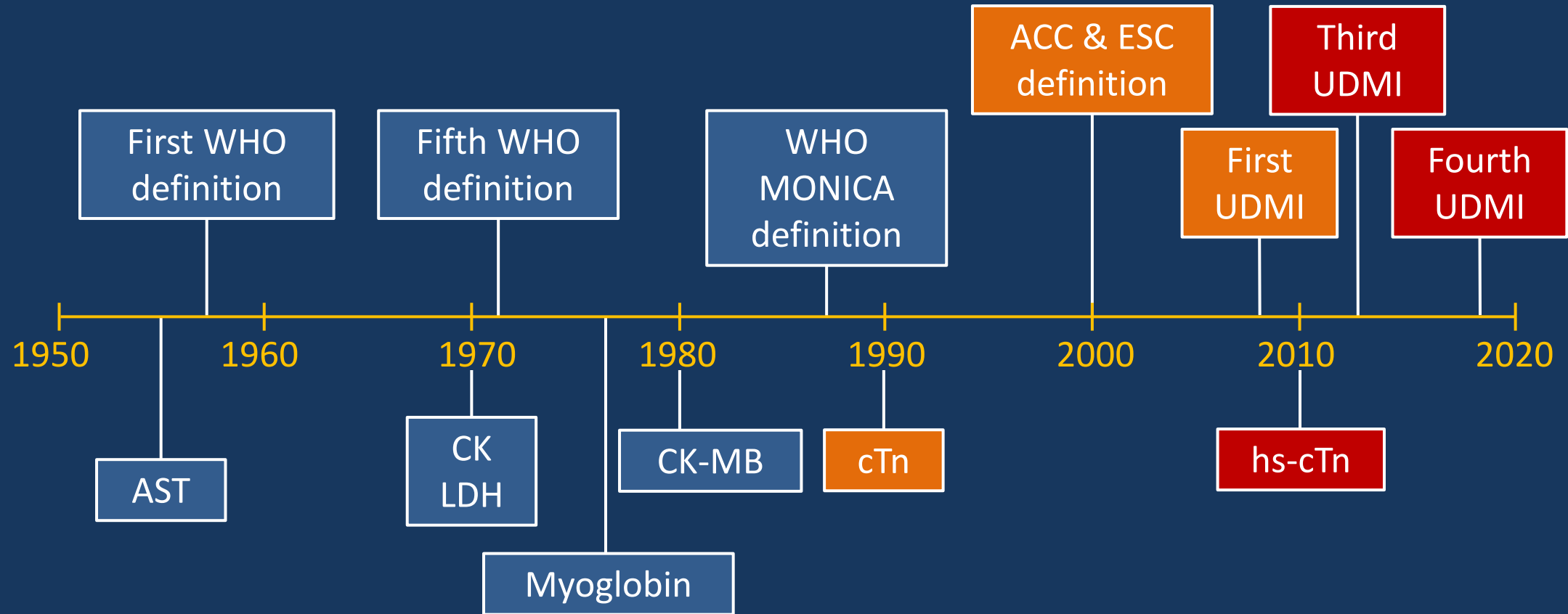# Does the 99ᵗʰ Percentile cTn Value Mean Anything to the Clinician?

M. Odette Gore, MD, MSCS

University of Colorado Denver School of Medicine
Denver Health and Hospital Authority
Colorado Prevention Center

Timeline of MI definitions and use of biomarkers

Adapted from Thygesen *et al. J Am Coll Cardiol.* 2018 Oct 30;72(18):2231-2264
and Garg *et al. Intern Emerg Med.* 2017; 12(2): 147–155.

Fourth Universal Definition of MI

- **Myocardial injury:** Cardiac troponin (cTn) > 99th percentile

- **Acute myocardial injury:** Serial measurements detecting a rise or fall in cTn, with at least one value > 99th percentile

