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

Critical Path to TB Drug Regimens 2017 Workshop
Washington DC – March 22, 2017

Jan Trøst Jørgensen, M.Sc.Pharm., Ph.D.
Dx-Rx Institute
Fredensborg, Denmark
E-mail: jan.trost@dx-rx.dk

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

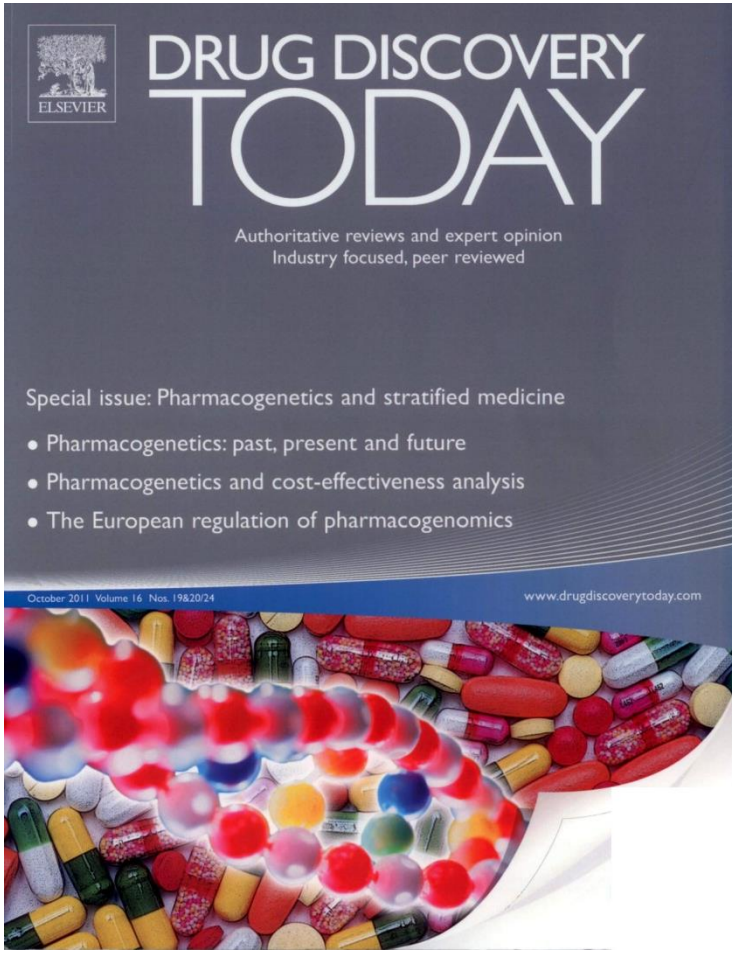
- Introduction and History
- Companion Diagnostics and Assay Technologies
- Drug-Diagnostic Co-development Model
- What can be achieved?
- Summary and Conclusion

Tuberculosis & Cancer

Similarities	
	Major global public health concern
	High unmet medical needs
	Drug susceptibility testing
	Drug resistance
Differences	
	Etiology and pathophysiology
	Global incidences
	Pharmaceutical companies' interest
	The availability of new drugs

Disease Heterogeneity

"In order to achieve a more effective pharmacotherapy we need to recognize that most diseases are heterogeneous and thus develop drugs accordingly."[1]



