ACC Accreditation Services™

Troponin Essential Guidelines: A Practical Implementation Guide

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Speaker Overview

Ruth Cantu, BSN, RN, AACC

Accreditation Product and Programs Development

No disclosures

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Objectives

Participants will be able to:

1) Discuss the differences in the testing methodologies
2) Summarize the latest Troponin guidelines/research
3) Describe the role Troponin plays in the clinical environment
4) Appraise the potential effects of Troponin on clinical care
5) Describe the integration of Troponin requirements within the Chest Pain Center (CPC) Accreditation Tool
6) Share quality practices to optimize care and outcomes of the Acute Coronary Syndrome Patients (ACS)

American College of Cardiology (ACC)

Mission:

To transform cardiovascular care and improve heart health.

Vision:

A world where innovation and knowledge optimize cardiovascular care and outcomes.

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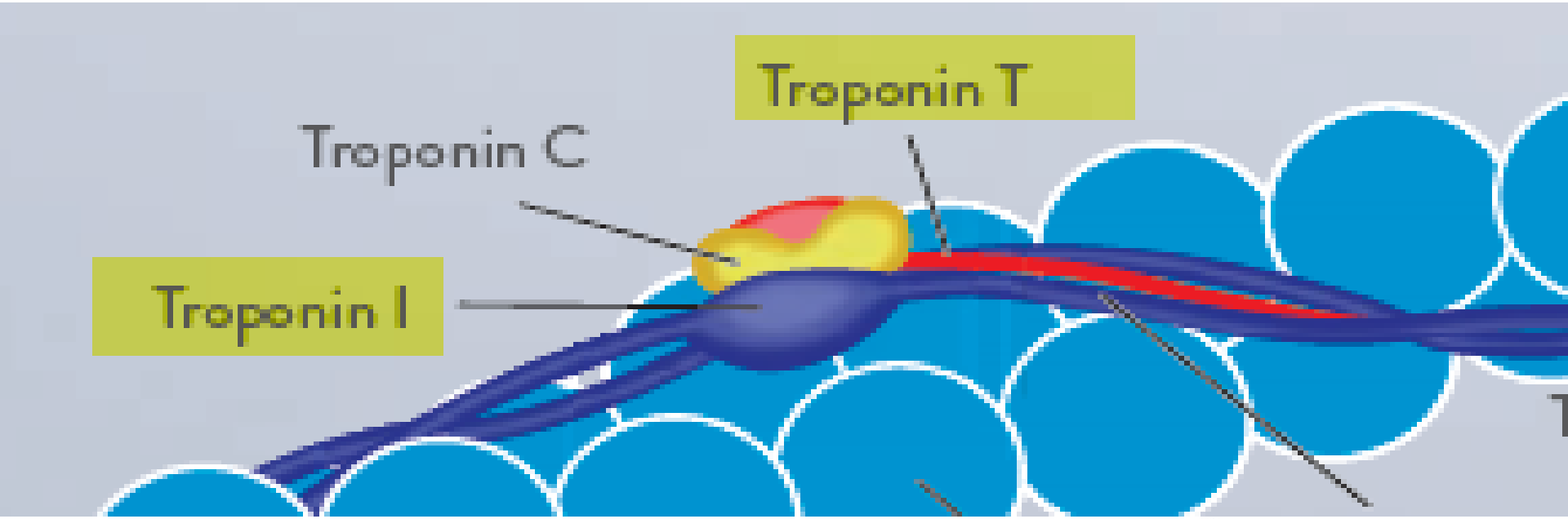
ACC Position Statement: Laboratory

- Focuses on ID and Management of MI and ACS
- Each facility responsible for vendor relationships
  - —ACC provides Guidance and Education
- Facility should know the recommendations
- Facility should review their protocols for Troponin

Troponin I and Troponin T

- Biomarkers of myocardial necrosis (heart tissue damage) with high cardiac-specificity
  - Troponin I (cTnI) and T (cTnT) are generally cardiac-specific
- Preferred biomarker for dx of MI
- Protein complex (not an enzyme)



Source: ACC Accreditation Services Troponin Brochure_2017

3rd Universal Definition of (MI) - 2012

1st worldwide consensus document

- **TROPONIN (I or T) - preferred** biomarker overall
- Diagnosis of acute MI = **a rise and/or fall**
- 99th percentile URL ***designated*** **as the decision level**
- Coefficient of Variation (CV) <20% at the 99th %ile
- > 20% CV at URL should not be used
- Blood samples 1st assessment; repeated 3– 6 h later

Third Universal Definition of Myocardial Infarction (MI)
Kristian Thygesen, Joseph S. Alpert, Allan S. Jaffe, Maarten L. Simoons, Bernard R. Chaitman and Harvey D. White
Circulation. published online August 24, 2012

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4th Universal Definition Summary - 2018

- **Further expands on the 3rd Universal Definition of MI**
- "The new document discusses at length the various forms of **non-ischemic myocardial injury**…"

  For example: Sternal trauma, diabetic patients, myocarditis, chemotherapy, renal failure
- "…contains material concerning an unusual form of myocardial infarction, **myocardial infarction with non-obstructed coronary arteries (MINOCA)…"**
- "…new material on **takotsubo**…use of **high-sensitive troponin (hs-cTn) assays**…expanded section of **non-invasive testing**
- "…regulatory issues…**all 5 subtypes have…ICD 10 codes…"**

Joseph S. Alpert MD , The Fourth Edition of the Universal Definition of Myocardial Infarction, The American Journal of Medicine (2018), doi: 10.1016/j.amjmed.2018.06.016

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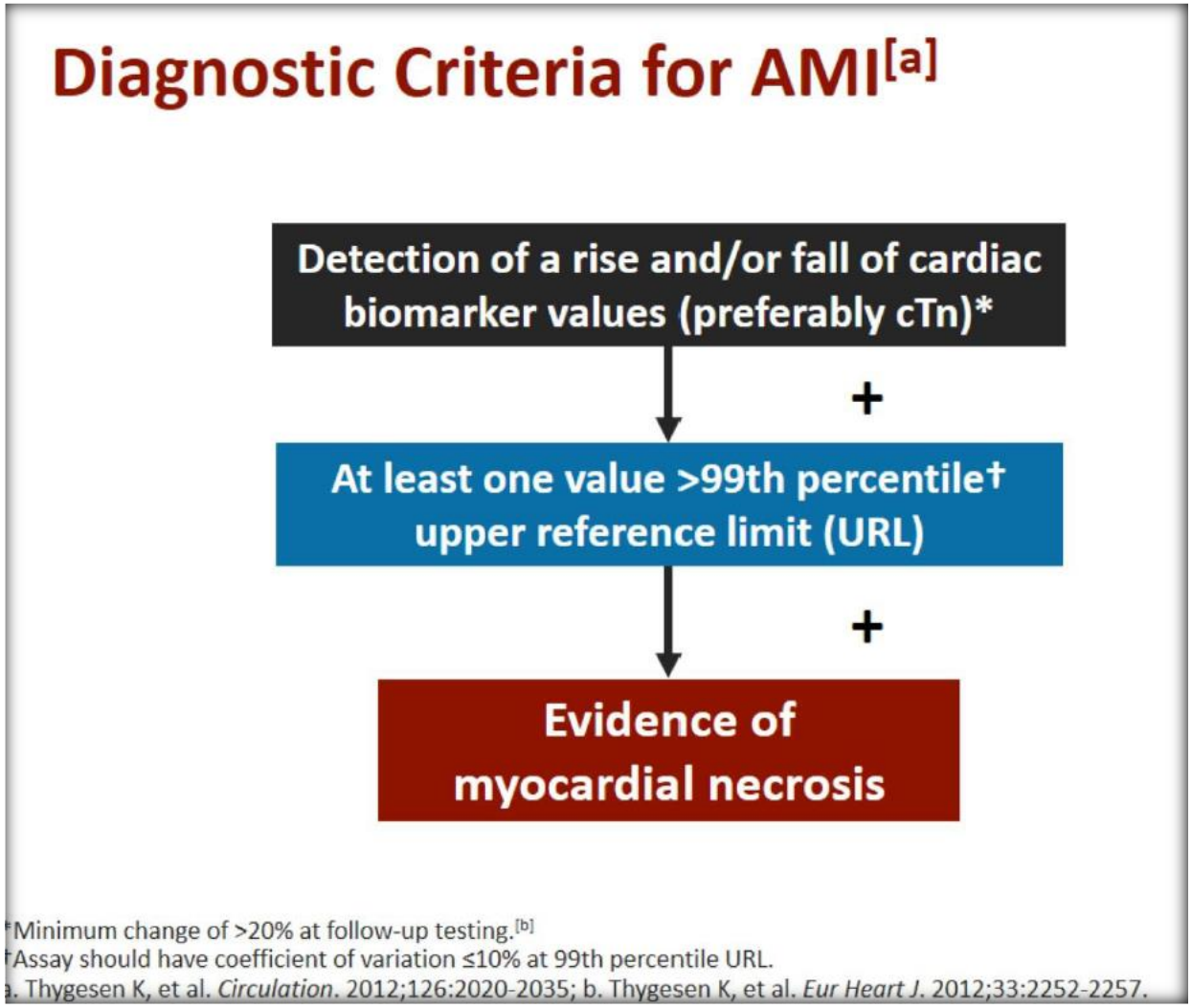
Educational Presentations: Medscape



https://www.medscape.org/viewarticle/884837

Coefficient of Variation (CV)

Q: When the test is run multiple times on the same sample, how frequently do you get the same result?

A: The standard answer is…rarely, if ever.

In real world terms, measured by running sample at least 20 times and identifying the percentage (%) of variation within that set of results.

The Universal Definition of MI advocates from 10% to 20%

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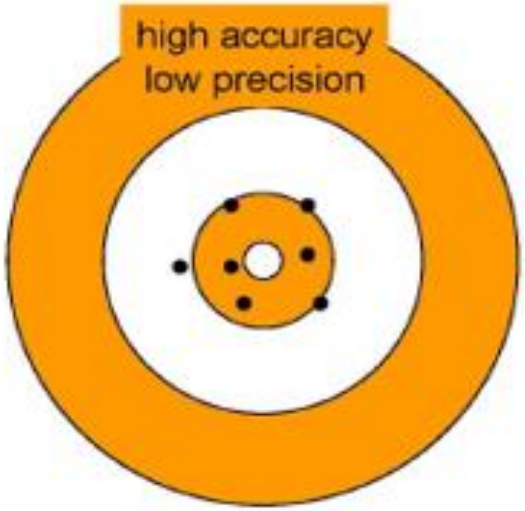
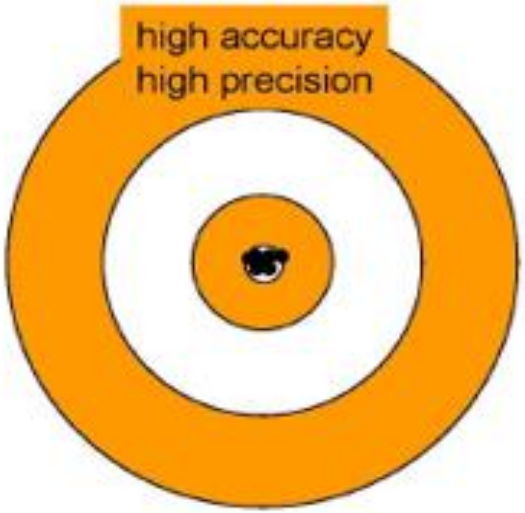
High Accuracy, Different Precision



18% CV



10% CV

Contemporary Cardiac Troponin Assays are more precise

Courtesy of Dr. Robert Christenson, University of Maryland; SCPC Webinar 10/14/15

99th Percentile

Troponin (cTn):
One of few analytes where 99th % ile reference range is recommended

The reason:

- Goal of early prediction
- Identify results early in the elevation cycle
- Ensures standardization

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Review of Facility Processes Related to Troponin

