LSI Medience Corporation

PATHFAST™

hs-cTnI

high sensitivity troponin I

IFCC & ESC compliant

0/1 h NSTEMI rule-out/rule-in algorithm

POCT – whole blood/plasma

Results in < 17 minutes

PATHFAST™ hs-cTnI: early and immediate diagnosis of MI in the emergency department (ED)

PATHFAST™ hs-cTnI is a chemiluminescent enzyme immunoassay (CLEIA) for quantitative measurement of cardiac troponin I (cTnI) concentration in whole blood or plasma at the point of care (POC).
Low concentrations of cTnI can be analysed by using high sensitivity cardiac troponin (hs-cTnI) assays which meet the criteria defined by IFCC and ESC (1,2). PATHFAST™ provides high accuracy and precision of test results similar to central lab analyser, combined with the flexibility of a POCT assay within 17 minutes out of whole blood and plasma by all in one cartridge solution.
The new PATHFAST™ hs-cTnI assay fits for the recommendations on the IFCC and ESC guidelines for the early detection of AMI(1-3,9).

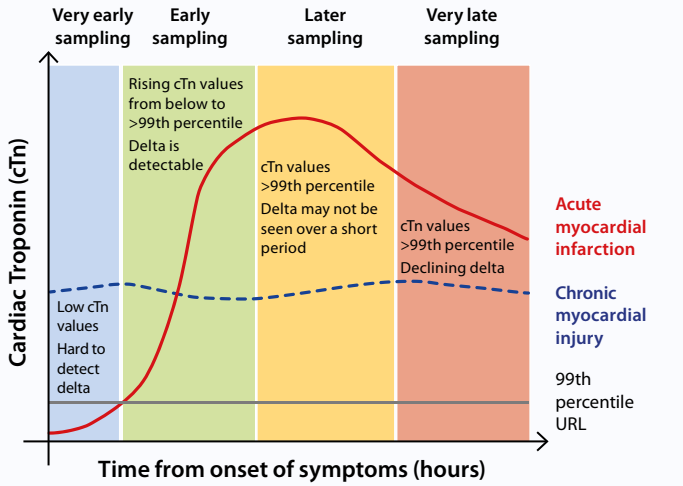
Clinical benefits of hs-cTn assays

hs-cTnI assays detect troponin levels at low concentrations with high accuracy and precision at the earliest point of time. They measure low levels of troponin released by ischemia/micro-necrosis (Fig. 1) and allow even detection and quantification of troponin levels of healthy individuals (4).

The European Society of Cardiology (ESC) recommend the use of hs-cTn assays (2, 3) for early rule-in and rule-out of Acute Myocardial Infarction (AMI) and differentiation from patients with non-coronary artery cardiac diseases. High-sensitivity troponins can detect small changes for a short time accurately even at the early phase of the disease and differentiate acute disease from chronic state (Fig.1, 9).

In addition to the diagnosis of AMI, detection of low cardiac troponin levels may make it possible to predict information (risk stratification) in terms of short- and long term mortality of patients (5).

Fig. 1: cTnI kinetics after acute myocardial injury including acute myocardial infarction

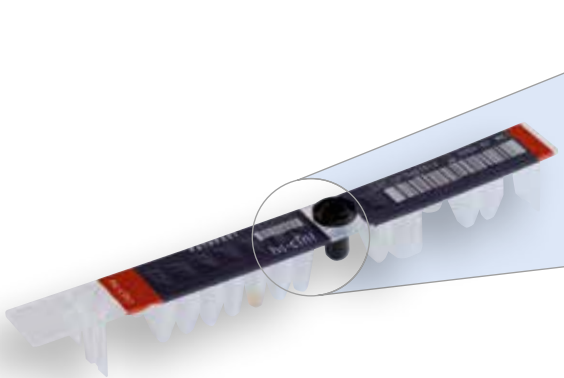


Time course of acute and chronic myocardial infarction (8)

99th **29.0 ng/L**

CV **6.1 %**

In clinical studies PATHFAST™ hs-cTNI has been evaluated for a 99th percentile upper reference limit of 29.0 ng/L at an imprecision of 6.1%, which is less than 10% and fits for the criteria of hs-cTnI, declared by IFCC (1).



