Expert Review of Molecular Diagnostics

ISSN: 1473-7159 (Print) 1744-8352 (Online) Journal homepage: informahealthcare.com/journals/iero20

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To cite this article: Jan Trøst Jørgensen (2015) Companion diagnostics: the key to personalized medicine, Expert Review of Molecular Diagnostics, 15:2, 153-156, DOI: 10.1586/14737159.2015.1002470

To link to this article: https://doi.org/10.1586/14737159.2015.1002470

Published online: 17 Jan 2015.

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Companion diagnostics: the key to personalized medicine

Expert Rev. Mol. Diagn. 15(2), 153–156 (2015)

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This special focus issue of *Expert Review of Molecular Diagnostics* on *in vitro* companion diagnostics aims to provide the reader with up-to-date knowledge on this fast-evolving area of medical research. Companion diagnostics takes up a central role in the development of targeted drugs and to a large extent, the success of this type of therapy depends on their performance. Companion diagnostic assays have a single patient as a point of reference and they will be decisive for the move toward a more precise and individualized pharmacotherapy. The 'first generation' of companion diagnostic assays relies on single biomarker detection but with our increasing understanding of disease pathophysiology a new generation of assays is under development, which will be based on patient profiling and multiplex platforms.

Much of today's pharmacotherapy is characterized by 'trial and error' and the success rate after treatment is consequently low [1]. Such an approach can have serious medical consequences for the individual patient as well as economically for the healthcare system and the society as a whole. For most serious chronic diseases, early diagnosis and early intervention are two elements of key importance. For cancers, an incorrect or delayed treatment decision will often result in disease dissemination with no or very low chances of cure and even result in death. Similarly, for a disease such as rheumatoid arthritis (RA), a delayed or incorrect treatment can result in irreversible joint destruction and disability to the patient. Optimally, any pharmacological treatment decision should be timely and rely on an in-depth understanding of the disease biology and the mechanism of the action of the drug. We are far from being there yet but within a few disease areas, the advances in molecular medicine and molecular diagnostics have given us sufficient insight to allow us to practice a more rational pharmacotherapy, which has led to the development of companion diagnostics (CDx) assays.

What is a CDx assay? According to the US FDA guidance document issued in August 2014, a CDx assay is defined as an *in vitro* diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product [2]. Furthermore, the FDA specifies several areas in which such an assay could be essential and overall these can be summarized as outcome prediction (efficacy and safety) as well as therapy monitoring. No doubt, the predictive characteristic of the CDx assay, especially with regards to efficacy, has attracted most attention so far. As we are moving toward a more precise and individualized pharmacotherapy, the CDx assays will play a central role in these efforts by having a single patient as its point of reference. In this context, it is also important to remember that the success of individualized targeted therapy is linked to the performance of the corresponding CDx assay.

The concept of having a predictive assay in conjunction with a drug was first introduced in relation to the development of trastuzumab (Herceptin®, Roche/Genentech) for treatment of advanced breast cancer [3]. Trastuzumab obtained FDA approval in September

EXPERT REVIEWS

KEYWORDS: companion diagnostics • oncology • personalized medicine • precision medicine • rheumatology

 10.1586/14737159.2015.1002470 © 2015 Informa UK Ltd ISSN 1473-7159

1998 and on the same day the immunohistochemical assay for HER2 overexpression (HercepTest™, Dako) was approved [4]. The current drug–diagnostic codevelopment process is very much inspired by the way that Genentech developed trastuzumab in the 1990s, and a number of targeted cancer drugs and corresponding CDx assays have obtained regulatory approval since then [5]. A couple of these recent drugs are crizotinib (Xalkori®, Pfizer) and ceritinib (Zykadia®, Novartis), which have been approved for the treatment of non–small-cell lung cancer (NSCLC) in patients with *ALK* rearrangement [6,7]. For both the compounds, the development time has been remarkably short and the approvals granted based on small open-labeled non-randomized Phase I/II studies. However, this would never have happened without an in-depth molecular understanding of the disease biology and the mechanism of action of the drugs. This knowledge was used to develop a CDx assay based on the FISH technology (Vysis LSI ALK Break Apart Rearrangement Probe Kit, Abbott Laboratories) intended for preselection of NSCLC patients with *ALK* rearrangement. CDx assays related to crizotinib and ceritinib are also discussed in an editorial by Conde *et al.* in the current special focus issue on *in vitro* companion diagnostics [8].

This special focus issue of *Expert Review of Molecular Diagnostics* aims to provide the reader with up-to-date knowledge on different topics related to CDx assays. Through a number of mainly review articles, both basic scientific and clinical aspects as well as regulatory challenges will be covered. Despite a lot of research ongoing within different therapeutic areas, CDxs are still more or less solely related to oncology, which this special focus issue will also reflect, however, rheumatology is addressed in a comprehensive review article.

