Learning from the Impact of the Drug-Diagnostics Strategy in Oncology

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Disclosures: Jan Trøst Jørgensen has worked as a consultant for Dako, Agilent Technologies and Euro Diagnostica and has given lectures at meetings sponsored by AstraZeneca, Merck Sharp & Dohme, and Roche.
Drug-Diagnostics Co-development in Oncology

- Introduction and History
- Companion Diagnostics and Assay Technologies
- Drug-Diagnostic Co-development Model
- What can be achieved?
- Summary and Conclusion
# Tuberculosis & Cancer

<table>
<thead>
<tr>
<th><strong>Similarities</strong></th>
<th></th>
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<tbody>
<tr>
<td>Major global public health concern</td>
<td></td>
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<tr>
<td>High unmet medical needs</td>
<td></td>
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<tr>
<td>Drug susceptibility testing</td>
<td></td>
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<td>Drug resistance</td>
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<table>
<thead>
<tr>
<th><strong>Differences</strong></th>
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<tbody>
<tr>
<td>Etiology and pathophysicsology</td>
<td></td>
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<tr>
<td>Global incidences</td>
<td></td>
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<tr>
<td>Pharmaceutical companies’ interest</td>
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<tr>
<td>The availability of new drugs</td>
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</table>
Disease Heterogeneity

“In order to achieve a more effective pharmacotherapy we need to recognize that most diseases are heterogeneous and thus develop drugs accordingly.”

“A high degree of correlation between response and positive estrogen-receptor assay suggests the value of the diagnostic test as a means to select patients for tamoxifen treatment”


A CDx assay is an in vitro diagnostics device that provides information that is essential for the safe and effective use of a corresponding therapeutic product:

1. Identify patients who are most likely to benefit from the therapeutic product
2. Identify patients likely to be at increased risk as a result of treatment with the therapeutic product risk for serious adverse reactions
3. Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness
4. Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population

Companion Diagnostics in Oncology
The Current FDA Approved Assay Technologies

- **Immunohistochemistry (IHC)**
  - HercepTest (Dako/Agilent) – *Drugs: Trastuzumab, Pertuzumab, Ado-trastuzumab emtansine*
  - PD-L1 IHC 22C3 pharmDx (Dako/Agilent) – *Drug: Pembrolizumab*

- **In Situ hybridization (FISH/CISH)**
  - PathVysion *HER-2* DNA Probe Kit (Abbott Molecular) – *Drug: Trastuzumab*
  - Vysis *ALK* Break Apart FISH Probe Kit (Abbott Molecular) – *Drug: Crizotinib*

- **Real-time Polymerase Chain Reaction (RT-PCR)**
  - Therascreen *EGFR* RGQ PCR Kit (Qiagen) – *Drug: Gefitinib*
  - Cobas *EGFR* Mutation Test v2 (Roche Molecular Diagnostics) – *Drug: Osimertinib*

- **DNA sequencing/Next-Generation Sequencing (NGS)**
  - FoundationFocus CDxBRCA Assay (Foundation Medicine) – *Drug: Rucaparib*

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1. US FDA. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Updated: December 22, 2016. ([http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm](http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm)).
Drug-Diagnostic Codevelopment

Phase I to III Clinical Development\(^1,2\)

**Drug Development**

- Discovery Research
- Pre-clinical
- Clinical Phase I
- Clinical Phase II
- Clinical Phase III
- Regulatory Approval
- Post Approval Phase

**CDx Development**

- Biomarker Selection
- Feasibility Studies
- Prototype Assay(s)
- Analytical Validation
- Clinical Validation & Utility
- Regulatory Approval
- Post Approval Phase

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Drug-Diagnostic Co-development

Enrichment Design\(^1,2\)