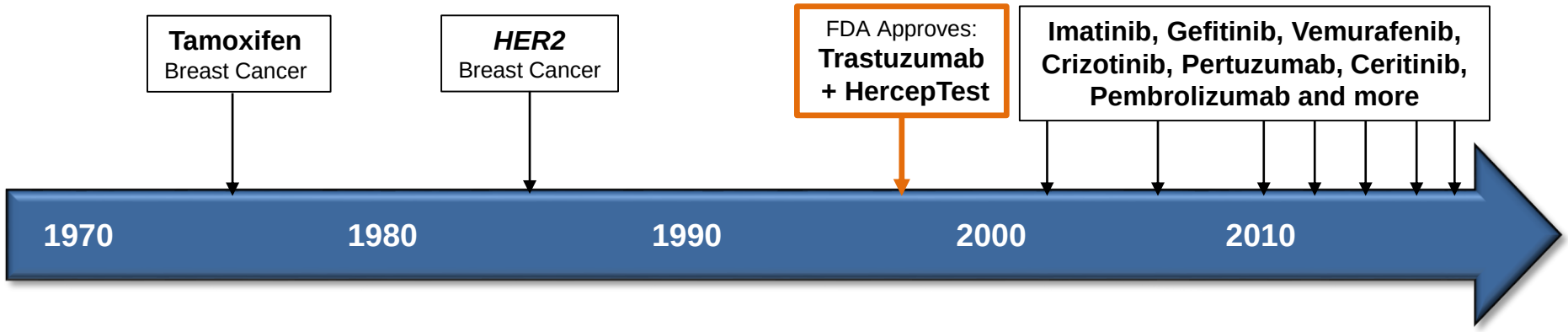
1. Jørgensen JT. A challenging drug development process in the era of personalized medicine. Drug Discov Today 2011;16: 891-897

Drug-Diagnostic Combinations

Oncology[1]

"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"

Lerner HJ et al. Phase II study of tamoxifen: report of 74 patients with stage IV breast cancer. Cancer Treat Rep. 60,1431-1435 (1976).



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Companion Diagnostics (CDx)

US Definition[1]

U.S. Department of Health and Human Services
Food and Drug Administration

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

1. In Vitro Companion Diagnostic Devices. Guidance Document. FDA, August 6, 2014. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf

Companion Diagnostics in Oncology

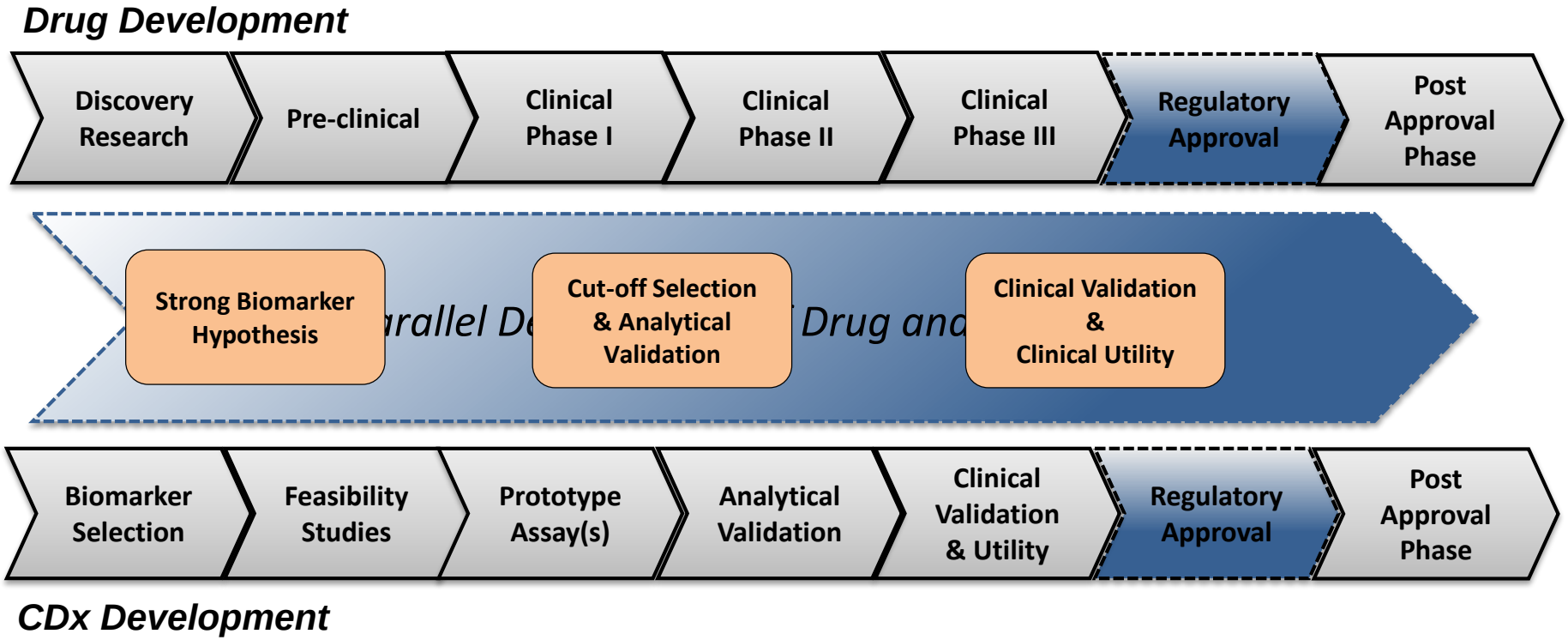
The Current FDA Approved Assay Technologies[1]

