



# Cardiac Biomarker History, Characterization of Troponin Assays & Impact on Cardiac Care

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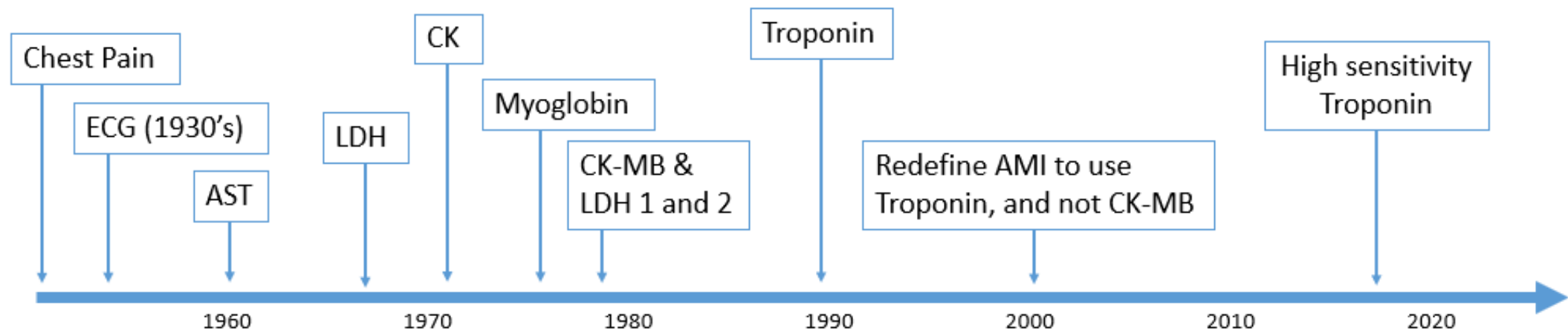
# Disclosures

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None

# History of Cardiac Biomarkers

- Biomarker – “A measurement taken that helps improve diagnosis or predict response to disease”
  - Cardiology – early adopter of Biomarkers
- Mid 1950’s – Observations that AST and ALT rose sharply after MI’s
- Era of “Cardiac Enzymes”

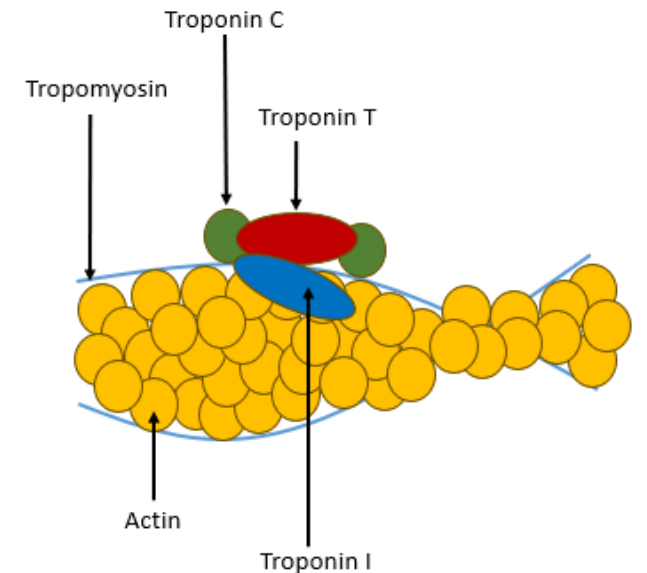


Garg P, Morris P, Fazlanie AL, et al. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. *Internal and Emergency Medicine*. 2017;12(2):147-155. doi:<https://doi.org/10.1007/s11739-017-1612-1>

# History of Cardiac Biomarkers

## •What is Troponin?

- Review: Muscle Tissue → Bundles → Myocytes (Muscle cells or muscle fibers) → myofibrils (1000's) → sarcomere (contractile units) → actin, tropomyosin & troponin
- Complex of 3 subunits
  - Troponin T – anchor to actin, cardiac isoform
  - Troponin C – binds to calcium, found in skeletal & cardiac muscle
  - Troponin I – inhibits interaction of actin with tropomyosin when there is not enough calcium present , cardiac isoform
- Helps regulate the interaction of actin and tropomyosin
- Calcium triggers contraction by making troponin complex move so tropomyosin and actin can cross-bridge and contract



Thin Filament of Sarcomere

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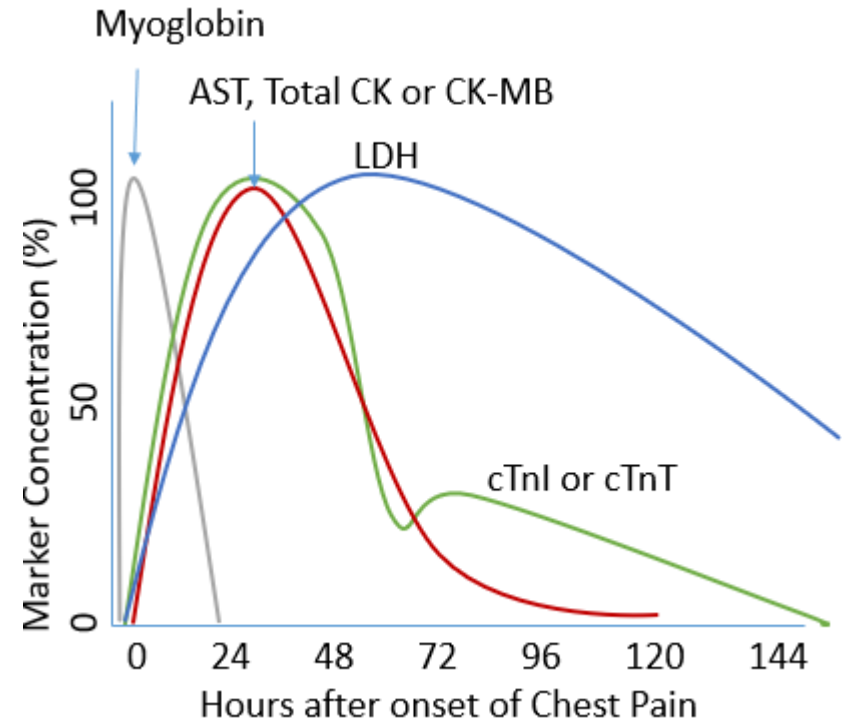
# History of Cardiac Biomarkers

