High Sensitivity Cardiac Troponin Assays Are Coming Soon

By: Chris Farnsworth, PhD and Mitch Scott, PhD

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. In August 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, provided by Abbott Laboratories, which was cleared by the FDA in November 2019. The hsCTnI assay detects troponin concentrations in blood approximately ten times lower than current methods, with superior analytic precision. The limit of accurate quantification (LOQ) of the hsCTnI method is 4 ng/L (0.004 ng/mL) versus 30 ng/L (0.03 ng/mL) with our current method.

By definition, hsCTnI assays quantify circulating cTn above the LOQ in >50% of healthy subjects (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, which 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 of MI in females. Also, note that the units for reporting troponin will change to ng/L to avoid many zeroes in the result field. (continued on page 2)
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Analytic characteristics and the 99th% URL of the current method and the new hscTnI method.

<table>
<thead>
<tr>
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<th>Limit of Quantification</th>
<th>99th% URL</th>
<th>Imprecision (%CV) at 99th% URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Method</td>
<td>30 ng/L</td>
<td>28 ng/L - Overall</td>
<td>20</td>
</tr>
<tr>
<td>High Sensitivity Method</td>
<td>4 ng/L</td>
<td>17 ng/L - Female</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 ng/L - Male</td>
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</tbody>
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For over 5 years, hscTn tests have been successfully implemented by healthcare systems across the world, and they have demonstrated several diagnostic advantages over current assays. Key among these include: (i) permitting the establishment of rapid “rule-out” and “rule-in” protocols for myocardial infarction, (ii) stronger diagnostic sensitivity to detect non-ischemic myocardial injury, and (iii) superior capacity to assess a patient’s future cardiac risk.

The superior sensitivity and precision of hscTnI assays has enabled development of accelerated diagnostic protocols (ADPs) for ruling in or out myocardial infarction 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 (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%). The ADP that will be implemented at BJH is based on one using the Abbott Laboratories’ hscTnI method at the University of Minnesota, Hennepin County Hospital and is shown on the next page. In this algorithm, patients are considered low risk for MI when symptom duration >2 hours is coupled with an hscTnI value <4 ng/L (LOQ). For hscTnI testing at 2 hours after the baseline sample, patients are considered low risk for MI when the 2 hour value remains <99th % sex-specific URL and the delta between the 0 and 2 hr values is <5 ng/L. In contrast, the accelerated classification defines patients as high risk if hscTnI values are ≥99th% URL with consistent clinical risk factors or when deltas exceed predetermined values set according to a high positive predictive value (>70%).

Serial testing is critical for diagnosing acute MI, particularly when index troponin concentrations are ≥99th% URL but <100 ng/L. Patients with chronic comorbidities that can cause non-ischemic cardiac injury (e.g., cardiomyopathy, end-stage renal failure, etc.) will often have hscTnI values falling within this range. Thus, the initial differential at these hscTnI concentrations must be kept broad and include conditions responsible for insidious and acute causes of myocardial injury: heart failure, chronic kidney disease, myocarditis, cardiotoxic drugs, cardiomyopathy, amyloidosis and sepsis. All of these can result in non-ischemic cardiac injury, but unlike acute myocardial infarct, these comorbidities will not result in significant deltas when serial hscTnI testing is performed over several hours unless their onset is acute.

The Division of Laboratory & Genomic medicine is working with the Division of Cardiology, the Department of Emergency Medicine, and the BJH laboratory to prepare educational materials that will promote the best utilization of hscTnI testing that can be found at https://bjhlab.testcatalog.org/show/hsTrop-1. (continued on page 3)
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High Sensitivity Troponin I Algorithm

Possible Ischemic Presentation

Immediate 12-lead electrocardiogram and clinical risk assessment a

NSTEMI?

Baseline hs-cTnl (0h) b

2-h Sample

0 & 2h < Sex specific 99th % URL AND < 5ng/L change AND Symptoms > 4h

0 or 2h > sex specific 99th % URL

Yes

No

Low risk for acute myocardial injury

Acute Myocardial Infarction

Repeat hs-cTnl at 4h and 6h (if necessary)

Insufficient delta & Low Risk

Yes

No

Myocardial Ischemia

Significant Delta de

Acute myocardial infarction

Acute cardiac injury

Yes

No

Promote Cardiac Evaluation

Higher Risk Acute Myocardial Infarction

**STEMI Guidelines**

> Sex specific 99th % URL & high-risk a,c

99th % URL

Male: 35 ng/L
Female: 17 ng/L

a Risk score eg. HEART, EDACS, TIMI,
b If 0h hs-cTnl 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-cTnl >200 ng/L Proceed to 2h sample if clinically indicated
d If baseline is <100 ng/L if baseline ≥ 100ng/L

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

*At least one cTnl 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.
Molecular Testing for SARS-CoV-2 at BJH

By: Neil Anderson, KB

On March 16th, 2020 the Barnes Jewish Hospital (BJH) Laboratory began molecular testing for SARS-CoV-2. This response to the ongoing COVID-19 pandemic has been a joint effort from the BJH Microbiology Laboratory, BJH Molecular Infectious Disease Laboratory, and Washington University faculty. Since implementation, these teams have worked together to rapidly grow testing across a variety of platforms, resulting in increase from a test capacity of approximately 50 specimens a day to approximately 1,200 tests per day. This has allowed Barnes Jewish Hospital to provide testing for patients across different clinical sites throughout the BJC healthcare network and the Saint Louis region.

