MITSUBISHI CHEMICAL EUROPE

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

LSI Medience Corporation

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 (2015) for the use of high sensitivity troponin assays (1,2).

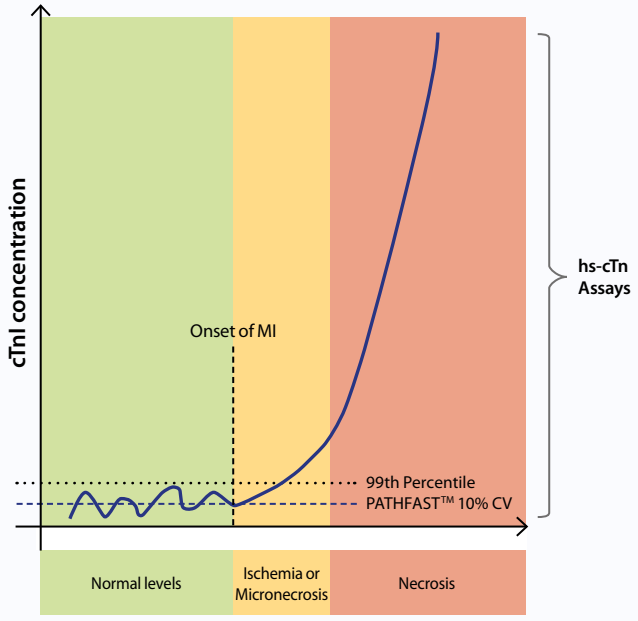
Clinical benefits of hs-cTn assays

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/micronecrosis (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.

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).

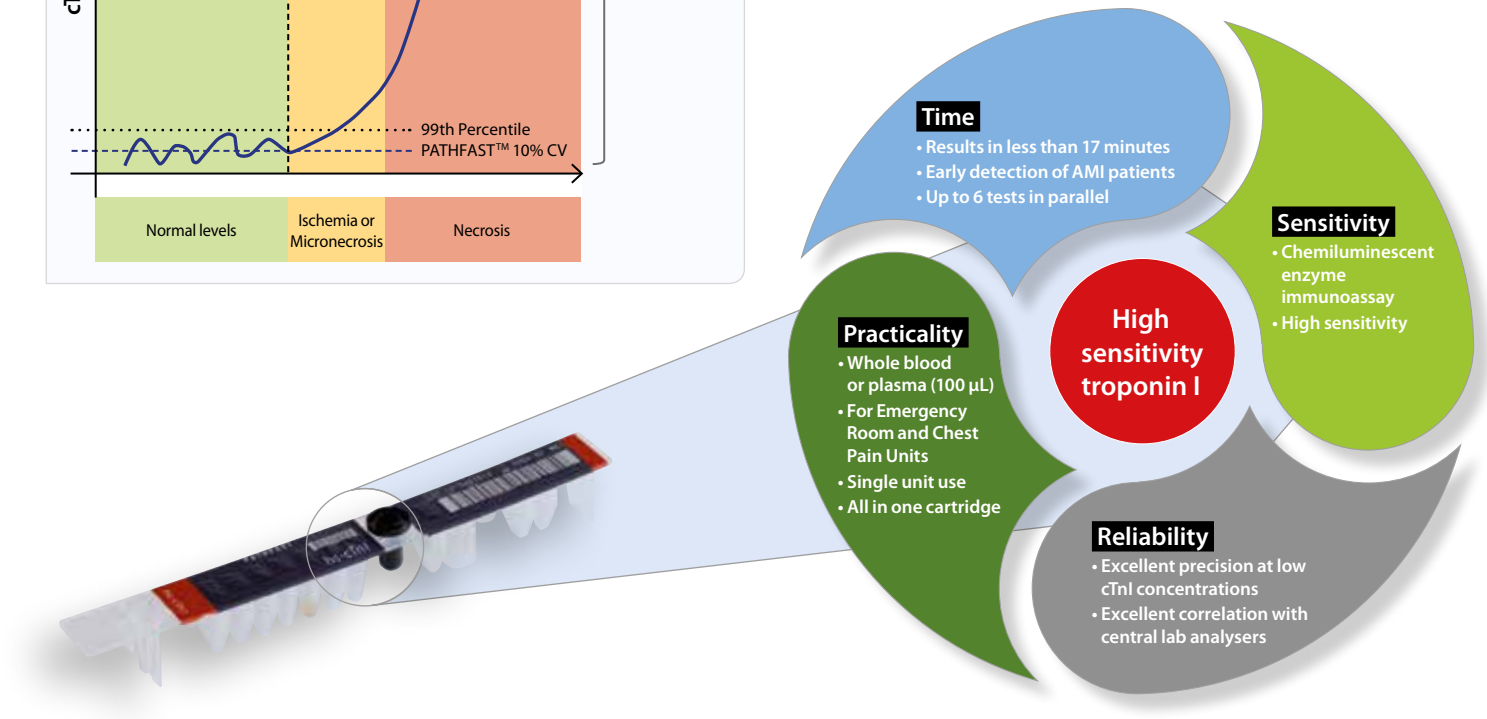
Fig. 1: cTnI levels in different clinical situations