Drug-Diagnostic Combinations

Regulatory Approval – Efficacy Data

# Drug-Diagnostic Combinations

## Objective Response Rates – Oncology

### Table 1. Objective response rates for anticancer drugs with and without a CDx assay linked to their use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>CDx Assay(s)</th>
<th>Platform</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab (Perjeta)</td>
<td>Breast cancer (HER2+)</td>
<td>HercepTest (Dako)/HER2 IQFISH pharmDx (Dako)</td>
<td>IHC/FISH</td>
<td>80.2%</td>
</tr>
<tr>
<td>Crizotinib (Xalkori)</td>
<td>NSCLC (ALK+)</td>
<td>Vysis ALK Break Apart FISH probe kit (Abbott)</td>
<td>FISH</td>
<td>65.0%</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>NSCLC (EGFR+)</td>
<td>Cobas EGFR mutation test (Roche)</td>
<td>PCR</td>
<td>65.0%</td>
</tr>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>Colorectal cancer (EGFR+/KRAS)</td>
<td>EGFR pharmDx (Dako)/KRAS RGQ PCR kit (Qiagen)</td>
<td>IHC/PCR</td>
<td>57.0%</td>
</tr>
<tr>
<td>Ceritinib (Zykadia)</td>
<td>NSCLC (ALK+)</td>
<td>Vysis ALK Break Apart FISH probe kit (Abbott)</td>
<td>FISH</td>
<td>54.6%</td>
</tr>
<tr>
<td>Imatinib Mesylate (Gleevec)</td>
<td>GIST (CD117+)</td>
<td>c-Kit pharmDx (Dako)</td>
<td>IHC</td>
<td>53.9%</td>
</tr>
<tr>
<td>Dabrafenib (Tafinlar)</td>
<td>Melanoma (BRAF+)</td>
<td>ThxID BRAF kit (BioMérieux)</td>
<td>PCR</td>
<td>52.0%</td>
</tr>
<tr>
<td>Afatinib (Gilotrif)</td>
<td>NSCLC (EGFR+)</td>
<td>EGFR RGQ PCR kit (Qiagen)</td>
<td>PCR</td>
<td>50.4%</td>
</tr>
<tr>
<td>Vemurafenib (Zelboraf)</td>
<td>Melanoma (BRAF+)</td>
<td>Cobas 4800 BRAF V600 mutation test (Roche)</td>
<td>PCR</td>
<td>48.4%</td>
</tr>
<tr>
<td>Ado-trastuzumab emtansine (Kadcyla)</td>
<td>Breast cancer (HER2+)</td>
<td>HercepTest (Dako)/HER2 IQFISH pharmDx (Dako)</td>
<td>IHC/FISH</td>
<td>43.6%</td>
</tr>
<tr>
<td>Olaparib (Lynparza)</td>
<td>Ovarian cancer (BRCA+)</td>
<td>BRACAnalysis CDx (Myriad)</td>
<td>PCR</td>
<td>34.0%</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Colorectal cancer</td>
<td>No CDx</td>
<td>–</td>
<td>45.0%</td>
</tr>
<tr>
<td>Ixabepilone (Ixempra)</td>
<td>Breast cancer</td>
<td>No CDx</td>
<td>–</td>
<td>34.7%</td>
</tr>
<tr>
<td>Paclitaxel protein-bound particles (Abraxane)</td>
<td>NSCLC</td>
<td>No CDx</td>
<td>–</td>
<td>33.0%</td>
</tr>
<tr>
<td>Pemetrexed (Alimta)</td>
<td>NSCLC</td>
<td>No CDx</td>
<td>–</td>
<td>27.1%</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>Melanoma</td>
<td>No CDx</td>
<td>–</td>
<td>24.0%</td>
</tr>
<tr>
<td>Ziv-aflibercept (Zaltrap)</td>
<td>Colorectal cancer</td>
<td>No CDx</td>
<td>–</td>
<td>19.8%</td>
</tr>
<tr>
<td>Cabazitaxel (Jevtana)</td>
<td>Prostate cancer</td>
<td>No CDx</td>
<td>–</td>
<td>14.4%</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>Thyroid carcinoma</td>
<td>No CDx</td>
<td>–</td>
<td>12.0%</td>
</tr>
<tr>
<td>Eribulin mesylate (Halaven)</td>
<td>Breast cancer</td>
<td>No CDx</td>
<td>–</td>
<td>11.0%</td>
</tr>
<tr>
<td>Ipilimumab (Yervoy)</td>
<td>Melanoma</td>
<td>No CDx</td>
<td>–</td>
<td>10.9%</td>
</tr>
<tr>
<td>Sunitinib malate (Sutent)</td>
<td>GIST</td>
<td>No CDx</td>
<td>–</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

2. Drugs@FDA: FDA Approved Drug Products. (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).
Success Rates in Oncology Drug Development
Melanoma and NSCLC\textsuperscript{1,2,3}

Cumulative success rates

Drugs without CDx  \hspace{1cm} Drugs with CDx

\begin{itemize}
\item Melanoma:
  \begin{itemize}
  \item 6%\textsuperscript{1}
  \item 11%\textsuperscript{2}
  \end{itemize}
\item NSCLC:
  \begin{itemize}
  \item 62%\textsuperscript{3}
  \item 47%\textsuperscript{2}
  \end{itemize}
\end{itemize}

Cost of Drug Development
Traditional vs Drug-Diagnostic Strategy\textsuperscript{1,2}

Summary and Conclusion

• Today 20 anticancer drugs have a CDx linked to their use
• Key requirements for CDx assay development:
  – Strong biomarker hypothesis
  – Analytical validity
  – Clinical validated and demonstrated clinical utility
• The drug-diagnostic co-development model:
  – Increased drug efficacy in the target population
  – Increased development success rate
  – Reduction of cost and time
• Can the drug-diagnostic strategy used in oncology be translated into other disease areas?
Companion diagnostics—a tool to improve pharmacotherapy

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1De Re Instituttet, Rosensvangen 76, DK-4490 Frederiksberg, Denmark; 2Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen, Denmark.