High sensitivity troponin I

Time
- Results in less than 17 minutes
- Early detection of AMI patients
- Up to 6 tests in parallel

Sensitivity
- Chemiluminescent enzyme immunoassay
- High sensitivity

Practicality
- Whole blood or plasma (100 µL)
- For Emergency Room and Chest Pain Units
- Single unit use
- All in one cartridge

Reliability
- Excellent precision at low cTnI concentrations
- Excellent correlation with central lab analysers

Criteria for a high sensitivity cTn assay

Recommendation from IFCC (1)	
99th percentile of hs-assays should be measured with an analytical imprecision of <10% CV	✓
hs-cTn assays should measure cTn above the limit of detection (LOD) in 50% of healthy individuals	✓
Gender specific 99th percentile values should be established for men and women	✓

Recommendation from ESC guideline (2,3)	
New ESC guidelines of 2015 advises to use 0 h /3 h rule-out or a 0 h /1 h rule-in/rule-out algorithm by using high sensitivity troponin assays as an alternative to the established 0 h /3 h /6 h procedere (2).	✓

For PATHFAST™ hs-cTnI assay the 99th percentiles values were determined in 734 healthy individuals and are listed in Table 1. Gender specific 99th percentile cut offs for overall, females and males are 27.9 ng/L (this value is not significantly different from the FDA cleared overall 99th percentile of 29.0 ng/L before exclusion of individuals with abnormal NT-proBNP, HbA1c and eGFR), 20.3 ng/L, and 29.7 ng/L respectively (6).

Tab. 1: Gender specific 99th percentile by PATHFAST™ hs-cTnI assay

	N	Gender specific 99th percentile (ng/L)	% measurable concentrations > LoD
Overall	734	27.9	n= 487 (66.3%)
Males	382	29.7	n= 301 (78.8%)
Females	352	20.3	n= 186 (52.8%)

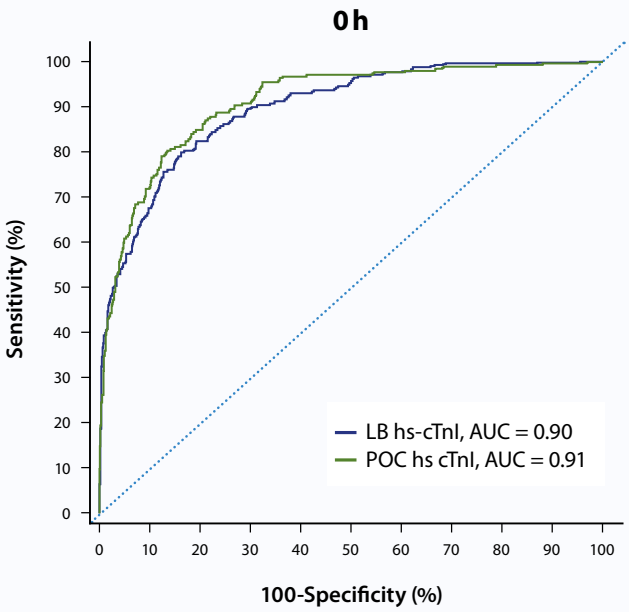
Gender specific 99th percentile and measurable number of healthy subjects between LoD and 99th percentile after exclusion of individuals with abnormal NT-proBNP, HbA1c and eGFR (6)

Troponin concentrations were measured with the PATHFAST™ hs-cTnI assay in EDTA plasma.

The ROC analyses of PATHFAST™ hs-cTnI and of a guidelines recommended well established laboratory-based highsensitivity troponin assay (LB hs-cTnI) revealed comparable discriminatory ability for the diagnosis of NSTEMI. The ROC analysis showed the AUC at 0 h (n=1.244) was 0.91 (95% CI, 0.89–0.93) for PATHFAST™ hs-cTnI, and 0.90 (95% CI, 0.87– 0.92) for the LB hs-cTnI. After 1 h (n=1.251), AUC values increased to 0.94 (95% CI, 0.93– 0.96) for PATHFAST™ hs-cTnI and 0.94 (95% CI, 0.92–0.96) for the LB hs-cTnI assay (Fig. 2A and 2B) (7).