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- Why does Troponin get released into the bloodstream?
  - Extended ischemia → irreversible damage to myocytes → cell membrane degrades → necrosis → releases complexes bound to myofibrils, including Troponin
  - Cell membrane permeability and degradation, which can happen during sepsis or inflammation
  - Normal turnover of myocytes
- When are high concentrations of troponin detected by troponin assays?
  - Acute thrombotic occlusion of a coronary artery → Acute Myocardial Infarction
  - Events that can cause Type II MI:
    - Myocarditis
    - Myocardial Contusion
    - Atrial fibrillation
  - Non-ischemic myocardial injury:
    - Heart Failure
    - Renal Failure
    - Sepsis
    - Pulmonary Embolism

# History of Cardiac Biomarkers

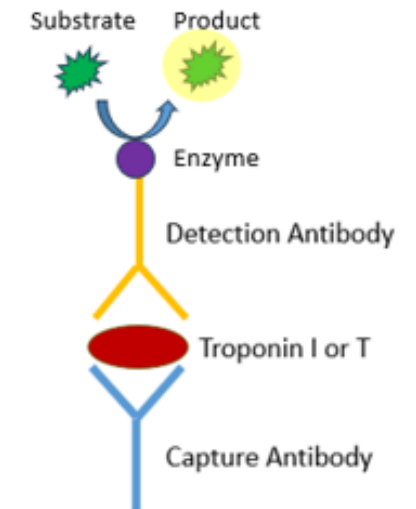
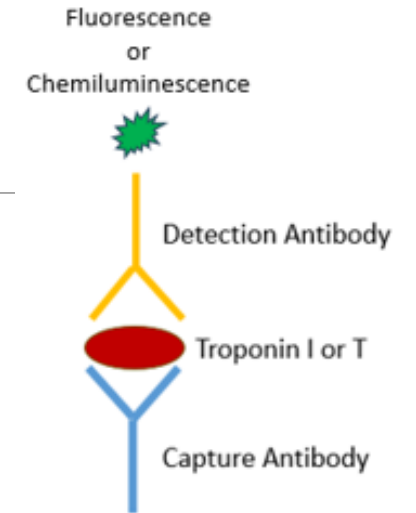
- Discovered in 1965, eventually came to be known as “Troponin”
- Troponin appears in 4-10 hours after an acute cardiac event (contemporary assays); less than 1 hour with high sensitivity assays
- Peaks around 12-48 hours
- Stays elevated for 4-10 days
- Heart-specific marker, not disease-specific marker



# Evolution of Troponin Assays

- How is troponin measured?

- Immunoassays
  - Capture Antibody
  - Detection Antibody
  - Detection Antibody tags can be enzymatic, fluorescent or chemiluminescent
- Radioimmunoassay – 1987
- Enzyme-linked immunosorbent assay (ELISA) – 1992
- Manufacturers use different capture and detection antibodies, to recognize epitopes on Troponin I or T
- No standard reference material for Troponin
- 2000 - Global Task Force with European Society of Cardiology & American College of Cardiology
  - Troponin is the preferred cardiac biomarker
  - Increase required for diagnosis of MI
  - Troponin above the 99<sup>th</sup> percentile, with a rise and/or fall, with evidence of cardiac ischemia, is sufficient for MI diagnosis



# Evolution of Troponin Assays

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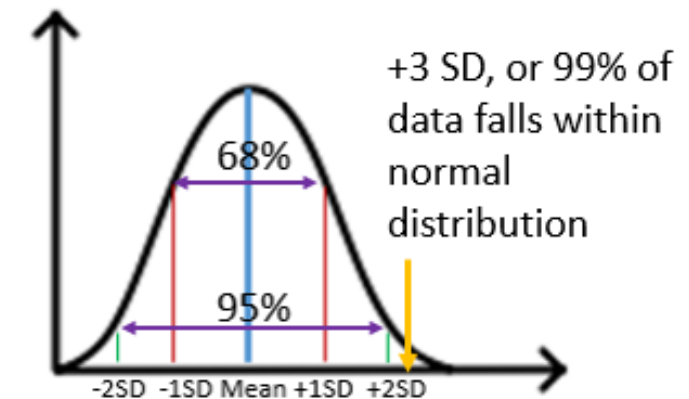
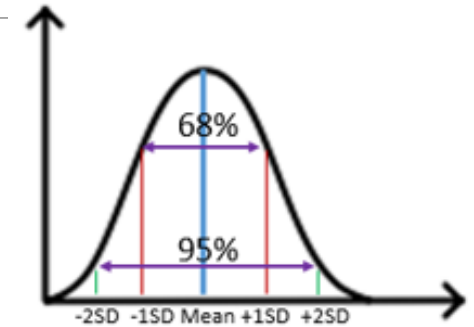
- High-sensitivity troponin (hs-cTn) assays have been used outside the US for over a decade
  - European Society of Cardiology has provided guidelines for hs-cTn since 2011
  - ESC 2020 guidelines recommend 0/1 hour & 0/2 hour rule-out algorithms
  - ESC also has assay-specific risk stratification thresholds that can help Providers understand hs-cTn results
- 2017 - FDA first approved hs-cTn assay for use in the US
  - Many assays available on the market now
  - Characteristics are tracked/updated every 4 months by the International Federation of Clinical Chemistry (IFCC)
  - Lack of guidelines in the US about how to include hs-cTn into clinical practice





# Characteristics of Troponin Assays

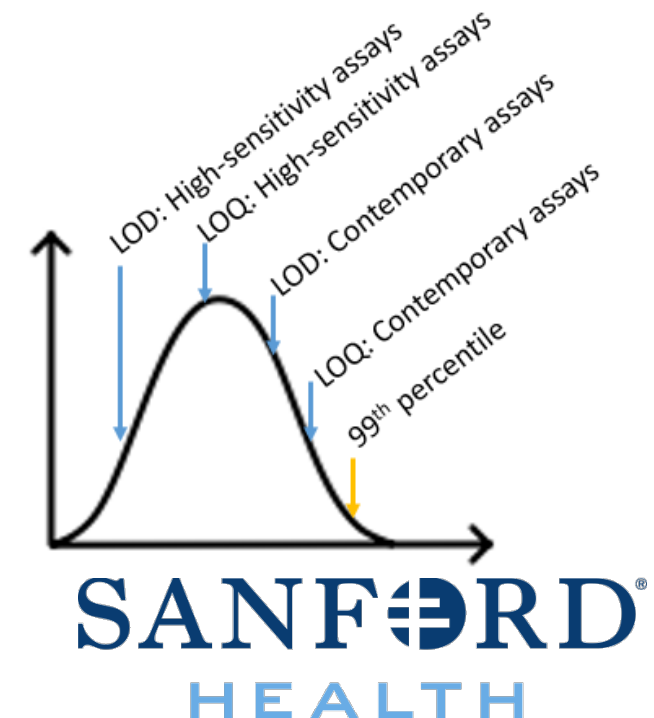
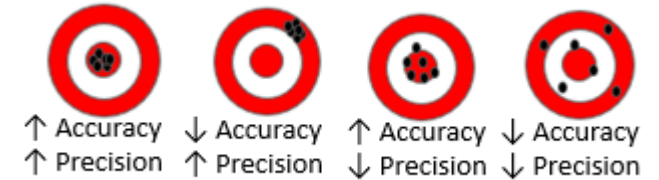
- Many Reference Intervals – 95<sup>th</sup> percentile reference limits
- Troponin – 99<sup>th</sup> percentile upper reference limit (URL)
- 99<sup>th</sup> percentile URL has played a major role in rule-in/rule-out of MI
  - Troponin > 99<sup>th</sup> percentile URL is diagnostic for myocardial injury
  - Contemporary – detect troponin in <50% of the healthy population
  - High sensitivity – detect troponin in >50% of a healthy population, for both males and females