- **MI:** Acute myocardial injury + at least one other clinical, ECG or imaging criterion consistent with ischemic injury.
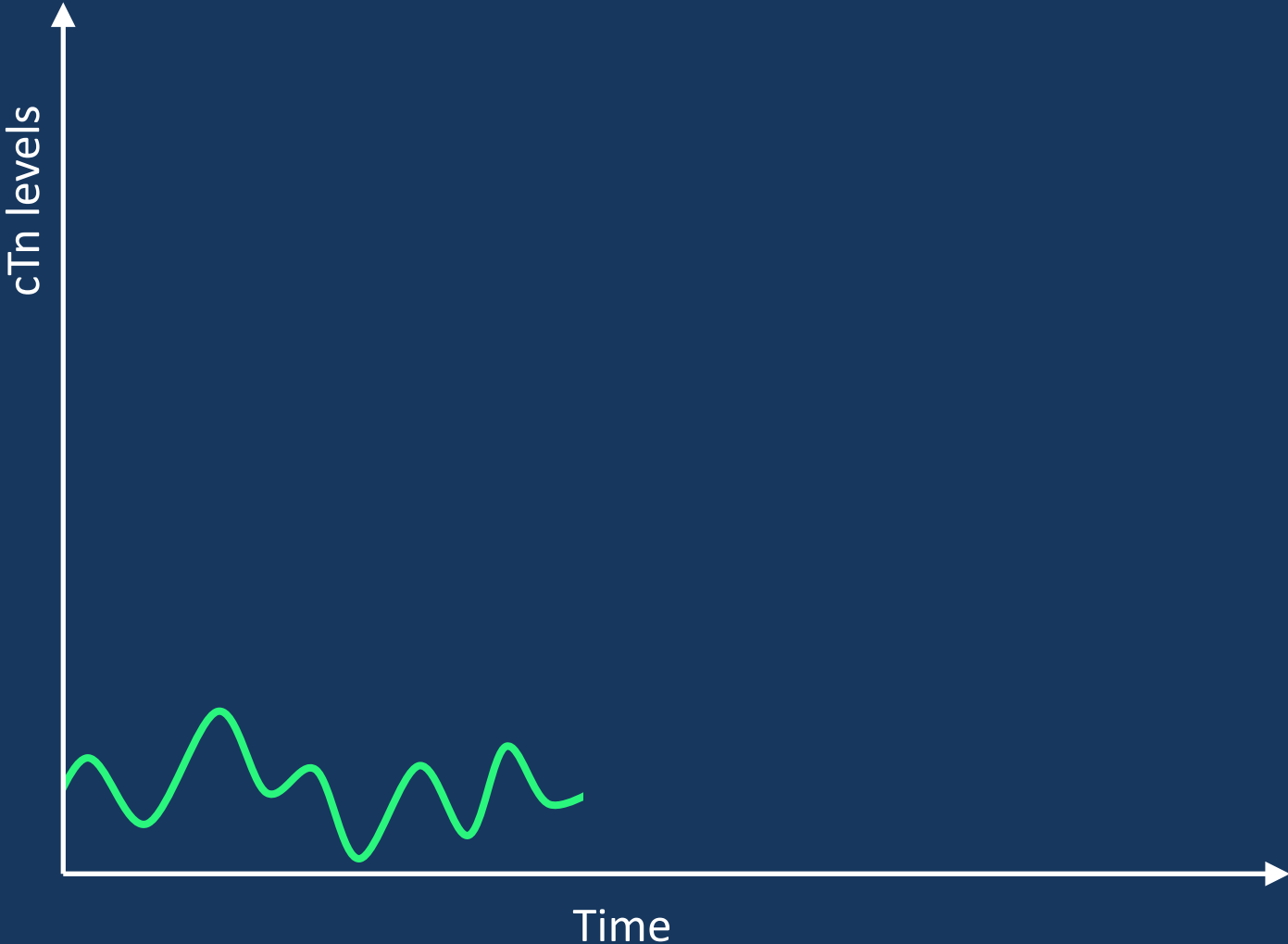
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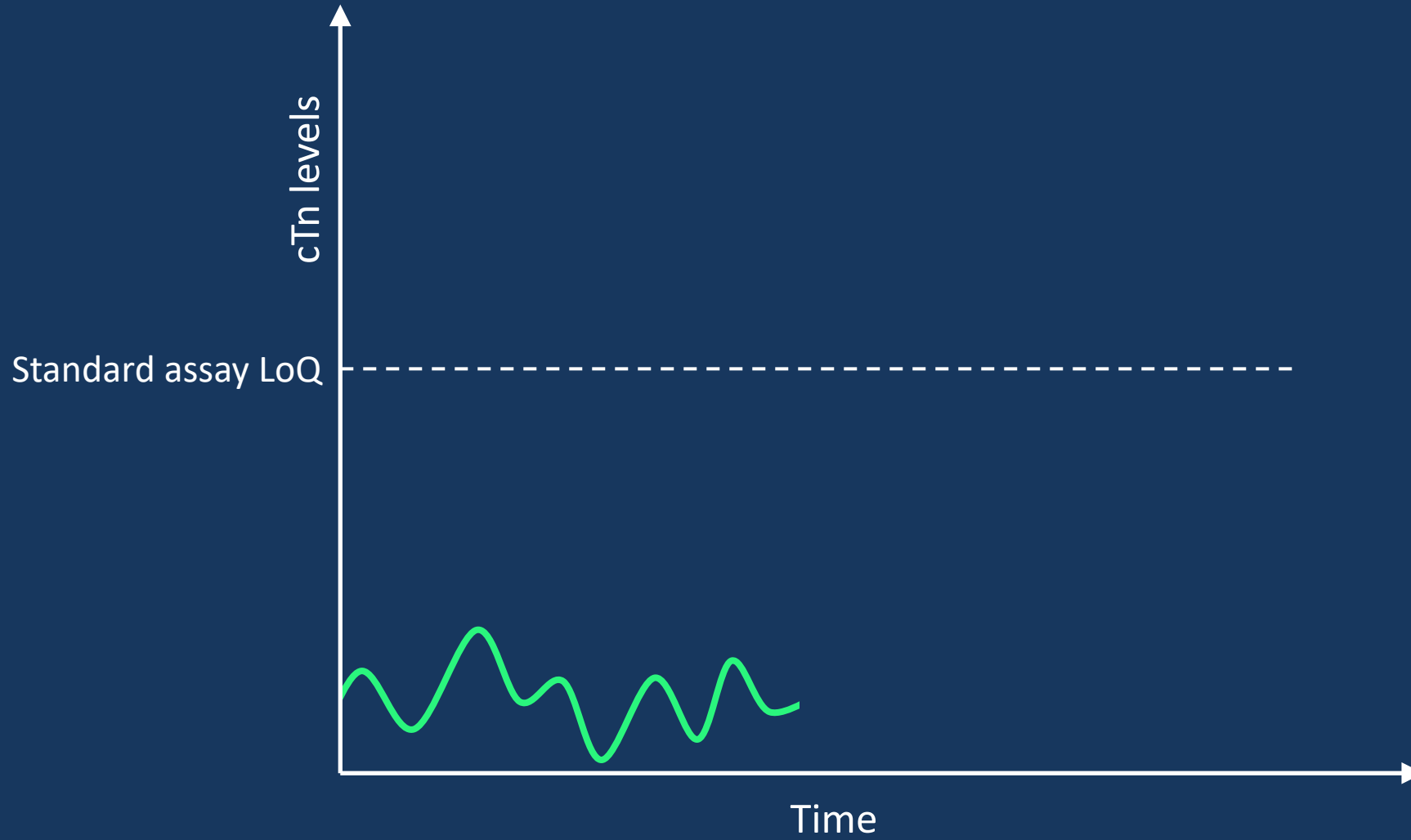- MI: Acute myocardial injury + at least one other clinical, ECG or imaging criterion consistent with ischemic injury.

