ELSEVIER

Drug Discovery Today: Technologies

Vol. 21–22, 2016

Editors-in-Chief
Kelvin Lam – Simplex Pharma Advisors, Inc., Boston, MA, USA
Henk Timmerman – Vrije Universiteit, The Netherlands

DRUG DISCOVERY TODAY TECHNOLOGIES

Translational pharmacology

Translational biomarkers: from discovery and development to clinical practice

Meena Subramanyam[1,*], Jaya Goyal[2]

[1]Global Biomarker Discovery and Development, Biogen, 300 Binney St., Cambridge, MA 02142, United States
[2]Value Based Medicine, Biogen, 300 Binney St., Cambridge, MA 02142, United States

The refinement of disease taxonomy utilizing molecular phenotypes has led to significant improvements in the precision of disease diagnosis and customization of treatment options. This has also spurred efforts to identify novel biomarkers to understand the impact of therapeutically altering the underlying molecular network on disease course, and to support decision-making in drug discovery and development. However, gaps in knowledge regarding disease heterogeneity, combined with the inadequacies of surrogate disease model systems, make it challenging to demonstrate the unequivocal association of molecular and physiological biomarkers to disease pathology. This article will discuss the current landscape in biomarker research and highlight strategies being adopted to increase the likelihood of transitioning biomarkers from discovery to medical practice to enable more objective decision making, and to improve health outcome.

Section editor:
Saileta Prabhu, Preclinical and Translational PKPD, Genentech, 1 DNA Way, South San Francisco, CA 94080, United States.

Introduction

Biomedical and technological innovations have created unprecedented opportunities to integrate decision-enabling biomarkers to support disease diagnosis, customize treatment options, and to de-risk therapeutic drug development. However, to realize the implicit value of biomarkers and justify the resource and financial investment, a strong collaboration between key stakeholders is needed to develop a translational road map. Such a road map is useful to define the key parameters that have to be taken into consideration for qualifying the clinical utility and defining the benefit/risk of implementing the biomarker test as a companion to a therapeutic or as a complementary diagnostic in a specific context [1]. Typically the biomarker is qualified for use in a disease natural history study with no drug intervention, or as part of an investigational drug clinical trial. Companion diagnostics, as defined by FDA, are biomarker tests that provide information for the safe and effective use of a corresponding therapeutic product. Complementary diagnostic tests, on the other hand, help identify a subset of patients, for instance cancer patients expressing PD-L1, who may respond particularly well to a specific class of therapeutic. Adoption of such qualified biomarker tests in drug development and in routine medical practice can enable better precision and objectivity in decision-making, and increase the overall value to the health care system as shown in Fig. 1. For example, a biomarker-driven disease diagnosis in the preclinical or sub-clinical stage will enable the physician to initiate a suitable treatment program in patients who will

*Corresponding author: M. Subramanyam (meena.subramanyam@biogen.com)