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Troponin Analyzers: Name versus Location

LAB – main or central laboratory analyzer

- Various types of analyzers

POCT – point-of-care testing

- Catch-all phrase: Refers to any testing conducted outside a traditional central lab

NPT – near patient testing

- May be a static analyzer or hand-held
- Also referred to as a "bench-top" analyzer

BSM or BST – bed-side markers or bed-side testing

Results may print out as "ED POC"

Decision Making Options

- **Troponin:**
  - POC
  - Stat Lab
  - Central Lab

ED

OBS

- **Troponin:**
  - POC
  - Stat Lab
  - Central Lab

- **Troponin:**
  - Central Lab

In-Pt

Rule-Out

OR

Observe

Observe

Rule-out / Rule-in

Rule–in

Testing

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Understanding the Differences

Troponin:

- Each assay has it own pattern of sensitivity, specificity, and imprecision characteristics
- Each assay has its own normal range and a specific numerical values
- Each assay is reliable on its own terms, but absolute concentrations between different assays cannot be compared

Adapted from: Lexington Medical Center Laboratory Bulletin and ACC Accreditation Troponin Brochure

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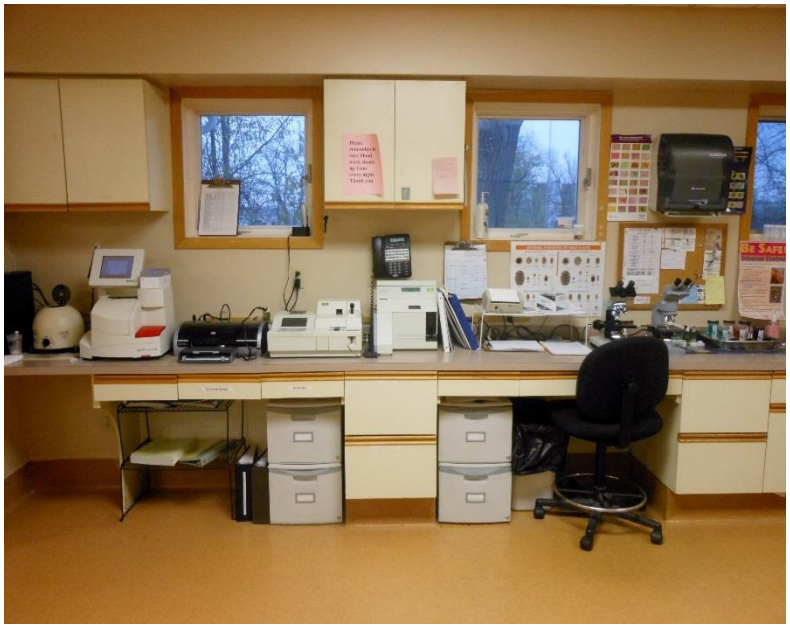
Understanding the Differences

Troponin results within the facility require comparison studies and protocols

POC/NPT



Central Lab

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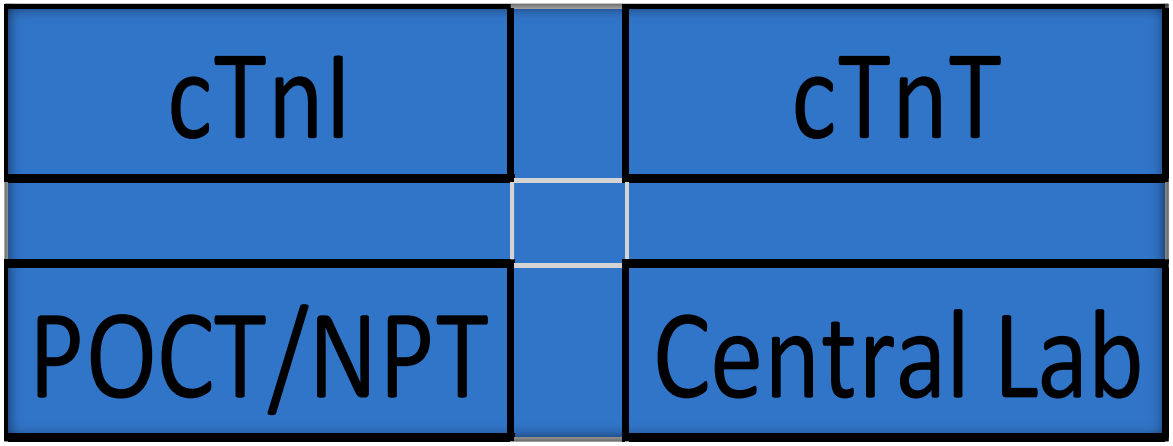
Understanding the Differences

Not interchangeable

- Troponin T (cTnT) and Troponin I (cTnI)
- cTnI and cTnI

No single reference standard in laboratory medicine for cardiac troponin I assays

- POC and NPT and Central Lab



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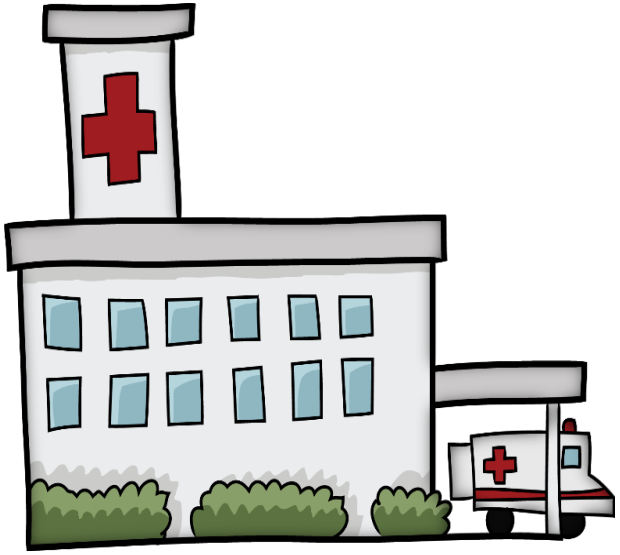
Understanding the Differences

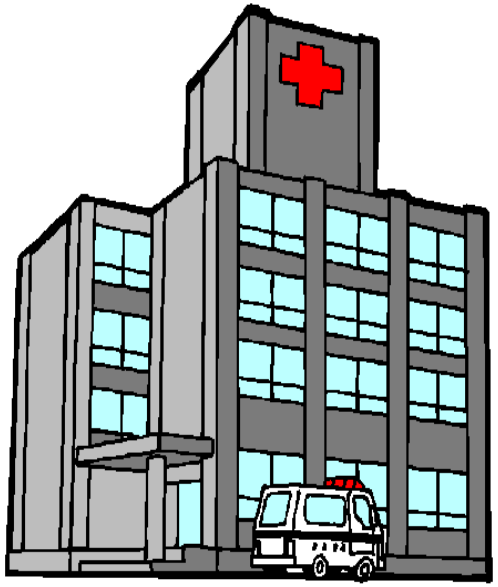
Troponin results from one facility to the next are not interchangeable.

Troponin Type X*



Transfer Facility

Troponin Type Y*



Receiving Facility

* Unless pre-determined to be the same assay and analyzer – typically within a system

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Understanding the Differences

Troponin assay protocols:

Protocols must be implemented for serial strategy assessments if using POC in ED and/or Dedicated Observation area versus Central Lab for in-patient

For Example:

A policy directive to hold blood from the patient's original blood-draw in the main/central lab:

- For re-base-lining
- To be comparable to subsequent determinations, once the patient is admitted to the hospital

Adapted from: Lexington Medical Center Laboratory Bulletin and ACC Accreditation Troponin Brochure

Responsibility to Share Information

Clinical Committees responsibility is to share information with Laboratorians

Laboratorians responsibility to share information with Clinicians

"...As the field continues to absorb the guidelines, panelist and others advised laboratorians to take time to know the documents so they can have constructive discourse about them with physicians..."

Clinical Lab News, Feb 2014, vol 40, no 2

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Review of Troponin in Clinical Practice

