Editorial

Personalized Medicine

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The era of personalized medicine: mechanistic or correlative biomarkers?

"…a successful personalized medicine-oriented biomarker development should not solely rely on traditional hypothesis-driven approach that is restricted by conventional mechanistic insights in order to take advantage of rapidly growing omics world."

Keywords: biofluid • blood • correlative biomarkers • disease process • dynamic biomarkers • genome-wide • longitudinal • personalized medicine

Victor Levenson
Author for correspondence:
Catholic Health Initiatives Center for Translational Research,
801 West Baltimore Street, Ste 302,
Baltimore, MD 21201, USA;
Tel.: +1 443 948 5436;
victorlevenson@catholichealth.net

Yuriko Mori
Catholic Health Initiatives Center for Translational Research, Baltimore, MD, USA

Personalized medicine & its components

It is generally accepted that tectonic shifts are underway in modern medicine – from population-wide approaches that use common features of the disease as the driving forces for its detection, diagnosis and treatment, we move to a person-centric universe with emphasis on attributes that are specific for a particular individual. This new level of understanding does not negate already accumulated knowledge of the most common aspects of disease, but rather reveals more intimate details of disease- and treatment-induced changes within an individual. From averaging across diverse groups we now move to personalized medicine (PM).

In this editorial we will consider the following elements as components of PM: detection of a diseased state and identification of the nature of the disease in an individual (detection and differential diagnosis [DDx]); prognosis of outcomes; prediction of an individual's sensitivity to treatment; and monitoring of response during treatment. Indeed, these elements encompass all aspects of a person's encounter with a disease, from detection and DDx to treatment and outcomes. It should be noted, however, that selection of treatment is determined not only by the real needs of the individual but also by the limited universe of current treatment options thus restricting its personalization.

PM requires accurate and real-time (or predictive) data about the disease and its sensitivity to treatment, for which obective characteristics (biomarkers) of the disease are vital. In this editorial we cover desirable biomarker characteristics and practical issues to be considered for biomarker development, highlighting the importance of "dynamic biomarkers," longitudinal measurement, correlative biomarkers (in contrast to mechanistic or hypothesis-driven biomarkers), and biomarker development in biofluids.

Roles of biomarkers in PM

One of the greatest achievements of modern medicine is undoubtedly its standard of care, ensuring that established protocols are equally available to patients in the metropolitan areas and in community hospitals. To move the same standards to the era of PM requires objective evaluation of selected traits to differentiate patients resistant to a treatment from those who will respond, patients with a disease X1 from those with disease X2, and so on. Objectively measured biomarkers thus become a keystone of PM, and their development becomes one of the most pressing issues of PM advance.

In 1998, the NIH Biomarkers Definitions Working Group defined a biomarker 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" [1]. Disease and its treatment are continuous and uninterrupted processes that cannot be adequately defined by 'static biomarkers' – biomarkers that can be measured only once (e.g., tissue-based biomarkers in solid tumors) or as biomarkers that once arising, do not change in the course of disease

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development (e.g., somatic mutations). We believe that static biomarkers have limited value for PM because they present only a snapshot of the continuity of the disease. To characterize an ongoing process, to follow transition from a benign lesion or an inflammatory process to a malignant tumor or from a non-invasive to invasive form of the disease, to rapidly detect emergence of a drug-resistant clonal subpopulation, and so on, we need dynamic biomarkers that reflect the process rather than the state. This basic requirement stipulates the need for repeated or even continuous measurement, which significantly limits the choice of media for testing (discussed later in this editorial).

What is the prerequisite for a biomarker that serves as an indicator of different processes, normal, pathogenic and induced by treatment? Conventional answer often involves an established mechanistic link to the process: for instance, a biomarker for pharmacologic response is also the target of the drug [2]. While intellectually comforting, mechanistic interpretation relies on established knowledge, neglecting the unimaginable universe of as yet unknown events, links, and processes. In order to consider this universe as a whole, the prerequisite for biomarkers has to shift from mechanistic explanations to correlation with the actual clinical observations, as has been done already for genome-wide association studies (GWAS). This shift from mechanistic to correlative biomarkers is already introduced into multiple areas of biomarker development [3]. We believe that relinquishing the need for mechanistic explanations aligns biomarker development process with the general process of knowledge advancement – from associations to mechanistic explanations and then to the control over the underlying mechanisms [4].