Testing for COVID-19 can be ordered in Epic using the orderable “COVID-19 Coronavirus” (Lab Number LAB4920). The preferred specimen type is a nasopharyngeal (NP) swab collected in Universal Transport Media (UTM). Testing on lower respiratory specimens (bronchoalveolar lavages, bronchial washings, tracheal aspirates, and sputum) is also available and should be considered when patients with strong clinical suspicion for infection initially test negative by NP swab.

Testing is performed 24 hours a day and results are available within 12-24 hours of specimen receipt within the BJH Microbiology Laboratory. A limited supply of rapid testing kits are available (4-hour turnaround time upon laboratory receipt) and the testing is reserved for situations in which a rapid result is clinically necessary. This is determined by a series of questions developed by clinical and laboratory leadership posed at the point of ordering in Epic.

By broadly offering molecular testing we hope to be poised to best serve our patients during the COVID-19 pandemic. If you have any questions, please contact BJH Laboratory Customer Services (314-362-1470) or refer to the BJH COVID-19 FAQ document (https://wustl.box.com/v/CoronavirusCOVID19).

DID YOU KNOW?

As of July 8, 2020, 50,614 COVID test results have been reported by BJH
Serologic Testing for SARS-CoV-2 at BJH

By: Neil Anderson, K B

On May 4th, 2020 the Barnes Jewish Hospital Core Laboratory began serologic testing for COVID-19 using the Abbott SARS-CoV-2 IgG serologic assay.

The Abbott SARS-CoV-2 IgG assay allows for the qualitative detection of SARS-CoV-2 IgG which has been suggested to play a role in COVID-19 diagnosis, identification of patients with presumptive immunity and identification of convalescent plasma donors. Serologic testing has important limitations which should be carefully considered when used for these purposes.

1) Diagnosis of COVID-19:
Serologic testing SHOULD NOT be used to rule in or rule out COVID-19 infection. False positive results can occur due to past exposure to seasonal coronaviruses (types OC43, 229E, HKU1, and NL63). False negative results can occur early in disease. Data from BJH patient testing suggests a sensitivity of <10% within 3 days of symptomatology and <44% at ≤14 days. If active COVID-19 infection is suspected, PCR testing of a nasopharyngeal swab, oropharyngeal swab or lower respiratory tract specimen should be ordered for COVID-19 diagnosis (Epic Order: COVID-19 Coronavirus RNA).

2) Identification of patients with presumptive immunity:
Currently all serologic assays for SARS-CoV-2 are designed only to determine past infection with the virus. There are no currently available serologic assays that can reliably predict immunity.

3) Identification of convalescent plasma donors:
The use of convalescent plasma to treat COVID-19 is based upon finding donors with high concentrations of SARS-CoV-2 antibodies. The majority of commercial serologic assays available are qualitative (including the Abbott IgG assay) and none are able to reliably predict success of convalescent plasma treatment.

Testing will be performed on plasma (submitted in EDTA pink or purple top tubes) or serum (submitted in red top or serum separator tubes) and will be batched once per day. Providers can expect a 24-48 hour turnaround time from specimen receipt in the laboratory. Positive results will not be flagged as abnormal and will be reported to the Missouri Department of Health. Testing can be ordered with Epic order “SARS-CoV-2 (COVID-19) Antibody IgG” (LAB3959). This test should be ordered no earlier than 14 days after symptom onset to maximize positive and negative predictive value.


For additional information regarding SARS-CoV-2 testing performed at BJH providers should reference the laboratory FAQ document, which is updated daily (https://wustl.box.com/v/CoronavirusCOVID19).
Meeting the Laboratory Informatics Challenges of the COVID-19 Pandemic

By: Ron Jackups, KB, PhD

The COVID-19 pandemic has presented clinical and strategic challenges across BJC and WUSM; clinical laboratories were no exception. Members of the Laboratory and Genomic Medicine (LGM) Division in the Department of Pathology and Immunology sprang into action as the first cases appeared in the St. Louis area, both by implementing clinical testing as soon as they became available. When convalescent plasma from donors previously exposed to COVID-19 became a therapeutic option, LGM provided critical leadership in making this option available to patients.

These challenges presented an opportunity to find effective solutions in our information systems and other informatics resources. LGM, in concert with BJC’s laboratory information services (LIS), quickly built an order in Epic (LAB4920) that would facilitate molecular tests requests to address both clinical need and the unprecedented risk of managing a scarce inventory of testing options. The current order employs order questions (Figure 1), asking about a patient’s symptoms and the indication for testing, in order to determine the urgency of testing and preserve the laboratory’s ability to perform rapid testing for patients whose clinical management hinges on a swift diagnosis (e.g. patients being admitted to a clinical floor directly from the emergency department). In addition, LGM has built or contributed to several dashboards that provide clinical leaders essential information and testing statistics to make strategic decisions about how to employ future testing and therapeutic options (Figure 2).

As convalescent plasma became recognized as an adjunct therapy for select patients with COVID-19, blood banks across BJC needed to address the challenge of ensuring that this critical resource be available for such patients. LGM and LIS once again worked together to modify the existing plasma transfusion orders to facilitate the ordering of this unique product as well as tools to track its use across the system.

To date, over 50,000 patients have been testing for COVID-19 across BJC. The laboratories at our hospitals, laboratory information services, and the members of the Division of LGM will continue to support the diagnosis and care of these patients as we address new challenges in the future. (continued on page 7)
Meeting the Laboratory Informatics Challenges of the COVID-19 Pandemic (continued from page 6)

**Figure 1:** Example of COVID-19 RNA test order (inpatient view)

**Figure 2:** Example of laboratory dashboard for COVID-19 RNA testing