2018 MID-ATLANTIC
CONFERENCE

8th ANNUAL CURRENT CONCEPTS IN
VASCULAR THERAPIES

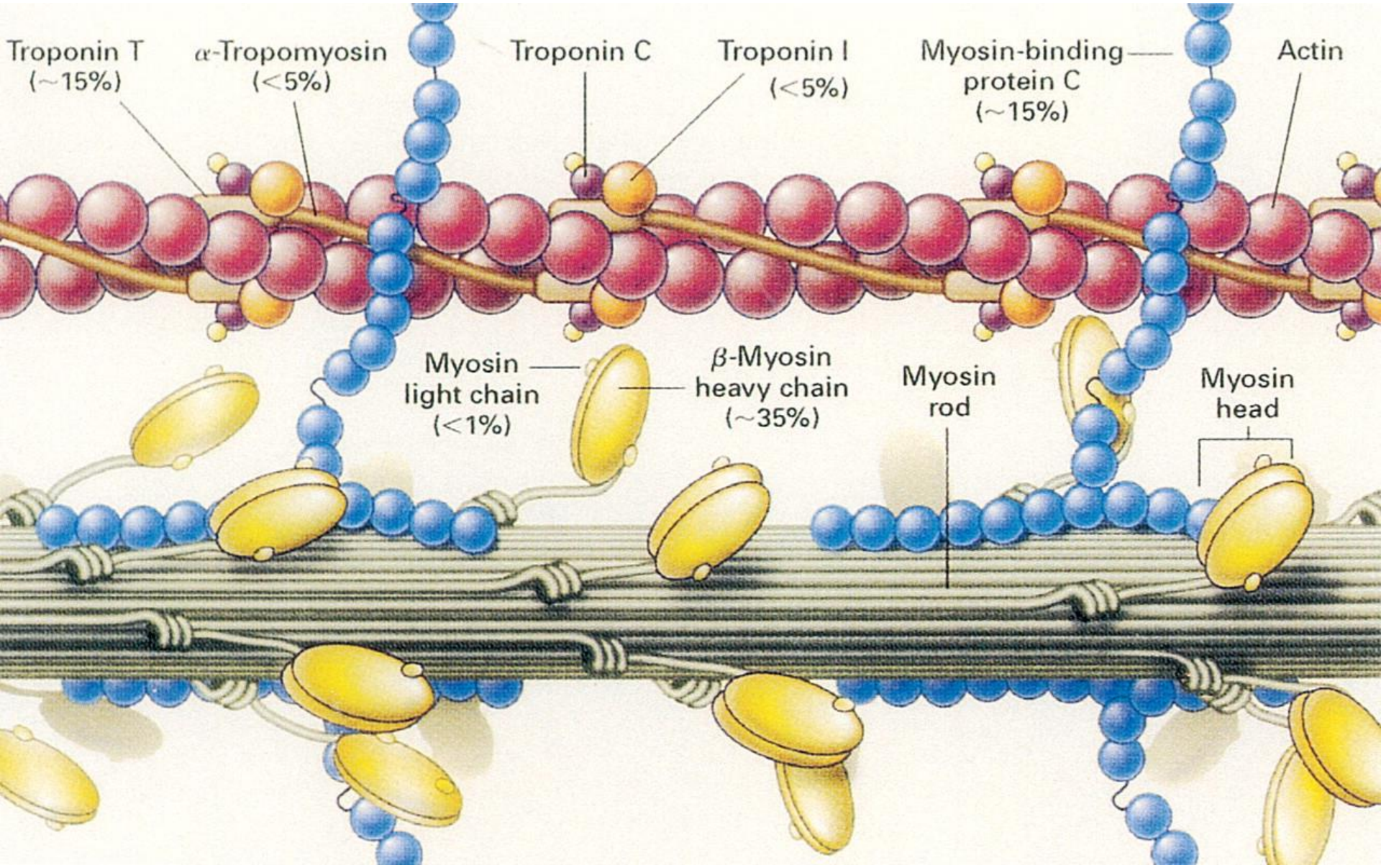
2018

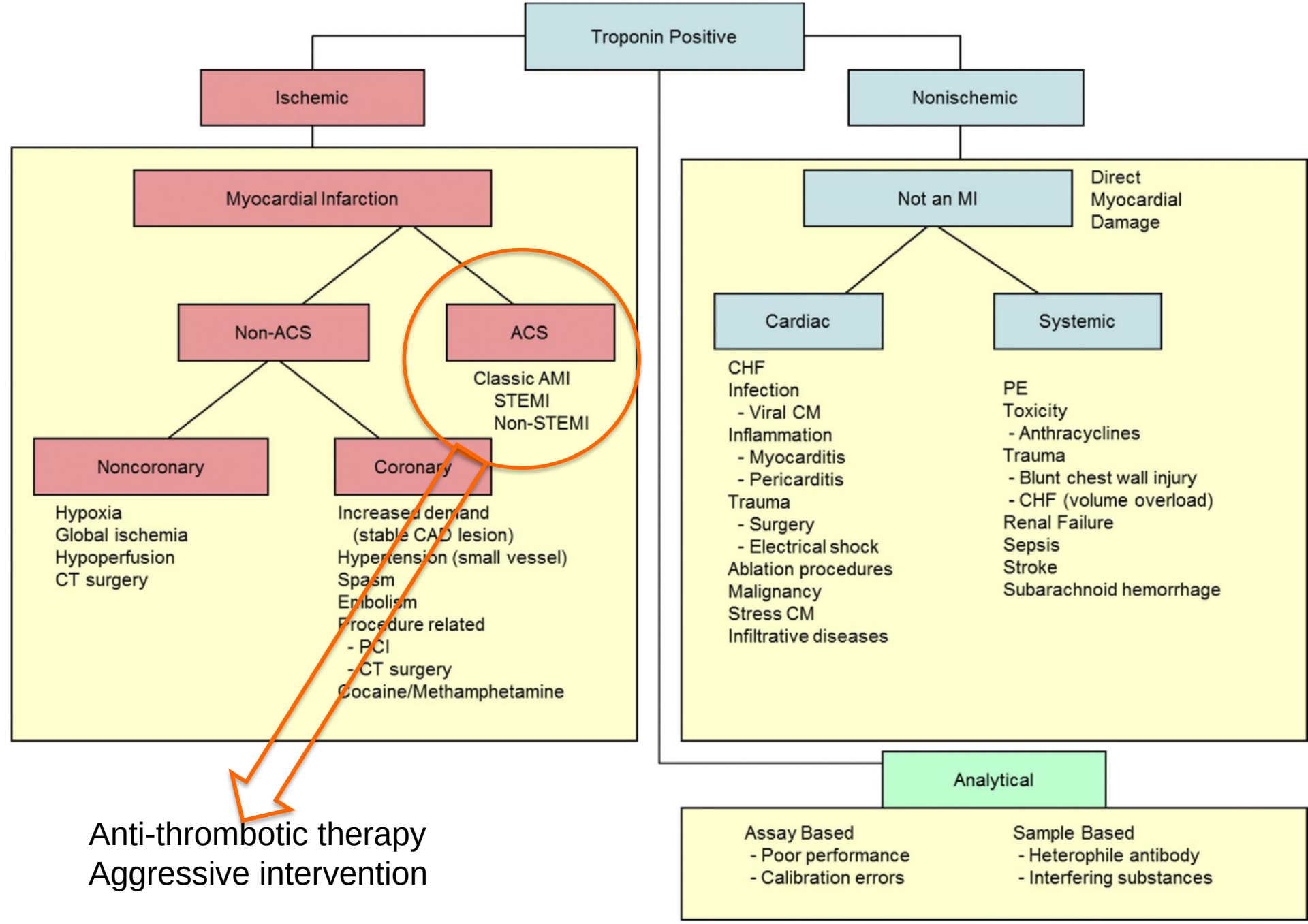
John E. Brush, MD, FACC
SMG and EVMS
April 27, 2018

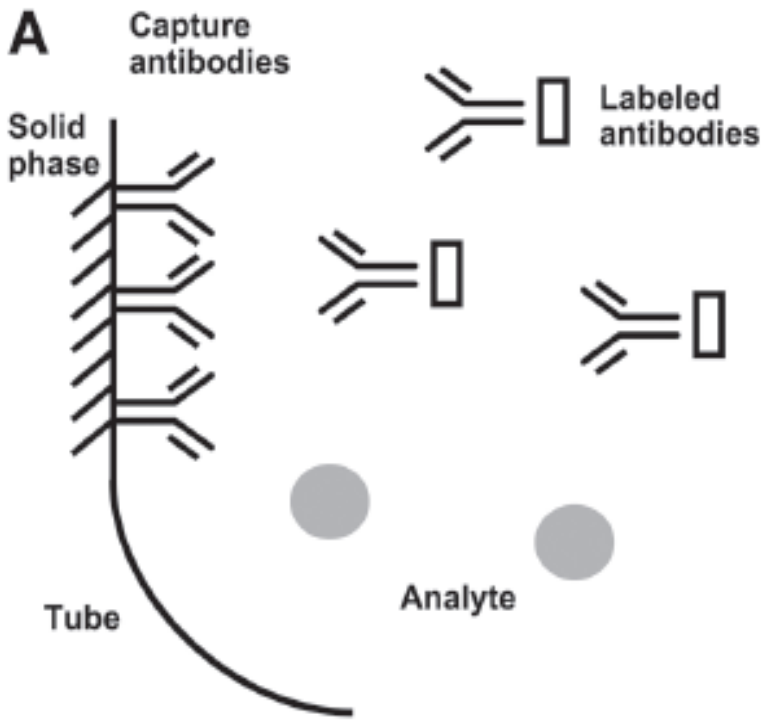
Cardiovascular Biomarkers

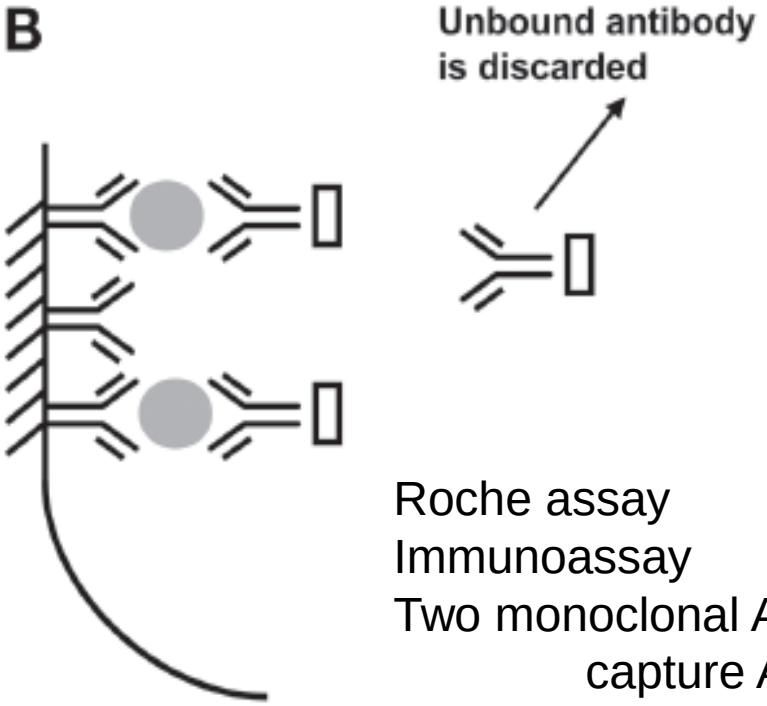
Cardiovascular Biomarkers – 15 min.