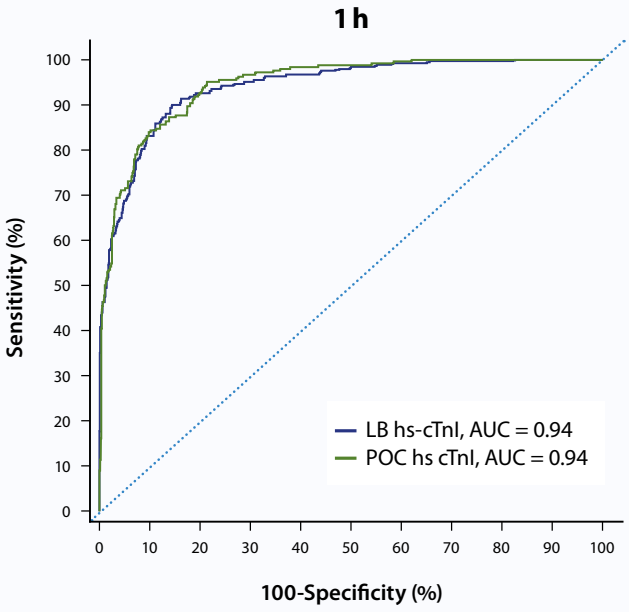
PATHFAST™ hs-cTnI assay offers the opportunity for chest pain units and emergency units to test hs-cTnI in less than 17 min.

Fig. 2A: Comparison ROC of PATHFAST™ and one central LAB assay for NSTEMI patients at admission



Performance of PATHFAST™ hs-cTnI and a LAB Method (hs-cTnI) in NSTEMI patients (7), modified from Sörensen NA et al. Clin Chem 2019; (65): 1592-1601 (7)

Fig. 2B: Comparison ROC of PATHFAST™ and one central LAB assay for NSTEMI patients after one hour

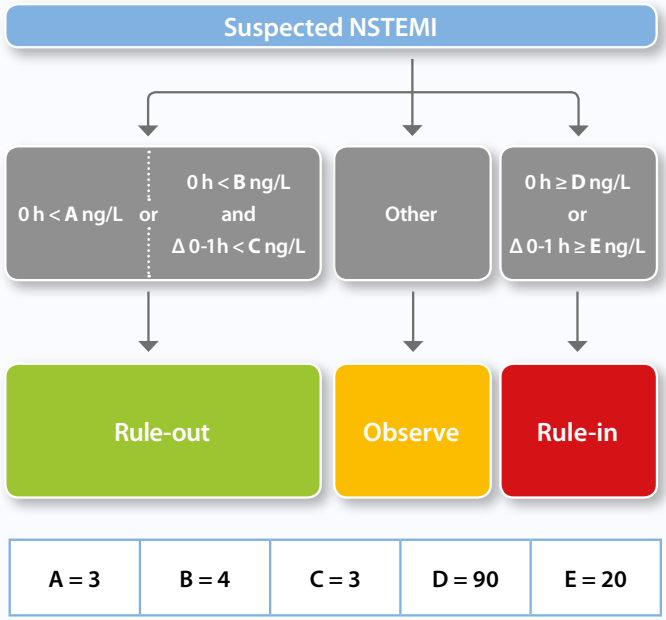


Performance of PATHFAST™ hs-cTnI and LAB method (hs-cTnI) in NSTEMI patients, modified from Sörensen NA et al. Clin Chem 2019; (65): 1592-1601 (7)

Diagnostic algorithms for PATHFAST™ hs-cTnI

The ESC guidelines recommended rule-in and rule-out algorithms using hs-cTn assays in patients admitted with suspected NSTEMI to the ED (2).