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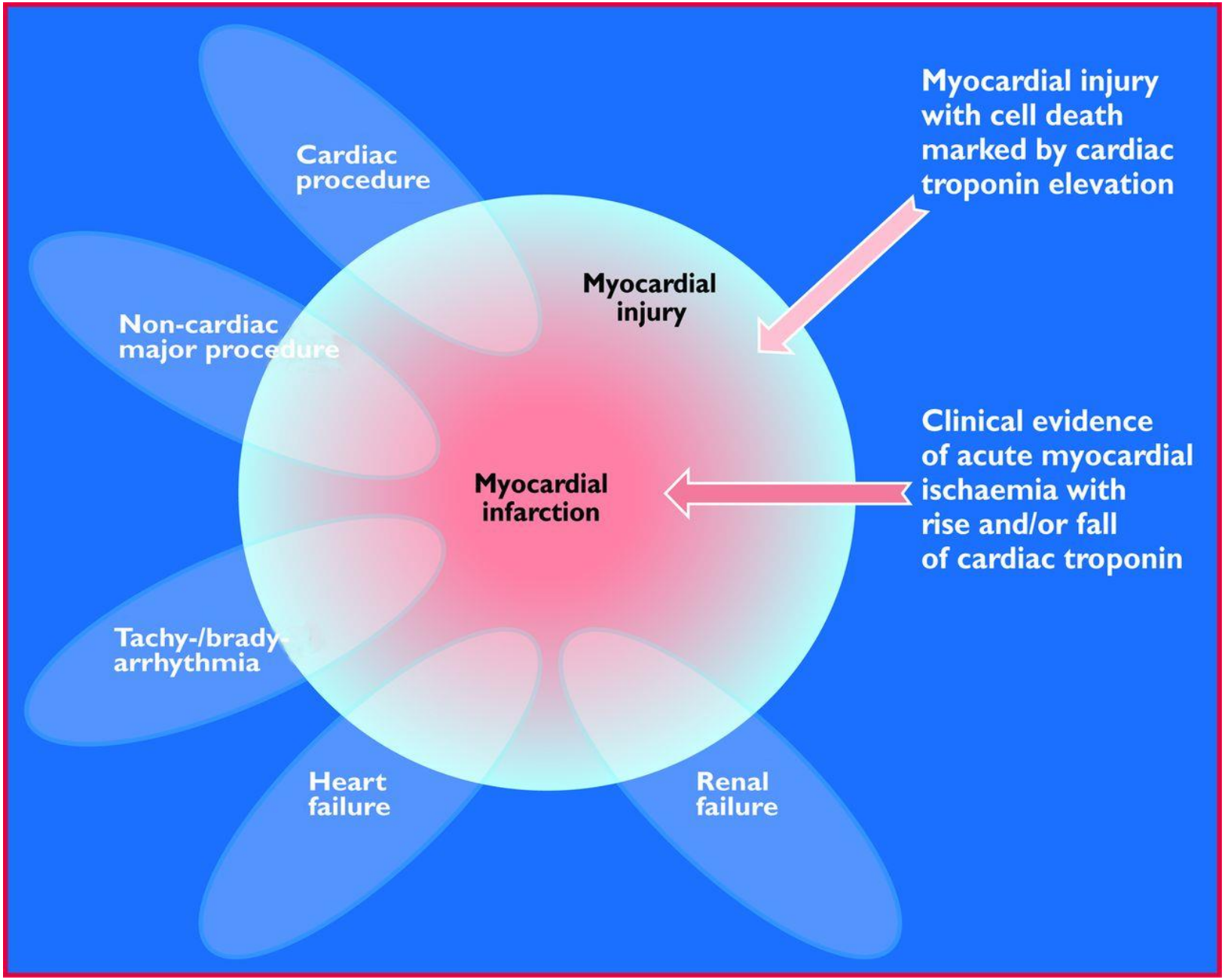
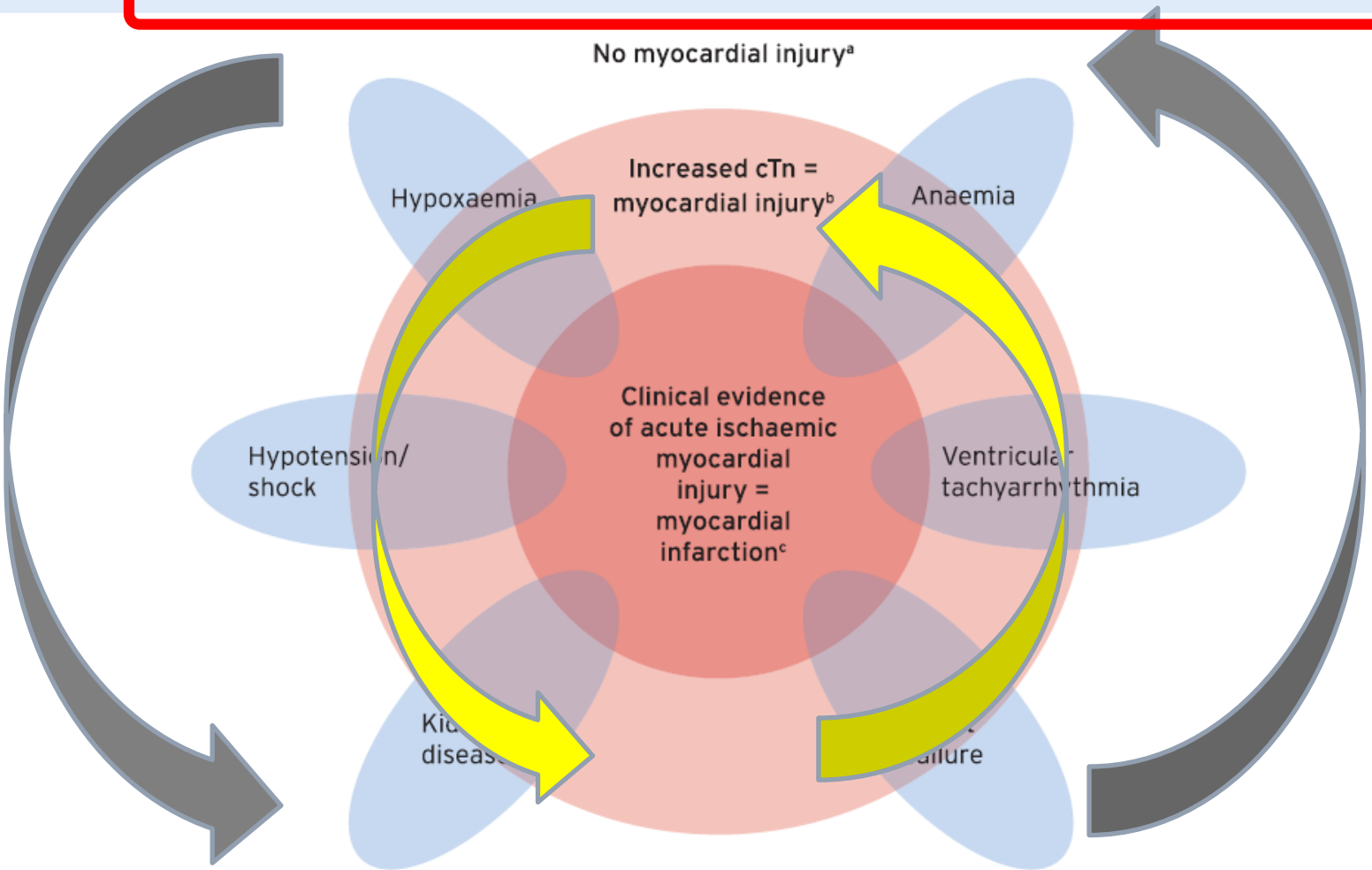
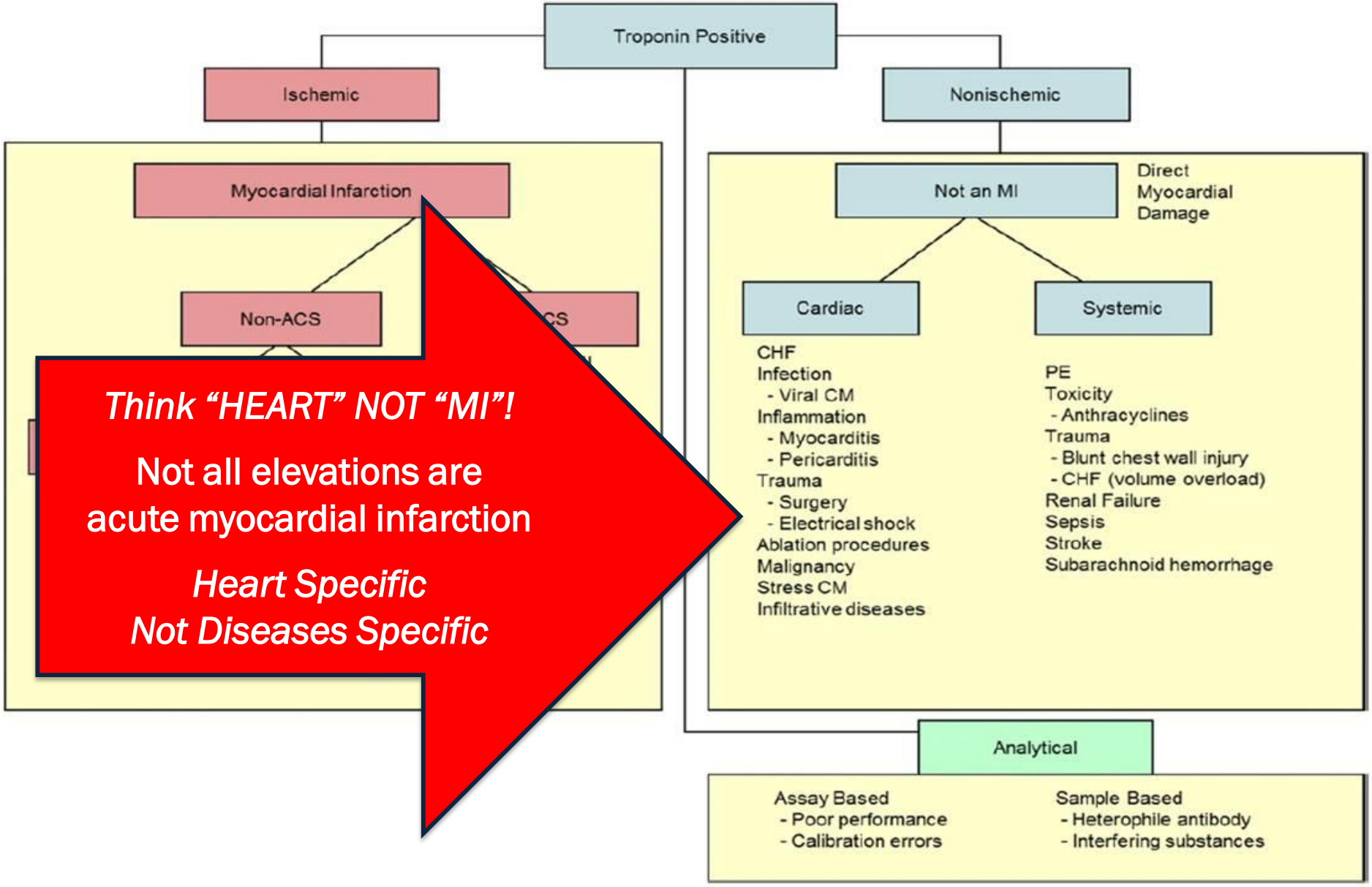


Thygesen K et al. Circulation 2012;126:2020-2035

FIGURE 2 Spectrum of myocardial injury, ranging from no injury to myocardial infarction. Various clinical entities may involve these myocardial categories, e.g. ventricular tachyarrhythmia, heart failure, kidney disease, hypotension/shock, hypoxaemia, and anaemia. cTn = cardiac troponin; URL = upper reference limit. [a]No myocardial injury = cTn values ≤ 99th percentile URL or not detectable. [b]Myocardial injury = cTn values > 99th percentile URL. [c]Myocardial infarction = clinical evidence of myocardial ischaemia and a rise and/or fall of cTn values > 99th percentile URL.



Joseph S. Alpert MD , The Fourth Edition of the Universal Definition of Myocardial Infarction, The American Journal of Medicine (2018), doi: 10.1016/j.amjmed.2018.06.016



ACCF 2012 Expert Consensus Document on Practical Clinical Considerations in the Interpretation of Troponin Elevations. (2012). Newby LK, Journal of the American College of Cardiology, 60 (23), 2012.

Explanation of 99th Percentile

"The use of the 99th percentile cutoff for cTn positivity does not imply that 1% of the population suffers from myocardial damage....useful ...with **a high pretest probability** of ACS.

...context of... clinical history, ECG findings...cardiac imaging to establish the correct diagnosis.

A positive troponin in the setting of a **low pretest probability** for ACS may be suggestive but clearly is not indicative of a coronary event."

How to Interpret Elevated Cardiac Troponin Levels *Vinay S. Mahajan, and Petr Jarolim*
Circulation: Volume 124(21):2350-2354; November 22, 2011

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Clinician Awareness of Interferences

Biotin (vitamin B7)

A beauty supplement; when taken at levels well above the daily recommended intake **may cause interference in immunoassays, including for cTn.**

- **FDA released a safety communication in November 2017**
  - FDA received an increase in the number of reported adverse events related to biotin interference, including one death.
  - This patient had been taking a high dose of biotin, which led to a false negative cTn result.

ACTION: Verify if patient use of Biotin is an assessment question

https://www.aacc.org/publications/cln/articles/2018/janfeb/meeting-the-biotin-challenge

American Association for Clinical Chemistry: Date: JAN/FEB and MAR.1.2018 // Source: Clinical Laboratory News
https://www.aacc.org/publications/cln/articles/2018/march/the-future-of-cardiac-troponin-testing

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Clinician Awareness of Interferences

- **Biotin** (vitamin B7)
  - Is this question addressed in the facility lab report?

EXAMPLE:

```
 Order Entry Note 1:
ALERT: This test could potentially be affected if the patient is taking high dos
es of Biotin/Vitamin B7 found in many multivitamins and hair, skin and nail grow
th supplements. Interpret results with caution if result doesn't fit the clinica
l picture.

 Order Entry Note 2:
For [redacted]: Please annotate in comments if the patient is currently taking Biotin,
 the approximate dosage and the time of the last dosage.
```

Other Resource Article:

Cardiac troponin and natriuretic peptide analytical interferences from hemolysis and biotin: educational aids from the IFCC Committee on Cardiac Biomarkers (IFCC C-CB)

Clin Chem Lab Med 2018; Amy Saenger et. al, https://doi.org/10.1515/cclm-2018-0905

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NSTE-ACS 2014 Guidelines

Class I

- Cardiac- …oponin I or T when a contemporary assay is used) levels should b… …sentation and 3 to 6 hours after symptom onset in all patients … …ymptoms consistent with ACS to identify a rising and/or falling p… …dence: A)*

- Additior… …hould be obtained beyond 6 hours after symptom onset in p… …erial examination when electrocardiographic cha… …tion confer an intermediate or high index of suspicion for AC…

- If the time o… …nset is ambiguous, the time of presentation should be considered the … …f onset for assessing troponin values. *(Level of Evidence: A)*