Practical considerations on PM-oriented biomarker development

If we look to develop a dynamic biomarker that can be measured repeatedly, changes to reflect the natural history of the disease and is developed using GWAS-like approach, we need to determine the practical questions: what is the media most appropriate for such development? What are the limits of utility for the developed biomarker measured in that media? What are the chemical structures most amenable for use as biomarkers? What are the characteristics of these chemicals that are most likely to serve as biomarkers? A comprehensive review of these questions is outside of the scope of this paper, thus we will present an outline of potential solutions.

An ideal media for biomarker development and analysis should be easily accessible, collected with a simple and minimally invasive procedure, require no or minimal processing, and be stored without the need for expensive and otherwise burdensome factors. Tissue, a widely favored medium, is far from this ideal due to the difficulties of access, collection procedure that requires surgery and either significant processing (formalin-fixed paraffin-embedded [FFPE] tissues) or storage at ultra-low temperature. In addition, longitudinal testing of tissues is impossible (response to chemotherapy cannot be measured in tumor tissue if the tumor has been already removed) or excessively invasive or, in cased of tissue-based DDx, requires precise identification of disease sites prior to the tissue collection. At the same time, tissue is a valuable resource for predictive tests to determine the sensitivity to a treatment because they provide direct access to the diseased area. In addition, predictive tests are by definition one-time determinations that do not require longitudinal re-sampling. Tissue-based tests also have some value for prognosis of outcomes [5], although changes in the initial tumor make-up (e.g., acquired drug resistance due to secondary mutations) can render initial tissue-based prognosis inaccurate [6].

> “…research on non- or minimally invasive testing media, such as blood and urine, rather than traditionally favored tissue, will further facilitate the development of clinically useful dynamic biomarkers for personalized medicine.”

Biological fluids, especially saliva, sweat, tears and urine, and to a lesser degree interstitial fluid and blood, are much more accessible for test development and analysis. Even more significantly, they can be tested repeatedly and (in case of interstitial fluid) even continuously [7]. Acknowledged relationship between blood and a number of biological fluids may create possibilities for development of a biomarker in one type of media (e.g., in blood) with subsequent transfer to another (e.g., urine). The possibility of repeated testing in biofluids is offset by the absence of a direct link to a tissue-based process for different diseases (hematologic malignancies are the most notable exception), which can lead to significant problems for biomarker development when a test developed for tissues does not perform as well in blood [8,9]. It appears likely that discovery and testing should be done in the same tissue to avoid potential differences in biomarker performance.

Blood is the most explored biofluid, and potential biomarkers described range from proteins to miRNA [10] to epigenetic modifications (methylation of cell-free DNA, histone modifications and miRNA [11]). Probably the closest contender is urine, where methylation [12] and genetic analysis in cell-free DNA [13] and proteins [14] are actively explored as potential biomarkers. Saliva can probably provide biomarkers for oral cancer and potentially for cancers of other organs [15], although the range of applications for this media

is largely unexplored. Even less work has been done in sweat, although the presence of volatile organic compounds in sweat is well established [16] as well as their potential value for detection of myocardial infarction [17] or hypoglycemia in diabetics [18].

Conclusion & future perspective

As the focus in medical progress shifts from population-based care to PM, the relevance of objectively measurable biomarkers in assuring standard of care has become greater than ever. In order to realize the highest standard of PM in both diagnostic and therapeutic aspects, there is a dire need for the development of dynamic biomarkers that reflect the longitudinal process of disease progression and treatment effects in individuals and can be measured repeatedly or continuously with minimal invasiveness. We argue that a successful PM-oriented biomarker development should not solely rely on traditional hypothesis-driven approach that is restricted by conventional mechanistic insights in order to take advantage of rapidly growing omics world. We also believe that research on non- or minimally invasive testing media, such as blood and urine, rather than traditionally favored tissue, will further facilitate the development of clinically useful dynamic biomarkers for PM.

Technological advances have and will continue to promote the realization of optimal biomarker-guided PM. Progress in analytical technologies on samples with limited quantity makes blood the medium of choice in biomarker development. Rigorous efforts are now allotted to establishing standard operation procedures for optimal and practical blood processing that is required for consistent analysis of biomarkers [19]. New targets of omics (e.g., metabolomics and microbiome) will continue to expand potential molecular targets for biomarker development. Finally, ongoing efforts on establishing standard study designs and bioinformatics tools will enhance the probability of success for biomarker candidates developed by integrative omics technologies similar to GWAS [20].

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