- Troponin
  - Molecule
  - Assay
    - Cutoff
    - High sensitivity
  - Clinical use
    - Spectrum bias
- BNP
  - Molecule
  - Assay
  - Clinical use
    - Diagnostic
    - Prognostic
    - Guiding therapy

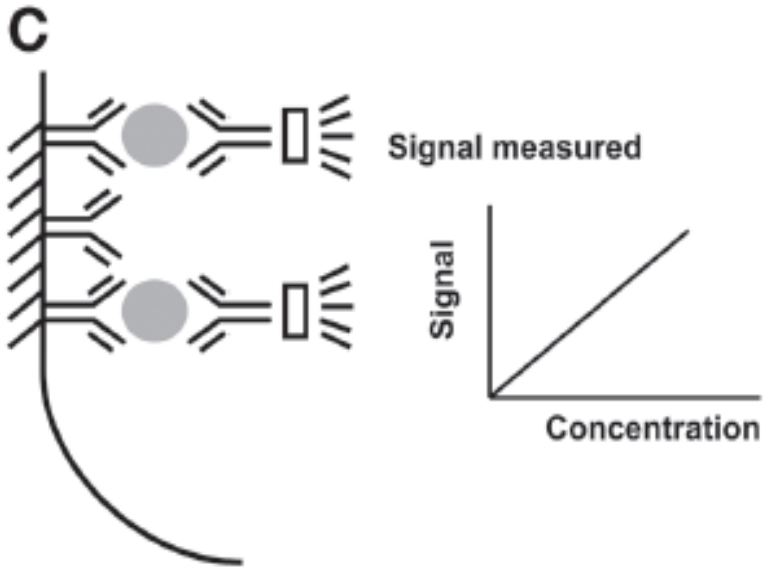

Troponin T
(~15%)
α-Tropomyosin
(<5%)
Troponin C
Troponin I
(<5%)
Myosin-binding
protein C
(~15%)
Actin
Myosin
light chain
(<1%)
β-Myosin
heavy chain
(~35%)
Myosin
rod
Myosin
head

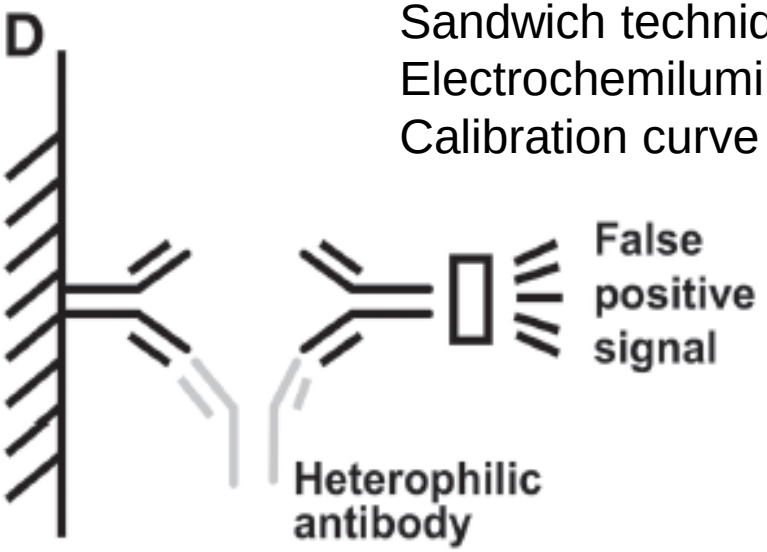

Troponin Positive
Ischemic
Nonischemic
Myocardial Infarction
Non-ACS
ACS
Classic AMI
STEMI
Non-STEMI
Noncoronary
Coronary
Hypoxia
Global ischemia
Hypoperfusion
CT surgery
Increased demand
(stable CAD lesion)
Hypertension (small vessel)
Spasm
Embolism
Procedure related
- PCI
- CT surgery
Cocaine/Methamphetamine
Not an MI
Direct
Myocardial
Damage
Cardiac
Systemic
CHF
Infection
- Viral CM
Inflammation
- Myocarditis
- Pericarditis
Trauma
- Surgery
- Electrical shock
Ablation procedures
Malignancy
Stress CM
Infiltrative diseases
PE
Toxicity
- Anthracyclines
Trauma
- Blunt chest wall injury
- CHF (volume overload)
Renal Failure
Sepsis
Stroke
Subarachnoid hemorrhage
Analytical
Assay Based
- Poor performance
- Calibration errors
Sample Based
- Heterophile antibody
- Interfering substances
Anti-thrombotic therapy
Aggressive intervention



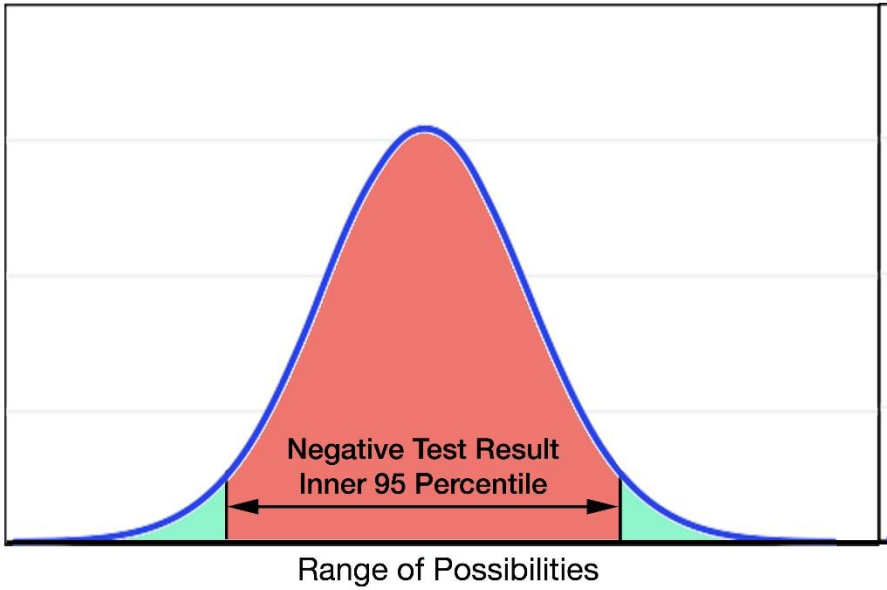


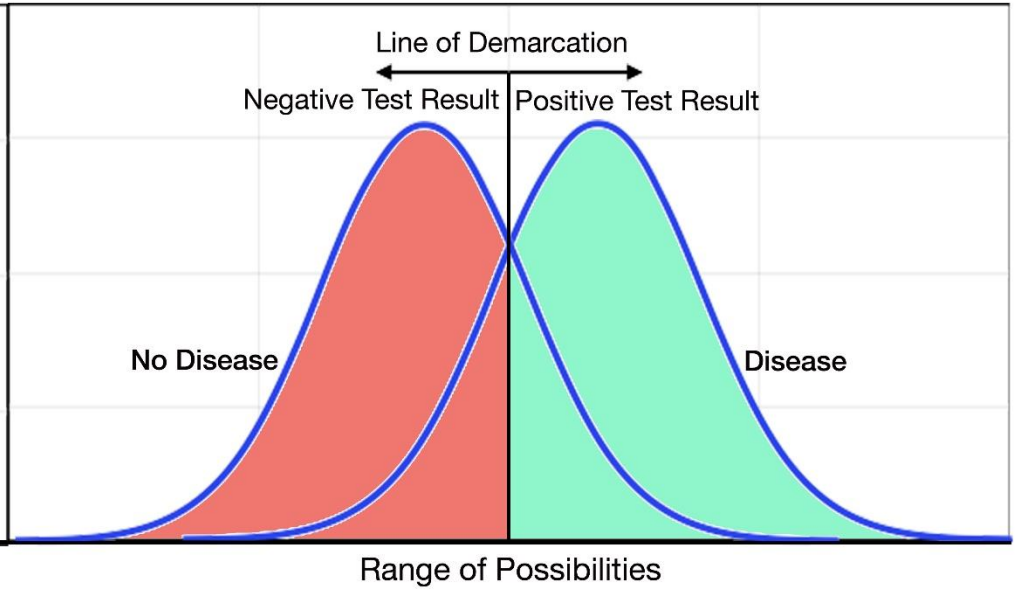
Roche assay
Immunoassay
Two monoclonal Abs
capture AB
Signal AB
Sandwich technique
Electrochemiluminescence
Calibration curve

