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Letter to the editor

Validation and implementation of the fifth-generation high sensitivity Troponin T (hs-TnT) assay at a large teaching county hospital. A laboratory-driven multi-speciality effort

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ABSTRACT

We describe the validation and implementation of the new 5th generation high sensitivity Troponin T assay (Roche Diagnostics®). In addition to the assay improved sensitivity, the numerical values, reporting units, reference intervals, and critical limits are markedly different. We describe the use of clinical correlation as the basis for implementation and validation of the fifth-generation hs-TnT assay at a large teaching county hospital.

To the Editor,

Clinical laboratories frequently introduce new diagnostic tests and update those in use when the implementation process requires performance validation activities governed by both regulatory guidelines [1] and manufacturer's recommendations. When applying an update to an existing test, usually associated with calibration set points, new assay formulation, or changes to dilution protocols, there is often little or no clinically significant change in reportable values. Rarely, an assay measuring the same analyte offers either completely different reportable values or reports values are not interchangeable with the prior generations of the assay. Evaluation of the performances of such assays requires clinical correlation and outcomes analysis as part of the technical validation and implementation.

The FDA recently approved for clinical use a fifth generation highly sensitive Troponin T assay (hs-TnT). In addition to the assay's improved sensitivity, the numerical values, reporting units, reference intervals, and critical limits are markedly different from the prior generation of the assay. The improved sensitivity of the assay makes possible new protocols with shorter “rule out” AMI times. Clearly the changes in assay and protocol engendered with the fifth generation assay impacts all health care personnel caring for patients with chest pain and suspected of myocardial ischemia.

A multi-speciality team drawn from Clinical Chemistry, Cardiology, Emergency Medicine, Laboratory Administration, Information Technology, Nursing, Hospitalist Medicine, and Performance Improvement departments was set up. The team initially met on a bi-weekly basis, then weekly during the last 2 months prior to implementation of the new hs-TnT assay and diagnostic protocol. During the frequent sessions an implementation protocol was developed and progress of the assay technical and clinical validation was reviewed (Fig. 1). Meetings were hosted and mediated by a representative from the hospital Performance Improvement division.

The performance of the hs-TnT assay was validated on the Cobas® 6000 system, e601 immunoanalyzer (Roche Diagnostics) as per protocol for the following: analytical reportable range, imprecision, limit of detection, and for calibration verification studies. Quality control ranges were also established. Manufacturer's reported reference intervals were verified using samples from healthy laboratory volunteers (20 males and 20 females). All technical validations were within acceptable limits. Assay reportable range was verified from 6 to 100,000 ng/L following a 1:10 dilution (Table 1). Gender stratified manufacturer's reference intervals were verified at < 14 ng/L for females, and < 22 ng/L for males, and < 19 ng/L for both genders combined. 969 samples from 541 patients (56% men, 44% women) being investigated for acute coronary syndrome were analysed using both 4th and 5th generations hs-TnT assays.

The imprecision of the hs-TnT assay was assessed according to the CLSI EP5-A3 protocol [2]. To facilitate assessment over a wide hs-TnT concentration range, the assay imprecision was extensively assessed using three sets of quality control material obtained from 2 different suppliers, Liquichek™ Cardiac Markers Plus and Cardiac Troponins quality control materials from Bio-Rad and Cobas® PreciControl Troponin control material from Roche. Within assay imprecision (obtained by forcing samples thru each of 2 measuring cells of 3 automated analysers) as well as between assays imprecisions (over 20 days) were assessed. Within assay imprecision was 0.9% at 16 ng/L (Cardiac Troponin), 1.47 and 0.83% at 28 and 1970 ng/L (PreciControl), and 3.2, 4.0% at 240 and 4789 ng/L (Cardiac Markers) respectively. Similarly, intraassay imprecisions were 2.6% at 16 ng/L (Cardiac Troponin), 2.12 and 1.5% at 28 and 1970 ng/L (PreciControl), and 3.1, 2.6, and 4.1% at 240, 1024, and 4789 ng/L (Cardiac Markers) respectively. Total imprecision for all control materials was 2.7, 2.6, 4.5, 3.3, 1.7, and 5.7% at 16, 28, 240, 1024, 1970 and 4789 ng/L hs-TnT respectively. The differences between different material may be due to possible matric differences. However, when using plasma samples, the following within assay imprecision was observed 4.7, 3.3, 2.2, and 3.9% at 12, 16, 24, and 53 ng/L respectively.

