



Precision medicine and cardiac troponin biomarkers: new practice recommendations advance diagnostic precision

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A review of the historic use of cardiac biomarkers for evaluation of coronary syndromes creates a twisting network of timelines and advances that illustrate the scientific method of precision medicine. Publication of clinical practice guidelines have established milestones along those timelines and the recent consensus recommendations for use of cardiac troponins (cTn) (1) exists in the context of previous accomplishments and the challenges ahead.

The first milestone was the laboratory medicine practice guideline on cardiac markers by the National Academy of Clinical Biochemistry (NACB) published in 1999 which outlined the use of creatine kinase MB isoenzyme and the emerging biomarkers cTn T and cTn I (2). While the concept of precision medicine was not articulated in 1999, the first guideline defined the identification of patient subpopulations relative to onset of chest pain, ECG changes and serial changes of cardiac biomarkers characteristic of acute myocardial infarction. The second milestone is comprised of the NACB practice guidelines and the Third Universal Definition of Myocardial Infarction that both appeared between 2007 and 2012 and these refined the analytic and clinical applications of cardiac biomarkers with coronary syndromes. Historically, the second milestone emerged as the general concepts of precision medicine were established (3). Precision medicine was described by the National Research Council Committee in 2011 as:

“the tailoring of medical treatment to the individual characteristics of each patient... the ability to classify individuals into subpopulations that differ in their susceptibility to a

particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment.” (3).

The third and current milestone from the NACB will consist of expert-opinions [published in January 2018 (1)] and evidence-based recommendations (under preparation). This milestone provides constructive suggestions to enable consistent cTn analyses for patients including suggested quality control practice, objective definitions for describing assay performance (e.g., limit of detection, limit of quantitation and limit of blank), recommended reporting units (ng/L without decimal places for patient results) as well as definitions to distinguish contemporary and high sensitivity cTn assays. These recommendations are also intended for clinical trials to improve comparability of studies involving measurement of cTn. The third NACB set of recommendations advances diagnostic precision by advocating high sensitivity cTn assays be reported with sex-specific 99th percentile upper reference limits, rather than a common 99th percentile associated with contemporary cTn assays. Although the clinical utility of sex-specific ranges has yet to be definitively established, this consensus statement encourages their implementation. Laboratories and clinicians have been slow to adopt such ranges for high sensitivity cTn and the NACB has recommended better communications between these groups to promote understanding of pre-analytic and analytic concerns regarding cTn assays. Stat testing in hospital central laboratories commonly aims for a 1-hour turn-around time

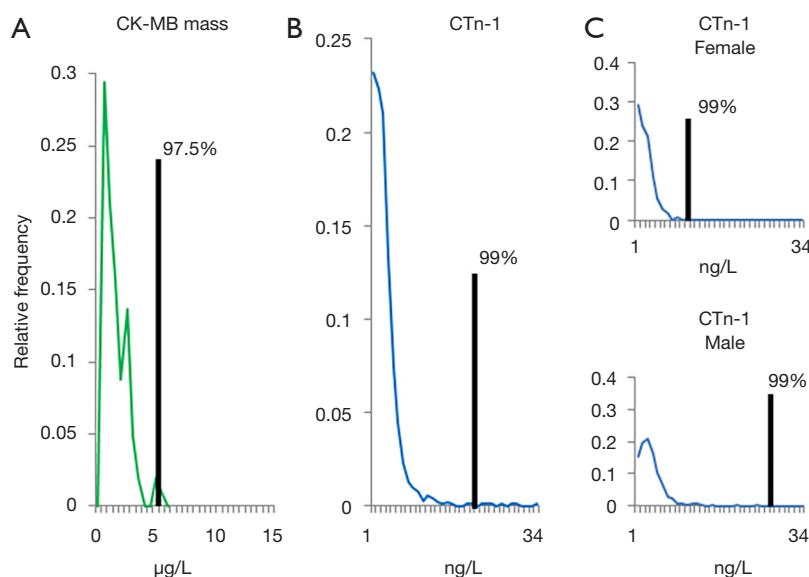


Figure 1 Milestones in the cardiac biomarker timeline. Historic development of cardiac biomarkers has followed the principles of precision medicine by classifying individuals into sub-populations to tailor medical treatments. (A) Reference population frequency of creatine kinase MB isoenzyme mass with the 97.5th percentile for the assay indicated as a black bar (4). (B) Reference population frequency of cardiac troponin I with the 99th percentile for the assay indicated (5). (C) Sex-specific reference population frequencies of cardiac troponin I with the 99th percentile for the assay indicated (5).

interval once the specimens have arrived in the laboratory. The current practise recommendations acknowledge this turn-around time goal but encourage efforts to improve service delivery. Although point of care methods provides an appealing alternative testing platform, their implementation has been limited for numerous reasons including clinical specificity and sensitivity as well as standardization and harmonization issues.

The scientific method of precision medicine is exemplified in the series of NACB recommendations or milestones for use of cTn in acute coronary syndromes as each guideline has advanced the tailoring of medical treatments for patients in specific sub-populations (Figure 1). The most recent set of recommendations continues that tradition. It should also be noted that improved measurements of cTn have contributed to resolving the pathobiology of cardiac diseases and establishing new relevant sub-populations that will be the subject of future advances and timelines that continue to be revealed.

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