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).



Criteria for a high sensitivity cTN assays

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.

Samples from 993 patients obtained at 0 hour, 1 hour and 3 hours after admission to the Chest Pain Unit (CPU) with suspicion of acute coronary syndrome, were used. 219 AMI patients were identified (23.5%) by two independent cardiologists with blinded cTnI values.

The ROC analysis for the discrimination between AMI and non-AMI patients including the clinical sensitivity and specificity, as well as the Positive and Negative Predictive Values (PPV and NPV) based on the 99th percentile value are explained in Table 2 for PATHFAST™ hs-cTnI assay. Comparison with one established central laboratory methods (troponin I) showed comparable diagnostic validity for AMI (NSTEMI and STEMI) (Fig. 2A) and NSTEMI patients (Fig. 2B) (7).

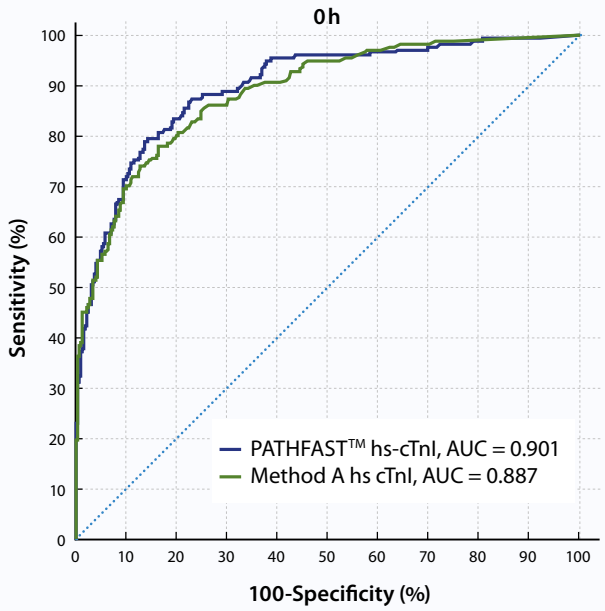
PATHFAST™ hs-cTnI assay offers the opportunity for chest pain units and emergency units to test hs-cTnI in less than 17 minutes.

Tab. 2: ROC analysis for diagnosis of AMI at 0,1,3 hour after admission

Time point after admission	0 h	1 h	3 h
RO-AUC	0.901	0.949	0.964
Sensitivity, % (95% CI)	65 (58-72)	81 (75-86)	91 (86-94)
Specificity, % (95% CI)	92 (90-94)	93 (90-94)	91 (89-93)
PPV, % (95% CI)	73 (66-79)	77 (71-82)	75 (69-80)
NPV, % (95% CI)	89 (86-91)	94 (92-96)	97 (96-98)

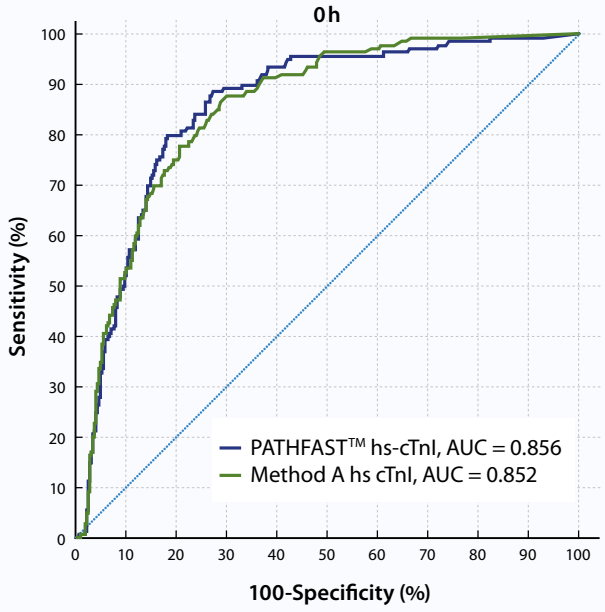
Diagnostic performance criteria of PATHFAST™ hs-cTnI (7)