The technical implementation of the assay was initially completed by the ‘Rapid Response’ laboratory performing over 5000 Troponin tests a month and serving the critical care areas. This was followed, 6 weeks later, by implementation of the assay by the Core Laboratory supporting the inpatient non-critical units and the outpatient clinics. Acceptable correlation studies between the two testing laboratories were obtained.

To assess if the new hs-TnT assay facilitated an improved AMI rule-out protocol, we first added an additional blood sample acquisition at 1 h following baseline cTnT to our existing AMI 3-h rule-out protocol

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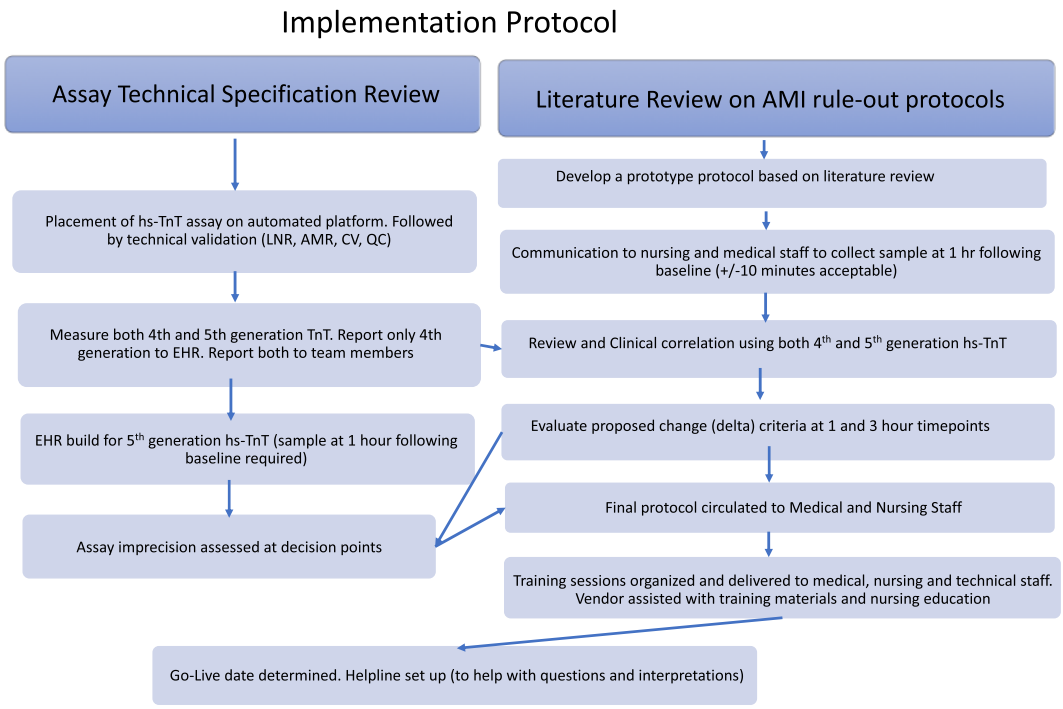

Fig. 1. Implementation protocol. Flow diagram showing both technical and clinical validation of the new 5th generation hs-TnT and the development of the diagnostic protocol.

Table 1
Comparison of performance characteristics and utility of the 4th and 5th generation Troponin T assays.

