J. of Cardiovasc. Trans. Res. (2013) 6:447–448
DOI 10.1007/s12265-013-9477-9

Biomarkers and Heart Disease: What is Translational Success?

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Received: 9 May 2013 / Accepted: 17 May 2013 / Published online: 4 June 2013

The term "biomarker" is a generic term that encompasses any measurable biological variable that is reflective of the presence, progression, or therapeutic response to disease. Thus, biomarkers in cardiovascular disease could arguably include clinical measurements such as heart rate, imaging modalities such as cardiac MRI, or biochemical measurements of fluid samples such as blood and urine. It is this latter category which has received considerable attention in terms of potential clinical application in the early screening, detection, risk stratification, diagnosis, and prognosis of heart disease. Clear examples of translational success of heart disease biomarkers exist for risk stratification (e.g., lipid profiling and atherosclerosis) and for diagnosis (e.g., troponins and the diagnosis of ischemic injury). However, where can biomarker measurements take us in terms of disease management and therapy assessment? In this issue of the *Journal of Cardiovascular Translational Research* (JCTR), the current potential of protein and small nucleotide (i.e., microRNA) biomarkers are examined in different clinical contexts of heart disease. The overriding question that arises from this featured series is: *How do we characterize translational success?*

With that question arise several key issues for translational success: (1) defining a biomarker's purpose, (2) understanding the biomarker's relationship to the disease, (3) assessing the promise of multimarker approaches, (4) determining when a biomarker is ready for "prime time" clinical utility, (5) integrating the biomarkers into standard clinical practice, and (6) maximizing medical resource allocation.

The first issue to address, in terms of the overarching question, is to define the specific expectations and purpose of a biomarker test. For example, is the purpose of the biomarker measurement to improve the sensitivity and accuracy of a currently available test? In this case, high sensitivity troponin measurements have certainly improved the sensitivity of diagnosing acute coronary syndromes when compared to ECG criteria. On the other hand, troponin levels hold poor specificity or predictive value in terms of predicting clinical and functional outcomes such as adverse left ventricular remodeling and the progression to heart failure. Thus, a very careful definition of the purpose of the biomarker must be established.

A second consideration is that although biomarkers may be reflective of underlying disease processes, such as the release of cardiac myocyte enzymes with ischemia or mediators of profibrotic pathways in hypertensive heart disease, a functional role in disease may not be a necessary criterion for the biomarker's usefulness. For example, while inflammatory markers may be highly informative in terms of evaluating heart disease progression, their functional roles in specific pathologies are still being defined. Presented in this issue of JCTR there are several reviews and reports investigating inflammatory pathways and their relevance to the development and progression of heart disease [1–6].

The third theme, and one that is becoming recognized with greater frequency, is that multimarker analyses have become technically feasible. While a single biomarker may provide sensitive and specific insight, analyses of multiple biological pathways will likely allow a better discrimination of the multifactorial nature of heart disease and may facilitate more personalized heart disease management. The study and assembly of subsets of biomarkers via statistical modeling, such as receiver operating curves (ROCs) and cross-validation, are becoming more common place. Indeed, several of the papers presented in this featured issue of *JCTR* highlight promising multimarker approaches [2, 3, 7, 8].

A fourth critical question is: When does a biomarker transcend that of a laboratory based biochemistry measurement to become a reliable and practical tool for clinical use? Biomarkers may be used in a multitude of ways and a

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partnership between laboratory medicine/chemists, clinicians, and regulatory entities is necessary to validate the tests and clearly define usage guidelines. In the clinical context of cancer and inflammatory disease the binary and categorical use of biomarkers has taken hold. For example, breast cancers can be categorized as Her-2 positive or negative and autoimmune diseases, such as Raynaud's syndrome, can have positive or negative antinuclear antibody tests and be treated accordingly. However, the use of biomarkers, in terms of a categorical function, has not realized this type of clinical success in cardiovascular disease. On the other hand, if clinical decisions are to be made on continuous measurement results, then analytical performance across the measurement interval must be assured and nuanced guidance should be provided for clinical decision making. In this issue of *JCTR*, several examples of how biomarkers are being translated to clinical use for specific disease etiologies are provided including ischemic heart disease [3, 5, 9], dilated cardiomyopathies [4], heart failure with a preserved ejection fraction [2, 8], acute decompensated heart failure [1–3], and arrhythmias [7]. Authors from the FDA also provide their insights in this issue with an "*Evaluation of heart failure biomarker tests: a survey of statistical considerations*" [10].

While the identification of biomarkers that can provide important diagnostic and prognostic information with high sensitivity and specificity for a heart disease process would appear to be the major milestone in terms of defining translational success, it is but the beginning. Additional steps include commercial platform development (e.g., point of care and/or central laboratory tests), assay validation, regulatory approval, physician and patient education, integration into guidelines, and gathering evidence that appropriate clinical use of the biomarker is tied to positive outcomes so that the expense of the measurement can be justified. Biomarkers can also influence the development and utilization of therapeutics. To facilitate this, researchers should more aggressively explore how biomarkers can be used in clinical trials for patient selection and as indicators of treatment effectiveness. In addition, it is likely that biomarker profiling can be incorporated into treatments algorithms and used in clinical decision making for therapy selection and optimization. While these applications may seem somewhat optimistic, the articles presented in this featured issue certainly set the stage.

Finally, biomarker profiling may hold significant relevance in terms of utilization of medical resources. A biomarker panel that provides predictive value in terms of a successful outcome for a drug or device, or for that matter assists the clinician in the development of a judicious disease management strategy, would likely be a significant advancement in effectively reducing medical care costs. It should also be recognized that a growing segment of patients are becoming empowered with information and are increasingly seeking out genomic and biomarker tests to guide their medical care. Thus, the integration of biomarker profiling in terms of heart disease diagnosis and management appears to be on the horizon whether driven by clinicians or the patients themselves. In this issue of the *Journal of Cardiovascular Translational Research* we wish to highlight many biomarkers that are demonstrating success at different stages in the hope that our celebration of the successes will spur continued biomarker translational research and ultimately better care for patients with heart disease.

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