hs-cTn assays and early diagnosis of MI

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cTn levels

Standard assay LoQ

Time

hs-cTn assays and early diagnosis of MI

cTn levels

MI

Detection with standard assay
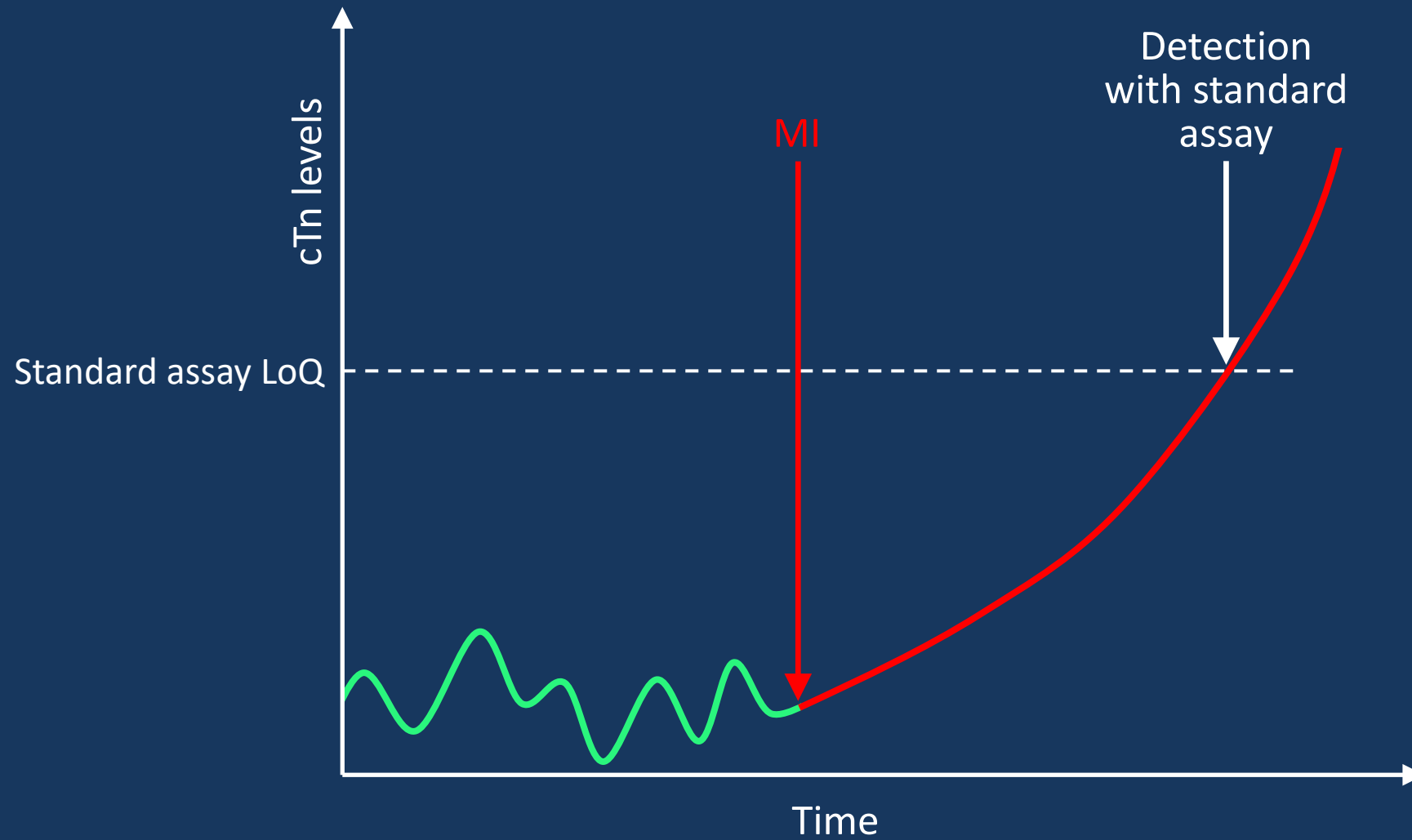
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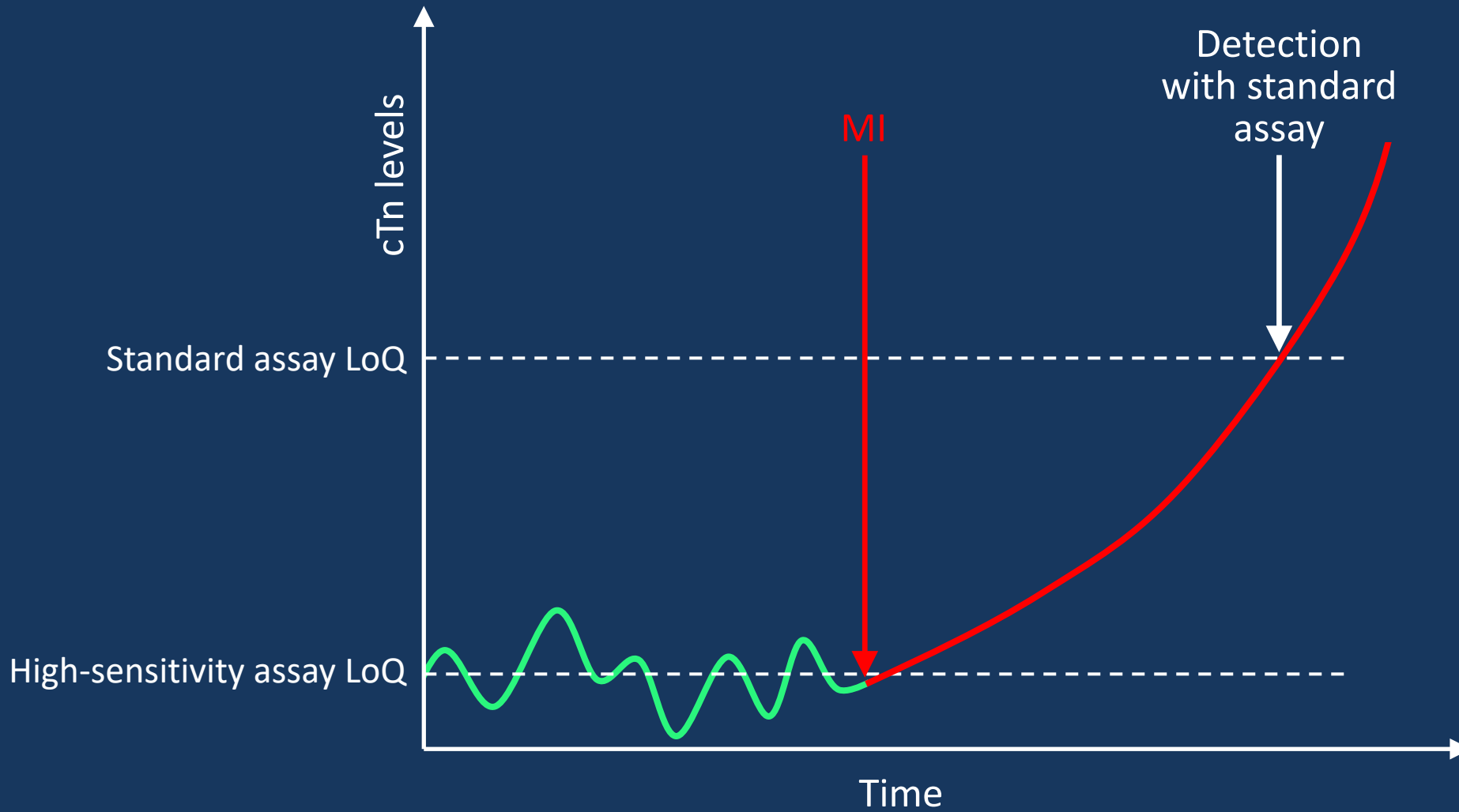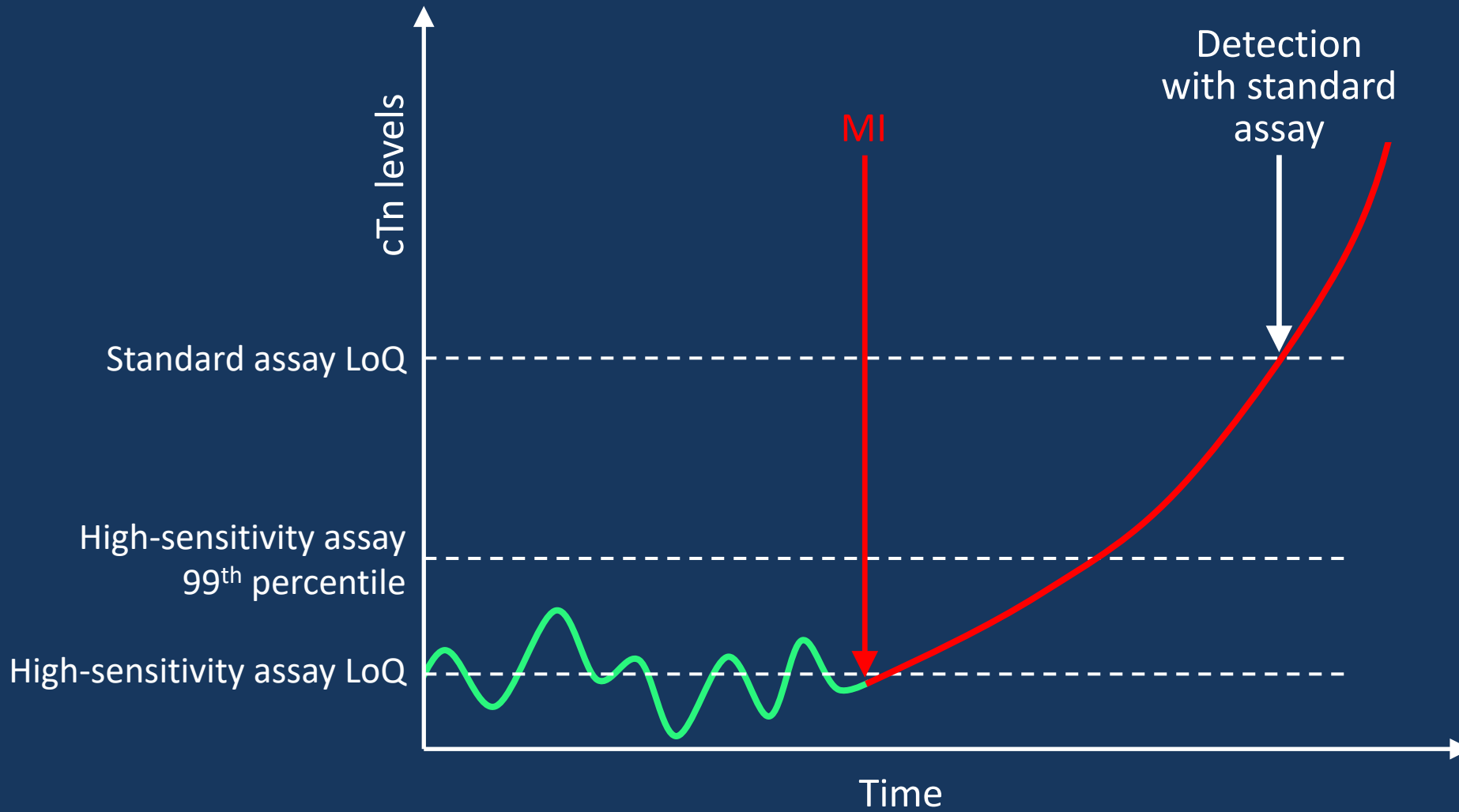# hs-cTn assays and early diagnosis of MI