- **Immunohistochemistry (IHC)**
  - HercepTest (Dako/Agilent) – *Drugs: Trastuzumab, Pertuzumab, Ado-trastuzumab emtansi*ne
  - 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*

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).

Drug-Diagnostic Codevelopment

Phase I to III Clinical Development[1,2]



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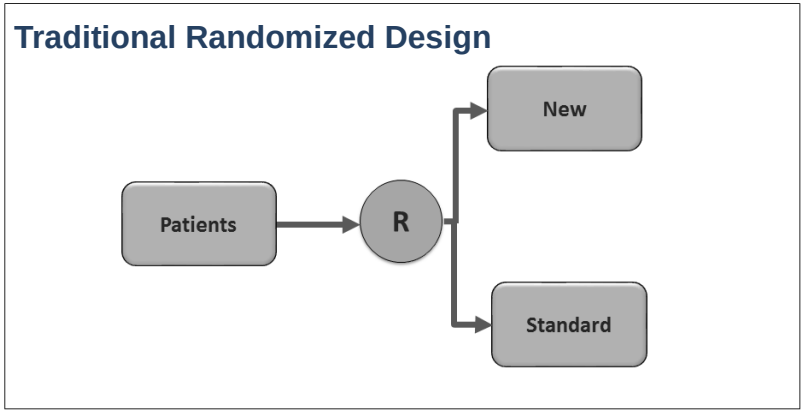
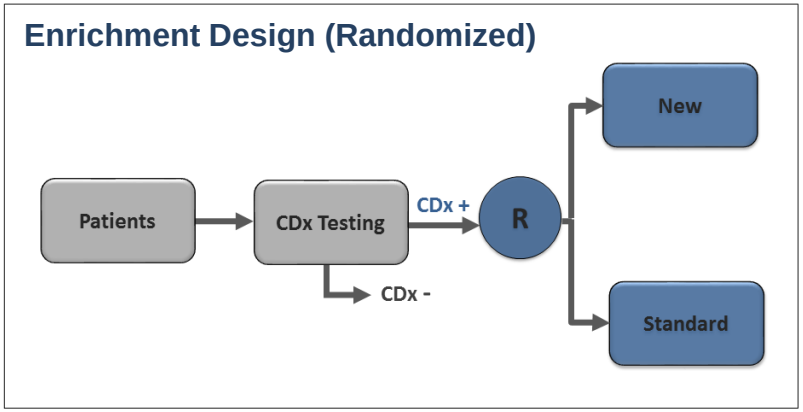
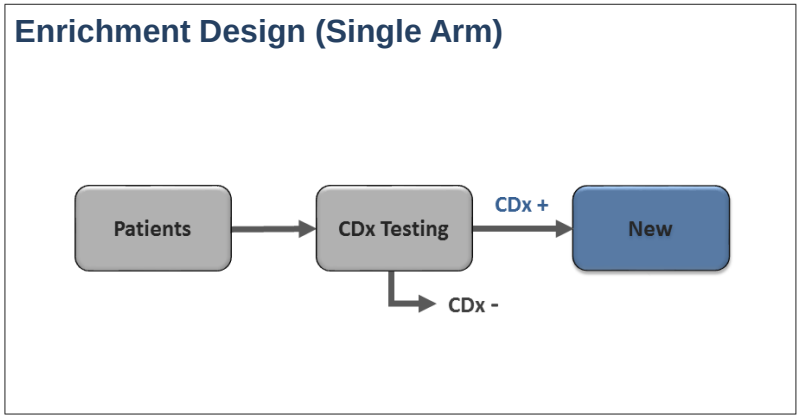
2. US FDA. Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product. Draft Guidance, July 15, 2016. (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM510824.pdf)