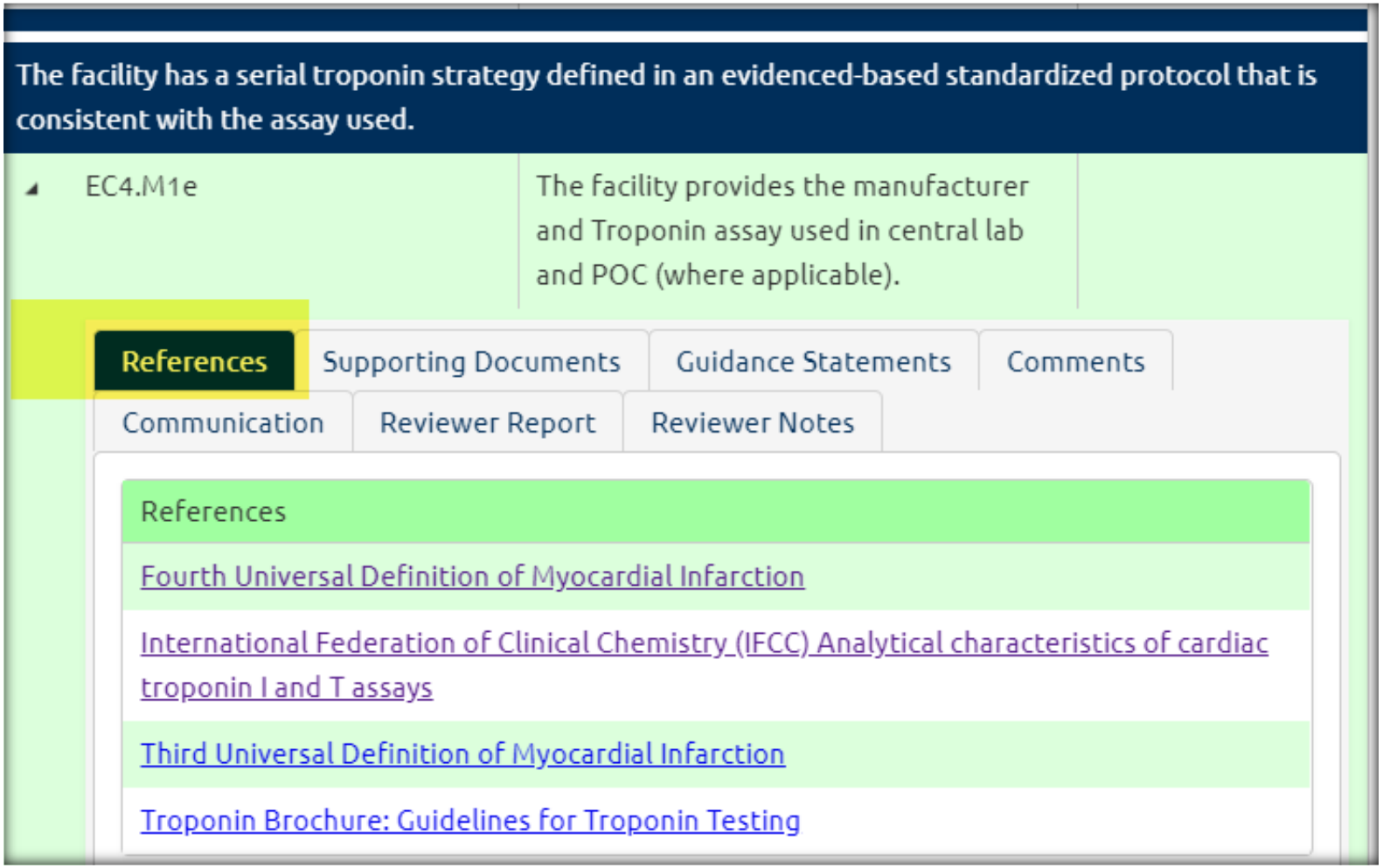
CPC v6 assessment:
Standing orders/Cardiac panel should no longer include:
CK-MB
MYO
Total CK

Class III: No Benefit

- With contemporary troponin assays, creatinine kinase myocardial isoenzyme (CK-MB) and myoglobin are not useful for diagnosis of ACS. *(Level of Evidence: A)*

Amsterdam, E., et al, 2014 AHA_ACC Guideline for the Mgmt of Pts with NSTEMI ACS, Circulation 2014.

References for Support



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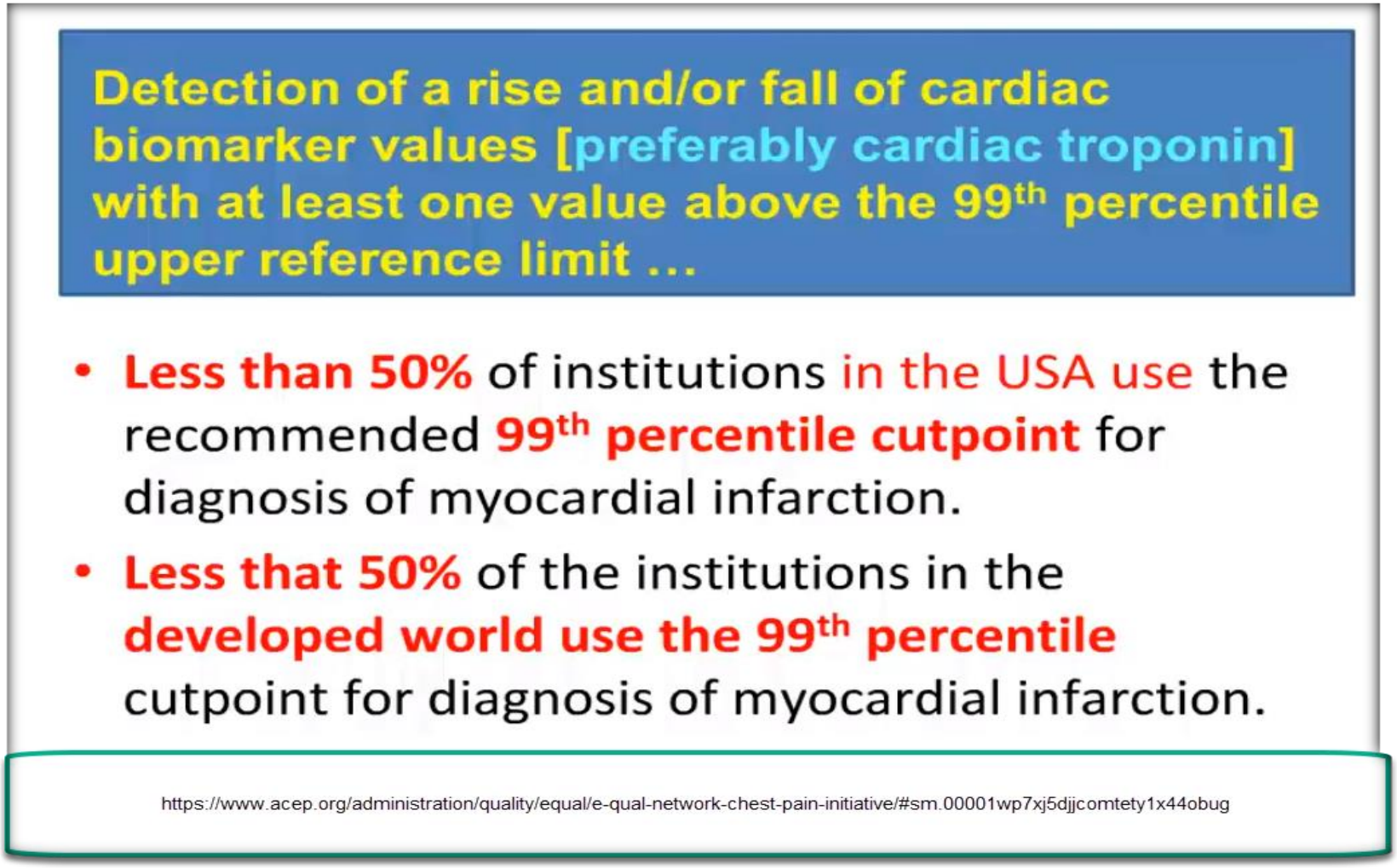
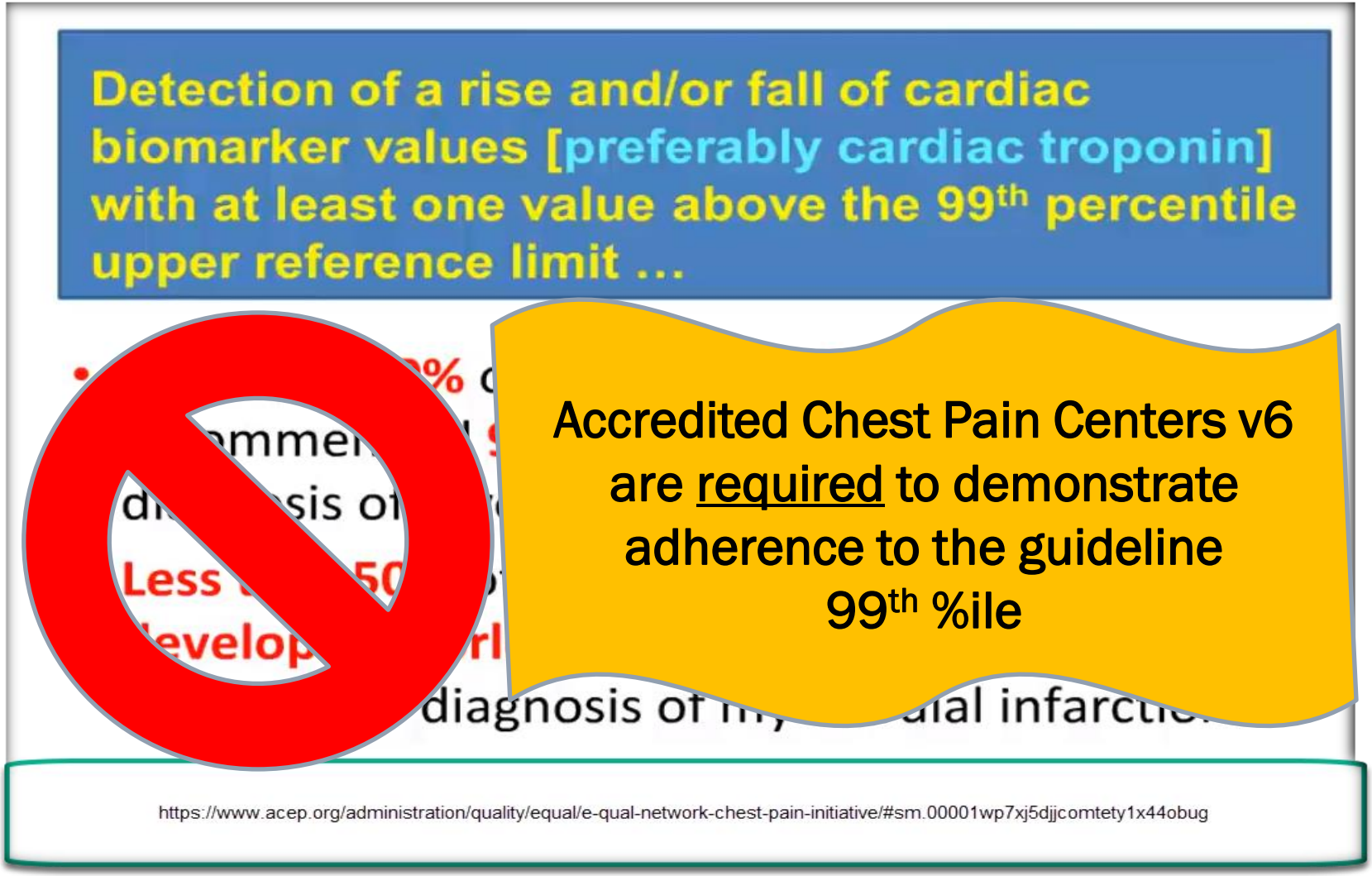
Educational Presentations



Dr. Robert Christenson, Cardiac Troponin: Current Status and Future Promise
https://www.whitehatcom.com/POCWebMtgs/Slides/R_Christenson_Cardiac_Troponin_041118.pdf