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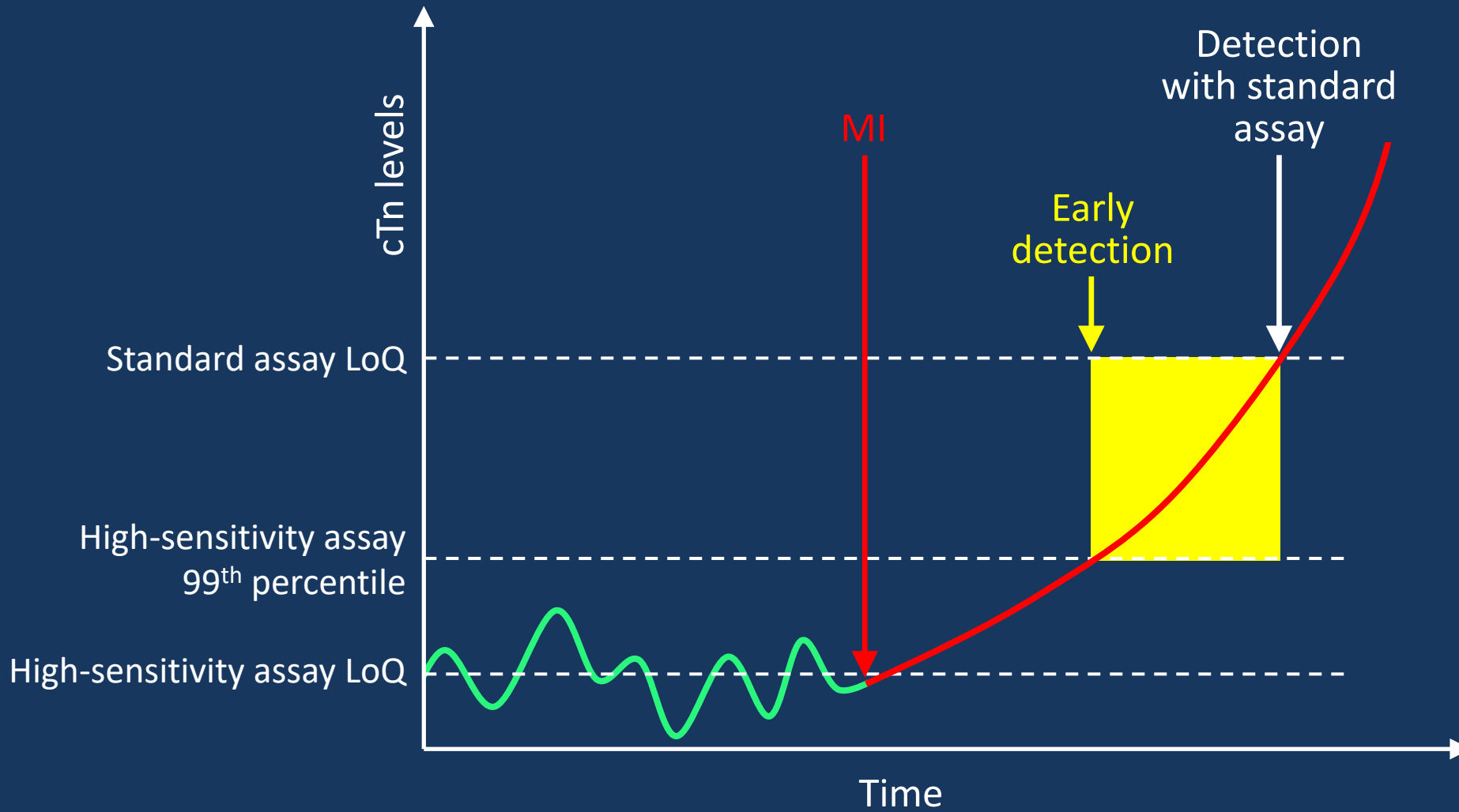
Diagnostic performance

Data from 786 consecutive patients who presented to the ER with symptoms suggestive of MI with onset <12 hrs

	Standard cTnT (LoQ 35 ng/L)	hs-cTnT (99th percentile 14 ng/L)
Sensitivity	72	95
Specificity	97	80
Positive predictive value	85	50
Negative predictive value	94	99

Reichlin *et al.* N Engl J Med. 2009 Aug 27;361(9):858-67

How is the 99ᵗʰ percentile hs-cTn defined?