Fig. 2A: Comparison ROC of Method A for AMI (STEMI and NSTEMI) patients



Performance of PATHFAST™ hs-cTnI and Method A (hs-cTnI) in AMI patients (7)

Fig. 2B: Comparison ROC of Method A for NSTEMI patients

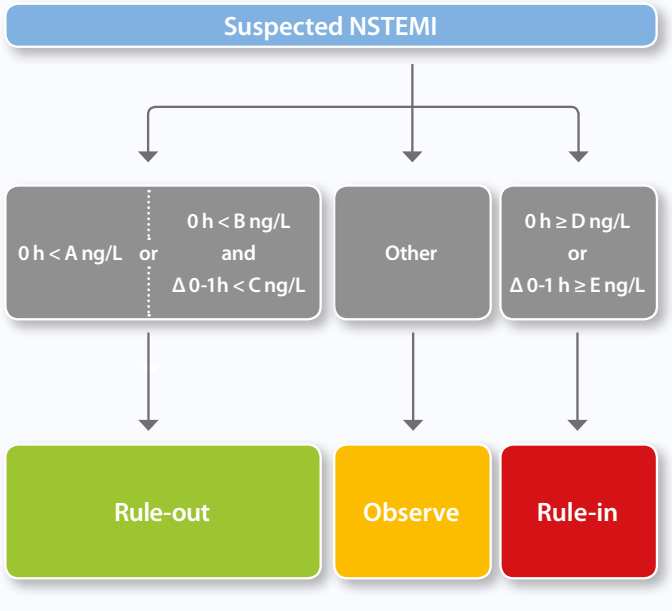


Performance of PATHFAST™ hs-cTnI and Method A (hs-cTnI) in NSTEMI patients (7)

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 according to 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) preliminary study data using a cut off level **A** of 3 ng/L revealed the following results (7):

NPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	% ruled-out (95% CI)	Total N
100,0 (97.6, 100,0)	100,0 (95,8, 100,0)	44,4 (39,1, 49,7)	35,8	441

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

Rule-out is possible by the combination of a baseline level below a cut off level (**B**) and below of an increase within 1 hour (**C**). In large validation cohorts the NPVs for rule-out of NSTEMI exceeded 98%. For PATHFAST™ hs-cTnI the following cut off levels have been examined with NPVs between 98.9% and 100% (8).

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, Table 3). In large validation cohorts the NPVs for rule-out of NSTEMI exceeded 98% (2). For PATHFAST™ hs-cTnI the following cut off levels have been examined for 669 patients with suspected NSTEMI and NPVs between 98.9% and 100% (8).

Tab. 3: Rule-out of NSTEMI with serial sampling for PATHFAST™ hs-cTnI within one hour

0 h ≤ B (cTnI, ng/L)	Δ 0-1h ≤ C (cTnI, ng/L)	NPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
3	1	100.0 (97.8, 100.0)	100.0 (97.3, 100.0)	30.5 (26.6, 34.6)
	2	99.6 (97.5, 100.0)	99.3 (95.9, 100.0)	41.9 (37.7, 46.2)
	3	99.6 (97.8, 100.0)	99.3 (95.9, 100.0)	46.9 (42.6, 51.2)
4	1	100.0 (98.1, 100.0)	100.0 (97.3, 100.0)	36.1 (32.0, 40.3)
	2	99.6 (98.0, 100.0)	99.3 (95.7, 100.0)	51.0 (46.7, 55.3)
	3	99.7 (98.2, 100.0)	99.3 (95.7, 100.0)	56.6 (52.3, 60.9)
5	1	99.5 (97.3, 100.0)	99,3 (97.1, 100.0)	38.3 (34.2, 42.6)
	2	99.3 (97.6, 99.9)	98,5 (94.7, 99,8)	55.9 (51.6, 60.1)
	3	99.4 (97.9, 99.9)	98,5 (94.7, 99,8)	62.1 (57.8, 66.2)
6	1	99.1 (96.7, 99.9)	98,5 (94,7, 99,8)	40.6 (36.4, 44.9)
	2	99.1 (97.3, 99.8)	97,8 (93,6, 99.5)	59.3 (55.0, 63.4)
	3	98.9 (97.2, 99.7)	97.0 (92,5, 99,2)	66.0 (61.8, 70.0)