Educational Presentations



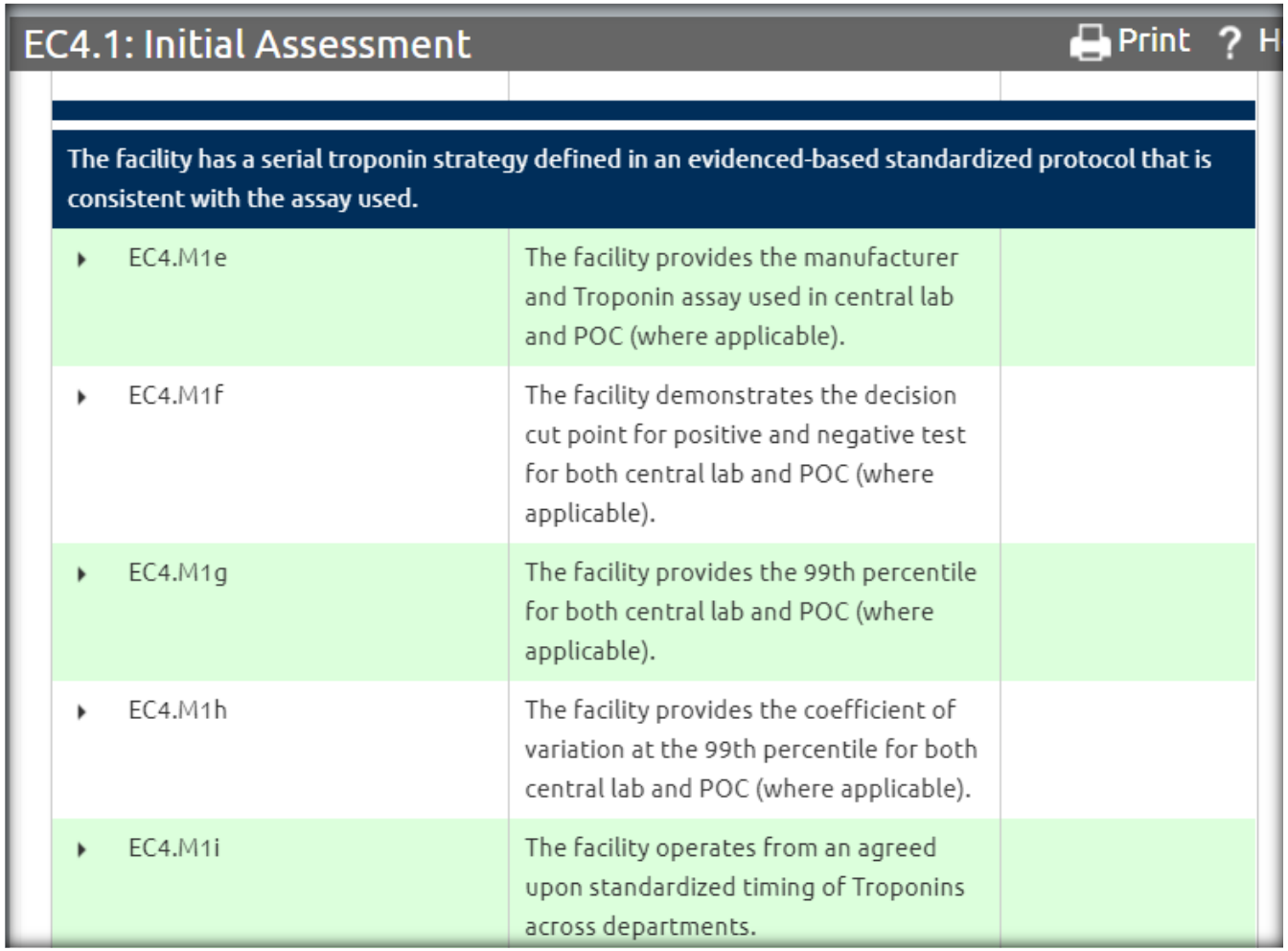
Dr. Robert Christenson, Cardiac Troponin: Current Status and Future Promise
https://www.whitehatcom.com/POCWebMtgs/Slides/R_Christenson_Cardiac_Troponin_041118.pdf

Accountability for use of the 99th Percentile

"Clinical laboratorians in the wake of this new definition could take several **measures to help physicians appropriately use** and interpret hs-cTn results, Jaffe continued. **Consistent use of the 99th percentile protocol is one such approach. Labs sometimes decide that the 99th percentile is something else and use their own cutoffs. This undermines the guidance the Universal Fourth Definition is trying to achieve,** Jaffe said. "It's hard to suggest approaches to evaluate changing patterns or results or when to consider other possibilities when these are set up as if one is using the assays properly and someone else is using different cutoffs. Then it doesn't work well. **It's important that labs start to come together and stop deciding that the 99th percentile is something else."**

Allan Jaffe, MD, Cardiologist, Mayo Clinic, Rochester, Minnesota
https://www.aacc.org/publications/cln/cln-stat/2018/september/20/discerning-myocardial-injury-from-infarction

Accreditation Quality Assessments



EC4.1: Initial Assessment

Print ? H

The facility has a serial troponin strategy defined in an evidenced-based standardized protocol that is consistent with the assay used.		
EC4.M1e	The facility provides the manufacturer and Troponin assay used in central lab and POC (where applicable).	
EC4.M1f	The facility demonstrates the decision cut point for positive and negative test for both central lab and POC (where applicable).	
EC4.M1g	The facility provides the 99th percentile for both central lab and POC (where applicable).	
EC4.M1h	The facility provides the coefficient of variation at the 99th percentile for both central lab and POC (where applicable).	
EC4.M1i	The facility operates from an agreed upon standardized timing of Troponins across departments.	

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CPC Troponin Assessments

For both CENTRAL LAB and POC/NPT Troponin

- Manufacturer
- Analyzer
- 99th Percentile
- CV at 99th%
- **Review use of outdated assays**
- Troponin Turn-Around-Time (TAT) % Door-to-Result – 60 minutes

- Reviewing the ***Interpretive Comments test results*** **print out**
  - Assess guideline adherence
- **IFCC**
- ***Instructions for Use (IFU)***

- **Ensuring facilities are no longer using or referencing outdated WHO criteria from IFU or outdated reference ranges, discrepancies, grey zone, assays etc.**

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Accreditation Quality and Adherence: v6

EC4.M1g

EC4.M1g	The facility provides the 99th percentile for both central lab and POC (where applicable).	

The Lab must be consulted for this item.

Facilities should establish and use the 99th percentile concentration for the Troponin cut point. For optimal precision for AMI diagnosis, the use of Troponin with a coefficient of variation (CV) at the 99th percentile upper reference limit (URL) of less than or equal to 10%, is preferred. Assays with CV of greater than 20% at the 99th percentile URL should not be used.

Reference Guidance:

1. *Third Universal Definition of Myocardial Infarction*: Detection of a rise and/or fall of the measurements is essential to the diagnosis of acute MI. An increased cTn concentration is defined as a value exceeding the 99th percentile of a normal reference population [upper reference limit (URL)]. This discriminatory 99th percentile is designated as the decision level for the diagnosis of MI and must be determined for each specific assay with appropriate quality control in each laboratory.
2. IFCC – Use this guide to find the facility Troponin assay 99th percentile and CV at the 99th percentile to validate use of the 99th percentile.

Supporting documentation includes a policy or protocol specifically outlining the required information. The facility must provide the Troponin interpretive results with the reference range.

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NCDR® Chest Pain - MI Registry™

(formerly the ACTION Registry®)

Troponin Quality Assessments:
99th percentile URL
Central lab and POC

NCDR® **Data Collection Form v3.0** Chest Pain – MI Registry™

F. LABS		
CARDIAC MARKERS		
Troponin Counter[12255]:	**1**	**2**
Troponin Collected Date/Time[12405]:	mm / dd / yyyy / hh:mm:ss	mm / dd / yyyy / hh:mm:ss
→ **If any value,Troponin Result Date/Time**[12406]:	mm / dd / yyyy / hh:mm:ss	mm / dd / yyyy / hh:mm:ss
Troponin Test Location[12544]:	O Lab O POC	O Lab O POC
→ **If Lab, Troponin Assay, URL**[12409]:	*Lab Assay, URL* _____	*Lab Assay, URL* _____
→ **If POC, Troponin Assay, URL**[12543]:	*POC Assay, URL* _____	*POC Assay, URL* _____
Troponin Value[12408]:	_____ O ng/mL O ng/L O µg/L	_____ O ng/mL O ng/L O µg/L

https://cvquality.acc.org/NCDR-Home/registries/hospital-registries/chest-pain-mi-registry

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IFCC: Updated

The International Federation of Clinical Chemistry (IFCC) – Updated versions now in v5 or v6 tool

http://www.ifcc.org/media/463447/PoCT_CardTroponin_I_T_Assay_v060617.pdf

http://www.ifcc.org/media/463450/ContemporaryCardiac__TroponinI_TAssay_v060617.pdf

http://www.ifcc.org/media/463453/HighSensitivityCardiacTroponinI_T_AssayAnalyticalCharacteristics_v060617.pdf

Commercially available assays - Company/ platform(s)/ assay	LoB [a] (µg/L)	LoD [b] (µg/L)	99th % (µg/L)	%CV at 99th %	10 % CV (µg/L)
Abbott AxSYM ADV	0.02		0.04	14.0	0.16
Abbott Architect	<0.01		0.028	14.0	0.032
Abbott Architect *STAT* hs-cTnI [e]	0.0007 - 0.001	0.0011 - 0.0019	0.0262 M: 0.0342 F: 0.0156	4.0 M: 3.5 F: 5.3	0.0047
Abbott i-STAT			0.08	16.5	0.10
Alere Triage SOB			NAD	NA	NA
Alere Triage Cardio 3			0.02	17.0	0.04
Beckman Coulter Access Accu			0.04	14.0	0.06
bioMerieux Vidas Ultra			.01	27.7	0.11
Mitsubishi PATHFAST cTnI [e]			.020	5.2	0.0031
Mitsubishi PATHFAST nI-II			.029	5.0	0.014
Ortho VITROS Trop			.034	10.0	0.034
Radiometer AQT				7.7	0.039
Radiometer AQ					0.026
Response Biom				.0	0.21
Roche Cardiac Reade			NAD	NA	NA
Roche cobas h 232 TnT			NAD	NA	NA
Roche E 2010 /cobas e 411 / E 170 / cobas e 601 / 602 TnT (4 gen)			NAD	NA	0.03
Roche E 2010/cobas e 411 / E 170 / cobas e 601 / 602 hs-TnT		.005	0.014	10.0	0.013
Roche E 2010/cobas e 411 / Roche E 170/cobas e 601 / 602 cTnI			0.16 [c]	NA	0.3
Siemens ADVIA Centaur® TnI-Ultra™	0.00		0.04	8.8	0.03
Siemens Dimension® EXL™ TNI	0.010	0.017	0.056	10.0	0.05
Siemens Dimension® RxL CTNI	0.04 [d]		0.07	15 - 22	0.14
Siemens Dimension VISTA® CTNI	0.015		0.045	10.0	0.04
Siemens IMMULITE® 1000 Turbo [e]	0.15		0.30	14	0.59
Siemens IMMULITE® 1000 [e]	0.1		0.19	11	0.22
Siemens IMMULITE® 2000 XPi [e]	0.2		0.29	10.3	0.32
Siemens IMMULITE® 1000 Turbo [f]	0.15		NA	NA	0.64
Siemens Stratus® CS cTnI	0.03 [d]		0.07	10.0	0.06
Tosoh ST AIA-PACK	0.06		0.06 [c]	8.5	NA

PREVIOUS IFCC VERSION

IFCC Updated: 3 Separate

Contemporary Cardiac Troponin I and T Assay Analytical Characteristics Designated by Manufacturer

IFCC Task Force on Clinical Applications of Cardiac Bio-Markers (TF-CB) v060617

Company/Platform/Assay	LoB, µg/L	LoD, µg/L	% CV at 99th percentile	Conc at 20% CV µg/L	Conc at 10% CV µg/L	Reference Population N, Ages, Sex	Specimen Type	99th Percentile µg/L	Percent Normal ≥ LoD	Statistic Used to Calc 99th Percentile	Epitopes Recognizd by Antibodies	Country of Package Insert: Version Date

Point of Care Cardiac Troponin I and T Assay Analytical Characteristics Designated by Manufacturer

IFCC Task Force on Clinical Applications of Cardiac Bio-Markers (TF-CB) v060617

Company/Platform/Assay	LoB, µg/L	LoD, µg/L	% CV at 99th percentile	Conc at 20% CV µg/L	Conc at 10% CV µg/L	Reference Population N, Ages, Sex	99th Percentile, µg/L	Percent Normals Measure ≥ LoD	Statistic Used to Calc 99th Percentile	Specimen Type	Epitopes Recognized by Antibodies	Country of Package Insert: Version Date

High Sensitivity* Cardiac Troponin I and T Assay Analytical Characteristics Designated by Manufacturer

IFCC Task Force on Clinical Applications of Cardiac Bio-Markers (TF-CB) v060617

Company/ Platform/ Assay	LoB ng/L	LoD, ng/L	% CV at 99th percentile	Conc at 20% CV ng/L	Conc at 10% CV ng/L	Reference Population N, Ages, Sex	99th percentile Overall/M/F ng/L	Specimen Type	Percent Normals Measured ≥ LoD Overall/M/F	Statistic Used to Calc 99th Percentile	% RCV	Epitopes Recognized by Antibodies	Country of Package Insert: Version Date

IFCC now calls out assays with CV > 20% /
Some assays continue to state "Not Provided" for the various categories.