- "No expert opinion or consensus about specific criteria for how the 99ᵗʰ percentile [...] should be defined."

- 99ᵗʰ percentiles in current use were determined in "normal reference populations", but no consensus about criteria to define normal reference populations, or about statistical methods

Thygesen *et al. J Am Coll Cardiol.* 2018 Oct 30;72(18):2231-2264

How was the 99th percentile for hs-cTnT derived?

- **2010 –** Study of 616 apparently healthy volunteers and blood donors (mean age 44), with little information about subject selection and inclusion/exclusion criteria.

- **2011 –** Study of 533 apparently healthy individuals (mean age 37) selected based on a standardized questionnaire.

Giannitsis *et al*. *Clin Chem.* 2010 Feb;56(2):254-61; Saenger *et al*. *Clin Chim Acta.* 2011 Apr 11;412(9-10):748-54

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- **2012** – Recommendation of the IFCC Task Force on Clinical Applications of Cardiac Biomarkers: Normal reference populations for the determination of the 99ᵗʰ percentile value of cardiac troponin should be selected by detailed physician evaluation, including ECG, echo and NT-proBNP, and should include both younger and older subjects.

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Apple & Collinson. *Clin Chem.* 2012 Jan;58(1):54-61

Age- and sex-dependent 99th percentiles for hs-cTnT

Biomarkers

Age- and Sex-Dependent Upper Reference Limits for the High-Sensitivity Cardiac Troponin T Assay

CrossMark

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Vijay Nambi, MD, PhD,‡§ Robert H. Christenson, PhD,‖ Ibrahim A. Hashim, PhD,¶
Ron C. Hoogeveen, PhD,‡ Colby R. Ayers, MS,*# Wensheng Sun, MS,‡
Darren K. McGuire, MD, MHSc,* ** Christie M. Ballantyne, MD,‡ James A. de Lemos, MD* **

Dallas and Houston, Texas; and Baltimore, Maryland

Three large, well characterized, population-based cohorts

Study	Participants with measured hs-cTnT
Dallas Heart Study (DHS)	N = 3,546 Age 18 - 65 Dallas County
Atherosclerosis Risk in Communities (ARIC) Study	N = 9,698 Age 45 - 64 4 counties in North Carolina, Minnesota, Mississippi and Maryland
Cardiovascular Health Study (CHS)	N = 4,221 Age ≥ 65 4 counties in North Carolina, Maryland, Pennsylvania and California

de Lemos *et al. JAMA.* 2010 Dec 8;304(22):2503-12; deFilippi *et al. JAMA.* 2010 Dec 8;304(22):2494-502; Saunders *et al. Circulation.* 2011 Apr 5;123(13):1367-76

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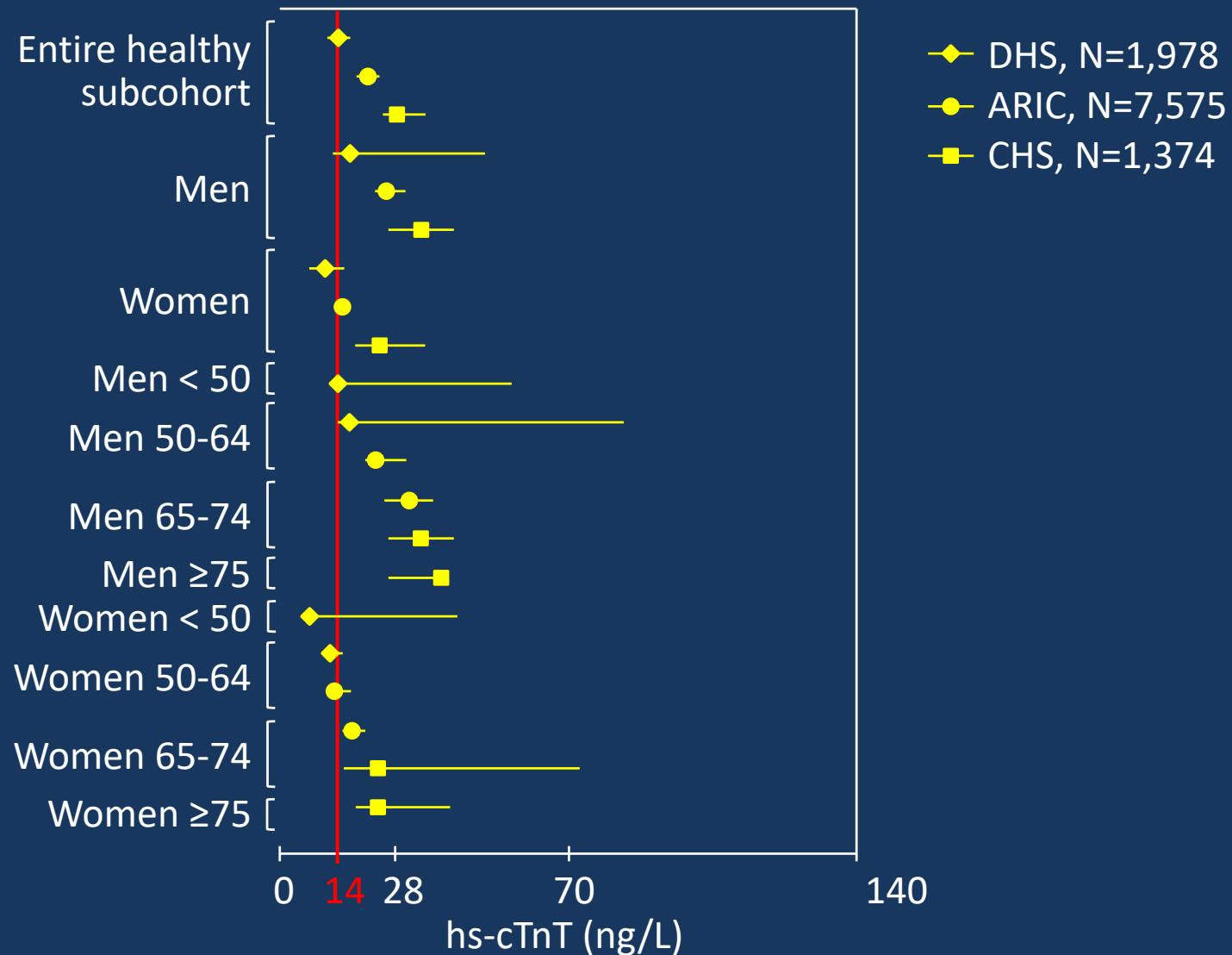Advantages vs. the studies used to derive the 14 ng/L 99th percentile for hs-cTnT:
- Detailed characterization (in excess of IFCC recommendations)
- Large number of participants
- Diverse races/ethnicities and wide age range