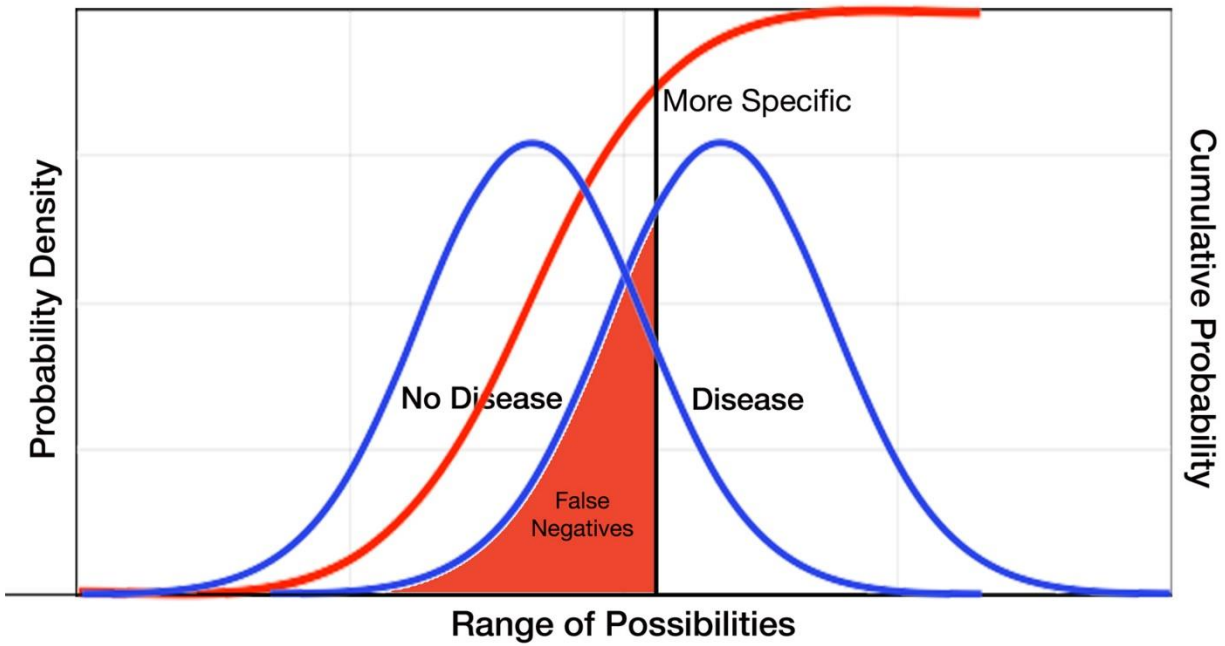


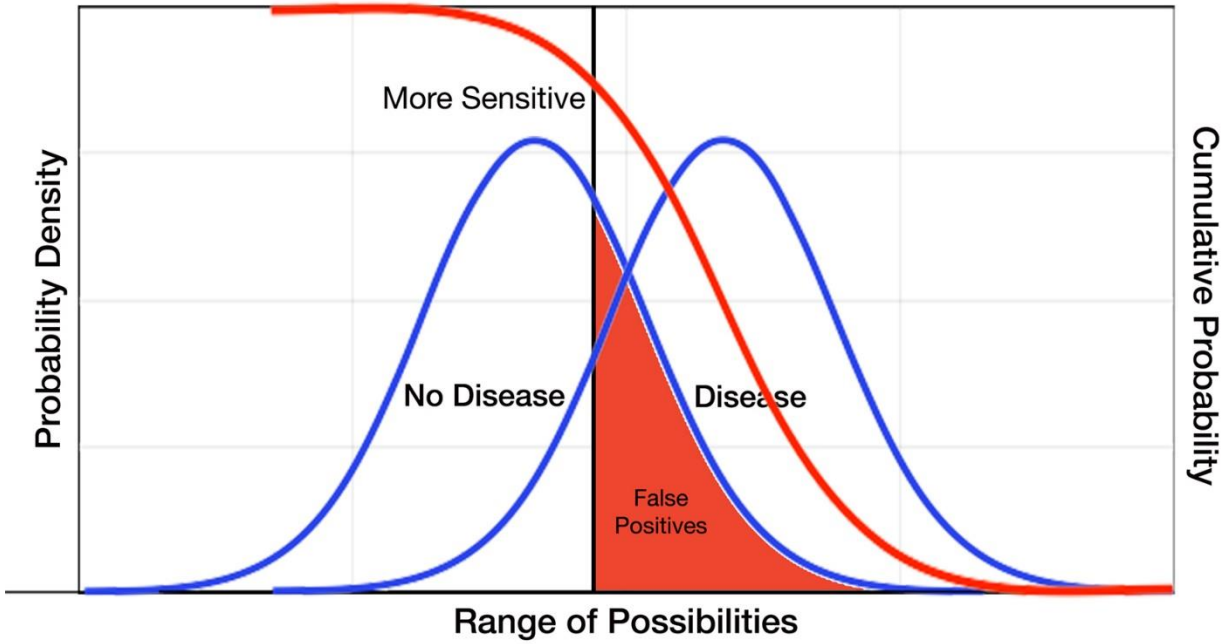


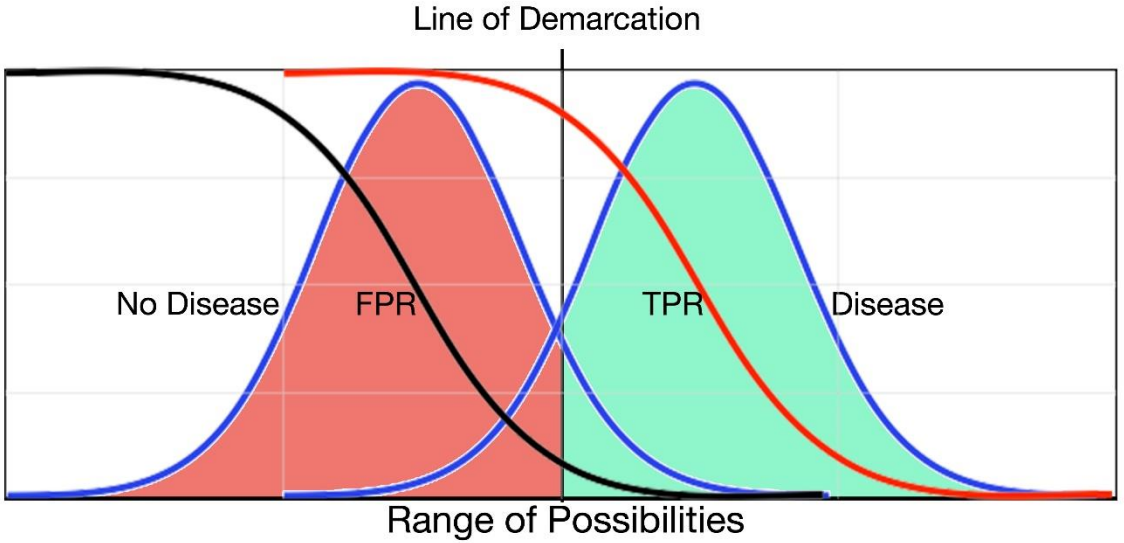
Defining Abnormal



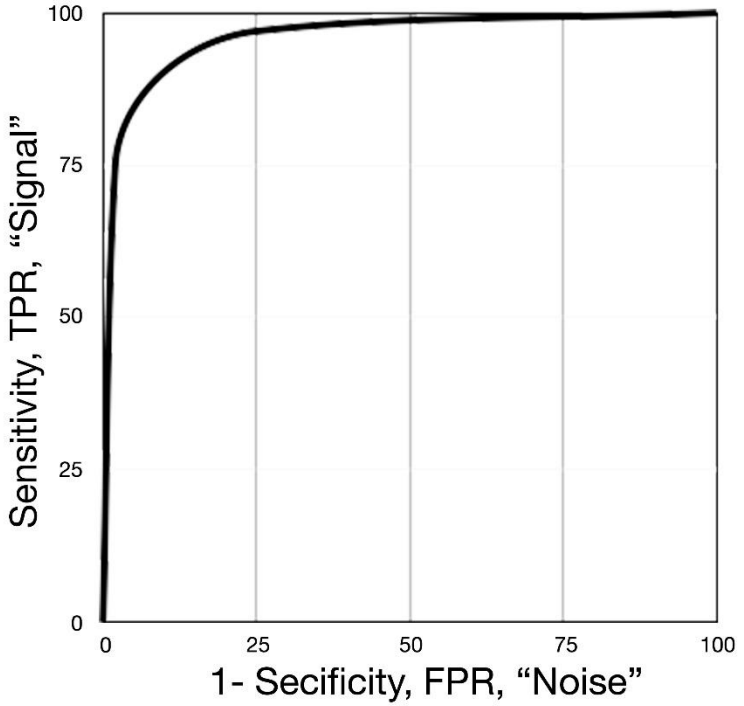



More Specific
Probability Density
Cumulative Probability
No Disease
Disease
False
Negatives
Range of Possibilities

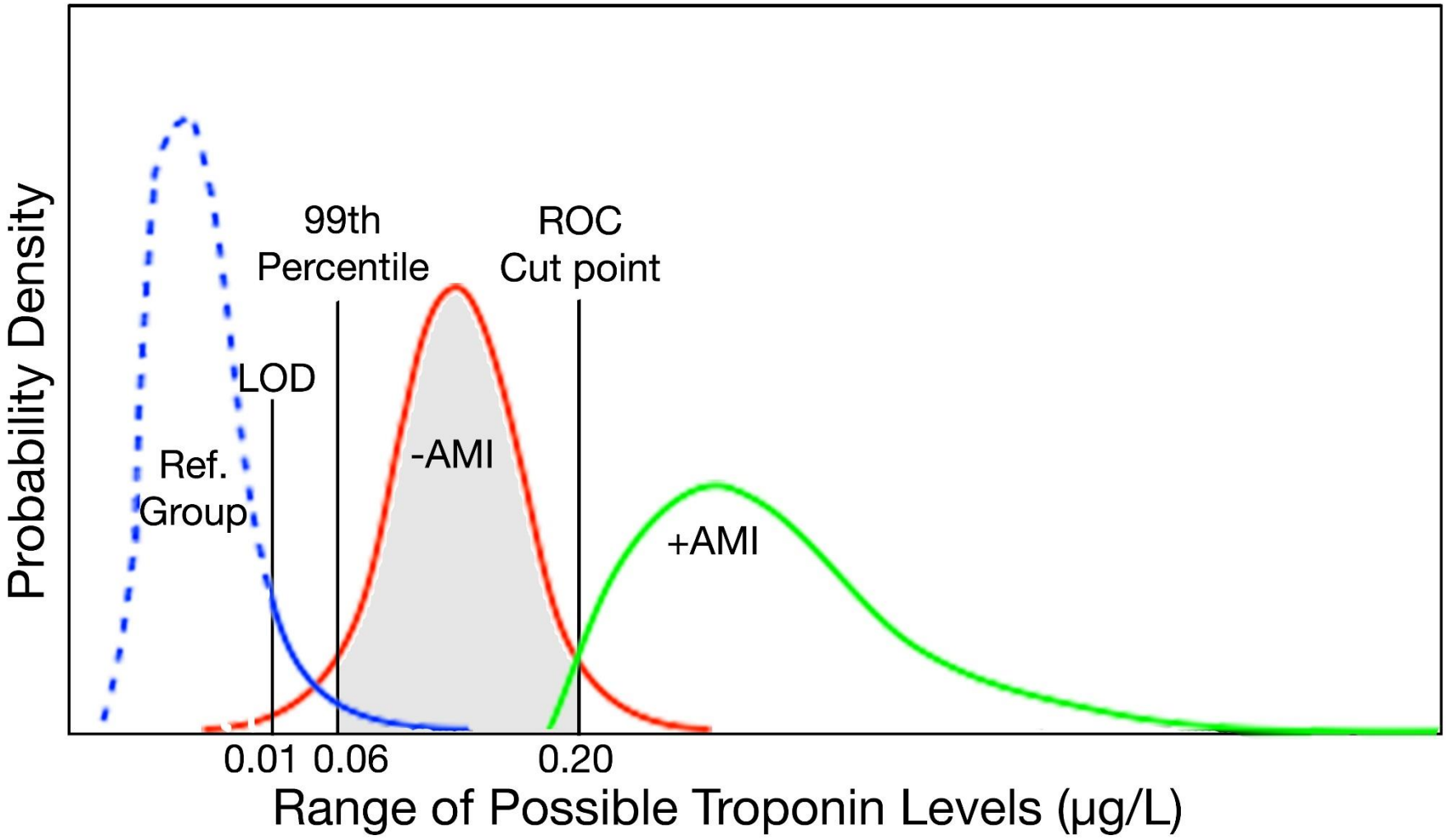

More Sensitive
Probability Density
Cumulative Probability
No Disease
Disease
False
Positives
Range of Possibilities