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Brief review of "high-sensitivity" Troponin

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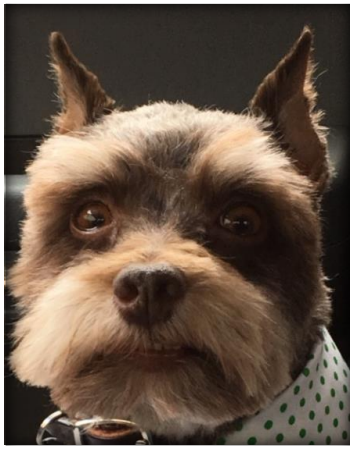
Sensitivity and Specificity

For Sensitivity think "SnOUT"



- Describes the ability of a test to identify true disease
- A high-sensitivity test has few False Negatives (FN) and is effective at ruling conditions "**out**" (SnOUT)
- Formula: (True Positive (TP)/TP+FN)

For Specificity think "SpIn"

- Describes the ability of a test to identify the absence of disease
- A high-specificity test has few False Positives (FP) and is effective at ruling conditions "**in**" (SpIn)
- Formula: (True Negative (TN)/TN+FP)

Dr. Rob Christenson – Cardiac Troponin: Current Status and Future Promise, 4/11/2018
https://whitehatcom.com/POCWebMtgs/Slides/R_Christenson_Cardiac_Troponin_041118.pdf

Clinical Lab Practice Recommendations

January 2018

…companion to National Association of Clinical Biochemistry (*now the American Association for Clinical Chemistry (AACC) Academy*) Laboratory Medicine Practice Guidelines on cardiac markers.

Concensus Document:

"…clinical laboratory practice recommendations for high-sensitivity (hs) cTn assays…"

REINFORCE REPORTING UNITS:

ng/L

Recommendation 3: Report hs-cTn in whole numbers, using ng/L without decimal points. For reporting QC values, we recommend 1 decimal point. For contemporary cTn assays, units are reported in µg/L to 2 significant figures, with QC values reported to 3 significant figures.

Clinical Chemistry 64:4, 645-655 (2018), page 4, Wu et al.
http://clinchem.aaccjnls.org/content/early/2018/01/08/clinchem.2017.277186

Reporting Units

Integer values (units of ng/L) reported for high-sensitivity cTn assays

Results of contemporary and earlier generation cTn assays were reported in units of ng/mL, causing results to appear as decimal values on patient and other documents. The recommendation of the AACC Academy and IFCC Task Force Consensus Guidelines [23] are to report hs-cTn results in units of ng/L, so that all results will be reported as whole number values. For example, a value of 0.07 ng/mL for a contemporary cTn assay will have value of 70 ng/L for a high-sensitivity test. Reporting high-sensitivity results as whole numbers will facilitate interpretation and allow differentiation of whether an assay is high-sensitivity, a contemporary, or earlier generation test. It is believed that expressing results as whole numbers, rather than as decimals as is recommended with contemporary and earlier generation cTn assays, will reduce error when interpreting cTn results [10].

R. Christenson: IMPACT OF HIGH SENSITIVITY TROPONIN ON THE EVALUATION AND TREATMENT OF PATIENTS WITH ACUTE CORONARY SYNDROME: EMCREG-International Monograph, August 2017, page 13

"High-sensitivity" Troponin Defined

What is High-Sensitivity Cardiac Troponin?

- IFCC defines high-sensitivity cTn test as one that can measure ≥ 50 % of healthy subjects above the Limit of Detection.
- Also, high-sensitivity cTn assays perform at the highest level of day-to-day precision, i.e. CV ≤ 10%.

Clin Biochem 2015;48(4-5):201-203

Dr. Rob Christenson – Cardiac Troponin: Current Status and Future Promise, 4/11/2018
https://whitehatcom.com/POCWebMtgs/Slides/R_Christenson_Cardiac_Troponin_041118.pdf

"High-sensitivity" Troponin Defined

"The assay should have a high enough analytical sensitivity (*i.e. be able to 'detect' very low troponin levels*) **to enable levels of troponin to be detected in at least 50% of "normal" individuals (AND females and males)** *i.e. apparently healthy people who do not have myocardial disease*.

With previous troponin assays, it was not possible to measure such small levels of troponin.

This meant that having any detectable troponin in the blood was *abnormal*, but now that technology has improved.

With a high sensitivity assay we will be able to detect Troponin in at least half of all healthy people."

Clinical Lab News, March 2017

Clinical Lab Practice Recommendations

Clinical Chemistry 64:4
645–655 (2018)

Special Report

Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine

Alan H.B. Wu,[1*] Robert H. Christenson,[2] Dina N. Greene,[3] Allan S. Jaffe,[4] Peter A. Kavsak,[5] Jordi Ordonez-Llanos,[6] and Fred S. Apple[7]

…e forms of cardiac troponin (T or I) being … The IFCC TF-CB proposed that for an …ned as high-sensitivity, 2 analytical criteria *(10)*. First, the %CV at the 99th percentile URL should be ≤10%. Second, measurable concentrations should be attainable at a concentration at or above the assay's LoD for >50% of healthy individuals *(10)*. Our guidelines expand on this second point by requiring both men and women individually attain measurable concentrations, with at least 50% measurable concentrations above the assay's LoD. The data to support these claims should be published in peer-reviewed journals, as well as by the manufacturer's package inserts.

"…both men and women…"

*LoD = Level of Detection

http://clinchem.aaccjnls.org/content/early/2018/01/08/clinchem.2017.277186

"Next Generation" Troponin: First in USA

March 2017:

The Food and Drug Administration (FDA) granted 510 (k) clearance to Roche for its *Elecsys Troponin T (TnT) Gen 5 Stat*

FDA termed: *Next Generation (Gen 5)* ***vs.*** *high-sensitivity**

Test characteristics: <10% CV at the 99th%-ile

*Defined to include both men and women

Clinical Lab News, March 2017, page 22

"High-sensitivity" Troponin: First 2 Troponin I

The Food and Drug Administration (FDA) granted 510 (k) clearance:

June 2018:

Beckman Coulter's *Access Troponin I (hsTnI)*

July 2018:

Siemens' *Atellica IM and ADVIA Centaur XP/XPT (TnIH)*

FDA termed both: *high-sensitivity*

Test characteristics: <10% CV at the 99th%-ile
for both men and women LoD > 50% of the healthy population

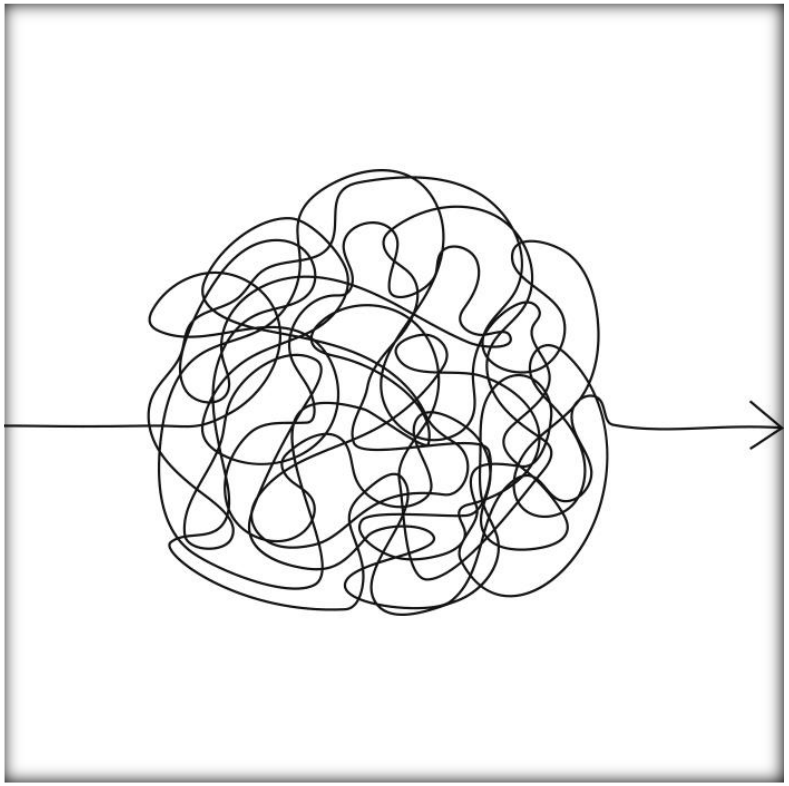
https://www.beckmancoulter.com/en/about-beckman-coulter/newsroom/press-releases/2018/q2/2018-june-27-us-fda-510k-clearance-of-hstnl

http://www.blockscientific.com/siemens-high-sensitivity-troponin-i-assays-get-fda-clearance/

On the topic of hs-cTn, what is next?

Open dialogue / Awareness of Guidelines / Accreditation REQ

Education, Education, Education



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IFCC Documents on hsTn

Clinical Applications of Cardiac Bio-Markers

The following resources have been prepared by the Task Force for Clinical Application of Cardiac Biomarkers (TF-CB):

- *Implementing High-Sensitivity Cardiac Troponin Assays in Practice - pocket format*
- *Using High Sensitivity Cardiac Troponin Assays in Practice - a Summary Document - pocket format*
- *Calculating Serial Change Values (Delta) for High-Sensitivity Cardiac Troponin Assays*
- *Using High Sensitivity Cardiac Troponin Assays in Practice*

http://www.ifcc.org/ifcc-news/news-archive-2014/2014-07-22-tf-cb-documents/

Other Articles:

High sensitivity, contemporary and point-of-care cardiac troponin assays: educational aids developed by the IFCC Committee on Clinical Application of Cardiac Bio-Markers

Clin Chem Lab Med 2018, Collinson, Saenger, Apple https://doi.org/10.1515/cclm-2018-1211

Educational Presentations/Offerings

Medscape:

Diagnostic Algorithms for ACS and High-Sensitivity Troponin: Where Are We Today?

https://www.medscape.org/viewarticle/884837

Medscape:

3-part series - Biomarkers

https://www.medscape.org/sites/advances/diagnostics

American Association Clinical Chemistry (AACC):

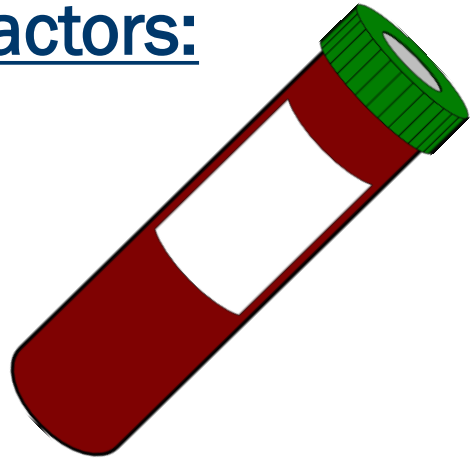
New Clinical Lab Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome

https://www.youtube.com/watch?v=XHTh96tZAZI&feature=youtu.be

Clinical Awareness/ Education: Collection

Clinical Considerations and Educational Requirements: Collection of blood relative to impacts on high-sensitivity Troponin

