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Guest Editor's Introduction

Transcriptional biomarkers

Biological markers (biomarkers) have been used for diagnostic testing for more than 50 years and have acquired immense scientific and clinical value. This process has accelerated in the 21st century, leading to their growing appeal as markers for routine diagnostic practice. There are numerous promising biomarkers, the most important of which are currently used for assessing the efficacy of treatment, development of new drugs, especially in the area of therapeutic medicine for cancer or cardiovascular diseases. In the past, biomarkers were defined as '*cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells, or body fluids*' [1]. Nowadays the term biomarker is defined as '*a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention or other health care intervention*' by the Biomarker Consortium of the Foundation for the National Institutes of Health (FNIH) [2]. A biomarker should be able to reveal a specific biological trait or a measurable change in the organism, which is directly associated with a physiological condition or disease status.

Early disease detection by biomarkers offers an effective opportunity for enhancing disease detection, improving patient prognosis and streamlining the use of drug therapy and assessing clinical outcomes of treatment. Hence biomarkers are potentially useful along several steps of the disease process:

- Before diagnosis, they provide the potential for screening and risk assessment.
- As part of the diagnostic process, biomarkers can determine staging, grading, and selection of initial therapy.
- Subsequently, in the treatment phase, they can be used to monitor therapy success, select additional therapies or monitor recurrent diseases [3].

Currently, biomarkers span a broad diagnostic sector and have been used since the earliest days of the application of molecular biology to increase our understanding of disease mechanisms. Thus, identifying biomarkers can include all diagnostic '-omics' layers, imaging technologies, and any other objective phenotypic measures of a person's health status. So, why is there today an increased amount of attention being paid to these molecular and cellular marker signatures? Genomics, epigenomics, transcriptomics, proteomics, imaging techniques, and other high throughput technologies allow us to measure more biomarkers than before. These analytical advances and high sophisticated technologies using '-omics' technologies have generated numerous candidate biomarkers with potential clinical value. At present, although encouraging, the practical value of most of these biomarkers, which are broadly scattered and derived from by high-throughput technologies as well as various analytical levels remains uncertain. The success, measured by successful translation of characteristic biomarker signatures into clinical practice, is highly dependent on continuing advances in the field of bioinformatics, which remains a bottleneck on the road to achieving a 'personalization' of treatment strategies and disease prevention in the near future.

Using bioinformatical tools to integrate the numerous biomarker data, it is possible to achieve a greater and broader understanding of disease pathways, their physiological interactions, the targets of interventions, and the pharmacologic consequences of medicines. Biomarkers help with the understanding of drug mechanisms or disease processes and are essential in helping shape any clinical decisions aimed at curing them. Thus, the use of biomarker signatures may play an important or even 'a definitive role in developing personalized medical health care'.

This issue focuses on the transcriptomic approach to the identification of "transcriptional biomarkers". The analysis of gene expression changes is the first level of exploration for any regulatory at the molecular and cellular levels [4]. Transcription of genes is a very dynamic process, allowing cells able to adapt rapidly to external, environmental or physiological changes affecting target tissues, organs or cells. Thus gene expression profiling is a very powerful means of identifying biomarkers that describe a given physiological status, a disease, an exposure to drugs, or other exogenous stimuli [5].

The scientific contributions describe the screening, the discovery, the quantification, and validation of transcribed biomarkers at both mRNA and microRNA levels. Various papers show ultra sensitive, high throughput, or RNA sequencing methods, and the implementation of integrative biostatistical tools for transcriptional biomarker identification, confirmation, and validation.

The first contribution will summarize the synonym 'transcriptional biomarkers', screening methods and the effective application of bioinformatical validation tools. The successful application of characteristic mRNA and microRNA expression patterns and their application in doping control or steroid biology are presented. Various publications describe the work-flow of biomarker development, their technical considerations, and deal with methodological questions. The focus is on sample quality: one report, based the SPIDIA European ring study, describes how RNA integrity in blood samples has an impact on transcriptional biomarker validity, and another details the challenges of heterogeneous sampling material and how this affects the gene expression profiling data. Further various RT-qPCR data analysis algorithms and methods are being presented and their effects on biomarker discovery, quality, and validity are described. The problem of biomarker detection in limited sample material, like single-cell or stem-cells studies is also addressed. A major focus of this issue is to show new emerging

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methods to discover 'transcriptional biomarkers', like RNA-Seq, high-throughput RT-qPCR, or digital PCR and its comparison with other quantitative methods and how they can be applied in personalized medicine or tumor biology.

The predictive value of microRNA and mRNA signatures in various cancer types is shown, in combination with epigenetic modifications. Finally the application of the MIQE guidelines [6] in clinical trials is described and how the biological relevance of transcriptional biomarker experiments can be improved.

In future, molecular biomarker signatures have the potential to identify a disease early, pinpoint individuals' susceptibility, or monitor health status and therapy success. In epidemiological studies they will allow us to look at whole populations as opposed to merely relying on the family disease history. Validated biomarkers show a disease from its earliest manifestation to the terminal stage. Therefore biomarker research and development supports a multitude of clinical technologies and applications, like molecular diagnostics, drug discovery, clinical trials, and advanced bioinformatical data analysis.

References

[1] B.S. Hulka, Overview of biological markers, in: B.S. Hulka, J.D. Griffith, T.C. Wilcosky (Eds.), Biological Markers in Epidemiology, Oxford University Press, New York, 1990, pp. 3–15.
[2] The Biomarkers Consortium is a public-private biomedical research partnership managed by the Foundation for the National Institutes of Health (<http://www.biomarkersconsortium.org>).
[3] A.J. Atkinson, Clin. Pharmacol. Ther. 69 (2001) 89–95.
[4] C.H. Sewall, D.A. Bell, G.C. Clark, A.M. Tritscher, D.B. Tully, J. Vanden Heuvel, G.W. Lucier, Clin. Chem. 12 (2) (1995) 1829–1834.
[5] I. Riedmaier, M.W. Pfaffl, H.H. Meyer, Drug Test. Anal. 2012 (Suppl. 1) (2012) 70–74.
[6] S.A. Bustin, V. Benes, J.A. Garson, J. Hellemans, J. Huggett, M. Kubista, R. Mueller, T. Nolan, M.W. Pfaffl, G.L. Shipley, J. Vandesompele, C.T. Wittwer, Rev. Clin. Chem. 55 (4) (2009) 611–622.

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