Abstract: The variability of pharmacotherapy can be of a significant magnitude, and the main causes for this is often disease heterogeneity. Patients who have similar diagnoses may very often respond differently to the same pharmacological intervention, with great variability in both efficacy and safety outcomes. Despite having developed personalization medicine for more than a decade, we still see that most drug regimens for severe chronic diseases are largely based on ‘trial and error’ and not on solid biomarker data. Moreover, with the advance of molecular diagnostics and a subsequently increased understanding of disease mechanisms, things are slowly changing. Within the last few years, we have seen an increasing number of predictive biomarker assays being developed to guide the use of specific drugs. This type of assay is called companion diagnostics and it must often develop in parallel to the drug using the drug-diagnostic development model. The development of companion diagnostics is a relatively new discipline and in this review, different aspects will be discussed including clinical and regulatory types. Furthermore, examples of such drugs, such as the ALK and PD-1/PD-L1 inhibitors, that have been approved together with a companion diagnostic will be presented.

Keywords: Companion diagnostics; companion diagnostic; PD-L1; ALK, EGFR, HER2; personalization medicine.

Introduction

Over the years, several publications have drawn our attention to the variability of pharmacotherapy, which in many cases can be of a significant magnitude (1-3). The main contributor to this variability is disease heterogeneity, and patients who have similar diagnoses may very often respond differently to the same pharmacological intervention, with great variability in both efficacy and safety outcomes. Despite having developed personalized medicine for more than a decade, we still see that most drug regimens are largely based on ‘trial and error’ and not on solid biomarker data. For serious chronic diseases, such an approach can have unforeseen medical consequences for the individual patients. However, with the advance of molecular diagnostics and subsequently an increased understanding of disease mechanisms, things are slowly changing. Within the last few years, we have seen an increasing number of predictive biomarker assays being developed to guide the use of specific drugs. This type of assay is called companion diagnostics and it must often develop in parallel to the drug using the drug-diagnostic development model. For a number of such drugs, companion diagnostics have taken up a central role in the development process, and the success of this type of targeted therapy largely depends on the performance of assays.

At the recent 4th Joint Congress of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCLM) and the European Union of Medical Specialties (UEMS) in Warsaw, Poland, the first author of this article gave a plenary lecture entitled “Clinical Application of Companion Diagnostics.”

Jan Trost Jørgensen

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Companion and Complementary Diagnostics: Clinical and Regulatory Perspectives

Jan Trost Jørgensen1, M.

Nearly 20 years ago, the US Food and Drug Administration (FDA) approved the first companion diagnostic assay and, today, this type of test governs the use of 18 different drugs. With the appearance of PD-L1 immunohistochemistry (IHC) assays linked to the use of different PD-1/PD-L1 immune checkpoint inhibitors, a new class of predictive biomarker assays has emerged: the complementary diagnostics. These predictive biomarker assays aid in the therapeutic decision process but are not prerequisites for receiving a specific drug, as is the case with companion diagnostics. Both types of assay have the individual patient as a point of reference and they will be decisive for the move toward a more individualized pharmacotherapy. They are also considered important elements in the realization of precision medicine.

Predictive Biomarker Assays

For decades, we have known that the response to a pharmacological intervention varies from patient to patient; however, it is often difficult to explain this variation and to predict who might be the responder (1). Notwithstanding, with the advent of molecular medicine and, subsequently, the increased understanding of disease mechanisms, things are slowly changing. Within the past couple of decades, we have seen an increasing number of predictive biomarker assays being developed. These predictive biomarker assays have the individual patient as a point of reference and they will be decisive for the move toward a more individualized anticancer therapy; in addition, they are considered important elements in the realization of precision medicine (1,4,5). The predictive biomarker assays linked to specific drugs have been named “companion diagnostics,” and more recently, we have seen the terms “complementary diagnostics” also being used. Here, I discuss both types of assay in relation to their clinical application as well as the current regulatory framework that governs their development and use.

Historical Aspects

Looking at the history of drug-diagnostic codelvelopment, the first time we saw molecular testing becoming an integral part of the drug development process was during the early 1990s. Here, we will discuss some important developments in this area.
“A bad tumor biomarker test is as bad as a bad drug”

Current president of ASCO, Daniel F. Hayes