de Lemos *et al. JAMA.* 2010 Dec 8;304(22):2503-12; deFilippi *et al. JAMA.* 2010 Dec 8;304(22):2494-502; Saunders *et al. Circulation.* 2011 Apr 5;123(13):1367-76

Age- and sex-dependent 99th percentiles for hs-cTnT

Gore *et al. J Am Coll Cardiol.* 2014 Apr 15;63(14):1441-8.

Age- and sex-dependent 99th percentiles for hs-cTnT

DHS, N=1,978
ARIC, N=7,575
CHS, N=1,374
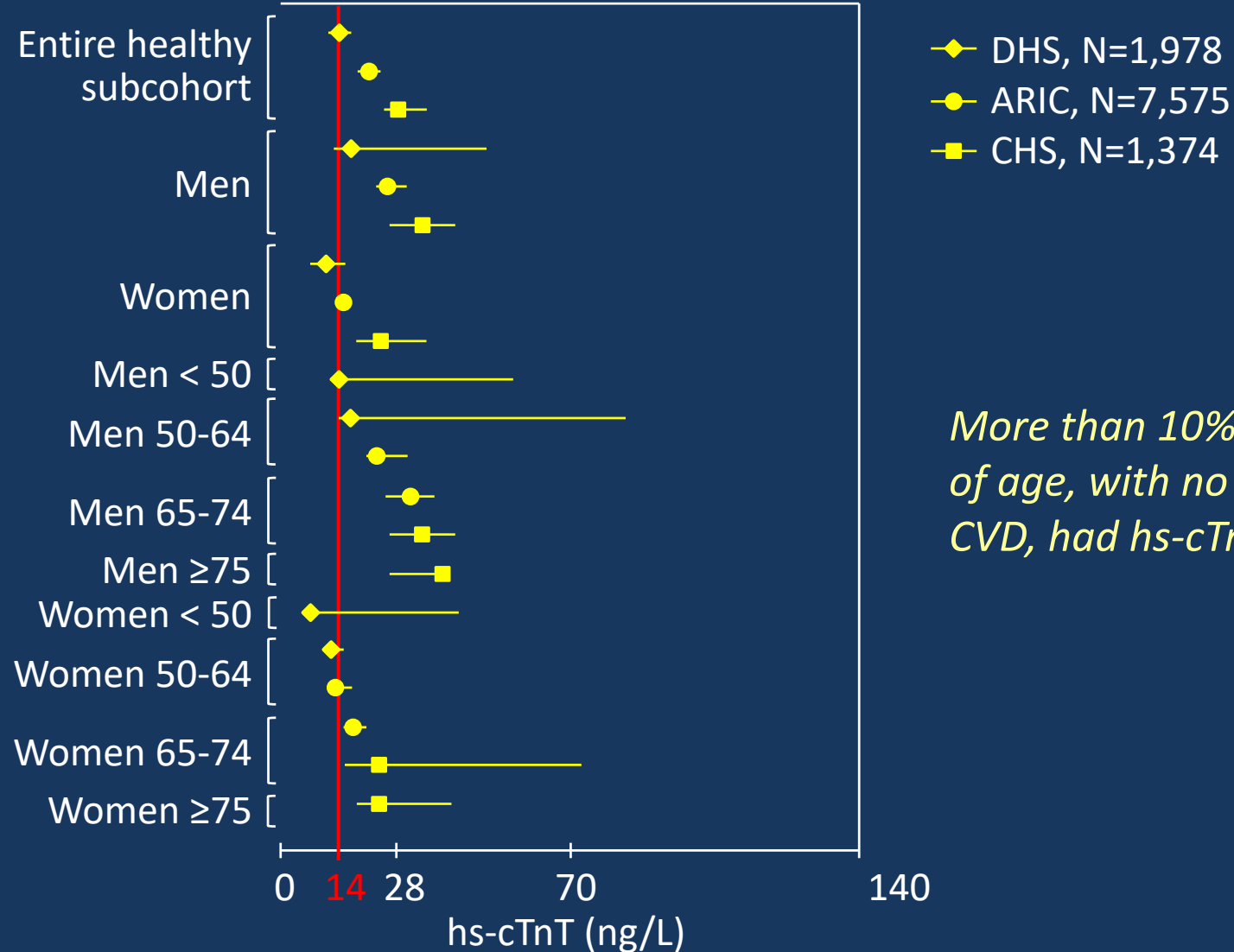
More than 10% of men 65 to 74 years of age, with no clinical or subclinical CVD, had hs-cTnT > 99th percentile