Fig. 3: Schematic depiction of rule-in and rule-out algorithms



Algorithms adapted and modified from Roffi M et al. Eur Heart J 2016; 37: p. 276 (2)

Rule-out of NSTEMI at admission for PATHFAST™ hs-cTnI (0 h)

According to the ESC guideline rule-out is possible already at admission (0 h) if the value is below a cut off level (**A**) and if onset of chest pain > 3 h. Regarding the LoD of 2.3 ng/L (6) recent s tudy data of PATHFAST™ hs-cTnI using a cut off level A of 3 ng/L with targeted NPV of 100% revealed the following results (7):

NPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	% ruled-out (95% CI)	Total N
100.0 (98.8, 100.0)	100.0 (97.7, 100.0)	46.5 (42.6, 50.5)	37.2	792

For 0 h rule-out only individuals with a symptoms onset over 3 h before presentation were used.

0 h / 1 h Rule-out algorithm of NSTEMI for PATHFAST™ hs-cTnI

A rule-out of NSTEMI is possible by the combination of a baseline concentration below a cut off level **B** and the delta from 0 h to 1 h < **C** (Fig. 3). 2015 ESC Guidelines recommend that in large validation cohorts the NPVs for rule-out of NSTEMI should exceed 98% (2). A diagnostic algorithm for a high-sensitive troponin I point of care assay was developed in a derivation dataset with 669 patients and validated in additional 610 patients. For PATHFAST™ hs-cTnI wide range of the combination was tested for 1.221 patients with suspected NSTEMI to achieve a NPV of above 99.5% with the highest number of patients ruled-out and the following cut off values have been identified (7-8, Table 2).

Tab. 2: Rule-out of NSTEMI with serial sampling for PATHFAST™ hs-cTnI within one hour (7,8)

0 h ≤ B (cTnI, ng/L)	Δ 0-1h ≤ C (cTnI, ng/L)	NPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
4	3	99.7 (98.8, 100.0)	99.1 (96.9, 99.9)	58.1 (54.9, 61.2)

0 h / 1 h Rule-in algorithm of NSTEMI for PATHFAST™ hs-cTn I

A rule-in for the likelihood of NSTEMI is possible if the hs-cTn value at admission (0 h) is measured above of a cut off level ≥ **D** or the hs-cTn concentration shows a rise within the first hour above the delta cut off level ≥ **E** (Table 3).

2015 ESC Guidelines recommend that the PPVs for validation cohorts should meet the rule-in criteria of 75-80% (2). For PATHFAST™ hs-cTnI the clinical study with 1.221 patients with suspected NSTEMI showed PPVs above 75% with specifities above 95%. The following cut off values have been identified (7-8, Table 3). Regarding the clinical situation of the individual patient the user may decide which cut off values may be applicable for optimal rule-out or rule-in.

Tab. 3: Rule-in of NSTEMI with serial sampling for PATHFAST™ hs-cTnI within one hour (E) (7,8)

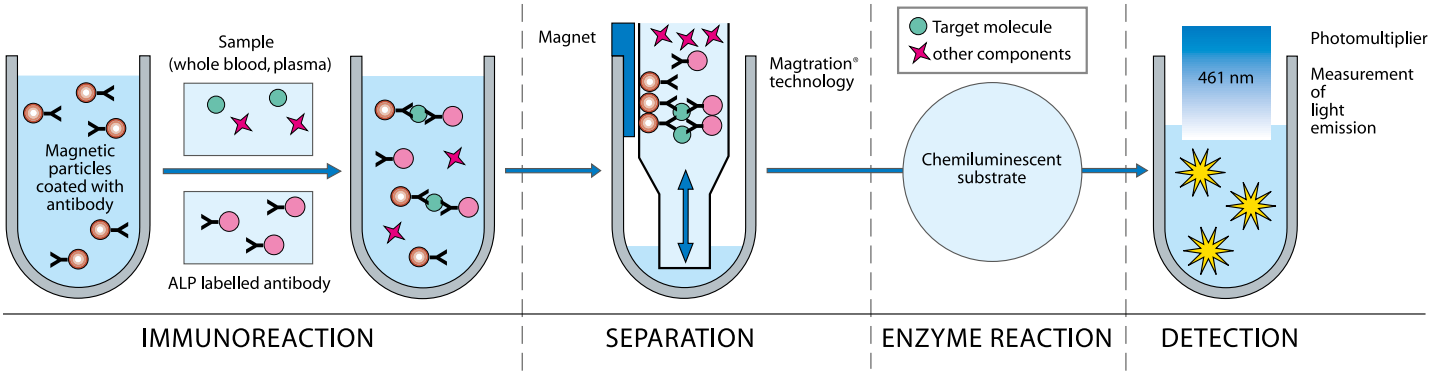
0 h ≥ D (cTnI, ng/L)	Δ 0-1h ≥ E (cTnI, ng/L)	PPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
90	20	80.1 (73.7, 85.5)	65.7 (59.2, 71.7)	96.2 (94.8, 97.3)

