Drug Discovery Today: Therapeutic Strategies
Vol. 10, No. 4 2013

Personalised medicine

Developing companion diagnostics for delivering personalised medicine: opportunities and challenges

Frank Desiere*, Thorsten S. Gutjahr, Ulrich-Peter Rohr

Roche Diagnostics, Basel, Switzerland

A greater understanding of disease biology processes, the opportunity to develop targeted drugs leading to further improved patient outcomes and technology advances, as well as increasing pressure on healthcare budgets have led to a shift towards personalised healthcare solutions. Personalised medicine has tremendous potential benefits for patients and healthcare providers, as well as for regulatory agencies and pharmaceutical and diagnostic companies, but the advancement of this innovative therapeutic strategy depends on identifying biomarkers functioning as companion diagnostics for the targeted drug. However, considerable practical, methodological, regulatory and economic issues must be addressed to fully realise the potential of this approach.

Introduction

Healthcare delivery has changed greatly in recent years. The traditional model of developing blockbuster drugs for an all-comer patient population is often not adequate any more as only a fraction of patients respond to several traditional therapies and healthcare spending is under intense pressure. Instead, treatment strategies are being sought to target new, innovative medicines only at patients who are more likely to have a favourable outcome. Recent advances in our understanding of disease pathophysiology, drug activity and biomarkers involved in these processes have resulted in a focus on tailoring treatment for specific patient subgroups based on their genetic makeup or other differentiating features (Fig. 1).

Biomarkers are defined as 'indicators of normal processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention' [1]. Here we review the key benefits and importance of, as well as the development challenges associated with, companion diagnostic tests that measure these biomarkers to identify appropriate patients for particular therapies.

Companion diagnostics

A companion diagnostic device has been described by the Food and Drug Administration (FDA) as 'an *in vitro* diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product' [2]. An *in vitro* diagnostic (IVD) companion device 'could be essential to identify patients most likely to benefit from a particular therapeutic product, identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product, or monitor response to treatment for the purpose of adjusting treatment (e.g. schedule, dose, discontinuation) to achieve improved safety and effectiveness' [2].

*Corresponding author.: F. Desiere (frank.desiere@roche.com), (fdesiere@yahoo.com)

 http://dx.doi.org/10.1016/j.ddstr.2013.05.002

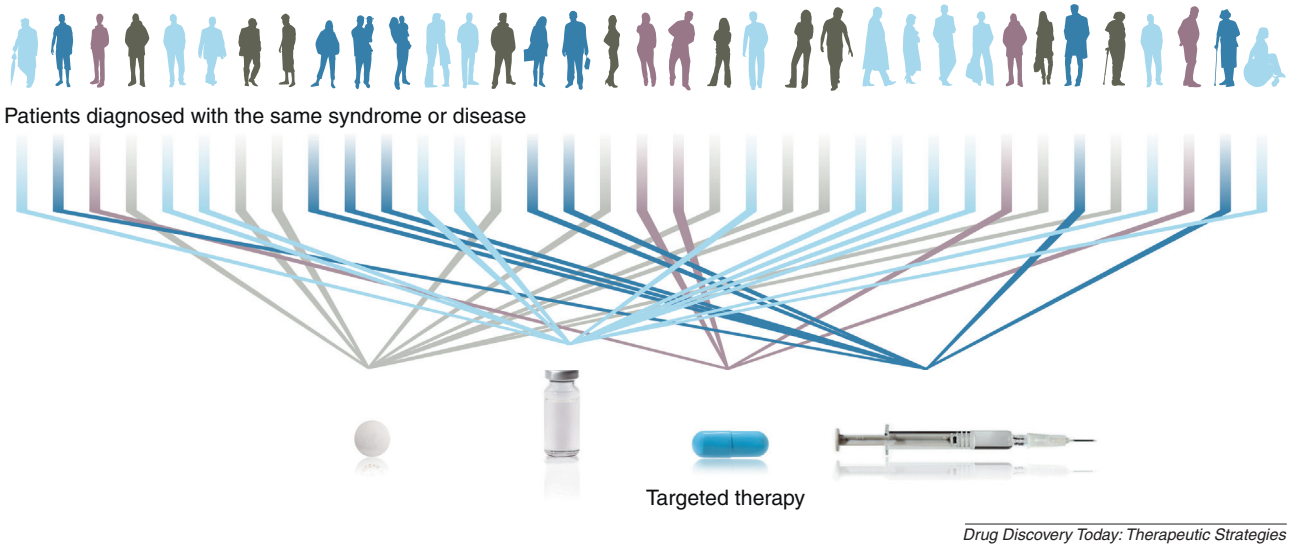

Figure 1. Personalised healthcare: improving patient outcome through targeting therapies to the 'right' subgroups. *Source*: Roche.

At present, 15 companion diagnostic tests are approved by the FDA [3], most of which are indicated for patients with cancer. In the European Union (EU), further tests have been commercialised as companion diagnostics under the current IVD directive [4]. Many more companion diagnostic tests are under development for use in cancer and other disease indications. A list of some of the drugs for which companion diagnostics are available is shown in Table 1.

Opportunities and challenges associated with personalised healthcare

Patients and their needs are at the centre of every new innovation in healthcare. The personalised healthcare approach is clearly focused on benefits for patients. However, there are other key stakeholders in the healthcare environment, including physicians, regulatory agencies, diagnostics companies, pharmaceutical companies and healthcare providers, all of whom may also benefit from the development and availability of companion diagnostic tests. These are summarised in Fig. 2.

The growing focus on personalised medicine inevitably calls into question traditional models of pharmaceutical development and it is anticipated that all-comer drugs will eventually become the exception rather than the rule. To fully illustrate the benefits of personalised medicine, challenges associated with this new approach need to be recognised and addressed. In the next sections, difficulties encountered at all stages of companion diagnostics development are described and discussed.

Biomarker discovery

The first step in developing personalised healthcare solutions is the identification of biomarkers that link the disease biology to the therapeutic agent in question. This requires an in-depth understanding of the pathways involved in the disease process, detailed characterisation of drug targets and identification of biomarkers that have demonstrated a relationship with and significance in the disease process, the mode of action of the drug, or play an important role in the relevant patient population.

Simultaneous and continuous development and optimisation of technologies and corresponding assays for measuring biomarkers are required alongside the biomarker identification and validation process. This usually requires the development of new reagents (recombinant proteins, monoclonal antibodies, probes, etc.), processes and even technology platforms. For example, the need for an accurate, rapid and robust assay for BRAF mutations in patients with melanoma led to development of the DNA-based cobas® BRAF V600 test [5]. Key challenges included developing procedures for reliable handling of formalin-fixed paraffin-embedded samples, DNA recovery, analysis of DNA fragments, and identification of extremely sensitive detection methods with a limit of detection of $\leq$5% mutant alleles [5]. There are many platforms currently available for detecting biomarkers, and selecting the correct one(s) is crucial to the success of both the diagnostic test and the drug.

Once the potential biomarker is identified, the rigorous process of development and validation can begin, starting with a prototype assay that may be used in early-phase clinical development trials, for example, for exploratory measurements of retrospectively collected samples, and further refined and developed into a companion diagnostic test as the clinical development of the drug progresses.

Co-development of drug and companion diagnostic

Concomitant development of a drug and its diagnostic test is considered to be best practice, bringing the drug and its