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Review – Part of the Special Issue – Pharmacology in 21st Century Biomedical Research

Biomarkers in pharmacology and drug discovery

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ABSTRACT

Biomarkers, quantitatively measurable indicators of biological or pathogenic processes, once validated play a critical role in disease diagnostics, the prediction of disease progression, and/or monitoring of the response to treatment. They may also represent drug targets. A number of different methods can be used for biomarker discovery and validation, including proteomics methods, metabolomics, imaging, and genome wide association studies (GWASs) and can be analysed using receiver operating characteristic (ROC) plots. The relative utility of single biomarkers compared to biomarker panels is discussed, along with paradigms for biomarker development, the latter in the context of three large-scale biomarker consortia, the Critical Path Predictive Safety Testing Consortium (PSTC), the NCI Early Detection Research Network (EDRN) and the Alzheimer's Disease Neuroimaging Initiative (ADNI). The importance of systematic optimization of many parameters in biomarker analysis, including validation, reproducibility, study design, statistical analysis and avoidance of bias are critical features used by these consortia. Problems including introduction of bias into study designs, data reporting or data analysis are also reviewed.

Contents

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1. Introduction

Biomarkers, where these exist and have been appropriately validated [1–7] can play a critical role in biomedical research, drug discovery and development, including:

- Their use as diagnostics to establish the presence of a disease.
- predicting disease progression and the stratification of disease severity.
- assessing and predicting the clinical benefit(s) or toxicity resulting from a therapeutic intervention.
- monitoring treatment response, including target engagement where appropriate.

Biomarkers can be used as part of a personalized medicine paradigm to customize treatment to the specific disease characteristics of an individual patient. They can also be used to better understand disease mechanisms and to identify novel disease targets.

Issues that are addressed in this review include: (i) biomarker discovery, development and analysis that requires a combination of careful study design to avoid distorting or negating results due to bias; (ii) systematic development of assays; (iii) larger scale collaborations involving multiple patient populations to develop and refine robust and reproducible assays and; (iv) for clinical validation [1–7], transparent data analysis (particularly when large datasets are involved), with statistical analyses appropriate for the specific use for which the biomarkers are being developed.

2. Defining biomarkers

Some biomarker definitions are listed in Table 1. These indicate their scope of use, which can include: application to various stages of the drug discovery process; characterization of animal disease models; use in clinical trials to stratify patients; use as diagnostics or companion diagnostics; or as indicators of therapeutic response.

Table 1
Definition of biomarker types.

Term	Definition
Biomarker	objectively measured characteristic evaluated as an indicator of normal biological or pathogenic processes, or pharmacological response(s) to a therapeutic intervention [8]
Surrogate	biomarker intended to substitute for a clinically meaningful endpoint; predicts clinical benefit, harm, or lack of either; a direct measure of how a patient feels, functions or survives [8,9]
Clinical endpoint	a characteristic or variable reflecting how a patient feels, functions, or survives [9]
Diagnostic	biomarker for the existence of (often asymptomatic) disease in an individual
Prognostic	characteristic predicting disease progression or outcome in an untreated individual [10,11]
Predictive	characteristic predicting patient benefit or toxicity from a specific intervention [10]
Pharmacodynamic	biomarker showing direct pharmacological effect of an NCE or drug [10]
Efficacy	characteristic predicting clinical benefit
Toxicity/safety	biomarker predicting clinical risk

Biomarkers, broadly defined, can be a variety of (ideally) quantitatively measured indicators of biological or pathphysiological processes, or the response to therapeutic intervention, including molecular entities, images or other measured activities or properties, or their combination as a biomarker panel. They include proteins, protein modifications, or activities, e.g., enzymes [12]. DNA-based biomarkers include DNA (e.g., circulating DNA can be used to diagnose genetic diseases such as Down's Syndrome in unborn children [13]), single nucleotide polymorphisms (SNPs), gene copy number variations (CNVs; DNA insertions, deletions, rearrangements such as inversions and translocations larger than 1 kb, and insertions/deletions less than 1 kb [14]), mRNA or long non-coding RNA [15]. Epigenetic biomarkers include methylated DNA (e.g., fecal DNA tests for detection of colorectal cancer [16]), microRNA (e.g., a microRNA panel for diagnosis of stage II-IV colon cancer [17]), or modified histones. Other more traditional biomarkers include gross phenotypes such as blood pressure, lung volume, blood sugar and urine volume, cellular metabolites or lipids and other physical measurements including structural (e.g., computed tomography or magnetic resonance) or functional (e.g., positron emission tomography) images as used in neuroimaging [18], or electroencephalograms [19]. Combinations of different biomarker types (e.g., fluid biomarkers, tissue images, allele expression [20], clinical imaging, and molecular biomarkers [21]) may be useful for improved diagnostic accuracy [22,23], particularly in complex disease states [24], and may be more effective than individual biomarkers (see Section 4.1).

The NIH Biomarkers and Surrogate Endpoint Working Group [8] has classified biomarkers into:

- Type 0 (reflects natural history of a disease, correlates with known clinical indices over the full range of disease states),
- Type I (reflects the effects of therapeutic intervention by the mechanism of action of a drug), and
- Type II biomarkers (surrogate endpoints, whose change predicts clinical benefit).

Biomarkers can also be subdivided by their application. A clinical biomarker is a predetermined, validated characteristic or variable reflecting how a patient feels, functions, or survives after treatment [8]. Surrogate markers or endpoints are intended to substitute for a clinical endpoint, reflect clinical benefit or harm, and/or directly measure patient function or survival. Definitions and examples of cardiovascular biomarkers include use of blood pressure- and/or HDL cholesterol-lowering for cardiovascular drugs [25,26] and the use of glycated hemoglobin (HbA1c) as a surrogate endpoint in diabetes [27]. Validation of surrogate endpoints requires extensive data, including large randomized clinical trials, that must demonstrate that the surrogate is prognostic for the true clinical endpoint, and the effect of therapy on the surrogate predicts its effect on the true endpoint [28]; as a consequence, such markers are rare.