High-sensitivity Troponin assay(s) requires special handling due to Hemolysis factors:



With Hemolysis:

- TnT results go down
- TnI results go up

Recommendation: Consult with Phlebotomy

ACTION: Teach staff to draw via venipuncture instead of through IV catheter (except for newly started IV line)

Al-Shidhani M, Saadi HA, Mula-Abed W, Riyami NBA (2015) Effect of Hemolysis on Plasma Cardiac Troponin Levels at Clinically Relevant Concentrations: An Experimental Study. Biol Med (Aligarh) 7: 217. doi: 10.4172/0974-8369.1000217

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Serial Strategy Assessments

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Serial Strategy and Stress Testing Timing

2014 NSTE-ACS Guideline Recommendations:

3.5.1. Discharge From the ED or Chest Pain Unit: Recommendations Class IIa

1. It is reasonable to observe patients …in a chest pain unit or telemetry unit **with serial ECGs and cardiac troponin at 3- to 6-hour intervals** (Level of Evidence: B)
2. It is reasonable for patients with possible ACS who have **normal serial ECGs and cardiac troponins** to have a treadmill ECG (Level of Evidence: A), stress myocardial perfusion imaging, or stress echocardiography before discharge or within 72 hours after discharge. (Level of Evidence: B)
3. **In patients with possible ACS and a normal ECG, normal cardiac troponins, and no history of CAD, it is reasonable to initially perform** (without serial ECGs and troponins) **coronary CT angiography** to assess coronary artery anatomy (Level of Evidence: A) or rest myocardial perfusion imaging…to exclude myocardial ischemia (Level of Evidence: B)

Reported PROTOCOLS from this guidance:

0h – 3h negative cTn– then stress

0h – 2h negative cTn – then CT angiography

Amsterdam, E., et al, 2014 AHA_ACC Guideline for the Mgmt of Pts with NSTEMI ACS, Circulation 2014.

Serial Strategy Assessment: v6

EC4.M1i

Guidance Statement

A patient's serial Troponin results should only be compared for those run on the same analyzer. The decision cut point for a Point-of-Care (POC) Troponin will not be the same as a central laboratory analyzer. If different analyzers are used during the serial strategy, ensure there is a protocol for comparison or re-base-lining should the patient move from the ED to a different environment. Per guideline recommendations, lab should report significant changes in serial samples through delta checks using the same assay.

A facility should provide protocols for the ED which then follow through to the hospital, e.g., ED = 0-2 hrs., OBS or inpatient continue at 6 hours or inpatient set at 0-3-6 hours which closely matches the ED 0-3-6 strategy. The facility should have a methodology to connect the different draw times between departments. Language examples, not limited to:

- "...if not done in the ED then Troponin on admission, then 3 and 6 hours ..."
- "...Troponin ED POC then 3 hrs. from original and 3 hrs. from second sample..."

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MI Definition and Serial Strategy

Serial Ordering Recommendations:

"…*This (MI) definition inherently requires* ***at least two cTn results,*** *which can* ***display either a rising or falling pattern****, over the initial 6-9 hours after a patient's presentation (0h)* ***with at least one value above the 99th percentile."***

"….*if the patient's initial two cTn results at* ***0h and 3h are below the 99th percentile***…and there is no diagnostic EKG or imaging findings, this would be sufficient to rule out MI in an otherwise low-risk patient, providing the ability to cancel subsequent outstanding …order. "

Cardiac Troponin Serial Ordering Recommendations: For Today and Tomorrow Sara Love, PhD and Fred Apple, PhD
Clinical Lab News, May 2014, vol 40, no. 5

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Serial Strategy Assessment: v6

(moved from v5 as Recommended to v6 as Mandatory)

EC4.M1i

ensure there is a protocol for comparison or re-base-lining should the patient move from the ED to a different environment. Per guideline recommendations, lab should report significant changes in serial samples through delta checks using the same assay.

Roche

Example of Reporting Strategy

BUN (Bld Urea Nitr...	8-24 mg/dL	48 '	23 Jan 08			
Chloride.....	100-108 mmol/L	110 '	23 Jan 08			
Bicarbonate, P/S,....	22-29 mmol/L	22	23 Jan 08			
Anion Gap.....	7-15	10	23 Jan 08			
CARDIAC CHEMIS...						
Troponin T, S.....	<0.01 ng/mL	0.11 '	23 Jan 08		0.11 '	
3H Troponin T, S.....	<0.01 ng/mL	0.12 '	23 Jan 08		0.12 '	
6H Troponin T, S.....	<0.01 ng/mL	0.15 '	23 Jan 08		0.15 '	
3H Delta.....	ng/mL	Not Sig @	23 Jan 08		Not Sig @	
6H Delta.....	ng/mL	Sig Delta @	23 Jan 08		Sig Delta @	
LIPIDS 63 AG						
LIPIDS 1 AG						
LDL Subfractionati...	100-200 g/dL	.@b0	23 Jan 08			
Beta LDL Choleste...	100-200 g/dL	.@b1	23 Jan 08			
Percentile Rank.....	100-200 g/dL	1.01 @b3	23 Jan 08			

3H Delta.....57001-ROCLIS

23 Jan 2008 15:38
Value: Not Sig
Facility: MCR
Reference Range: ng/mL
Comment:
No significant delta observed
Delta=.01
Entry User: INTERFACE USER, INTE
Accession Number: G9086672937
Performing Loc: DEPT LAB MED PATH

Partnering With Your Clinicians Through Changes in Troponin Testing
Amy Sanger PhD and Sherrie Smart, RN, MSN, Roche Webinar, 12-18-14

Serial Strategy Assessment: v6

Key Term: "Standardized throughout the facility…" transitioning process between ED and inpatient

EC4.M3b	The facility demonstrates the timing between serial troponins are standardized throughout the facility (timing strategy may include: 0, 2, 6 - 0, 3, 6 - 0, 3 etc.) with a mechanism to ensure continuity of serial strategy after the patient is moved to another unit.

…ment

…e of onset for assessing troponin values. A 0-3 hour protocol may be …en using laboratory based assays and the 99th% URL. Please refer to the IFCC …nce provided.

Facilities cannot use a serial strategy which denotes testing every 8 hours (e.g. 0-8-16 hour) intervals on any order sets.

It is important to ensure continuity of the serial strategy after the patient is transferred from one unit to another. A patient's serial Troponin results should only be compared for those run on the same analyzer. If different analyzers are used during the serial strategy, ensure there is a protocol for comparison or re-base-lining should the patient move from the ED to the inpatient environment.

The infamous "Grey Zone" existing in Troponin Testing

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Troponin History

- Early = CKMB
- **1999:** Troponin – poor assay precision created 2+ cut-points

The history of the grey zone was born!

"That set the stage for using whatever cutoff you want, and the field has never recovered from it." Jaffee et. Al. Clinical Chemistry 2008

- **2005:** Intro to 99%ile and CV </= 10%
- **2007:** Lab guidelines first attempt - cTn standardized
- **2012:** 3rd Universal Definition of MI
- **2018:** Clinical Lab Practice guidance updated
- **2018**: 4th Universal Definition of MI

Excerpt from internet presentation n.d. "Cardiac Markers: Why all the Confusion?" by R. Heitsman, Radiometer, National Accounts Manager

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CPC Guidance Language: v5 and v6

CPC v5: EC4.M1d3
CPC v6: EC4.M1f

The facility demonstrates the decision cut point for positive and negative test for both central lab and POC (where applicable).

Guidance Statement:

- The Lab must be consulted for these items.
- The facility must provide a policy, procedure or protocol to show the decision point for a positive test.
- The facility will be required to provide the Interpretive Comments for Troponin results.
- Decision cut points must be clearly documented by the facility and not open to interpretation.

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Interpretive Comments Assessment

- **TROPONIN T (TnT) 0.01 – 0.05 µg/L**

  Indicates minimal myocardial damage which with the appropriate clinical and ECG findings may be of prognostic significance in patients with ACS. However levels within this range may also be due to non-ACS causes *e.g. pulmonary embolus, heart failure, CRF, severe sepsis etc.*

  In ACS TnT starts to rise at 3-4h and reaches maximum sensitivity at 12-18h post symptoms and can remain elevated for up to 7-8 days. For exclusion of ACS levels should not be taken before 12h post symptoms.

- **TnT >0.05 µg/L would support a diagnosis of AMI**

Using the 99th% ile for decision point? Need more information
(see IFCC or other document)

Using a "Grey Zone"? No, there is a negative and a positive

Interpretive Comments Assessment

TROPONIN I

- <0.04 No evidence of myocardial damage provided sample is at least 12h post symptoms (event).
- 0.04 – 0.48 Suggest minor myocardial damage provided at least 12h post event
- >0.49 Indicates major myocardial damage

- Using the 99th% ile for decision point? Need more information (see IFCC or other document)
- Using a "Grey Zone"? YES

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Interpretive Comments Assessment

TROPONIN I

- <0.04 : Troponin appears normal or minor myocardial damage or other cause
- >0.04 : Consistent with Myocardial Infarction

This information is based on the recommendations of the **2012 Third Universal Definition of Myocardial Infarction** for Troponin to be at least one value above the 99th percentile upper reference limit.

- Using the 99th% ile for decision point? Probably (see IFCC or other document) – also cite the source (may see website links or PDF links)
- Using a "Grey Zone"? No, there is a negative and a positive

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Interpretive Comments Assessment

HIGH-SENSITIVITY TROPONIN T

- <19 ng/L

When assessing risk for Acute Coronary Syndrome (ACS): ….an initial hs-Troponin T less than 19 ng/L and a X hour delta…less than X ng/L should be considered very low risk….

Turn-Around-Time (TAT): Accreditation requirements and accountability

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TAT Tracking: Healthcare Implications

Studies and research support the following:

- Assessing the “whole process” (i.e.: arrival)
- Standardizing the definitions of turn-around-time (TAT)
- Assessing TAT with patient outcomes and length of stay

The advent of “Accelerated Diagnostic Protocols” for Troponin will require monitoring to ensure standardization of processes.

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TAT Advocated Since 2008 for Accreditation

Accreditation requirement for 10 years and continues to be determined as a “need”.

> Labs also need to work on turnaround time to prevent emergency department overcrowding. When the emergency department is overloaded, all patients suffer, Jaffe emphasized.“Finally, the lab needs to participate in development of protocols so that whatever approaches clinicians take reflect the joint input of the emergency department, lab, cardiology, and surgery departments that use these assays,” he said.

Allan Jaffe, MD, Cardiologist and chair of the division of clinical core laboratory services at Mayo Clinic in Rochester, Minnesota

Sept 2018 Clinical Lab News (CLN Stat)

https://www.aacc.org/publications/cln/cln-stat/2018/september/20/discerning-myocardial-injury-from-infarction

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TAT Tracking: Healthcare Implications

Study proposed concepts for TAT in the diagnostic process:

As a "Patient-oriented" view or the "whole process"

- **Diagnostic TAT** – arrival to reporting of results
- **Clinical TAT** – arrival to order
- **Laboratory TAT** – order to report/resulted

Ervasti et al, *Clin Chem Lab Med 2008*

"Guidelines do not exist delineating times frames for when a troponin test should optimally be resulted in association with improved patient outcomes."

"Prolonged laboratory TAT may delay recognition of conditions in the acutely ill , potentially affecting clinician decision-making and the initiation of timely treatment."

