**
  - CTCs $337.74 assay + $35.11 interpretation fee (Medicare Fee; covered in roughly half of the US)

- **Urine**
  - PCA3 $385

- **Image**
  - ?

The Future of Biomarkers in Prostate Cancer

- Two significant barriers:
  - the need for careful clinical validation,
  - the associated costs to the system.

- Incorporating of these biomarkers into ongoing and future clinical trials will be essential in developing and implementing them in clinic.
Acknowledgements

• Dr. Peter Black
• Dr. Richard Wassersug

Definitions

• **Accuracy** - The degree of agreement between the results of a measurement and the true value of the measurement.

• **Precision** - The degree of agreement between independent test results obtained under stipulated conditions.

• **Clinical (diagnostic) sensitivity** - The proportion of patients with a well-defined clinical disorder whose test values are positive or exceed a defined decision limit.

• **Clinical (diagnostic) specificity** - The proportion of patients who do not have a specified clinical disorder whose test results are negative or within the defined decision limit.

Definitions

- **Effectiveness** - The use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results in a significant portion of the target population.

- **Safety** - The probable benefit to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, will outweigh any probable risk.


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**The Cancer Biomarker Testing Market**

The increasing complexity of cancer tests in both execution and interpretation will result in more advanced testing facilities, such as key hospitals, cancer research centers, and specialized cancer testing laboratories. It’s expected that cancer patient management in the future will become analogous to chronic disease management, a key to the continued growth of the cancer biomarker testing industry.

**U.S. Cancer Biomarker Testing Market Value**

*Projected, billions USD*

<table>
<thead>
<tr>
<th>Year</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>$7.86</td>
</tr>
<tr>
<td>2017</td>
<td>$11.46</td>
</tr>
</tbody>
</table>
Relationship between biomarker publications and patents

![Graph showing relationship between biomarker publications and patents.]

Table 1

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Related drug</th>
<th>Indication</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Her-2/neu</td>
<td>Herceptin</td>
<td>Breast cancer</td>
<td>Path/Vyslony/RTSH</td>
</tr>
<tr>
<td>KR (CD117)</td>
<td>Gleevec/Glivec</td>
<td>Gastrointestinal</td>
<td>c-Kit pharmDX</td>
</tr>
<tr>
<td>EGFR</td>
<td>Eribulin/Tarceva</td>
<td>Colorectal/NSCLC</td>
<td>EGFR pharmDX NR</td>
</tr>
<tr>
<td>CD20</td>
<td>Rituxan/Bexar</td>
<td>NHL</td>
<td>Flow cytometry</td>
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<td>CD25</td>
<td>Ontak/Ozar</td>
<td>Lymphoma</td>
<td>Flow cytometry</td>
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<tr>
<td>CD3</td>
<td>Mylotarg</td>
<td>Leukaemia, CML</td>
<td>Flow cytometry</td>
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<td>Nolvadex</td>
<td>Breast cancer</td>
<td>Hormone receptor assay</td>
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<td>Maladine</td>
<td>Melanoma</td>
<td>Serology, DNA-based</td>
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<td>Philadelphia chromosome</td>
<td>Referon-A/Gleevec/Glivec</td>
<td>Leukaemia, CML</td>
<td>BCR-ABL chromosome translocation test</td>
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<td>T(15;17) translocation</td>
<td>Tibranex</td>
<td>Leukaemia, CML</td>
<td>Fluorescence in situ hybridisation (FISH)</td>
</tr>
<tr>
<td>PML/RAR α gene expression</td>
<td>Vesnonoid</td>
<td>Leukaemia, CML</td>
<td></td>
</tr>
</tbody>
</table>


Drucker E. Genome Medicine 2013.
A prognostic DNA signature for prostate cancer

Multivariate Cox proportional hazard model adjusting for clinical covariates (Gleason score and pretreatment PSA) in the low-risk and intermediate-risk groups (A) and when applied to the full pooled radical prostatectomy cohort (n=271) the signature for copy number alteration identifies patients who will fail rapidly (B).

Lalonde E. Lancet Oncology 2014.