The main purpose of developing a CDx assay in conjunction with a drug is to have a test that can predict whether a patient is likely to benefit from it or not. Hence, for many drugs, the CDx assays will take up a central role as a kind of 'decisive' stratification factor, both during the different clinical development phases and later after approval when the drug is to be routinely used in the clinic. The assay will then become a kind of 'gatekeeper' in relation to the treatment decision and with this central role in mind the regulatory requirements for CDxs need to be at the same level as for drugs [9]. This is also stressed in the interview with Daniel Hayes where he states that "A bad tumor biomarker test is as bad as a bad drug." He continues by saying that people need to value biomarker tests as much as they value drugs and that researchers should have to do a biomarker study with the same amount of rigor as therapeutic trials [10]. This opinion was also expressed by Hayes et al. in a recent article published in *Science Translational Medicine* [11].

Having the critical role of CDx assays in mind it seems only natural that a number of countries now have stringent regulatory requirements. These countries include Australia, Canada, China and Japan; however, for the EU it has taken some time to realize the critical importance of CDx assays in relation to the patient management. It is only recently that the discussions about a more up-to-date regulation for IVD medical devices including CDx assays have started, but it seems that new legislation now will be in place for the European countries within a reasonable timeframe [12]. In the editorial by Rumiko Shimazawa and Masayuki Ikeda, the need for an international harmonization of the regulatory requirements on drug–diagnostic combinations is discussed [13].

Cancer is a very diverse group of diseases and genomic sequencing has shown that marked heterogeneity exists both between and within patients. Furthermore, it is a very dynamic disease, so the cancer that a patient is diagnosed with is likely different from the one that will cause a relapse at a later stage [14,15]. Based on this knowledge it seems obvious that analyzing a single biomarker at a certain point of time only will give us limited information. To have a broader and more complete picture of the disease with respect to the genes and pathways involved, multiplex assays are needed and here next-generation sequencing (NGS) will likely play a dominant role in the future. In the review article by Lin *et al.*, the authors give an introduction to the technology and its applications [16]. As NGS targets multiple genes and pathways, it could potentially provide valuable information on the underlying genomic alterations, which for the specific cancer might be useful in relation to determine susceptibility or resistance to a pharmacological anticancer intervention. Future NGS-based CDx will definitively be able to offer opportunities that do not exist with other technologies but there are also a number of challenges that needs to be overcome both in relation to the technology itself as well as the clinical validation, including documentation of clinical utility.

Multigene assays have already found their way into clinical routines when it comes to management of early stage breast cancer. In recent years, a number of molecular multigene profiling assays have been developed for the purpose of providing prognosis and therapy prediction in patients with early stage breast cancer. These assays are not based on NGS, but mainly on technologies such as RT-qPCR and DNA microarrays and cannot strictly be regarded as CDxs, because of the fact that they are not linked to a specific drug. However, these assays give valuable information on the disease prognosis for the individual breast cancer patient which is used to determine if treatment with chemotherapy should be initiated. In the research article by Issa *et al.*, the authors have performed at systematic literature search on different multigene profiling assays and subsequently conducted a meta-analysis [17]. For the 21-gene expression assay (Oncotype DX®, Genomic Health), their analysis showed that using the recurrence score resulted in change in treatment recommendations in 31.8% of all patients in the studies.

CDxs are not only aimed at outcome prediction but also to monitor response to treatment including acquired resistance to cancer therapy [2]. As a result of increased apoptotic and necrotic cell death or active secretion, DNA and RNA can be released from the tumor into the peripheral circulation. Measurement of these nucleic acids may potentially serve as a CDx for therapy monitoring in patients with advanced stage disease.

Detecting tumor DNA and RNA in blood could serve as a 'liquid biopsy,' which in some instances may be able to substitute for tumor tissue biopsies. This approach provides the possibility to perform repeated sampling in a convenient way and thus follow the disease changes as a consequence of treatment intervention [18]. In the article by Heidi Schwarzenbach, a comprehensive review of the literature is presented and the potential of using circulating nucleic acids as components of CDxs for predicting and monitoring chemotherapy response is discussed [19].

The advances in molecular medicine together with powerful computational and modeling tools have paved the way for the development of systems biology, which can be seen as a combined molecular and system-level approach to biological research. The systems biology methods are viewed as particularly appropriate for the search of biomarkers of disease processes and drug actions. Applying system biology methods in the understanding of the complexity of cancers and its drug–disease inactions seems to be obvious. However, system biology in relation to CDx research is still in its infancy. The review by Laura Caberlotto and Mario Lauria describes the ongoing activities and the potential of applying system biology methods in relation to CDx research [20].