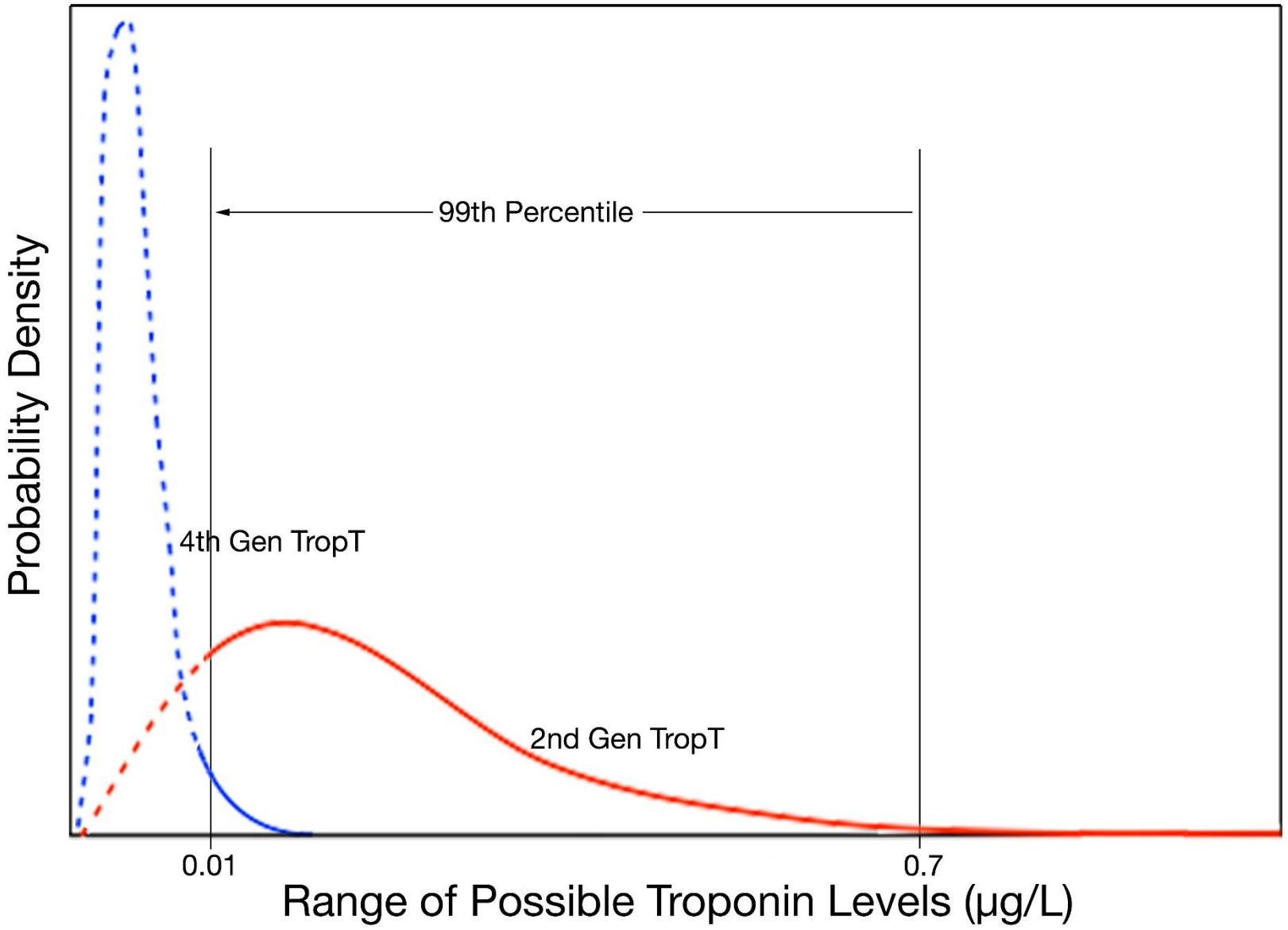


Plotting an
ROC curve
To maximize the TPR
And minimize the FPR

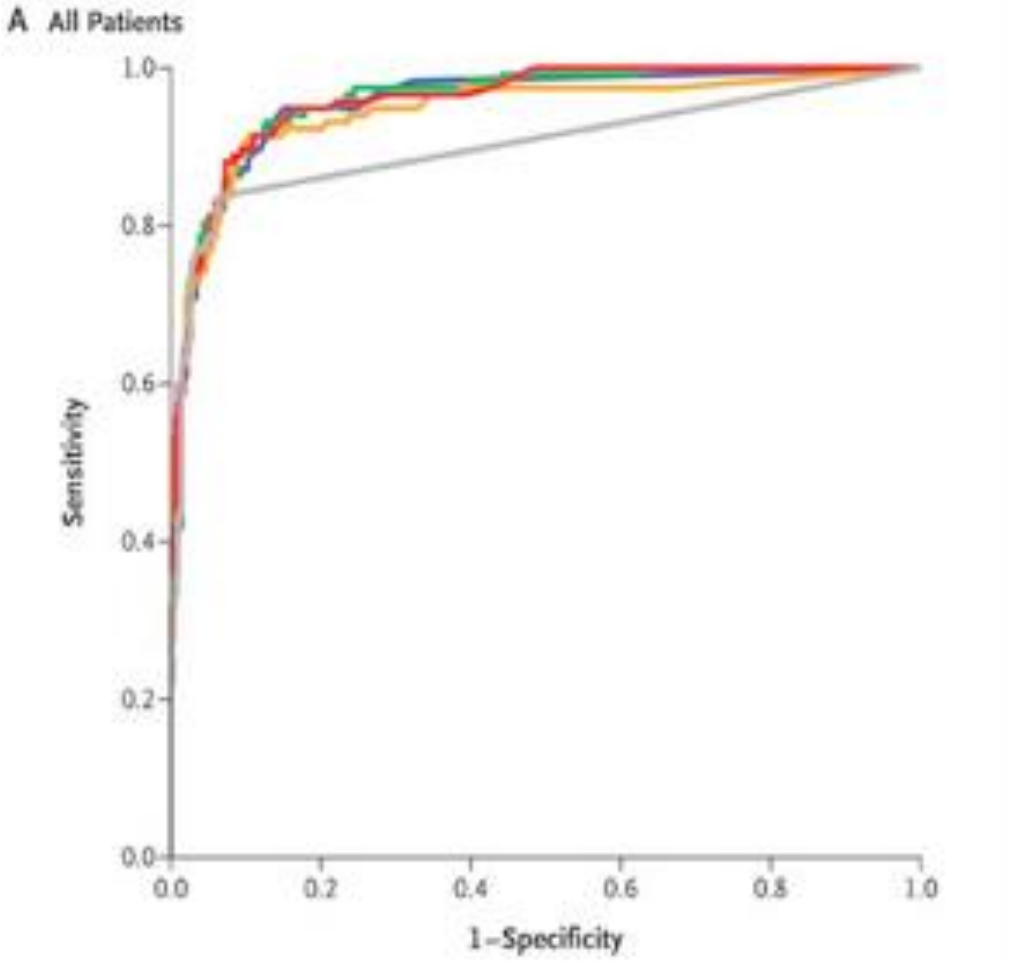


Setting the cut-point

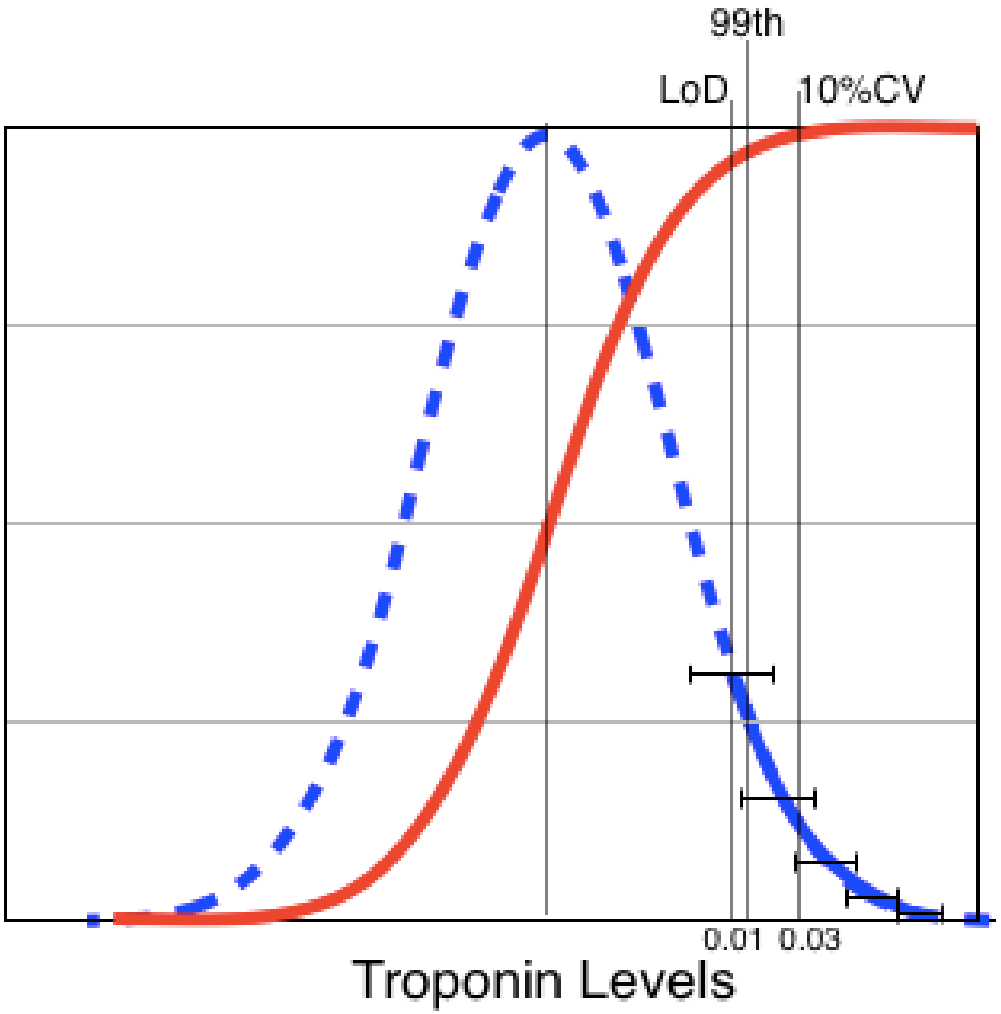



Probability Density
99th Percentile
4th Gen TropT
2nd Gen TropT
0.01
0.7
Range of Possible Troponin Levels (µg/L)