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# Characteristics of Troponin Assays

- CV – coefficient of variation, aka imprecision, variability, or reproducibility
  - Contemporary & High-sensitivity  $\rightarrow \leq 10\%$  CV at the 99<sup>th</sup> percentile
- LOD – lowest troponin concentration that the assay can reliably detect
- LOQ – lowest troponin concentration that can be measured at  $\leq 10\%$  CV
  - LOD, LOB and LOQ are much lower for high-sensitivity troponin assays than contemporary
- LOB – background noise signal of a troponin concentration at zero
- High-sensitivity troponin assays  $\rightarrow$  More precise, more sensitive, more specific for troponin measurement and diagnosing myocardial injury and MI when using appropriate algorithms



# High-Sensitivity Cardiac Troponin (hs-cTn)

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- 2021 ACC/AHA guidelines – class I recommendation to use troponin and to preferably use hs-cTn
- Opportunities exist:
  - To educate clinicians about the analytics of hs-cTn assays
  - To develop/maintain evidence-based rapid risk stratification protocols for acute MI
  - To standardize sample collection protocols for rapid turnaround times for rule-in and rule-out algorithms
  - To help standardize reporting in Electronic Health Records
  - To ensure that our analytical quality controls in the Lab for hs-cTn are reliable for decisions
- Multi-disciplinary – Lab, Emergency Medicine, Internal/Family Medicine, Cardiology, Cardiology STEMI Coordinators

# High-Sensitivity Cardiac Troponin (hs-cTn)

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- 2021 ACC/AHA guidelines

- Prefer the use of hs-cTn
- Endorse using 99<sup>th</sup> percentile URL's
- Concentrations for hs-cTn should be reported in ng/L units and use whole numbers
  - Contemporary troponin uses ng/mL and decimals

- Important to understand how the 99<sup>th</sup> percentile URL for hs-cTn is established

- International Federation of Clinical Chemistry (IFCC) guidelines recommend the use of 400 healthy males and 400 healthy females
  - Use of questionnaires to exclude those with cardiovascular comorbidities, anyone on cardiovascular medications, use of biomarkers like NT-proBNP or BNP, Hemoglobin A1c, and/or eGFR to exclude anyone with subclinical disease
- Many medical centers still do not use the 99<sup>th</sup> percentile
  - Inconsistency between assays or not standardized/harmonized
  - Inconsistency between medical centers

# High-Sensitivity Cardiac Troponin (hs-cTn)

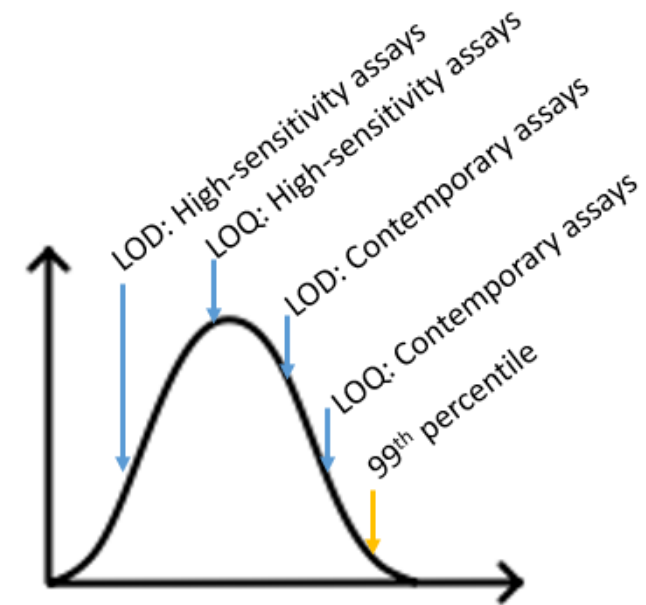
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- Gender-specific 99<sup>th</sup> percentile URL's for hs-cTn
  - Numerous studies show that women have lower 99<sup>th</sup> percentile URL's compared to men
  - 2021 ACC/AHA Guidelines for the diagnosis and evaluation of acute chest pain – Class IB recommendation
    - Acknowledge sex-specific hs-cTn 99<sup>th</sup> percentile URL's, but do not endorse or advocate their use
  - 2018 Fourth Universal Definition of Myocardial Infarction (UDMI) endorses sex-specific hs-cTn 99<sup>th</sup> percentile URL's
  - All FDA-approved hs-cTn assays have sex-specific 99<sup>th</sup> percentile URL's
- Questions about whether sex-specific 99<sup>th</sup> percentile URL's impact cardiac outcomes; studies are ongoing...