When it comes to CDxs the main focus has so far been on oncology, but in the review by Gibson *et al.*, the current applications of biomarkers in rheumatology is discussed [21]. A disease like RA is an obvious candidate for the development of CDx assays. Here, early diagnosis and effective therapy are crucial to prevent joint destruction and functional disability. The use of disease-modifying anti-rheumatic drugs are the mainstay of treatment in RA; however, prescription of these drugs are essentially based on a trial and error approach, rather than an informed decision related to targeted groups of likely responding patients. The uses of biological targeted agents, such anti-TNF-α drugs, have significantly improved the outcome for RA patients, but these drugs are expensive and approximately one-third of the patients do not respond adequately. A CDx assay that could stratify RA patients into likely responders or nonresponders of anti-TNF-α therapy is urgently needed. In the UK, such an assay is currently under development, which is based on a multiplex gene platform and hopefully it will be able to demonstrate clinical utility and be of benefit to the RA patients. In the review by Gibson *et al.*, a number of other CDx possibilities are discussed with regards to different 'omics' such as proteomics, genomics, microbiomics, imaging and bioinformatics.

In relation to the development of CDx assays, both the analytical and clinical performance needs to be documented carefully using different elements of the drug–diagnostic codevelopment model [9]. With regard to the economic evaluation the same kind of 'standard' does not exist. The review article by Doble *et al.* assessed published model-based economic evaluations in which a targeted oncology drug has been evaluated alongside its CDx assay [22]. Based on this assessment a checklist was prepared, which should be followed for future economic evaluations of drug–diagnostic combinations in oncology. In the article, the authors also point toward the importance of having information on the sensitivity and specificity of the CDx assays incorporated in the model.

George Poste *et al.* from the National Biomarker Development Alliance (NBDA) discuss in their review article the challenges that biomarker development is facing [23]. The content of this review is based on a series of workshops at Arizona State University involving a number of public and private stakeholders, which in the beginning of 2014 culminated in the launch of a new nonprofit entity, the NBDA. One of the concerns of NBDA is the poor productivity and lack of progress in biomarker research and development. According to the authors, this is reflected in the orders of magnitude asymmetry between the large number of publications claiming putative biomarkers and the small number that enter clinical validation trials and the even smaller group that achieve final regulatory approval and clinical adoption. When looking at the CDx assays approved through the Premarket Approval process at the FDA, a couple of things will draw attention [5]. First, the list is relatively short, and second, 10 out of the 19 assays on the list are measuring HER2, either as protein overexpression or as gene amplification. We have been working on the development of CDx-based assays for more than 15 years and despite this, only 19 CDx assays have had sufficient analytical and clinical documentation to obtain FDA approval, which supports the concerns of the NBDA with respect to poor productivity in biomarker research.

Despite the concerns with regard to the progress of biomarker and CDx research there are a few remarkable examples worth mention and one of these is the development of the ALK inhibitors for NSCLC patients with *ALK* rearrangement. Here the drug–diagnostic codevelopment model showed to be an exceptionally strong research tool both in relation to the development of crizotinib and also very recently for ceritinib. In the spring of 2014, ceritinib obtained an accelerated FDA approval based on efficacy data from only 163 metastatic NSCLC patients with *ALK* rearrangement enrolled in a Phase I single-arm, open-label clinical trial [24,25]. Such a result is only achievable with the use of a CDx that can preselect the patients likely to respond, which as for ceritinib resulted in a response rate of approximately 50%, even in a Phase I trial. Beside crizotinib and ceritinib, a number of other targeted cancer drugs have been successfully developed using the current drug–diagnostic codevelopment model. Most of these drugs have initially shown remarkably high response rates in selected groups of patients; however, after a period of time, resistance develops and the patients relapse. These observations put the current drug–diagnostic codevelopment model under pressure as it relies on single biomarker identification and subsequently 'monotherapy'. To overcome or delay resistance, we will have to move away from the 'one biomarker:one drug' approach toward a multimodal approach, which integrates more biomarkers and drugs simultaneously. Multiplex CDx assays need to be developed, which also will include NGS.

If here at the end I should speculate on the future direction for CDxs, I will turn to an article that I in fact wrote for this journal 6 years ago [26]. Here, I illustrated the move from 'blockbuster medicine' to 'personalized medicine' with a staircase and explained that we were slow moving up the stairs toward the middle step, which was 'stratified medicine.' For some parts of oncology, we have arrived at this middle step; for several targeted drugs, we are now using CDx assays to stratify the patients, applying the one biomarker:one drug approach. Unfortunately, we have learned that 'oncogenic addiction' only is a transient condition and resistance develops to all targeted drugs at some point of time. To overcome this situation, the next move – or the next step on the staircase – will likely be a multimodal one with multiple biomarkers and drugs. By doing this, we will move closer toward individualized or personalized medicine, but this next step will be challenging and neither easy nor cheap.

Financial & competing interests disclosure

JT Jørgensen is working as a consultant for Dako and Euro Diagnostica and has given lectures at meetings sponsored by Roche and AstraZeneca. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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