Drug-Diagnostic Co-development

Enrichment Design[1,2]







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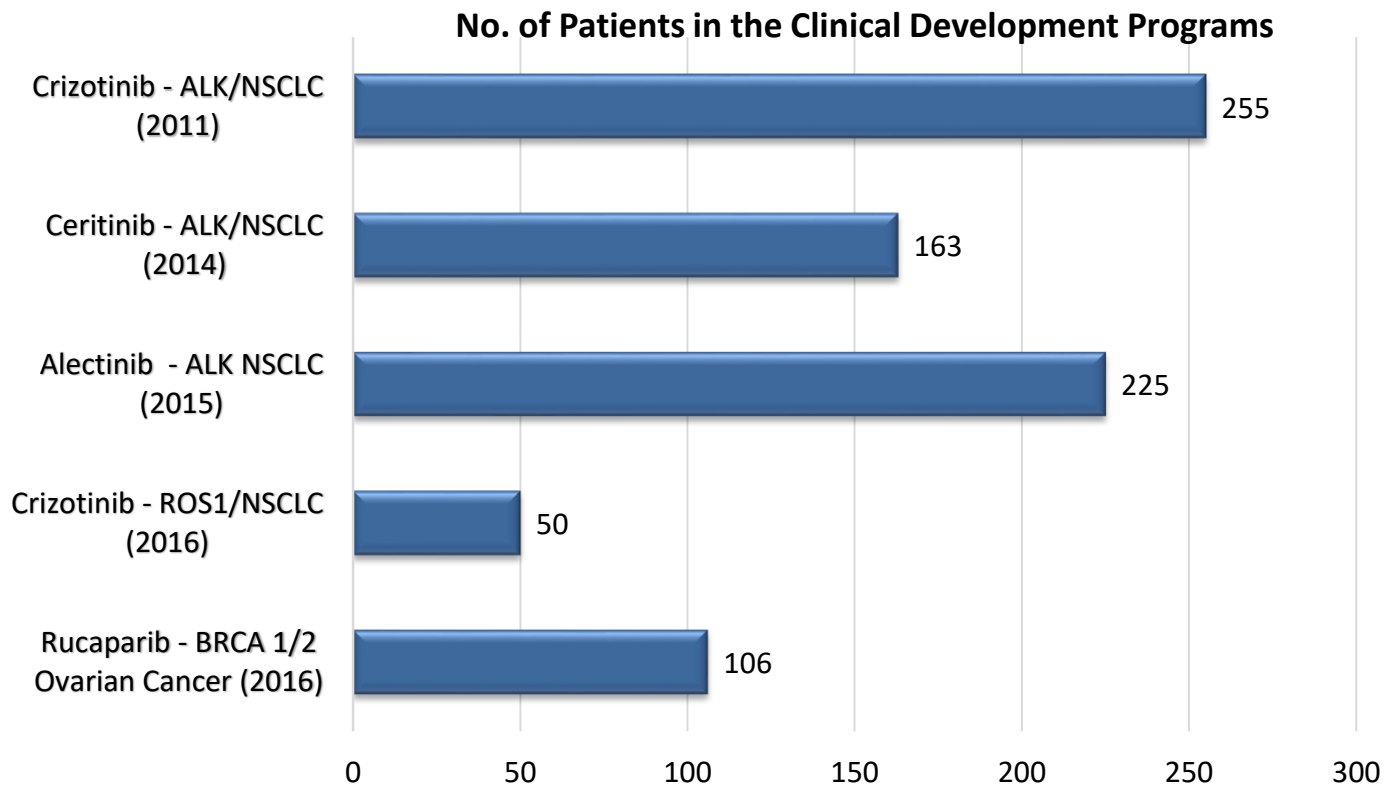
2. Jørgensen JT. Companion Diagnostics and Clinical Utility in Oncology - Current Status and Future Aspects . Oncology 2013; 85: 59-68.

