Companion & Complementary Diagnostics: Clinical and Regulatory Perspectives

Workshop on Companion Diagnostics
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Companion & Complementary Diagnostics

- Introduction and History
- Definitions
- Drug-Diagnostic Co-Development
- What can be achieved?
- Regulatory Aspects
- Conclusion and Future Perspectives
Disease Heterogeneity

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

Drug-Diagnostic Combinations
Oncology

“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”


Tamoxifen
Breast Cancer

HER2
Breast Cancer

FDA Approves:
Trastuzumab + HercepTest

Imatinib, Gefitinib, Vemurafenib,
Crizotinib, Pertuzumab, Ceritinib,
Pembrolizumab and more

Companion Diagnostics (CDx)  
US Definition¹

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 for serious adverse reactions as a result of treatment with the therapeutic product
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 (CDx)
Proposed EU Definition

A device which is essential for the safe and effective use of a corresponding medicinal product:

1. Identify, before and/or during treatment, patients who are likely to benefit from the corresponding medicinal product; or

2. Identify, before and/or during treatment, patients likely to be at increased risk for serious adverse reactions as a result of treatment with the corresponding medicinal product;

Complementary Diagnostics (CDx)

Preliminary US Definition

“A test that identify a biomarker-defined subset of patients that respond particularly well to a drug and aid risk/benefit assessments for individual patients, but that are not pre requisites for receiving the drug.”

Drugs with US FDA approved complementary diagnostic:

- Nivolumab for NSCLC and Melanoma (PD-L1 IHC 28-8 pharmDx)
- Atezolizumab for NSCLC and Urothelial Carcinoma (VENTANA PD-L1 (SP142) assay)

Companion & Complementary Diagnostics

The Use of Companion and Complementary Diagnostics

Drug-Diagnostic Co-Development\textsuperscript{1,2}

Phase I to III Clinical Development

\textit{Drug Development}

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

\textit{Parallel Development}

- Strong Biomarker Hypothesis
- Cut-off Selection & Analytical Validation
- Clinical Validation & Clinical Utility

\textit{CDx Development}

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

Drug-Diagnostic Co-Development\textsuperscript{1,2}
Phase I/II Clinical Development

\textbf{Drug Development}

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

\textbf{CDx Development}

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

\textbf{Strong Biomarker Hypothesis}

- Cut-off Selection & Analytical Validation

- Clinical Validation & Clinical Utility

\textbf{1. Olsen D, Jørgensen JT. Companion diagnostics for targeted cancer drugs - clinical and regulatory aspects. Front Oncol 2014; 4: 105.}

Immune Checkpoint Inhibitors

1st Line Treatment in NSCLC

- Pembrolizumab/PD-L1 IHC 22C3 pharmDx (KEYNOTE-024)
  - PD-L1 IHC 22C3 pharmDx is approved as a companion diagnostic
  - Assay cut-off: 50% PD-L1 expression
  - Treatment: Pembrolizumab (P) vs platinum-based chemotherapy (C), N=305
  - PFS: Median 10.3 mo (P) vs 6.0 mo (C); (HR 0.50, 95% CI 0.37-0.68, P<0.001)

- Nivolumab/PD-L1 IHC 28-8 pharmDx (CheckMate 026)
  - PD-L1 IHC 28-8 pharmDx is approved as a complementary diagnostic
  - Assay cut-off: 5% PD-L1 expression
  - Treatment: Nivolumab (N) vs platinum-based chemotherapy (C), N=541
  - PFS: Median 4.2 mo (N) vs 5.9 mo (C); (HR 1.15, 95% CI 0.91-1.45, P=0.25)

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(https://cslide.ctimeetingtech.com/library/esmo/browse/itinerary/5286/2016-10-09#2z94T0v3)
Drug-Diagnostic Co-Development

Enrichment Designs$^{1,2,3}$


Approved ALK & ROS1 Inhibitors in NSCLC
Regulatory Submissions – Efficacy Data¹,²,³

December 19, 2016
• FDA approved rucaparib, in conjunction with a NGS based CDx, for treatment of advanced stage ovarian cancer patients with BRCA1/2 mutations
• Efficacy was based on data from 106 patients in 2 single-arm, open-label studies.

