High-Sensitivity Cardiac Troponin I Assay Is Coming Soon

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The use of cardiac troponin (cTn) testing for diagnosing myocardial infarction (MI) has been standard of care for over 20 years because of its absolute specificity for cardiac muscle. For over 5 years, "high sensitivity" cardiac troponin (hscTn) tests have been successfully implemented by healthcare systems across the the world, and they have demonstrated several diagnostic advantages over our coventional cTn assays. Key among these include: (i) permitting the establishment of rapid “rule-out” and “rule-in” protocols for myocardial infarction, (ii) higher diagnostic sensitivity to detect non-ischemic myocardial injury, and (iii) superior ability to assess a patient’s future cardiac risk. On August 19, 2020, barring COVID-related delays, the BJH Core Laboratory will switch from our current cardiac troponin I test to a high sensitivity cardiac troponin I (hscTnI) test from Abbott Laboratories that was cleared by the FDA in November 2019.

hscTnI assays detect troponin concentrations in blood approximately ten times lower than current methods and accomplish this with superior analytic precision. Upon comparision, the limit of accurate quantification (LOQ) of our current method is 30 ng/L (0.03 ng/mL) while the LOQ of the hscTnI method is 4 ng/L (0.004 ng/mL).

By definition, hscTnI assays quantify circulating cTn above the LOQ in > 50% of healthy subjects (i.e., those with no history of, or risk factors for, cardiac disease) while having an imprecision of < 10% coefficient of variability (CV) at the 99th% concentration of a healthy population. The 99th% concentration in a healthy population is the upper reference interval (URL) used in the 4th Universal Definition of Myocardial Infarction which states, "*The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL.*"

The 99th% URL for the new hscTnI was determined in a cohort of 766 healthy males and 765 healthy females. Sex-specific 99th% URLs will be used to improve diagnostic sensitivity for MI in females. Also, note that the units for reporting troponin will change to ng/L to avoid many zeroes in the result field. Analytic characteristics and the 99th% URL of the current method and the new hscTnI method are depicted in Table 1.

Table 1	Limit of Quantification	99th% URL	Imprecision (%CV) at 99th% URL
Current Method	30 ng/L	28 ng/L - Overall	20
High-Sensitivity Method	4 ng/L	17 ng/L - Female 35 ng/L - Male	4

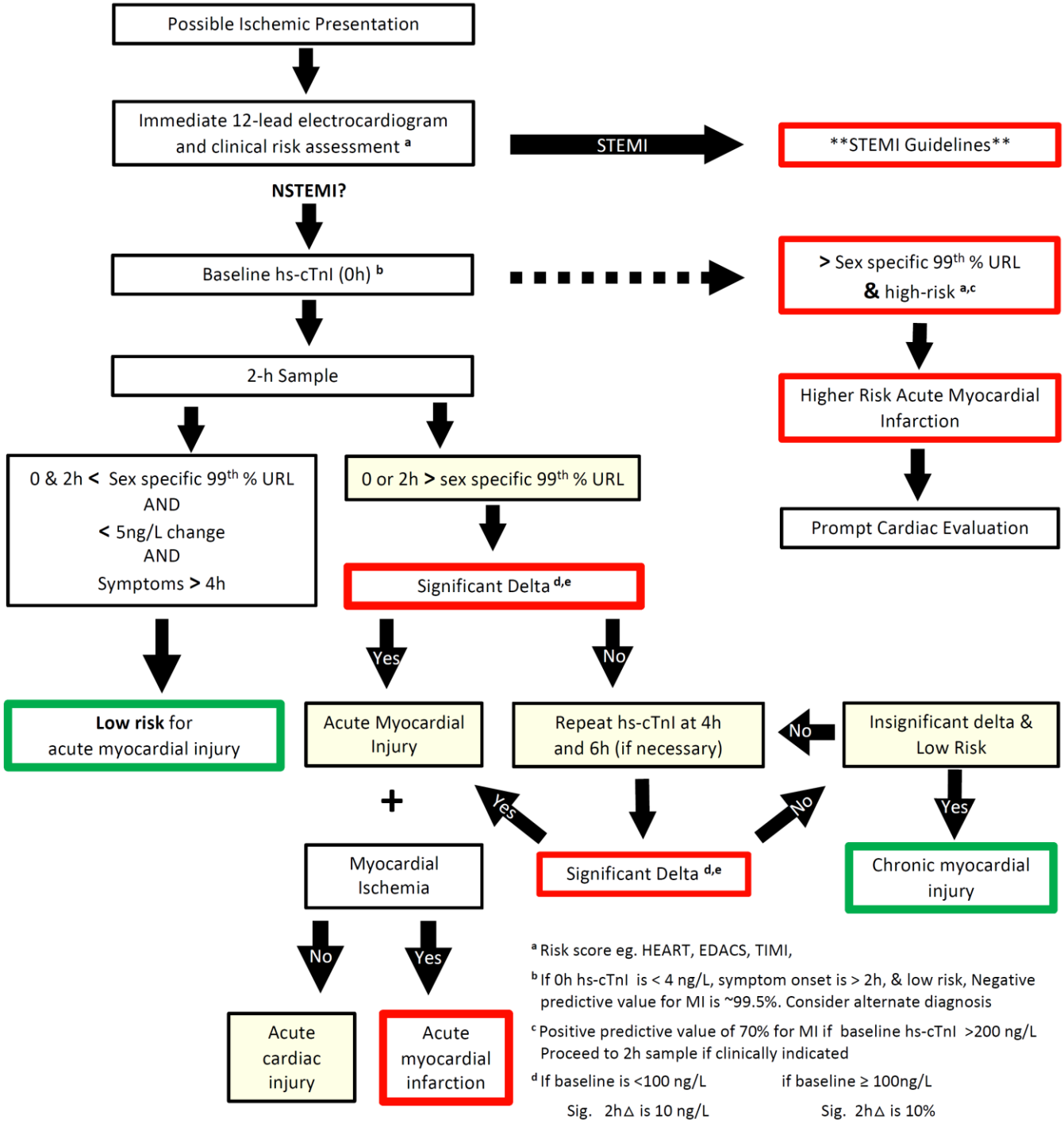
The superior sensitivity and precision of hscTnI assays has enabled the development of accelerated diagnostic protocols (ADPs) for ruling in or ruling out MI in emergent care settings. These protocols rely on both absolute hscTnI values above and below the sex-specific 99th% URL and the detection of changes (i.e., “deltas”) at predefined time points in combination with clinical risk factors. Numerous large scale studies have demonstrated that ADPs have exceptional negative predictive values (~ 99.5%). As such, ADPs using hscTn assays demonstrated an exceptional capacity to rapidly rule-out myocardial injury and/or infarction. The ADP that will be implemented at BJH is largely based on the algorithm developed at at the University of Minnesota, Hennepin County Hospital using the Abbott Laboratories’ hscTnI method and is shown in figure 1. In this algorithm, patients are considered low risk for MI when symptom duration is greater than 2 hrs is coupled and