Drug-Diagnostic Combinations

Regulatory Approval – Efficacy Data[1,2,3,4]



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2. McKeage K. Alectinib: a review of its use in advanced ALK-rearranged non-small cell lung cancer. Drugs 2015 ; 75: 75-82.
3. Swisher EM, Lin KK, Oza AM, et al. Lancet Oncol. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. 2017; 18: 75-87.
4. Jørgensen JT. The importance of predictive biomarkers in oncology drug development. Expert Rev Mol Diagn. 2016;16: 807-809.

Drug-Diagnostic Combinations

Objective Response Rates – Oncology[1,2]

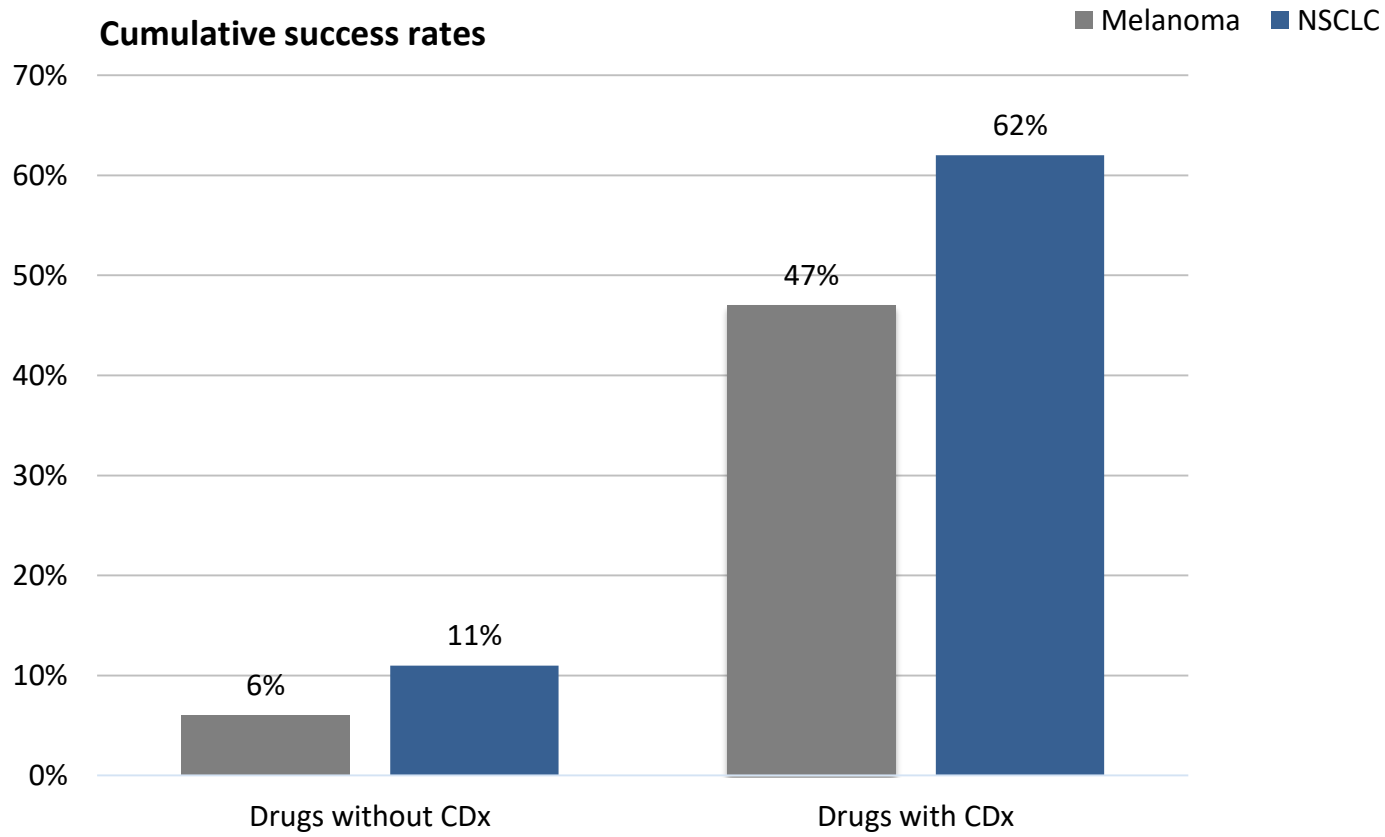
Table 1. Objective response rates for anticancer drugs with and without a CDx assay linked to their use[a,b]

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

1. Jørgensen JT. Clinical application of companion diagnostics. Trends Mol Med. 2015; 21: 405-7.
2. Drugs@FDA: FDA Approved Drug Products. (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).

