The Evolution of Companion Diagnostics from Signal Transduction to Immuno-Oncology

Nicholas C. Dracopoli, Ph.D.
Vice President, Head Oncology Diagnostics
Janssen R&D
Companion Diagnostics Forum
Princeton, NJ
December 6, 2017
The Biomarker Paradox

There are >80,000 biomarkers listed in GOBIOM database (4/4/2016)

but

only 29 FDA approved drugs with a CoDx

and only

3 are multiplex IVDs based on genomic profiles that predict response to therapy

~4 biomarkers for every gene in the human genome?

Why so few?

Why not more?
Probability of Successful Transition from Ph1 to Regulatory Approval for All Therapeutic Areas

- **25.9%** with a predictive biomarker
- **8.4%** without a predictive biomarker

Predicting Response to Therapy

Biomarker hypothesis:
• Simple target status marker
• Complex molecular profile

Correlative data:
• Multiple variables for correlation to clinical endpoints

Consistent endpoints:
• RR ≠ PFS ≠ OS

Sample size—Driven by data complexity to accommodate multiple testing:
• 1 training set
• ≥2 independent test sets
Oncology Drug Approvals Since Herceptin

Trends in Pharmacological Sciences

Dracopoli & Boguski, TIPS 38:41-54, 2017
## Multiplex CDx Tests Approved by the FDA in 2017

<table>
<thead>
<tr>
<th>Test</th>
<th>Genes</th>
<th>MSI</th>
<th>TMB</th>
<th>Drugs</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncomine Dx Target Test</td>
<td>23</td>
<td>No</td>
<td>No</td>
<td>3</td>
<td>NSCLC</td>
</tr>
<tr>
<td>F1CDx</td>
<td>324</td>
<td>Yes</td>
<td>Yes</td>
<td>15</td>
<td>NSCLC, Melanoma, Breast, Colorectal, Ovarian</td>
</tr>
<tr>
<td>MSK-IMPACT</td>
<td>468</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Common Features for Successful CDx

- Strong biomarker hypothesis
  - Large effect size for predictive biomarker
- Predictive marker test available in very early development:
  - Phase I extension or Phase II
- Single analyte test using established Dx technology:
  - PCR
  - Sequencing
  - Immunohistochemistry (IHC)
  - Fluorescent in situ hybridization (FISH)
- Dx platform must be globally available in all markets where the drug will be sold
Paradigm Shift Towards Immuno-Oncology

- Emerging proof of concept that the immune system can eradicate advanced metastatic cancers in a subset of patients
- New focus on increasing proportion of patients with long-term survival benefits
- Need to change biomarker strategy to identify these patients

Nivolumab

Brahmer et al at NEJM 2015
## Predictive Biomarkers for Different Drug Types

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Targeted</th>
<th>Immuno-Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved CoDx</td>
<td>0</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>Driver mutations</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug classes with CoDx</td>
<td>None</td>
<td>Mostly tyrosine kinase inhibitors</td>
<td>Checkpoint inhibitor</td>
</tr>
<tr>
<td>Drug targets</td>
<td>All rapidly dividing cells</td>
<td>Tumor cells with targeted MOA</td>
<td>Immune cells</td>
</tr>
</tbody>
</table>
| Mechanism of action            | • DNA synthesis  
• Microtubule function | • Signal transduction  
• DNA repair deficiency | • ADCC  
• Checkpoint inhibitors  
• Cancer vaccines  
• T-cell redirection  
• ex vivo modified T-cells |
Key Cdx Decisions

- Driver mutation
  - SOC
  - SOC + TKi

- Prior Immune Response
  - Checkpoint Inhibitor
  - Prime new immune response

Targeted Therapies

Immuno-Oncology Therapies
Biomarker Strategy for Immuno-Oncology Therapies

- Determine if there has been a prior suppressed immune response:
  - Release that response
  - Prime a new immune response
  - Modify T-cells to drive a response

- DNA testing for driver mutations is insufficient

- Need to use molecular, cellular and protein assays to monitor immune response

Prior Immune Response to the Tumor

Yes

Release inhibited immune response:
- Checkpoint inhibitor(s)

No

Prime new immune response:
- Vaccine
- T-cell redirection
- Ex vivo modification of T cells (CART etc)
Predicting response to checkpoint inhibitors in tumors with a suppressed immune response

**Biomarker Objective**
- Determine if there is evidence of a prior suppressed immune response

**Biomarker Assays**
- High clonal T-cell infiltration in the tumor
- PD-L1 expression in the tumor
- Mutation burden
- Neoantigen clonality
- Neoantigen presentation by MHC
Checkpoint Inhibitors

Deactivated T-cell

Activated T-cell

Predicting Response to Checkpoint Inhibitors

1. Ligand expression
2. T-cell clonality
3. Tumor mutation burden


Tumeh et al., Nature 515:568-571, 2014
Clinical response to Pembrolizumab Treatment

- Mismatch-repair status predicts response to checkpoint inhibitor
- Mismatch-repair deficient tumors ($\bar{x} = 1,782$) harbor >20-fold more mutations than mismatch repair proficient tumors ($\bar{x} = 73$)
- High somatic mutation loads are associated with extended PFS in patients treated with a checkpoint inhibitor

Le et al., NEJM 372:2509-2520, 2017
Clinical Benefit of Pembrolizumab Treatment According to Mismatch Repair Status

Le et al., NEJM 372:2509-2520, 2017
Predicting response to checkpoint inhibitors in tumors without a suppressed immune response

Biomarker Objectives

- Find alternative approach to prime or boost a novel immune response to the tumor

Biomarker Assays:

- Presence of epitopes for cancer vaccines
- Cell surface protein expression for targets for T-cell redirection
- Cell surface proteins for antibody or cellular cytoxicity
Antibody Mediated Cellular Cytotoxicity


https://upload.wikimedia.org/wikipedia/commons/0/09/Antibody-dependent_cell-mediated_cytotoxicity.png
T-cell Redirection

**Null Control**

**JNJ Duobody**

Staining for CD8+ cells

IHC images from JD Alvarez, Janssen Oncology
Cancer Vaccines

- Biomarkers for cancer vaccines will need to identify tumors expressing the targeted vaccine epitope.

HER2 expression in breast cancer
Conclusions

• Immuno-oncology drugs will require more complex biomarker tests
  • NGS or PCR for driver mutations are insufficient
• Need to measure the interaction of the immune system and the tumor
  • Cell and protein assays will be required in addition to NGS and PCR
• Complex molecular profiles are required to predict immune response
  • Single analyte tests are insufficient to deconvolute complex biological interactions
• Clinical strategies need to change to allow for development of more complex biomarker hypotheses
• Biomarker assay development needs to be started earlier to allow for routing co-development of drugs with companion diagnostics