the hs-cTn value is less than the LOQ (4 ng/L). At two hours, patients are considered low risk for MI when the 2 hr value remains less than the 99th% sex-specific URL and the delta between the 0 and 2 hr values is < 5 ng/L. In contrast, the accelerated classification defines high risk when hscTnI values are above the 99th% URL (when coupled with suggestive clinical characteristics) or when deltas exceed predetermined values, which are purposely set to have high positive predictive values (e.g., >70%). The orderable test for implementing this ADP will be "Troponin I high-sensitivity series (baseline, 2hr, 4hr, 6hr)" which will automatically place orders for baseline, 2, 4 and 6 hour samples. The new hscTnI test will require a 3 mL lavender top tube (K_2EDTA).

Serial cTn testing is essential for diagnosing acute MI, particularly when index troponin concentrations are above the 99th% URL but < 100 ng/L. Patients with chronic comorbidities that cause non-ischemic cardiac injury (e.g., cardiomyopathy, end-stage renal failure, etc.) will often have hscTn values falling within this range. Thus, the initial differential for hscTnI concentrations within this range must be kept broad, including non-ischemic conditions responsible for insidious (e.g., chronic kidney disease, cardiac amyloidosis, dilated cardiomyopathy) and acute (e.g., acute heart failure exacerbation, myocarditis, pulmonary embolism, sepsis, drug cardiotoxicity) myocardial injury. Unlike acute MI, myocardial injury due to non-ischemic etiologies will not ordinarily result in significant deltas when serial hscTn testing is performed over several hours, unless their onset is acute.

The Division of Laboratory & Genomic Medicine (LGM) worked with the Division of Cardiology, the Department of Emergency Medicine,and the BJH laboratory to prepare educational materials posted on a website that will promote the best utilization of hscTnI testing https://bjhlab.testcatalog.org/show/hsTrop-1 . Please contact either Chris Farnsworth (cwfarnsworth@wustl.edu) or Mitch Scott (mgscott@wustl.edu) of LGM if you have any questions.

High Sensitivity Troponin I Algorithm



99th % URL
Male: 35 ng/L
Female: 17 ng/L

[a] Risk score eg. HEART, EDACS, TIMI,

[b] If 0h hs-cTnI is < 4 ng/L, symptom onset is > 2h, & low risk, Negative predictive value for MI is ~99.5%. Consider alternate diagnosis

[c] Positive predictive value of 70% for MI if baseline hs-cTnI >200 ng/L Proceed to 2h sample if clinically indicated

[d] If baseline is <100 ng/L

Sig. 2hΔ is 10 ng/L
Sig. 4hΔ is 15ng/L
Sig. 6hΔ is 20ng/L

if baseline ≥ 100ng/L

Sig. 2hΔ is 10%
Sig. 4hΔ is 15%
Sig. 6hΔ is 20%

*At least one cTnI must be elevated for rules to apply

[e] If samples are collected >10-20h after onset of acute chest pain, troponin may have peaked and delta criteria may not apply. Declining troponin can be significant (ie. old MI). Same criteria are used with negative delta.