# High-Sensitivity Cardiac Troponin (hs-cTn)

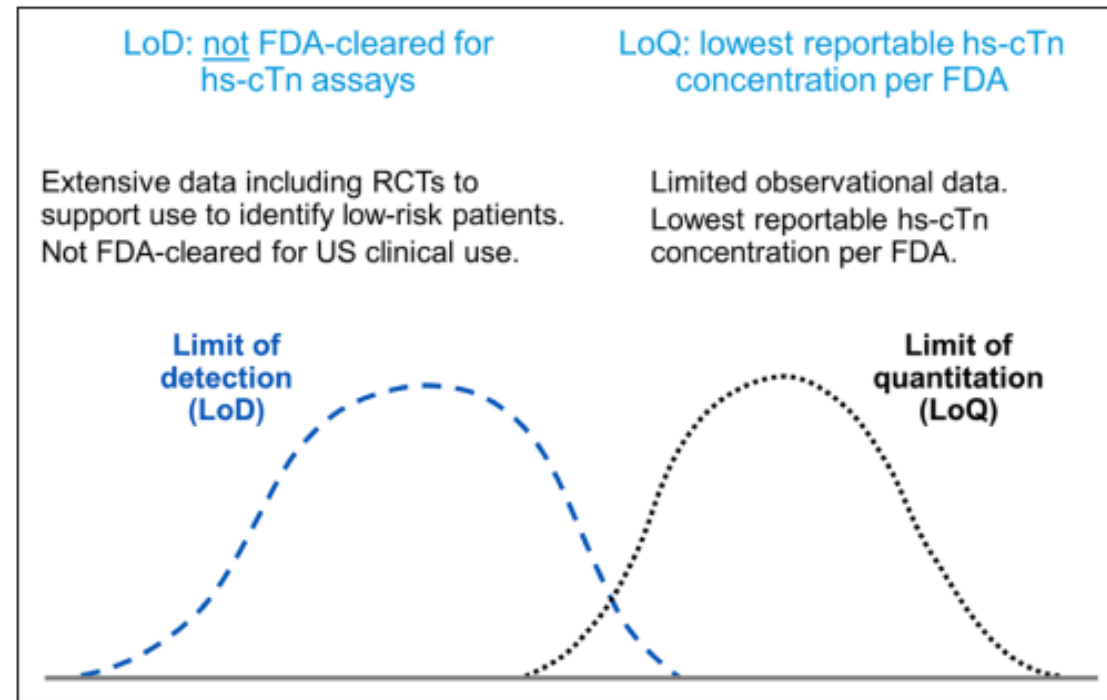
- Single Sample Rule-Out?
- Contemporary – 2 or 3 troponin results needed to rule-out, depending on presentation, troponin results/patterns and/or risk scores
- High-sensitivity troponin
  - Low risk patients: If not an early presenter (or less than 2 hours), many studies show that a single hs-cTn can rule out patients at low risk for acute MI
    - Reduce hospital overcrowding
    - Help with early discharge of low-risk patients
  - High risk patients: hs-cTn above the 99<sup>th</sup> percentile can indicate myocardial injury
    - Specific for myocardial injury
    - Not specific for MI
    - hs-cTn can be elevated in critical illness, end-stage renal disease,
  - Serial troponins over time (deltas) become more important to improve specificity



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# High-Sensitivity Cardiac Troponin (hs-cTn)

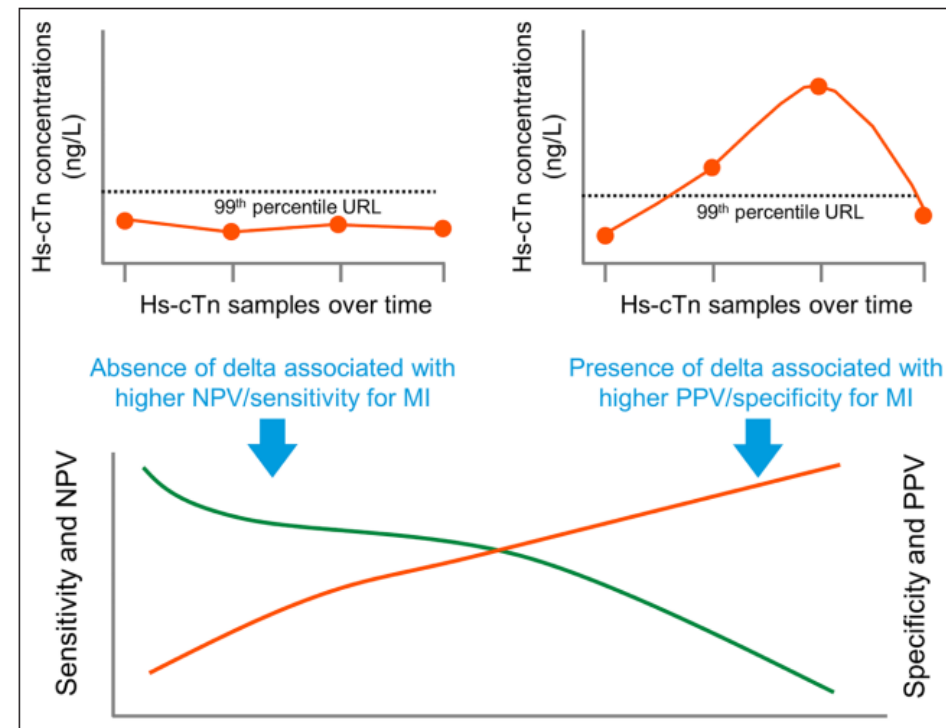
- 2021 ACC/AHA Guidelines – Class 2a recommendation for patients with acute chest pain, normal ECG, ACS symptoms begin at least 3 hours before arrival
  - Single high-sensitivity troponin that is below the LOD
- Problem: No FDA-approved assays allowed to report to the LOD, only to the LOQ



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# High-Sensitivity Cardiac Troponin (hs-cTn)

- What about hs-cTn values that change over time (Deltas)?
  - Absence of troponin changes over time identifies low risk patients
  - Presence of troponin changes over time identifies higher risk patients
    - Improved specificity
  - Not perfect for identifying MI
    - Deltas can represent any acute myocardial injury
    - Need to use other information including patient history, ECG, or imaging
  - Chronic Increases above 99<sup>th</sup> percentile, but absence of significant change (<20% change) indicates chronic myocardial injury
  - Still concern that small deltas could be missed with hs-cTn



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# High-Sensitivity Cardiac Troponin (hs-cTn)

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- Risk Stratification

- Evaluation of cardiovascular risk:
  - 2021 ACC/AHA Guidelines recommend using clinical decision pathways to help categorize patients with acute chest pain and acute coronary syndrome into low, intermediate and high-risk – Class IB recommendation
  - HEART score – History, ECG, Age, Risk Factors, Troponin
  - TIMI score – Thrombolysis in Myocardial Infarction
  - Risk scores help predict risk of 30-day major adverse cardiovascular events
- Low-risk:
  - Well defined group
  - hs-cTn can help with early identification and discharge of low-risk patients
  - Reduces ED overcrowding



# High-Sensitivity Cardiac Troponin (hs-cTn)

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- Risk Stratification

- Intermediate-risk

- Could be based on risk score alone
    - Should patients with hs-cTn below the 99<sup>th</sup> percentile have the same risk profile and care recommendations as patients with hs-cTn above the 99<sup>th</sup> percentile?
      - Likely different risks, depending on whether troponin changes show acute or chronic changes, and the magnitude of change could be important as well
    - Should transthoracic echocardiography, coronary angiography, and stress testing be applied to all intermediate patients, even if hs-cTn is below the 99<sup>th</sup> percentile?
      - No strong data for additional workup for patients without myocardial injury
      - Non-invasive evaluations in those with intermediate risk scores, but non-ischemic ECG's and hs-cTn's below the 99<sup>th</sup> percentile have low diagnostic yield and do not improve clinical outcomes
      - Over-testing could increase ED and hospital overcrowding, could increase length of stay