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

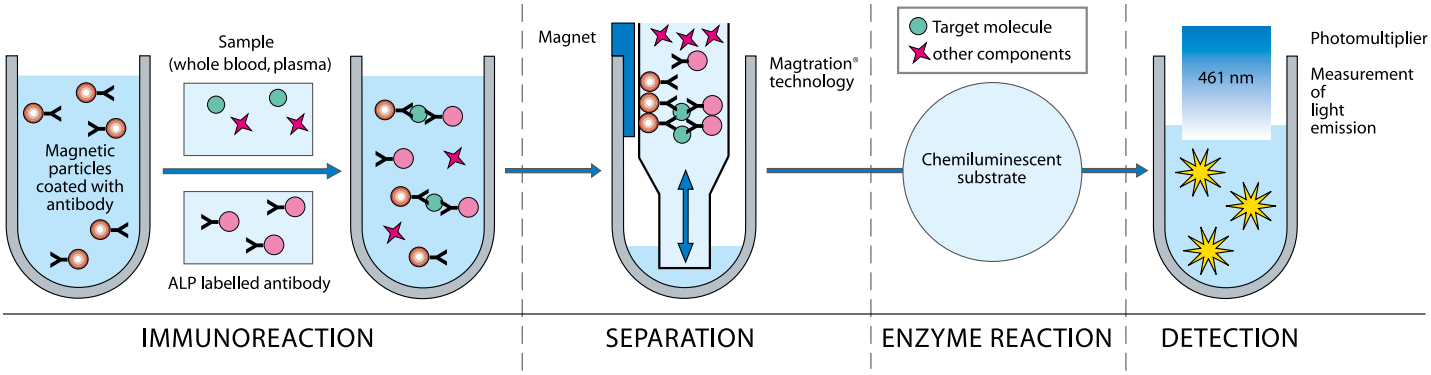
A rule-in for the likelihood of NSTEMI is possible if the hs-cTn value at admission (0 h) is measured above of a cut off level ≥ **D** or the hs-cTn concentration shows a rise within the first hour above the delta cut off level ≥ **E** (Table 4).

The PPVs for rule-in NSTEMI obtained from validation cohorts meet the rule-in criteria of 75-80% (2). PATHFAST™ hs-cTnI fulfilled these conditions in a clinical study with 669 patients with suspected NSTEMI. Cut off values with PPVs between 75.2% and 78.6% have been identified (8). 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. 4: Rule-in of NSTEMI with serial sampling for PATHFAST™ hs-cTnI within one hour (E)

0 h ≥ D (cTnI, ng/L)	Δ 0-1h ≥ E (cTnI, ng/L)	PPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
90	15	75.2 (66.5, 82.6)	67.9 (59.3, 75.7)	94.4 (92.1, 96.2)
	20	77.0 (68.1, 84.4)	64.9 (56.2, 73.0)	95.1 (93.0, 96.8)
	25	78.3 (69.2, 85.7)	61.9 (53.2, 70.2)	95.7 (93.6, 97.3)
	30	78.6 (69.5, 86.1)	60.4 (51.6, 68.8)	95.9 (93.8, 97.4)
100	15	74.8 (66.0, 82.3)	66.4 (57.8, 74.3)	94.4 (92.1, 96.2)
	20	76.6 (67.6, 84.1)	63.4 (54.7, 71.6)	95.1 (93.0, 96.8)
	25	77.9 (68.7, 85.4)	60.4 (51.6, 68.8)	95.7 (93.6, 97.3)
	30	78.2 (68.9, 85.8)	59.0 (50.1, 67.4)	95.9 (93.8, 97.4)

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
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7. Sörensen NA, Neumann JT, Ojeda F, et al. Diagnostic evaluation of a new high-sensitivity point-of-care troponin I assay. ESC Congress Munich 2018, P3181
8. Sörensen NA, Neumann JT, Ojeda F, et al. Diagnostic evaluation of a new high-sensitivity point-of-care troponin I assay. Personal Communication from the University Heart Center Hamburg, Germany

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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