Success Rates in Oncology Drug Development

Melanoma and NSCLC[1,2,3]



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2. Falconi A., Lopes G., Parker J.L. Biomarkers and receptor targeted therapies reduce clinical trial risk in non-small-cell lung cancer. J Thorac Oncol 2014; 9: 163-169.
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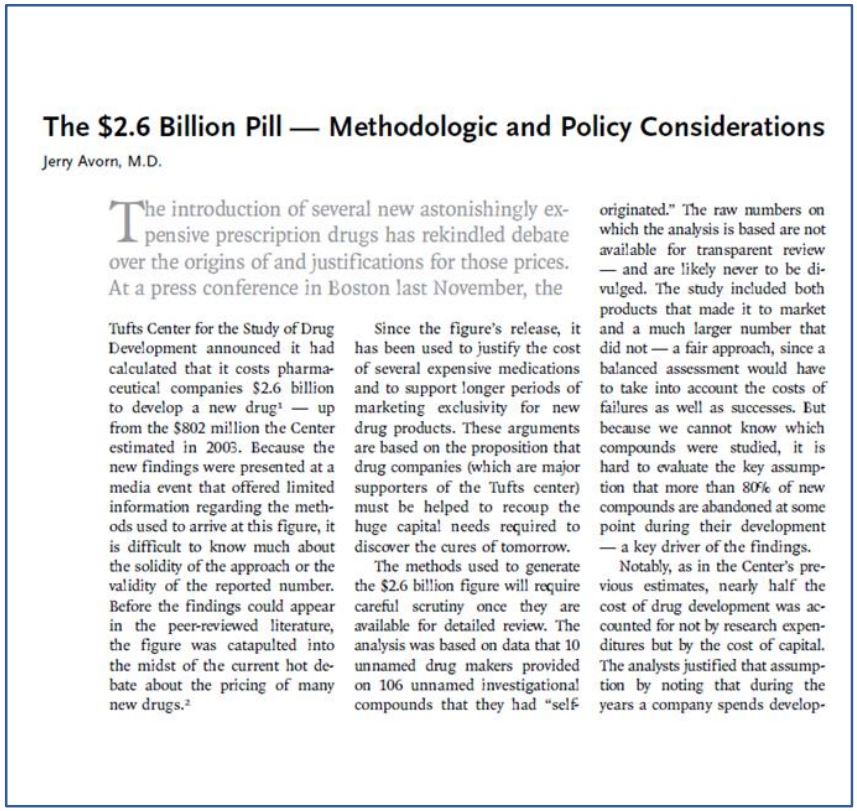
Cost of Drug Development

Traditional vs Drug-Diagnostic Strategy[1,2]