# High-Sensitivity Cardiac Troponin (hs-cTn)

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- Risk Stratification

- Intermediate-risk

- 2021 ACC/AHA Guidelines: Class 2a recommendation to manage intermediate risk patients in observation units that have acute chest pain
      - Can shorten length of stay, and is lower cost than inpatient admission
      - Studies show variability in benefit:
        - ED patients without initial diagnosis of MI, no change in 30-day outcomes between observation unit or hospital admission
        - Wide variation in admission rates and no improvements in outcomes with higher admission rates
    - Can patients with intermediate risk scores, without evidence of myocardial injury based on hs-cTn above 99<sup>th</sup> percentile, be evaluated in an outpatient setting (and not an observation unit or hospital admission)?



# High-Sensitivity Cardiac Troponin (hs-cTn)

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- Risk Stratification

- High-risk

- 2021 ACC/AHA Guidelines: Class 1 recommendation for patients with acute chest pain, suspected ACS, high-risk score, coronary angiography is recommended
    - Does not use hs-cTn or show proof of myocardial injury
    - Studies show that patients that have ACS and hs-cTn below 99<sup>th</sup> percentile, there is no benefit to routine invasive coronary angiography

- Unstable Angina and hs-cTn?

- hs-cTn assays work great in ruling out AMI
  - Unstable Angina diagnosis used much less often with hs-cTn, but unstable angina and severe stable obstructive coronary artery disease still happen
  - Should not be used as diagnosis without symptoms, even if proof of coronary artery disease with coronary angiography
  - Need caution in this area – some studies have shown that patients do benefit from coronary angiography when they have hs-cTn values above the 99<sup>th</sup> percentile, some studies have shown no benefit

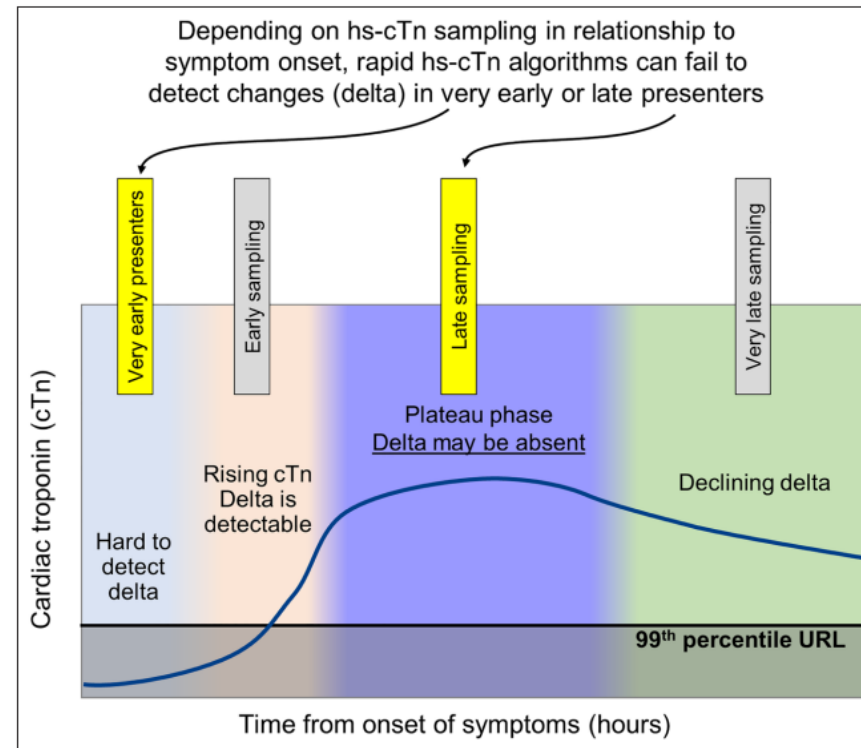
# High-Sensitivity Cardiac Troponin (hs-cTn)

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- Type 2 MI (or cardiac ischemia not due to CAD) is very common
  - Major increase in diagnosed MI events with hs-cTn assays is due to Type 2 MI's
  - US – data shows that there are more Type 2 MI's than Type 1 MI's
  - Heterogenous reasons for Type 2 MI's; angiography often needed
- Troponin Sampling Times are Important for hs-cTn!
  - Patients that present too early or too late may not look as if they are having an acute event (or not have a delta)
  - Early presenters may need additional hs-cTn samples or more time
  - The 2018 UDMI Guidelines do address this concern