	4th Generation Troponin T	5th Generation Troponin T
Lower decision limit	< 0.01 ng/mL	< 6 ng/L
Delta	N/A	3 at 1 h, 7 and 3 h
Critical value	≥ 0.01 ng/mL	≥ 52 ng/L
AMI rule -out protocol	3 h	0, 1 and 3 h

using the 4th generation cTnT assay. We then conducted a pre-implementation study of a new diagnostic protocol for AMI to model assay performance and to allow education and possible protocol modification prior to 'go-live' [3]. Samples received into the laboratory were analysed using both the conventional 4th generation cTnT assay and results reported in the usual manner, and the 5th generation hs-TnT but results for the later were not transferred to the electronic medical record (EMR). Formal adjudication of AMI events was performed by a panel of three cardiologists using all available clinical data and 30-day follow-up was obtained. Operating characteristics were compared for the 4th and 5th generation cTnT protocols, as was the proportion of individuals meeting criteria for 'rule-out AMI' at 0, 1, and 3 h following presentation and a protocol was developed [3]. The imprecision of the assay was re-assessed at the protocol recommended decision levels. The full complement of information technology build (results transfer to EMR) of the 5th generation hs-TnT was completed and tested.

The validity and implication of the developed rule-out protocol was discussed with emergency department clinical staff and hospitalists for feedback prior to implementation. Educational materials were prepared and training sessions conducted for pathology residents and technical staff by the clinical chemist, for nursing staff by representatives from nursing education department, and for medical staff by cardiologists and emergency department physicians. Roche diagnostics® provided technical support at the instrument level as well as scientific support staff to aid with training of nursing staff in the ED and other patient care areas.

Leaflets describing the new diagnostic protocol were distributed throughout the clinical care stations within the hospital. Chief residents of the various clinical specialities received copies and were tasked with ensuring distribution among residents. A memorandum and educational material were circulated to all hospital clinical staff.

Central to the success of the protocol is adherence to sample collection times at 1 and 3 h. This was achieved following training where median values were ± 9 and 12 min for 1- and 3-h samples respectively (Fig. 2).

The manufacturer's claim for fifth generation hs-TnT assay performance was successfully verified. Based on our earlier studies [4] and this report the use of detection limits was recommend when making clinical decision. A 3 step, 0, 1, and 3-h rule-out protocol was developed which utilized the higher sensitivity of the 5th generation hs-cTnT assay compared to its predecessor. The protocol [3] uses specific levels and relative change values rather than the 99th percentile decision limits, and allowed rule-out of AMI in 30% of patients at 0, 24% at 1 h, and 30% at 3 h. For the remaining 16%,13% had non-ischemic myocardial injury, 2% type 2 AMI, and 1% type I MI). In contrast, 4th generation assay required 3 h to rule out 80% of patients with the remaining 20% including 17% non-ischemic myocardial injury, 2% type II AMI, and 1% type I NSTEM.

Hospital leadership support, close collaboration and participation of health care providers from various clinical departments was essential. The project accumulated 31 h on operational discussions, 15 h on information technology structure, 20 h on physician training and 8 h on nursing training. Laboratory technical implementation and validation accumulated > 600 h. It is important to note that the implementation process described above is specific to our institution, as similarly stated for the rule out protocol, and that the process may not be directly implemented at other clinical or research settings without appropriate modifications. In addition to technical verification of the assay characteristics, the project highlights the need for clinical correlation as the basis for assay validation and serves as an example of a laboratory-driven process that facilitated the development of shorter AMI rule-out protocol.

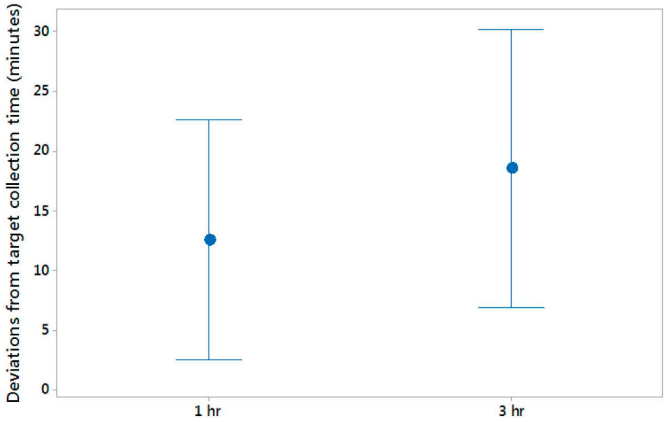

Fig. 2. Median and range deviations in minutes from target sample collection times scheduled for 1 and 3 h from presentation.

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