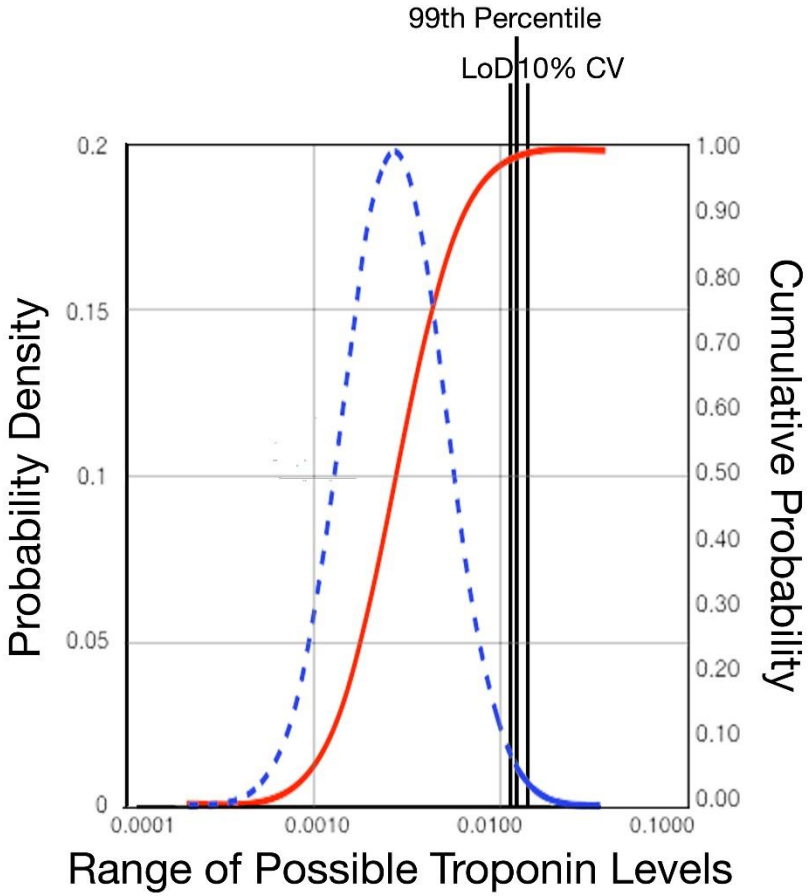
ROC for hs-troponin

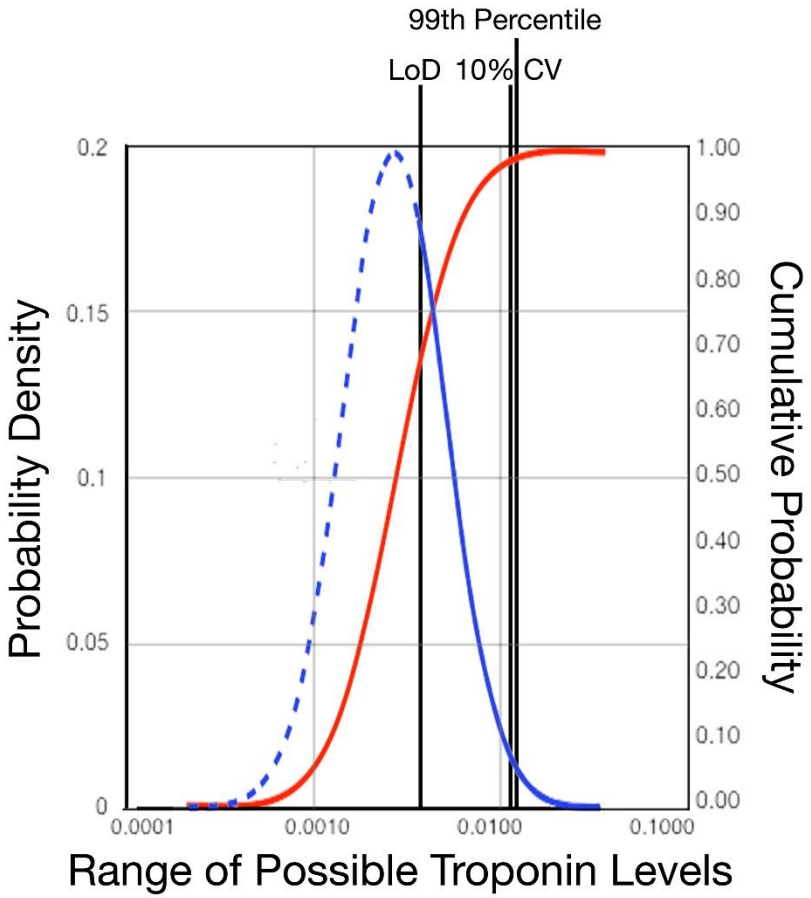


Analytical Characteristics of an Assay

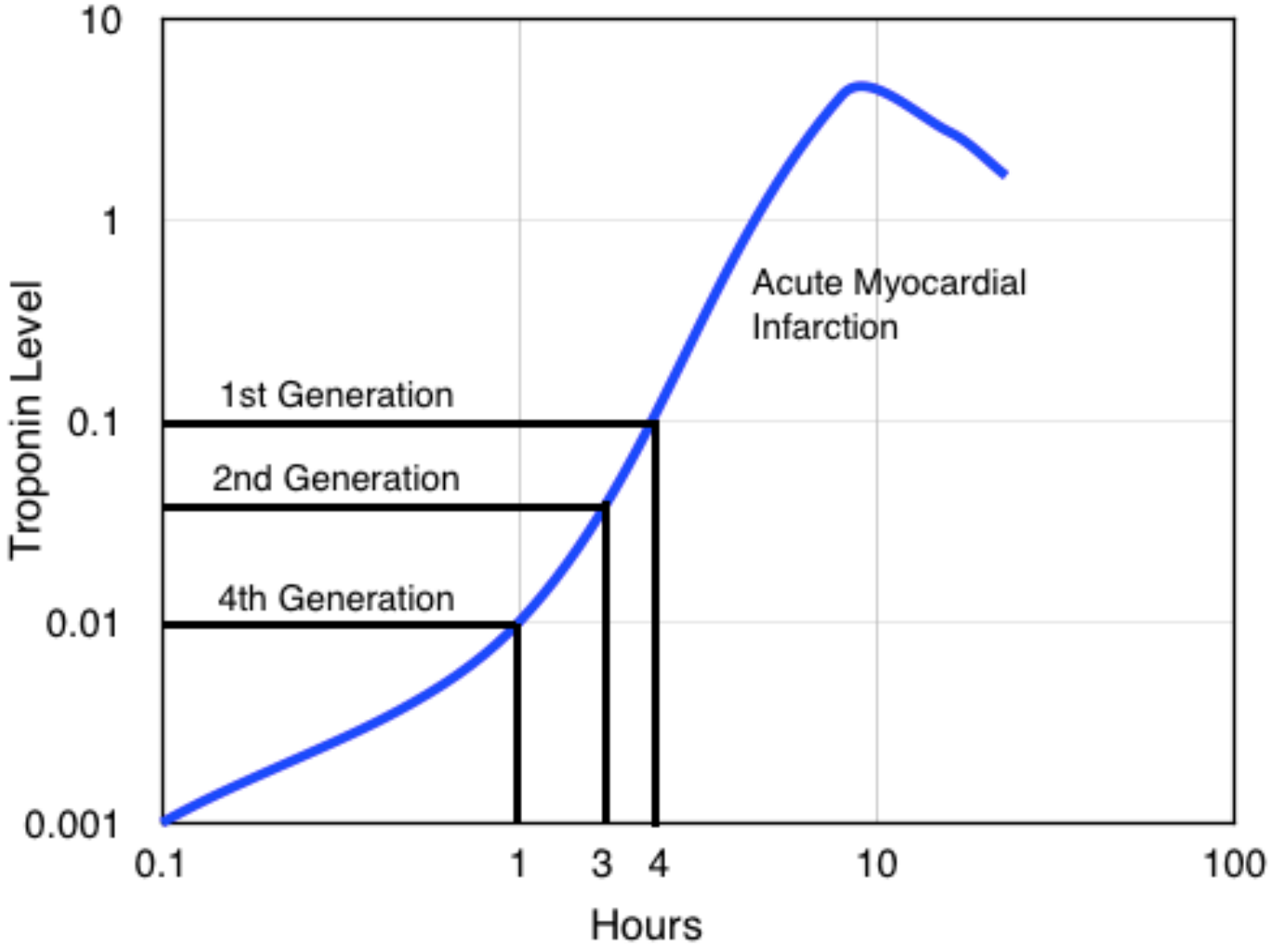


New hs-troponin assay

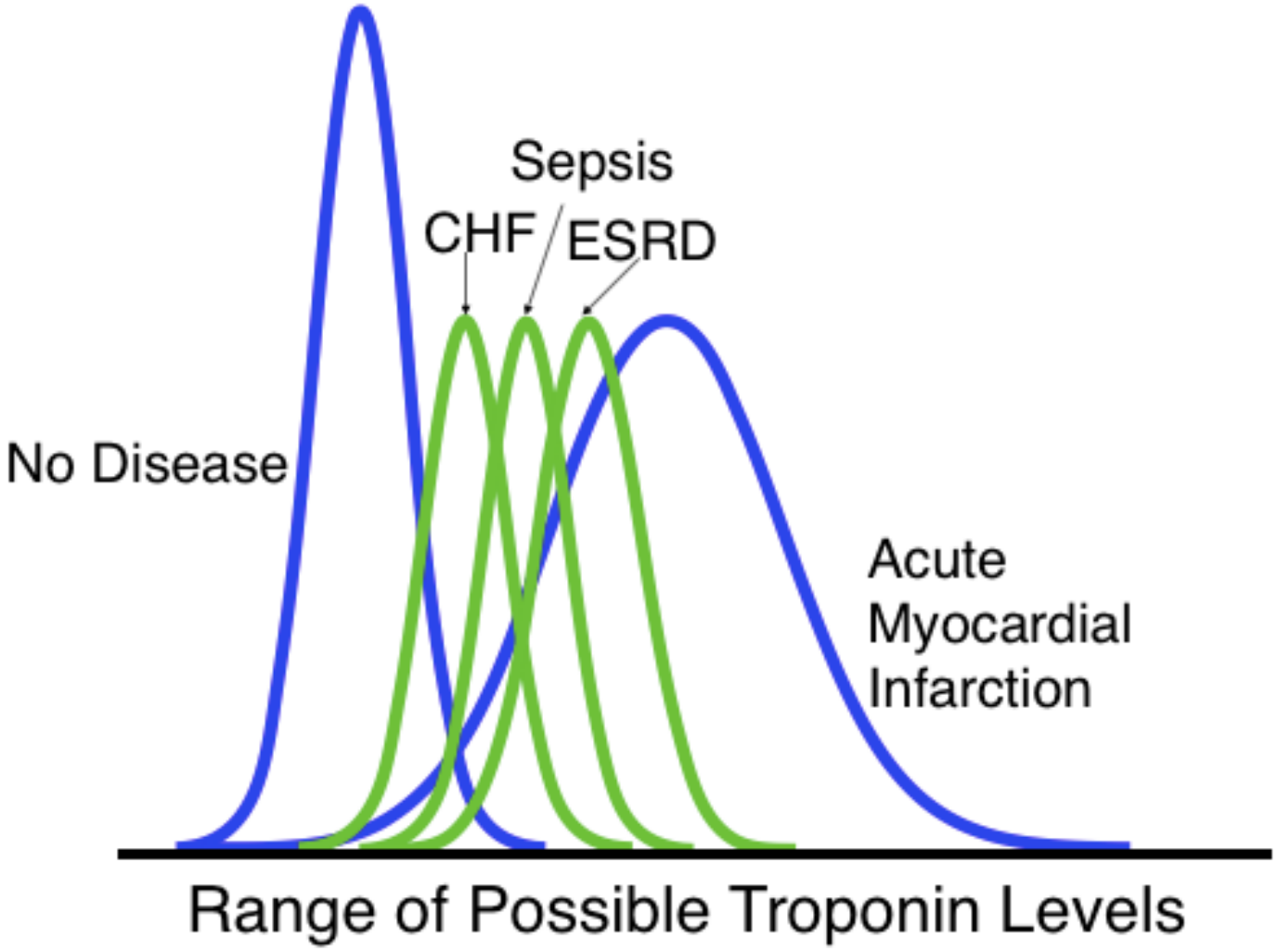




Advantage of Greater Analytical Sensitivity: Earlier Detection of AMI



Clinical Confounders in Common Practice



Spectrum Bias

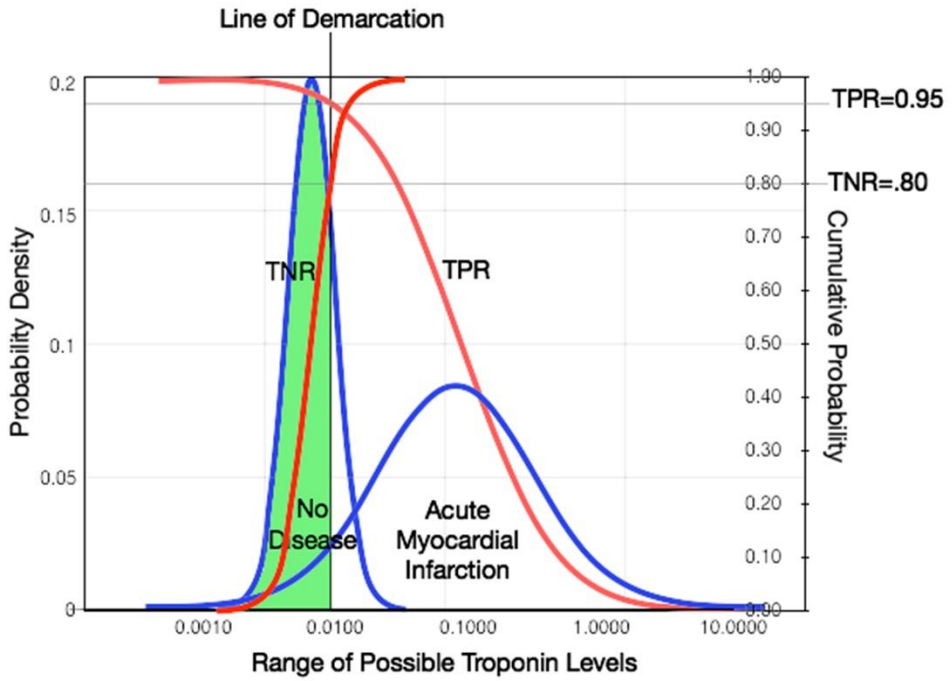
Reichlin, et al NEJM 2009; 361:858
High sensitivity troponin T assay: sensitivity=95%, specificity=80%
17% had an adjudicated diagnosis of acute myocardial infarction