# High-Sensitivity Cardiac Troponin (hs-cTn)

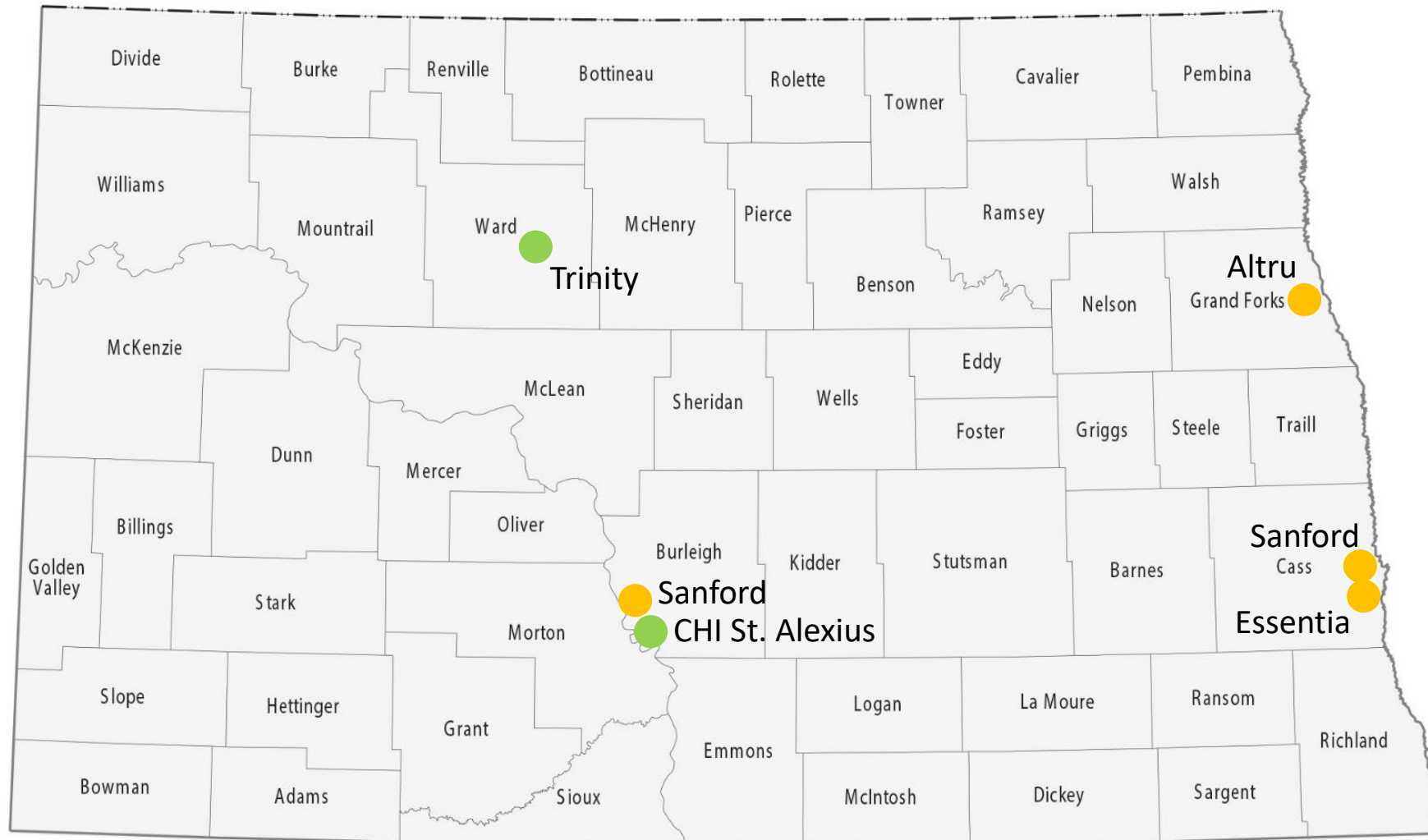


- Troponin Sampling Times are Important with hs-cTn! **SANFORD**<sup>®</sup>

Sandoval Y, Apple FS, Mahler SA, Body R, Collinson PO, Jaffe AS. High-Sensitivity Cardiac Troponin and the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guidelines for the Evaluation and Diagnosis of Acute Chest Pain. *Circulation*. 2022;146(7):569-581. doi:<https://doi.org/10.1161/circulationaha.122.059678>

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# Troponin Assays used in North Dakota STEMI Receiving Hospitals (as of Sept 2023)



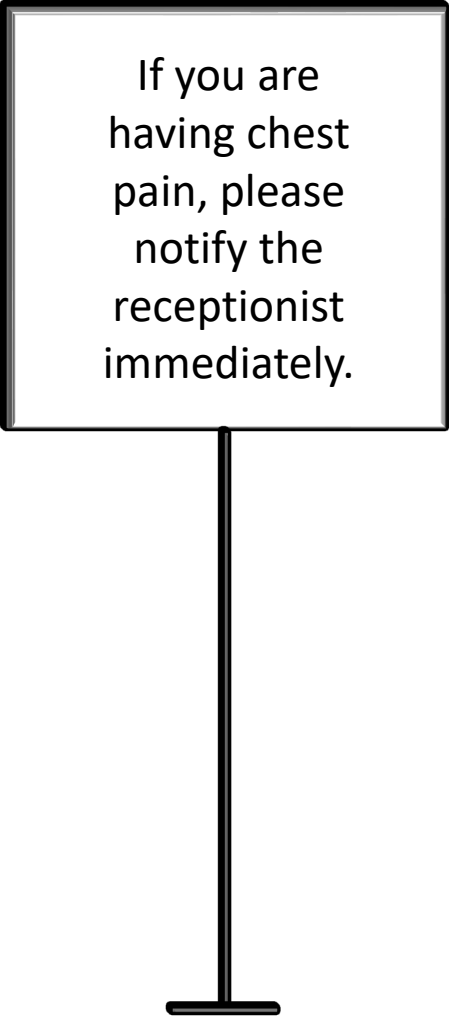
Marker	Troponin Assay
●	Contemporary (no plans to change)
●	Contemporary (plans to change to hs-cTn)
●	hs-cTn

# Chest Pain in the Emergency Department

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Second most common reason for adults to present to the Emergency Room in the US, accounts for >6.5 million visits annually, which is 5.5% of all ED visits in 2020

Only 5.1% of chest pain presentations account for acute coronary syndrome



If you are having chest pain, please notify the receptionist immediately.