 http://dx.doi.org/10.1016/j.ddtec.2016.10.001

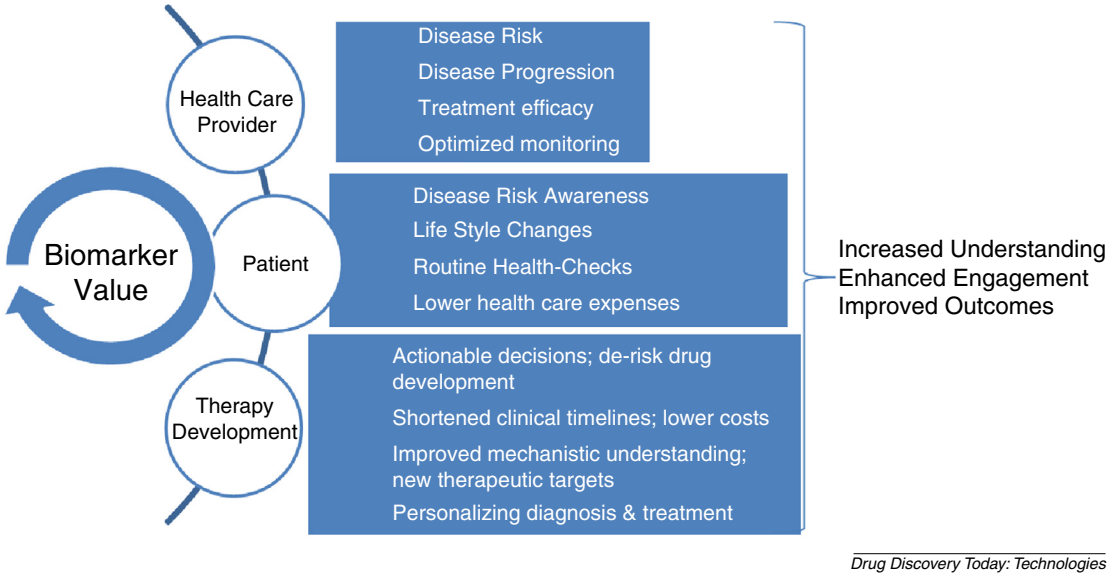

Figure 1. Contextualizing biomarker value. The key benefits derived from integration of qualified biomarkers for decision-making in medical practice for different stake-holders such as health care providers, patients and the drug development industry is illustrated.

likely benefit from treatment. Similarly, an increase in disease risk awareness at the patient level may trigger better lifestyle choices [2,3], as well as better adherence to treatment. In therapeutic drug development, biomarkers can potentially de-risk future investments by providing an early read, not only into the relevance of the target pathway in disease setting, but also on potential efficacy and safety considerations. The biomarker discovery process and technologies in use, as well as the dynamics of translating biomarkers from a conceptual idea to the clinic, is discussed below.

Biomarker discovery and development

The detection and phenotypic classification of disease pathophysiology requires data and knowledge integration at the molecular, physiological and clinical level. Much like therapeutic target discovery, the iterative process of novel biomarker discovery relies increasingly on the use of engineered cell lines to mimic disease states [4,5], patient-derived primary cells, body fluids and tissues [6,7], lineage-specific induced pluripotent stem cells [8] and/or transgenic rodent models [9]. Upon identification, the biomarkers are advanced into additional pre-clinical and clinical studies to assess clinical utility, as shown in Fig. 2, and to further characterize the behavior of the marker in disease (proof of mechanism) and upon therapeutic intervention (treatment monitoring). Response to therapeutic intervention may be evaluated using biomarkers in groups of patients with differing disease phenotype (prognostic (high/low risk; rapid/slow disease progression) to study clinical outcomes (proof of concept) and stratify effect (efficacy/safety; personalized or precision medicine). In some instances a single biomarker may be used for inferring several outcomes. For instance, amyloid plaque load in the brain detected by positron emission tomography (PET) can serve not only a diagnostic marker for Alzheimer's disease (AD), but in the case of therapies aimed at reducing the plaque burden, the reduction in the level of brain amyloid plaque can serve both as a pharmacodynamic marker and as a marker of treatment effect [10].

Biomarker technologies

The most significant development in biomarker sciences in the last several years has been the adoption of a systems biology based approach for the identification of disease- and drug-specific interaction networks within biological systems. This has greatly facilitated the construction of hierarchical models of interaction at the cellular and molecular level (interactome [11,12]). As illustrated in Table 1, high-throughput and high content genomic [13], proteomic [14], metabolomic [15,16], lipidomic [17] and epigenomic characterization technologies [18], autoantibody and microbiome profiling [19–21], in addition to molecular [22] and optical imaging [23,24] modalities and digital tools [25] are being increasingly used to study the interactions at the molecular and cellular level. Models built using this information is then used to interrogate the networks for discovery of novel molecules that drive disease processes, and biomarkers that uniquely reflect the interdiction of the various signaling nodes, pathway components and inter-pathway network, in the disease process. For example, molecular imaging technologies are increasingly used in neurodegenerative diseases to correlate structural and functional changes to disease process. Fluorine-18 fluorodeoxyglucose (F-FDG) PET imag-