The $2.6 Billion Pill — Methodologic and Policy Considerations

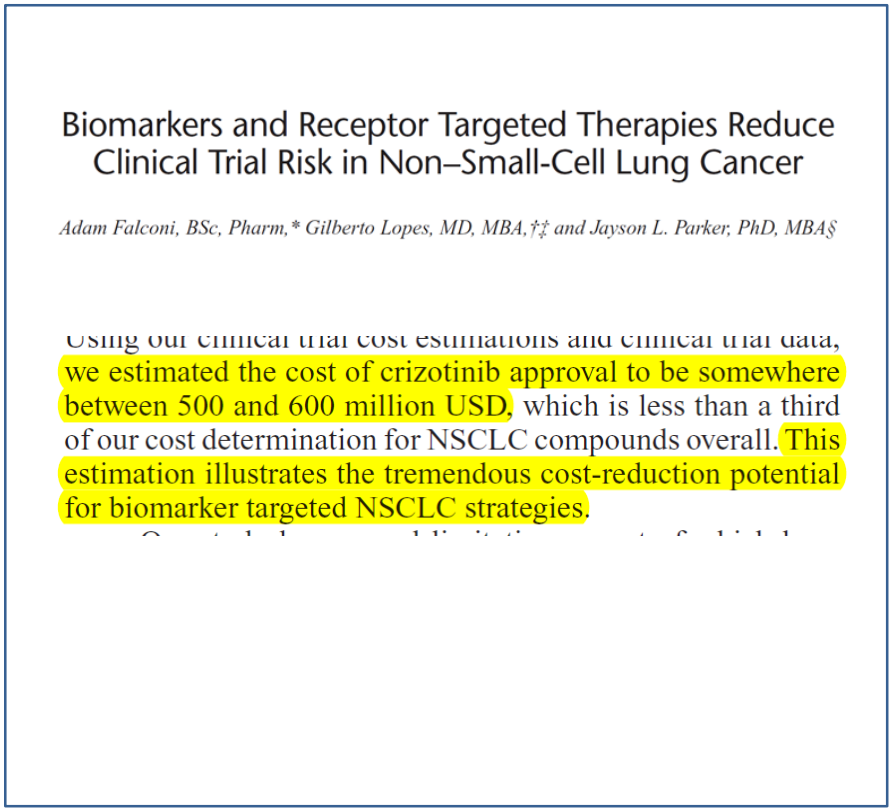
Jerry Avorn, M.D.

The introduction of several new astonishingly expensive prescription drugs has rekindled debate over the origins of and justifications for those prices. At a press conference in Boston last November, the Tufts Center for the Study of Drug Development announced it had calculated that it costs pharmaceutical companies $2.6 billion to develop a new drug[1] — up from the $802 million the Center estimated in 2003. Because the new findings were presented at a media event that offered limited information regarding the methods used to arrive at this figure, it is difficult to know much about the solidity of the approach or the validity of the reported number. Before the findings could appear in the peer-reviewed literature, the figure was catapulted into the midst of the current hot debate about the pricing of many new drugs.[2]

Since the figure's release, it has been used to justify the cost of several expensive medications and to support longer periods of marketing exclusivity for new drug products. These arguments are based on the proposition that drug companies (which are major supporters of the Tufts center) must be helped to recoup the huge capital needs required to discover the cures of tomorrow.

The methods used to generate the $2.6 billion figure will require careful scrutiny once they are available for detailed review. The analysis was based on data that 10 unnamed drug makers provided on 106 unnamed investigational compounds that they had "self-originated." The raw numbers on which the analysis is based are not available for transparent review — and are likely never to be divulged. The study included both products that made it to market and a much larger number that did not — a fair approach, since a balanced assessment would have to take into account the costs of failures as well as successes. But because we cannot know which compounds were studied, it is hard to evaluate the key assumption that more than 80% of new compounds are abandoned at some point during their development — a key driver of the findings.

Notably, as in the Center's previous estimates, nearly half the cost of drug development was accounted for not by research expenditures but by the cost of capital. The analysts justified that assumption by noting that during the years a company spends develop-



Biomarkers and Receptor Targeted Therapies Reduce Clinical Trial Risk in Non–Small-Cell Lung Cancer

Adam Falconi, BSc, Pharm, Gilberto Lopes, MD, MBA,†‡ and Jayson L. Parker, PhD, MBA§*

Using our clinical trial cost estimations and clinical trial data, we estimated the cost of crizotinib approval to be somewhere between 500 and 600 million USD, which is less than a third of our cost determination for NSCLC compounds overall. This estimation illustrates the tremendous cost-reduction potential for biomarker targeted NSCLC strategies.

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2. Falconi A., Lopes G., Parker J.L. Biomarkers and receptor targeted therapies reduce clinical trial risk in non-small-cell lung cancer. J Thorac Oncol 2014; 9: 163-169.

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?

Review Article

Companion diagnostics—a tool to improve pharmacotherapy

Jan Trost Jørgensen[1], Maria Hersom[2]

[1]Dx-Rx Institute, Baunevaenget 76, DK-3480 Fredensborg, Denmark; [2]Department of Pharmacy, Faculty of Health and Medical Sciences, Univer of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen, Denmark

Contributions: (I) Conception and design: JT Jørgensen; (II) Administrative support: M Hersom; (III) Provision of study materials or patients; authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (Final approval of manuscript: All authors.