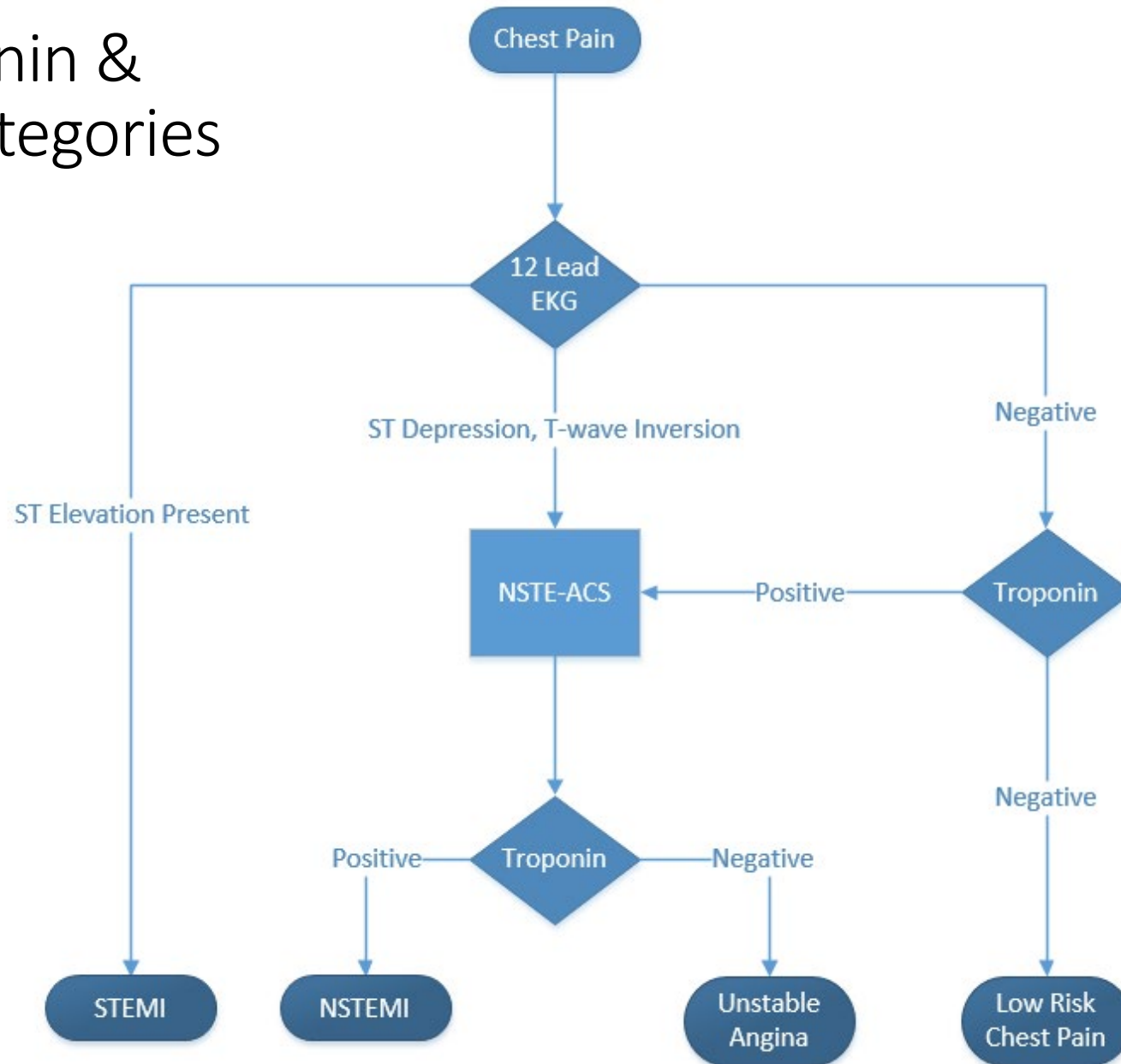
Cairns C, Kang K. National Hospital Ambulatory Medical Care Survey: 2020 Emergency Department Summary Tables. Published online December 13, 2022. doi:<https://doi.org/10.15620/cdc:121911>

Hsia RY, Hale Z, Tabas JA. A National Study of the Prevalence of Life-Threatening Diagnoses in Patients With Chest Pain. *JAMA Internal Medicine*. 2016;176(7):1029. doi:<https://doi.org/10.1001/jamainternmed.2016.2498>

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# EKG, Troponin & Registry Categories



# Criteria for Type 1 MI

## Fourth Universal Definition of Myocardial Infarction

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Detection of a rise and/or fall of cTn values at least 1 value above the 99<sup>th</sup> percentile URL and with at least 1 of the following:

- Symptoms of acute myocardial ischemia
- New ischemic ECG changes
- Development of pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy

# Types of Myocardial Infarction

## Fourth Universal Definition of Myocardial Infarction

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Type I: STEMI & NSTEMI

Type II: Demand Ischemia

Type III: Cardiac death with symptoms suggestive of myocardial ischemia (ischemic ECG changes or ventricular fibrillation)

Type IV: MI related to PCI procedure

Type V: MI associated with CABG

# Accelerated Diagnostic Protocols (ADP)

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Algorithms that combines troponin results, EKG results and a structured risk assessment to stratify ED patients according to their risk & determine their disposition

Allow for ACS to be quickly identified (ruled in) or excluded (ruled out)

## Three Categories

### 1. Rapid Rule-Out

- Use hs-cTN cut points and deltas

### 2. Focus on prediction of adverse cardiac events over a short timeframe (usually 30 days)

- Risk score or decision aid (HEART, EDACS, TIMI, GRACE, T-MACS, ADAPT)
- Various outcomes predicted – mortality, MACE (major adverse cardiac events)