Gore *et al. J Am Coll Cardiol.* 2014 Apr 15;63(14):1441-8.

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- Diagnostic performance: High sensitivity at the expense of low specificity, low PPV.

- Variability between different assays, primarily because of lack of consensus about criteria for deriving 99th percentiles.

AACC Universal Sample Bank: 99th percentiles for 12 hs-cTn assays

Modified from Apple *et al. Clin Chem.* in press *(published online on 1/27/2020)*
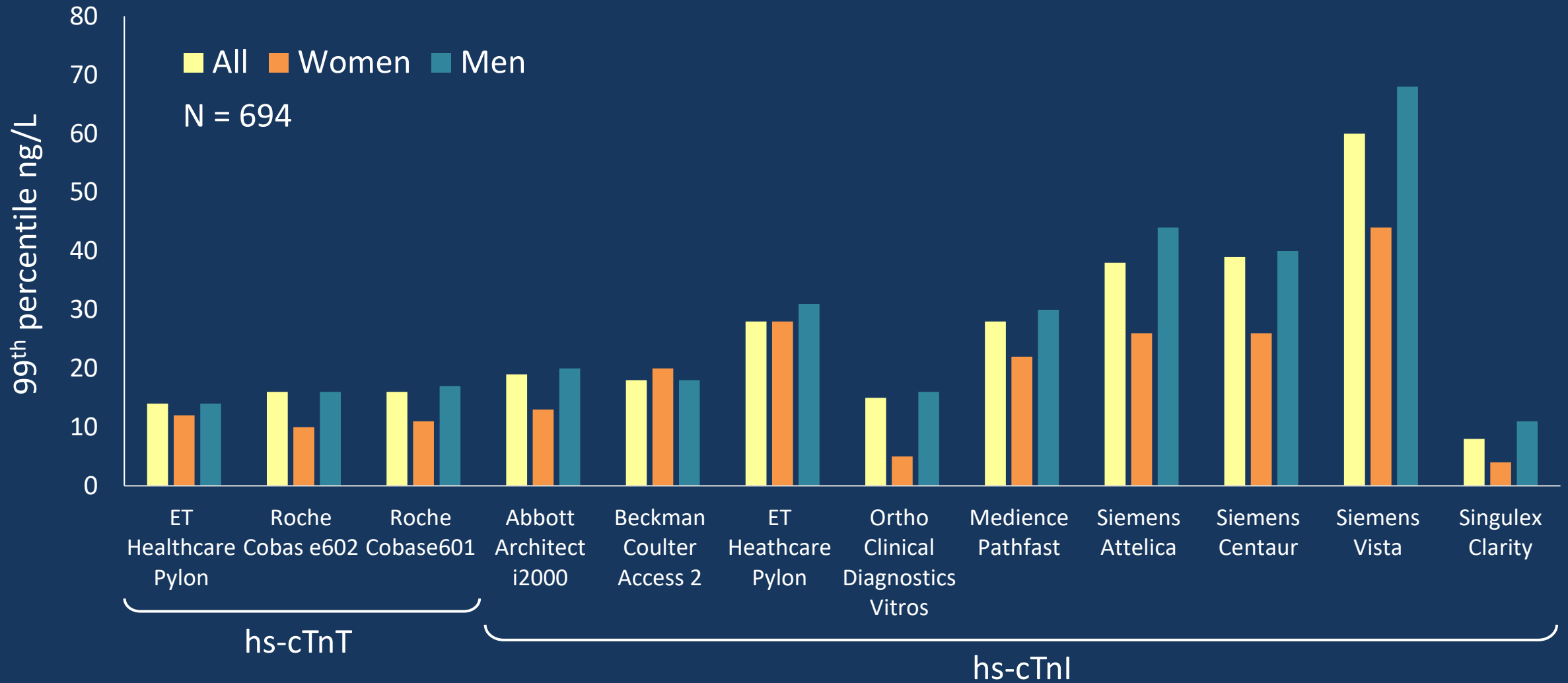
Implications for clinicians

- Avoid use of manufacturer-provided 99th percentile values to interpret hs-cTn qualitatively as normal vs. abnormal.

- Do not diagnose ACS based on a single hs-cTn > 99th percentile, in the absence of appropriate clinical context.

- Understand that hs-cTn > 99th percentile will have a higher sensitivity for non-MI troponin elevations compared with previous troponin assays.

Potential solutions for the future

- De-emphasize the use of 99th percentiles in clinical decision-making.

- More emphasis on serial change for MI rule-in
  (but no consensus on what constitutes a significant change).

- Benefit from the lower LoQ of hs-cTn assays in other ways
  (e.g. rapid MI rule-out).