Explicitly excluded patients with renal failure and sepsis

	Disease	No Disease	
Pos test	162	166	
Neg test	8	664	
	170	830	1000

	Disease	No Disease	
Pos test	108	416	
Neg test	8	468	
	116	884	1000

No RF or sepsis patients
Sensitivity = 95%
Specificity = 80%
LR(+) = 4.75
LR(-) = 0.063

Assume 250 (25%) confounders
Sensitivity = 93%
Specificity = 53%
LR(+) = 1.98
LR(-) = 0.132



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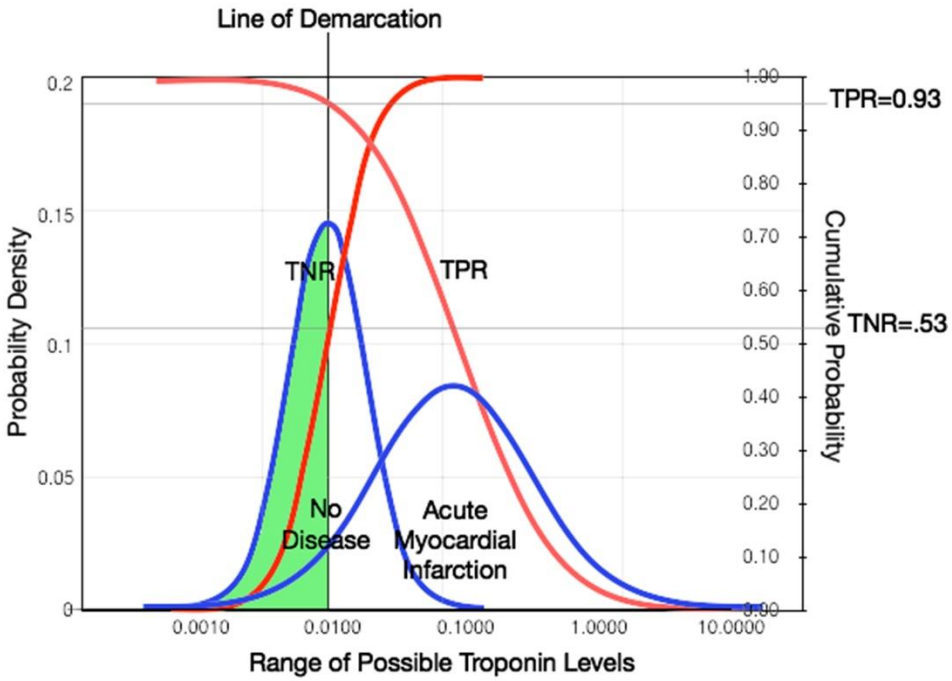

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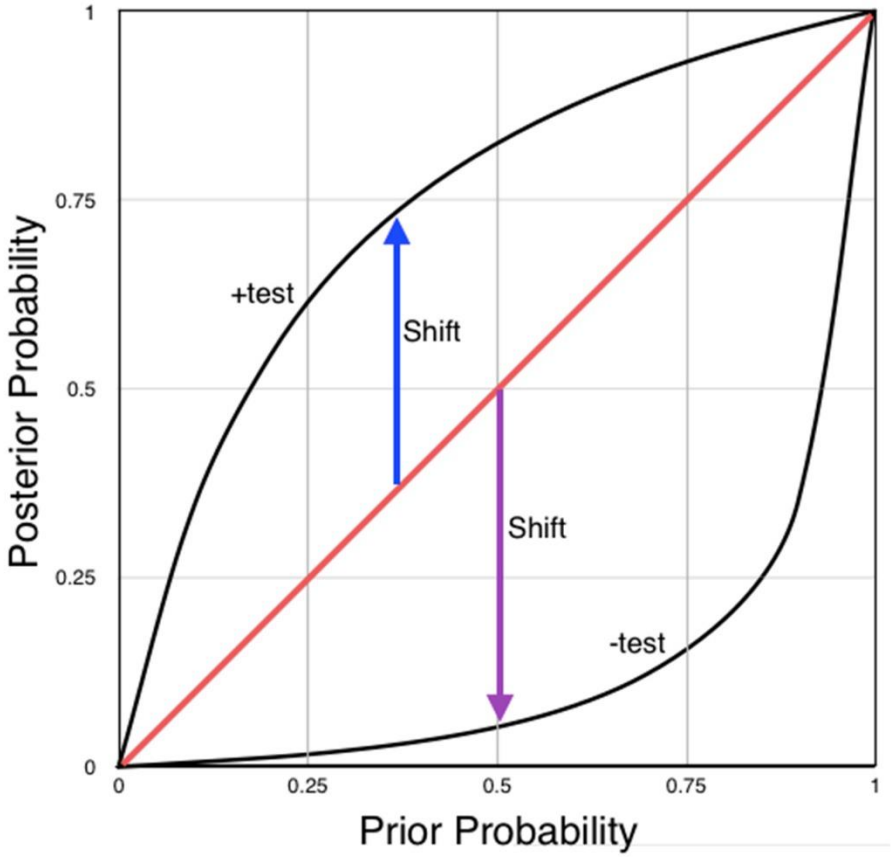
Specificity = 53%
LR(+) = 1.98
LR(-) = 0.132