Correspondence to: Jan Trøst Jørgensen. Dx-Rx Institute, Baunevaenget 76, DK-3480 Fredensborg, Denmark. Email: jan.trost@dx-rx.dk.

Abstract: The variability of pharmacotherapy can be of a significant magnitude, and the main reason for this is often diseases heterogeneity. Patients who have similar diagnoses very often respond differently to the same pharmacological intervention, with great variability in both efficacy and safety outcome. Despite having discussed personalized medicine for more than a decade, we still see that most drug prescriptions for severe chronic diseases are largely based on 'trial and error' and not on solid biomarker data. However, with the advance of molecular diagnostics and a subsequent 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 co-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 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 complimentary diagnostic will be given.

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

Submitted Nov 18, 2016. Accepted for publication Dec 06, 2016.
doi: 10.21037/atm.2016.12.26
View this article at: http://dx.doi.org/10.21037/atm.2016.12.26

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 diseases heterogeneity, and patients who have similar diagnoses very often respond differently to the same pharmacological intervention, with great variability in both efficacy and safety outcome. Despite having discussed personalized medicine for more than a decade, we still see that most drug prescriptions are largely based on 'trial and error' and not on solid biomarker data (1,4,5). For serious chronic diseases, such an approach can have unfortunate 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. Wit the last few years, we have seen an increasing numb of predictive biomarker assays being developed to gu the use of targeted cancer drugs. This type of assay called companion diagnostics and is most often develo in parallel to the drug using the drug-diagnostic development model (6). For a number of these drugs companion diagnostics have taken up a central role the development process, and the success of this type targeted therapy largely depends on the performance of assays.

At the recent 4th Joint Congress of the Internatio Federation of Clinical Chemistry and Laboratory Medic (EFLM) and the European Union of Medical Speciali (UEMS) in Warsaw, Poland, the first author of this arti gave a plenary lecture entitled "Clinical Applicati

Trends in Cancer

CellPress

Opinion

Companion and Complementary Diagnostics: Clinical and Regulatory Perspectives

Jan Trøst Jørgensen[1,*]

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 are predictive biomarker assays that aid the therapeutic decision process but are not a prerequisite 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. Here, I discuss both companion and complementary diagnostics.

Trends

An increasing number of cancer drugs will have a companion diagnostic linked to their use to aid the therapeutic decision process.

Companion diagnostics are predictive biomarker assays that are linked to the use of a specific drug, most often developed in parallel to the drug using the drug-diagnostic codevelopment model.

With the recent regulatory approval of PD-1/PD-L1 immune checkpoint inhibitors for different cancer indications, a new class of predictive biomarker assays has emerged: complementary diagnostics.

There have been recent debates as to the role of complementary diagnostics and how to distinguish them from other predictive biomarker assays, such as pharmacogenomic tests and companion 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 this variation and to predict who might be the responders [1]. Nevertheless, with the advance 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 codevelopment model. For several cancer drugs, these assays have taken a central role in the development process, and the success of this type of targeted drug largely depends on the performance of the assays. According to the recent personalized medicine survey performed by Tufts Center for the Study of Drug Development, 60% of the surveyed pharmaceutical company cancer drug pipelines rely on biomarker data during the late clinical phases [2]. 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 [1,3,4]. The predictive biomarker assays linked to specific drugs have been named 'companion diagnostics', and more recently, we have seen the name 'complementary diagnostics' also being used. Here, I discuss both types of assay in relation to their clinical application as well as the current regulatory frame that governs their development and use in the USA and Europe.

Historical Aspects

Looking at the history of drug-diagnostic codevelopment, the first time we saw molecular testing becoming an integrated part of the drug development process was during the early 1990s. Here,

[1]Dx-Rx Institute, Baunevaenget 76, 3480 Fredensborg, Denmark

*Correspondence: jan.trost@dx-rx.dk (J.T. Jørgensen).

“A bad tumor biomarker test is as bad as a bad drug”

Current president of ASCO, Daniel F. Hayes[1]

1. Hayes D., Raison C. Lessons for tumor biomarker trials: vicious cycles, scientific method & developing guidelines. Expert Rev Mol Diagn 2015; 15:165-169.