Conclusions from clinical studies

The clinical application of a 0/1 h diagnostic algorithm based on a novel PATHFAST™ POC hs-TnI assay is safe (7).

The diagnostic performance of PATHFAST™ POC hs-cTnI assay is comparable to a guideline-recommended established laboratory hs-cTnI assay (7).

PATHFAST™ Test Principle



PATHFAST™ Technical Specifications

Instrument type	Desktop Immunoassay Analyzer
Throughput	Up to 6 samples or parameters per run
Measuring time	<17 minutes for 6 samples using emergency markers or PATHFAST™ Presepsin
Sampling material	Whole blood, plasma, serum
Measuring principle	Chemiluminescence enzyme immunoassay technology (CLEIA) and Magtration® technology.
Reaction temperature	37 °C
Sample volume	100 µl
Data storage	Patient data: 1000, QC data: 1800, CAL data: 300
Datatransfer	ASTM and Fixed standard
Weight	28 kg
El. requirements	100 - 240 V AC (50/60 Hz)
Power consumption	360 VA
Monitor/keyboard	LCD touch-screen
Printer	Integrated
PC	Integrated, Handheld Barcodereader included
Interface	RS-232C and Ethernet Port
Calibration	Factory calibration, 2-point calibration every 4 weeks
24-h operation (stand-by)	Recommended

PATHFAST™ Dimensions

References

1. Apple FS, Jaffe AS, Collinson P, et al. IFCC educational materials on selected analytical and clinical applications of high sensitivity cardiac troponin assays. Clin Biochem 2015; 48: 201-203
2. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2016; 37(3): 267-315
3. Thygesen K, Alpert JS, Jaffe AS, et al. Third Universal Definition of Myocardial Infarction. Eur Heart J 2012; 33: 2551-256
4. Garg P, Morris P, Fazlanie AL, et al. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. Interm Emerg Med 2017;12: 147-155
5. Blankenberg S, Salomaa V, Makarova N, et al. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium. Eur Heart J 2016; 37: 2428-2437
6. Christenson RH, Duh S-H, et al. Validation of high-sensitivity performance for a United States Food and Drug Administration cleared cardiac troponin I assay. Clin Biochem. 2018 Jun; 56:4-10
7. Sörensen NA, Neumann JT, Ojeda F, et al. Diagnostic evaluation of a high-sensitivity troponin I point-of-care I assay. Clin Chem 2019; (65): 1592-1601
8. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019; (40): 237-269

Product List **PATHFAST™ for critical care and sepsis diagnostics**	Item number	Pack size
SYSTEM		
PATHFAST™ Immunoanalyser Analyzer for the detection of cardiac and other emergency parameters and sepsis	1114-0000	1 x 1
CONSUMABLES AND ACCESSORIES		
PATHFAST™ pipette tips	1114-1000	5 x 42 units
PATHFAST™ waste box	1114-1001	10 units
REAGENT KITS FOR CRITICAL CARE DIAGNOSTICS		
PATHFAST™ hs-cTnI	1110-5000	60 tests
PATHFAST™ Myoglobin	1110-2001	60 tests
PATHFAST™ CK-MB	1110-2002	60 tests
PATHFAST™ D-Dimer	1110-2003	60 tests
PATHFAST™ NTproBNP	1110-2004	60 tests
PATHFAST™ hsCRP	1110-2005	60 tests
REAGENT KITS FOR SEPSIS DIAGNOSTICS		
PATHFAST™ Presepsin	1110-4000	60 tests
PATHFAST™ Presepsin control set	1110-4001	4 x 1 ml

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