How a test result alters your probability estimate



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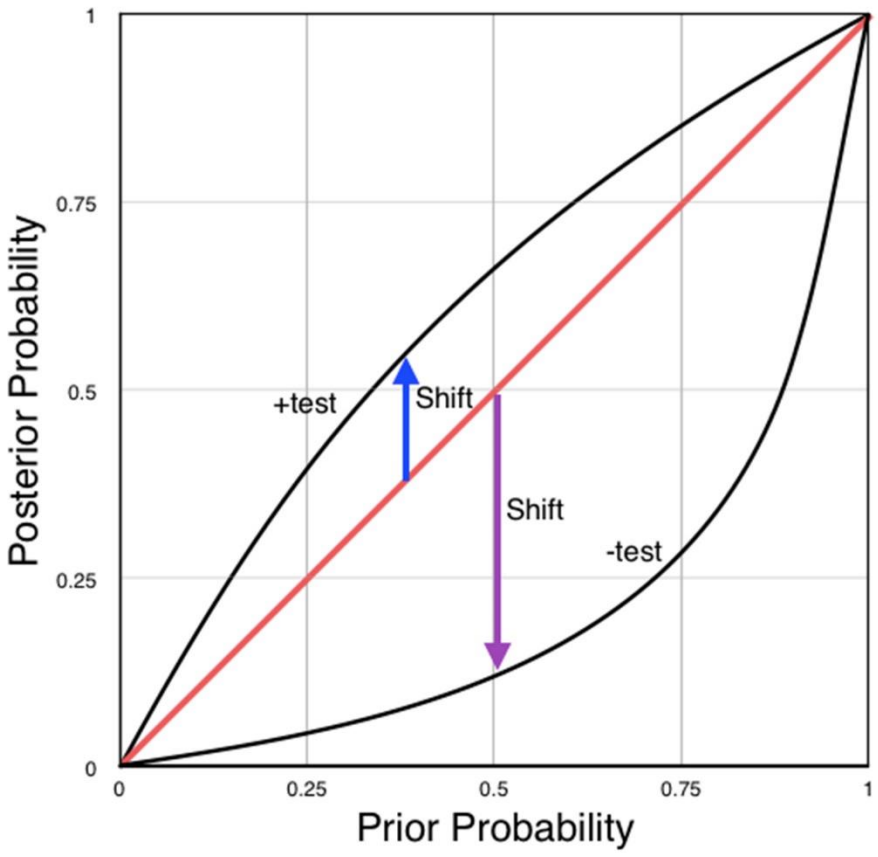

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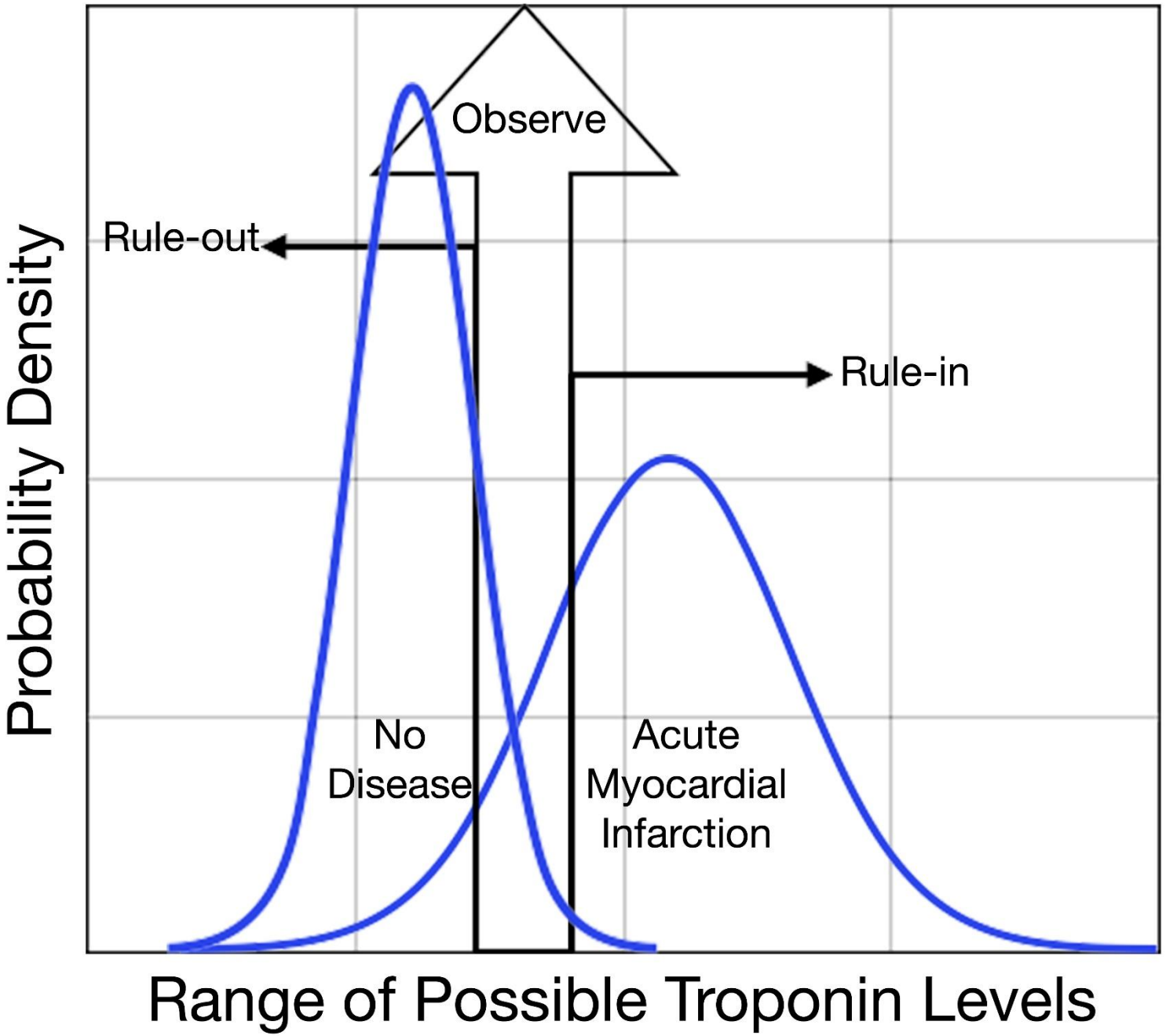
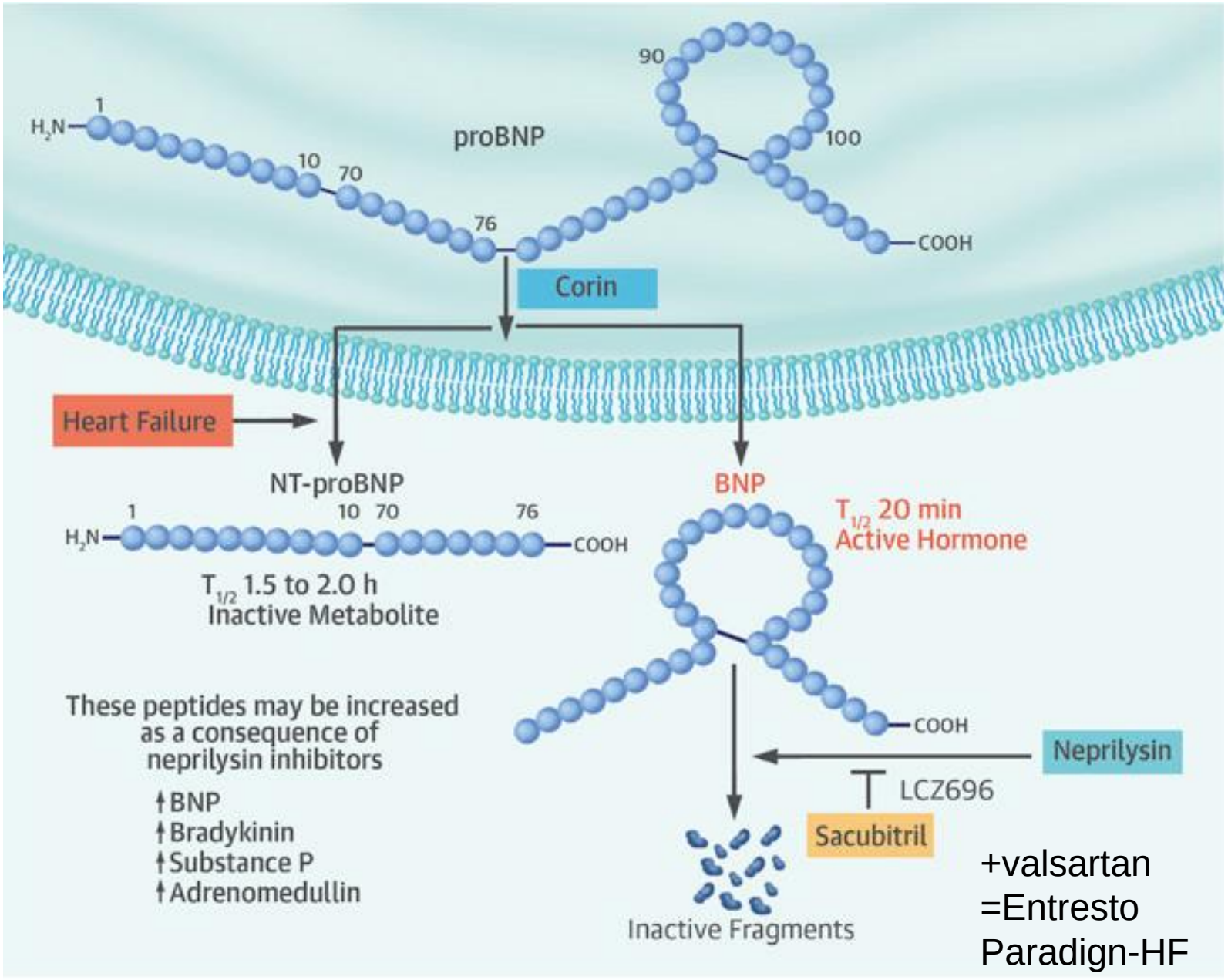
Specificity = 53%


Observe
Rule-out
Rule-in
No Disease
Acute Myocardial Infarction
Probability Density
Range of Possible Troponin Levels