### 3. Combination

hs-cTn flow chart

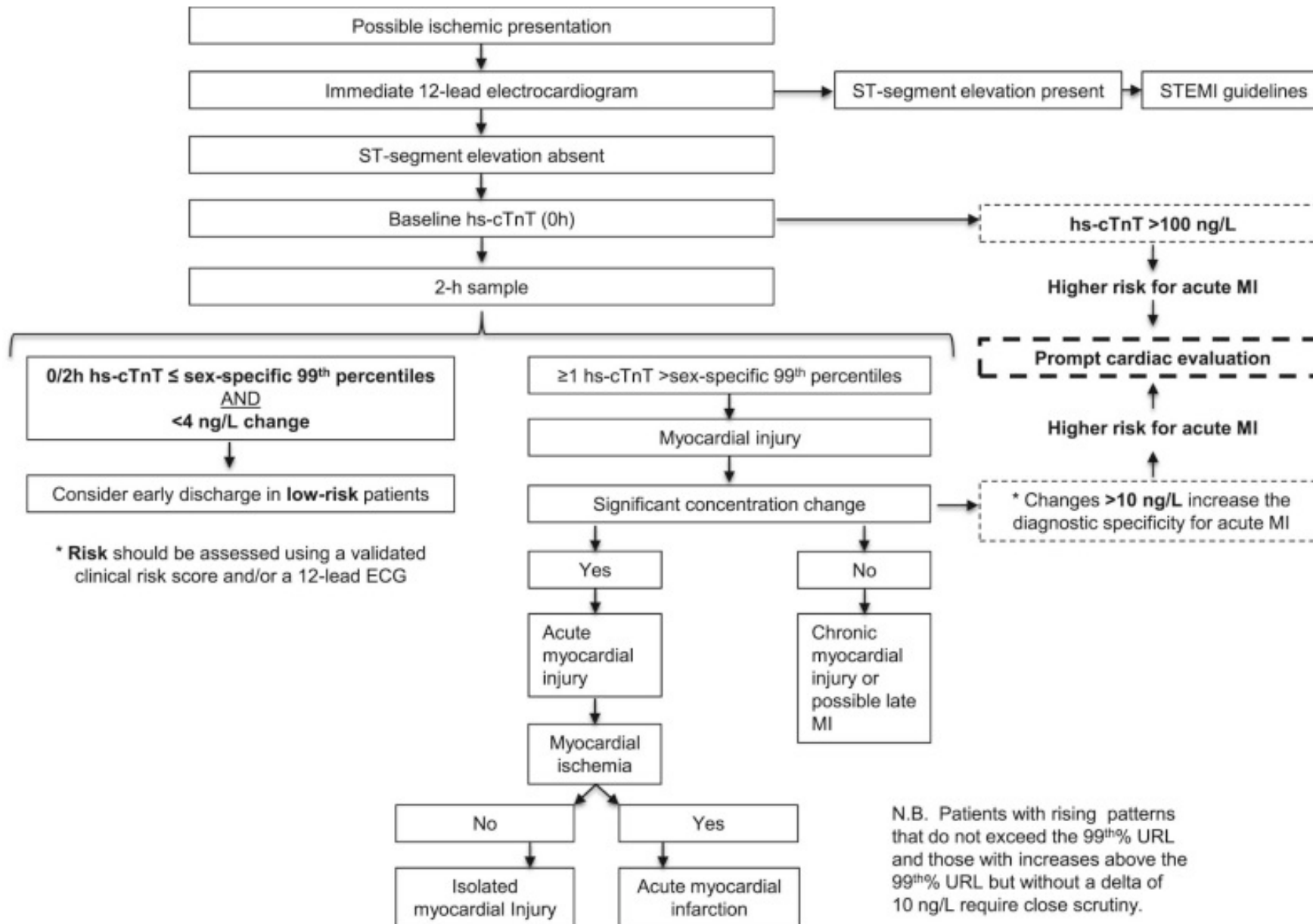
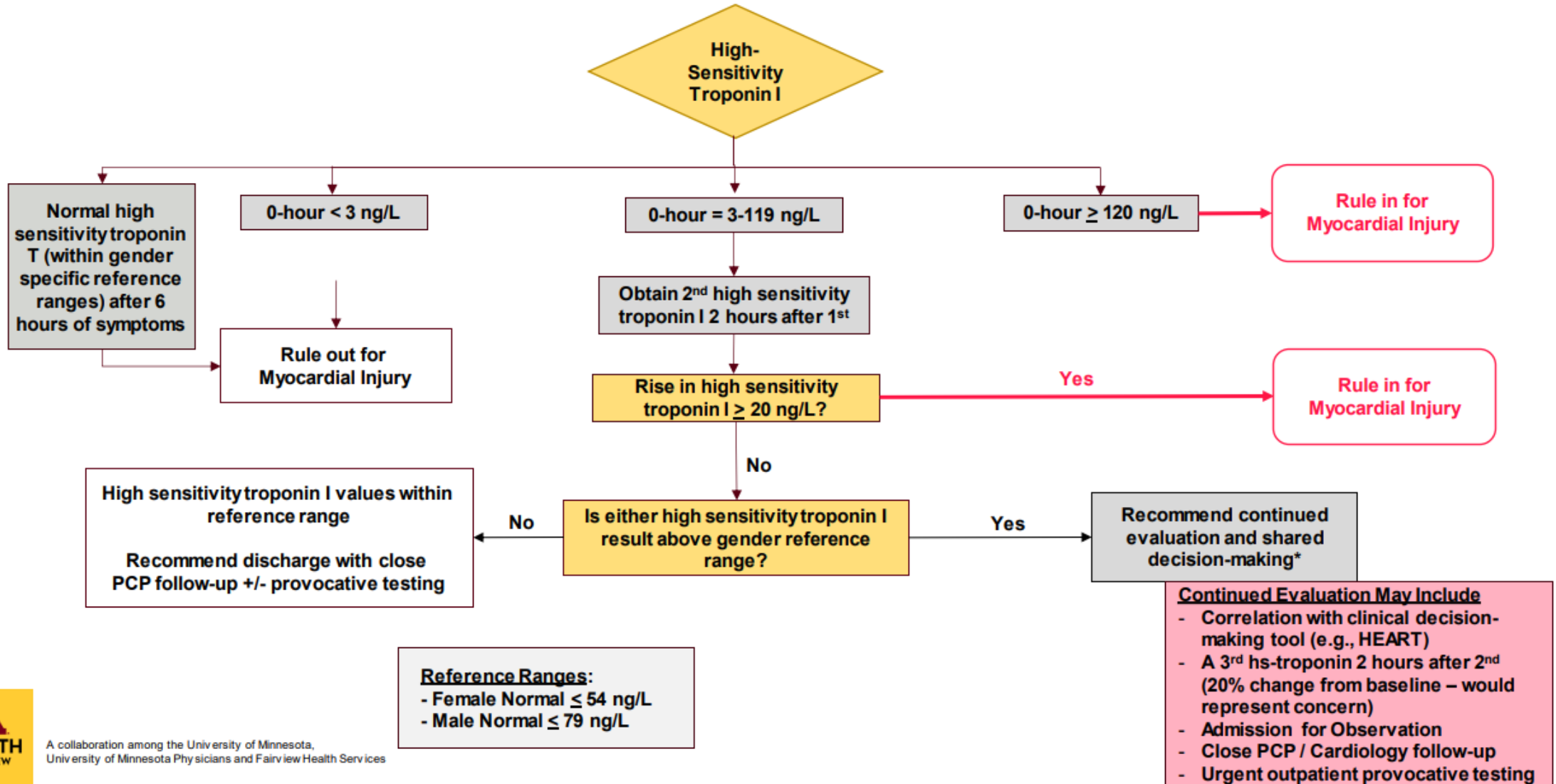


Figure used with permission.



# MHFV High-Sensitivity Troponin I Pathway for patients with symptoms of ACS



# Benefit of HS Troponin Assays

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Earlier identification of myocardial damage

Single troponin can rule out MI in patients presenting >2 hours after symptom onset

Sensitive but not specific for MI

Expedite the evaluation of patients with suspected ACS

- Decreased Length of Stay for Low Risk Chest Pain population
- Decrease ED overcrowding
- LOS Goal for ED <180 minutes

With HS Troponin utilization, Unstable Angina is diagnosed much less frequently, while there is an increase in Type II MI diagnoses

Utilization of whole numbers

Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;144(22). doi:<https://doi.org/10.1161/cir.0000000000001029>

Wassie M, Lee MS, Sun BC, et al. Single vs Serial Measurements of Cardiac Troponin Level in the Evaluation of Patients in the Emergency Department With Suspected Acute Myocardial Infarction. *JAMA Network Open*. 2021;4(2):e2037930. doi:<https://doi.org/10.1001/jamanetworkopen.2020.37930>



# Implementing HS Troponin – 6 Keys

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1. Identify other institutions' best practices
2. Assemble team of stakeholders and have regular meetings
3. Educate staff
4. Go-live with the change
5. Expect and prepare for uncertainty after the change
6. Evaluate the results



# Key Takeaways for Chest Pain in the ED

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Obtaining and reading a 12-lead EKG in less than 10 minutes for all patients presenting with acute chest pain

Use structured risk assessment

When ACS is suspected, troponin should be measured as soon as possible

hs-cTn preferred

Use clinical decision pathways

Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;144(22). doi:<https://doi.org/10.1161/cir.0000000000001029>



# Questions

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