Academic Emergency Medicine, 2010:17, Hwang et al

TAT Tracking: Healthcare Implications

July 2014 Clinical Laboratory News: Volume 40, Number 7

What Does Turnaround Time Say About Your Lab?

Key Quotes:

- " Every laboratorian knows that their colleagues in medicine see TAT as something almost as important as the quality of test results themselves."

- " In fact, surveys have found that 80% of labs get complaints about TAT."

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Turn-around-Time (TAT) Defined?

- Physicians “brain to brain”
- Laboratorians “receipt to result”
- Nurses “door or draw to result”
- Phlebotomist “collect to receipt in lab”

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TAT Article

Decreasing troponin turnaround time in the emergency department using the central laboratory: A process improvement study

Arlene M. Boelstler, Ralph Rowland, Jennifer Theoret, Robert B. Takla, Susan Szpunar, Shraddha P. Patel, Andrew M. Lowry, Margarita E. Pena

https://doi.org/10.1016/j.clinbiochem.2014.10.014

Highlights:

- A troponin turn-around-time (TAT) of **< 60 min Door-to-Results** can be achieved using central laboratory
- Multidisciplinary collaboration is central to process improvement success
- Optimizing workflow and processes is key to reducing Door-to-Result TAT
- Decreasing troponin TAT impacts emergency department length-of-stay (LOS)

Table 4
Summary of collaborative solutions before and after process improvement.

Pre-Process improvement	Post-Process Improvement
Door-to-order (Step 1) Patient taken back to an ED bed after triage; troponin order placed after the physician evaluates the patient	**Door-to-order (Step 1)** ED triage nurse-initiated cardiac panel blood draw protocol

Table 2
Emergency department length of stay, hemolysis rate, monthly ED volume and boarder hour data before and after process improvement.

Metric	TAT prior to PI Mean (min)	TAT after PI Mean (min)	p-value
ED Length of stay (h)	5.87 ± 2.73	5.15 ± 2.34	<0.0001
Hemolysis rate (%)	14.63 ± 0.74	3.36 ± 1.99	<0.0001
Monthly ED Volume	9771.50	9871.14	0.502
Monthly ED Boarder hours	438.13	891.09	0.010

(TAT = turnaround time; PI = process improvement; ED = emergency department)

Order-to-collect (min)	15 (23)	10 (12)
Collect-to-received (Min)	6 (8)	5 (5)
Received-to-result (min)	30 (12)	24 (11)
Door-to-result (min)	117 (60)	60 (40)

(TAT = turnaround time; PI = process improvement; IQR = Interquartile range).

Serial Strategy and TAT Assessment: v6

"Windows of Time" assess, how a facility ensures serial draws take

EC4.M3a

Guidance Statement

- EC4.M3a

The facility demonstrates Troponin protocols for the following:

- Serial marker strategy and Troponin turn-around-time (TAT) goals

If a 0-2-4 hr., 0-3-6 hr. or 0-90-180 minute protocol is in place, are those turn-around-times, beyond the zero time point, individually measured?

time (TAT) process. The facility should document the process for the monitoring of TAT, regardless of the patient's location, when the serial troponin is to be drawn (e.g., ED, OBS, inpatient). The recommendation is use of the 90th percentile (90%) defined as the goal time (benchmark) to measure how consistently cardiac biomarker results are delivered for the various time points (door-order-collect-received and resulted).

Provide meeting minutes, metrics, policies and protocols, lab-based educational newsletters to support this item.

TAT Assessed = Process Standardization

- Know the starting point
- Know the goal time for each phase
- Know the compliance goal

Time is muscle – think HEART!

PAST	PRESENT
Door to ECG = 10 minutes	Door to ECG READ within 10 minutes

REQUIREMENT

Time is muscle – think HEART!

PAST	PRESENT
Door to Reperfusion = 90 minutes	Door to Reperfusion "*as soon as possible*“ 90 min (100%)
	Door to Reperfusion 60 minutes (60%)
	First Medical Contact (FMC) to Reperfusion Less than 90 minutes
TRANSFER: Door in - Door out = 30 minutes	Door in - Door Ready = 25 minutes
Door to Thrombolytics = 30 minutes	*Same consideration; low utilization*

GOALS

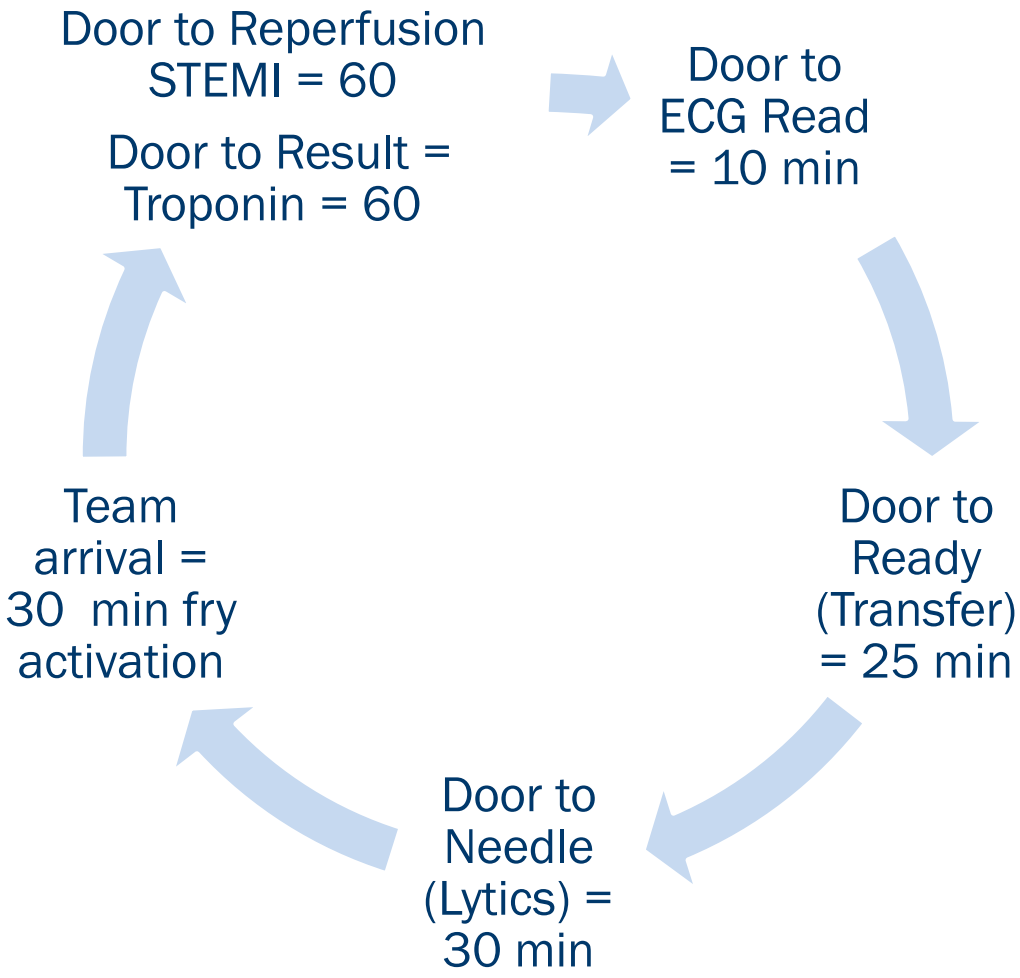
Time is muscle – think HEART!

PAST	PRESENT
Lab received to results = 60 minutes	Door to Troponin Results in 60 minutes *Facility sets % compliance –* *recommend assessments at 75% and 90%*
Order/Collect to results = 60 minutes	Order/Collect to results: % compliance = 90%

GOALS

Time is muscle – think HEART!

Benchmarks: From DOOR



Benchmarks and Requirements:

GOLDEN HOUR and QUALITY for the HEART

STEMI is a heart trauma:

60 minutes from "door"

SET NEW GOAL:

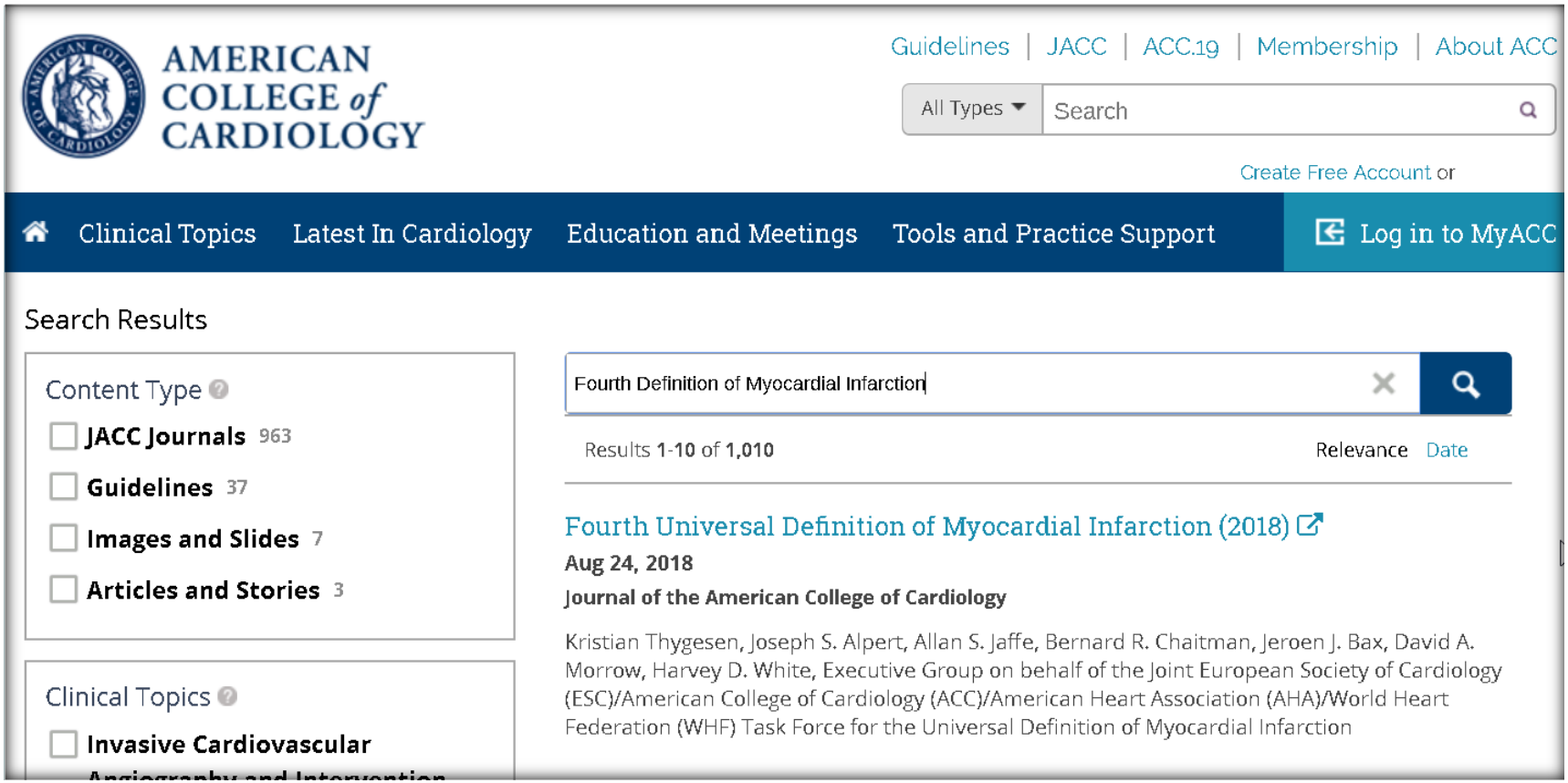
Door to Reperfusion in 60 minutes (60%)

SET NEW TAT GOAL and
ENSURE GUIDELINE COMPLIANCE SET:

Troponin assay at the 99th percentile

60 minutes from "door" (75%/90%)

Resources: www.acc.org



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Thank you!

Ruth Cantu, BSN, RN, AACC

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