## 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</th>
<th>Platform</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab (Perjeta)</td>
<td>Breast cancer (HER2+)</td>
<td>HerceptTest (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</td>
<td>Breast cancer (HER2+)</td>
<td>HerceptTest (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</td>
<td>NSCLC</td>
<td>No CDx</td>
<td>—</td>
<td>33.0%</td>
</tr>
<tr>
<td>particles (Abraxane)</td>
<td></td>
<td></td>
<td></td>
<td></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>

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Companion Diagnostics (CDx)  
Regulatory Aspects\(^1,2,3\)

- **Classification of CDx assays**
  - US: Class III (high risk IVD devices)
  - EU: General IVD (low risk IVD devices). In the near future Class C*

- **Documentation of analytical and clinical validity**
  - US: Review by FDA
  - EU: Self-certification and CE marking. In the near future review by independent notified body and national competent authorities and/or EMA

*Class C: High individual risk or moderate public health risk, where an erroneous result would put the patient in an imminent life-threatening situation or would have major negative impact on outcome

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Drug-diagnostics Codevelopment
Future Perspectives

Percentage of company pipeline relying on biomarker in late clinical development

- Oncology will continue to dominate
- Other therapeutic areas:
  - Central nervous system diseases
  - Cardiovascular diseases
  - Autoimmune diseases
- Drug and biomarker R&D will become a more flexible and iterative process

Summary & Conclusion

• The drug-diagnostic codevelopment model:
  – Increased drug efficacy
  – Reduction in time and resources spent\textsuperscript{1,2,3}
  – Increased development success rate\textsuperscript{1,2,3}

• Oncology drug development is currently undergoing major changes

• Key requirements for CDx assay development:
  – A clear intended use
  – Analytical validity
  – Clinical validated and demonstrated clinical utility

Companion diagnostics—a tool to improve pharmacotherapy

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Contributions: (1) Conception and design; (2) Administrative support; (3) Data collection; (4) Data analysis and interpretation; All authors; (5) Manuscript writing; All authors. Final approval of manuscript: All authors.

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Abstract: The variability of pharmacotherapy can be of a significant magnitude, and the main causes for this are often disease heterogeneity. Patients who have similar diagnoses very often respond differently to the same pharmacological intervention, with great variability in both efficacy and safety outcomes. Despite having developed personalized medicines for more than a decade, we still see that most drug development for serious diseases are largely based on “trial and error” and not on solid biomarker data. However, with the advancement of molecular diagnostics and a consequent 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 targeted cancer drugs. This type of assay is called companion diagnostics and is developed 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 assays will be discussed including clinical and regulatory issues. Furthermore, examples of drugs, such as the ALK and PD-1/PD-L1 inhibitors, that have been approved recently together with a companion or complementary diagnostic will be given.

Keywords: Companion diagnostics; complementary diagnostics; PD-L1; ALK; EGFR; HER2; personalized medicines

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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 very often respond differently to the same pharmacological intervention, with great variability in both efficacy and safety outcomes. Despite having developed personalized medicines for more than a decade, we still see that most drug development is largely based on “trial and error” and not on solid biomarker data (1,4,5). For serious chronic diseases, such as cancer, an approach can have unfortunate medical consequences for the individual patient. However, with the advancement 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 targeted cancer drugs. This type of assay is called companion diagnostics and is mostly developed in parallel to the drug using the drug-diagnostic development model (6). For a number of these drugs, companion diagnostics have taken a central role in the development process, and the success of this type of targeted therapy largely depends on the performance of these assays.

As the recent 4th Joint Congress of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the European Union of Medical Specialities (UEMS) in Warsaw, Poland, the last author of this article gave a plenary lecture titled “Clinical Applications of Companion Diagnostics in Cancer: Companion and Complementary Diagnostics.”

Trends in Cancer

Companion and Complementary Diagnostics: Clinical and Regulatory Perspectives

Jan Trost Jørgensen1,*

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 assay has emerged: the complementary diagnostics. These are predictive biomarker assays that use the therapeutic decision process but are not a prerequisite for receiving a specific drug, as is the case with companion diagnostics. Both types of assays 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. Here, I discuss both companion and complementary diagnostics.

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 and predict what might be the best treatment for each individual. Nevertheless, with the advancement 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 using the drug-diagnostic development model. For several cancer drugs, these assays have taken a central role in the development process, and the success of the use of targeted drug therapy depends on the performance of these assays.

At the recent 4th Joint Congress of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the European Union of Medical Specialties (UEMS) in Warsaw, Poland, the last author of this article gave a plenary lecture titled “Clinical Applications of Companion Diagnostics in Cancer: Companion and Complementary Diagnostics.”

Historical Aspects

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

Current president of ASCO, Daniel F. Hayes¹