Conclusion for Troponin

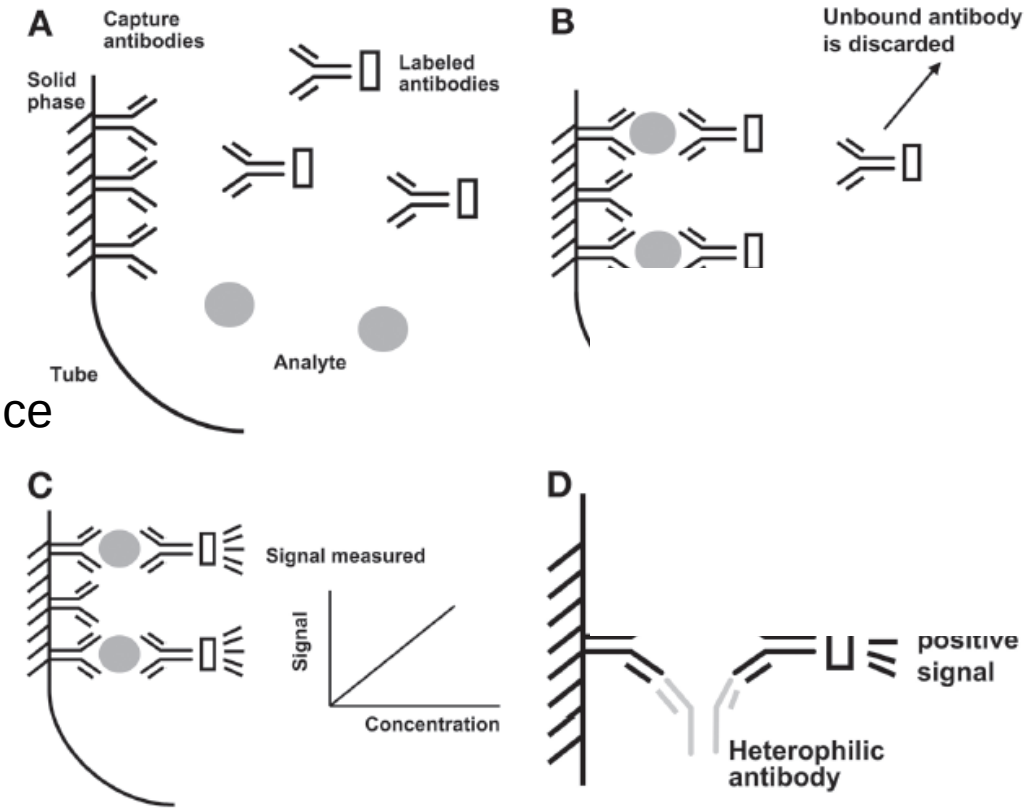
- Our medical reasoning needs to catch up with the analytical improvements in troponin testing.
- Better understanding of troponin testing is particularly important now, before high-sensitivity troponin tests are approved for use in the United States.
- Troponin testing should be ordered more judiciously, but this is hard to regulate.
- Better understanding of troponin testing will reduce the diagnostic error of over-diagnosis.
- New algorithms with more than a single cutoff may improve diagnostic accuracy and mitigate the error of over-ordering.

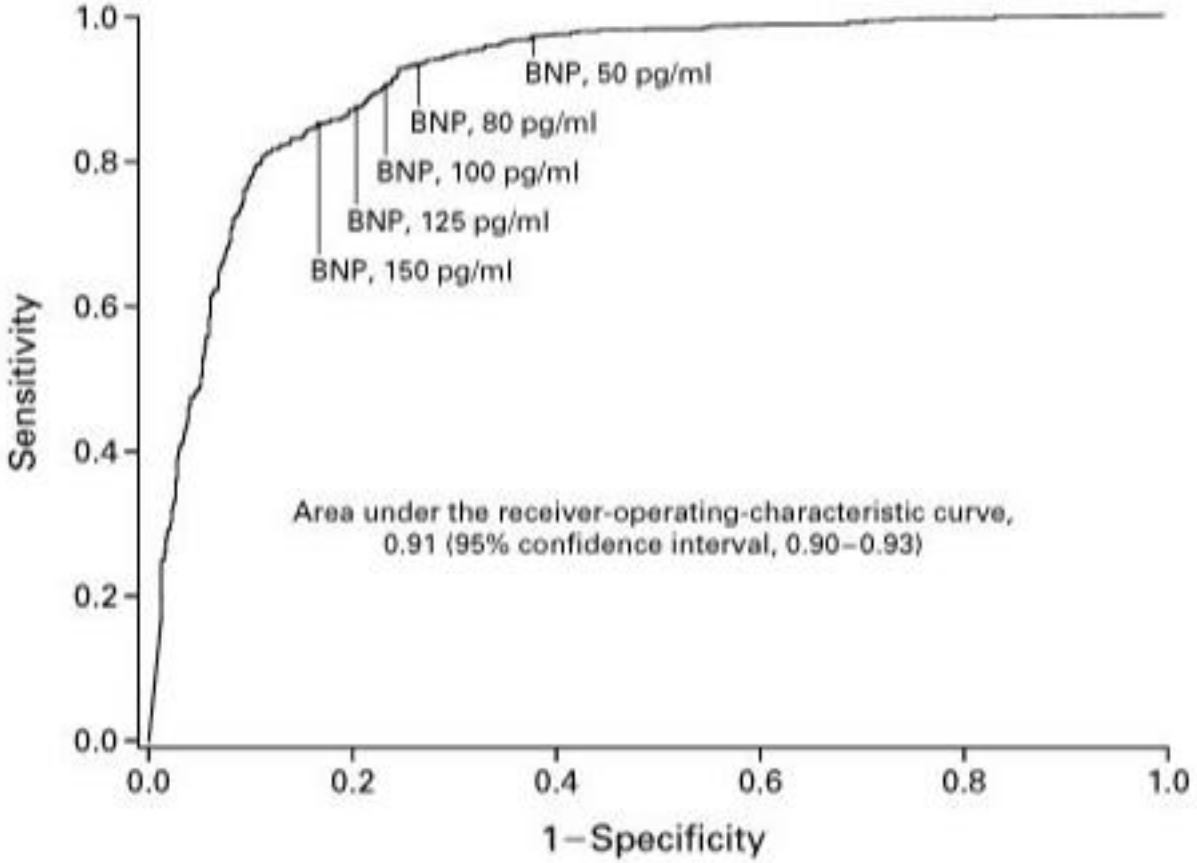
BNP


proBNP
H_2N
1
10
70
76
90
100
COOH
Corin
Heart Failure
NT-proBNP
H_2N
1
10
70
76
COOH
$T_{1/2}$ 1.5 to 2.0 h
Inactive Metabolite
BNP
$T_{1/2}$ 20 min
Active Hormone
COOH
These peptides may be increased as a consequence of neprilysin inhibitors
BNP
Bradykinin
Substance P
Adrenomedullin
Neprilysin
LCZ696
Sacubitril
Inactive Fragments
+valsartan
=Entresto
Paradign-HF

Similar Assay

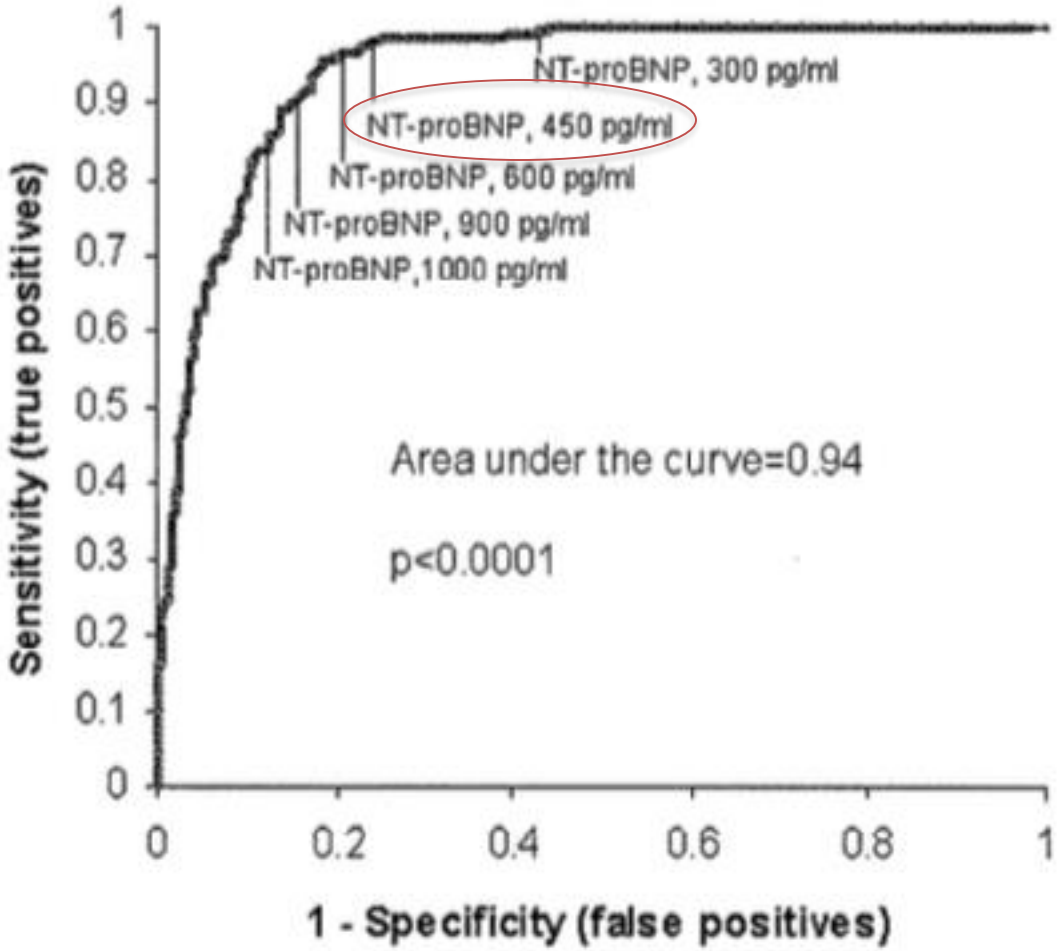
Roche assay
Immunoassay
Two monoclonal ABs
Sandwich technique
electrochemiluminescence





BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
	(95 percent confidence interval)				
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–95)	74 (70–77)	77 (75–80)	92 (89–94)	83
100	90 (88–92)	76 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	85 (82–88)	83 (80–85)	83 (80–85)	85 (83–88)	84

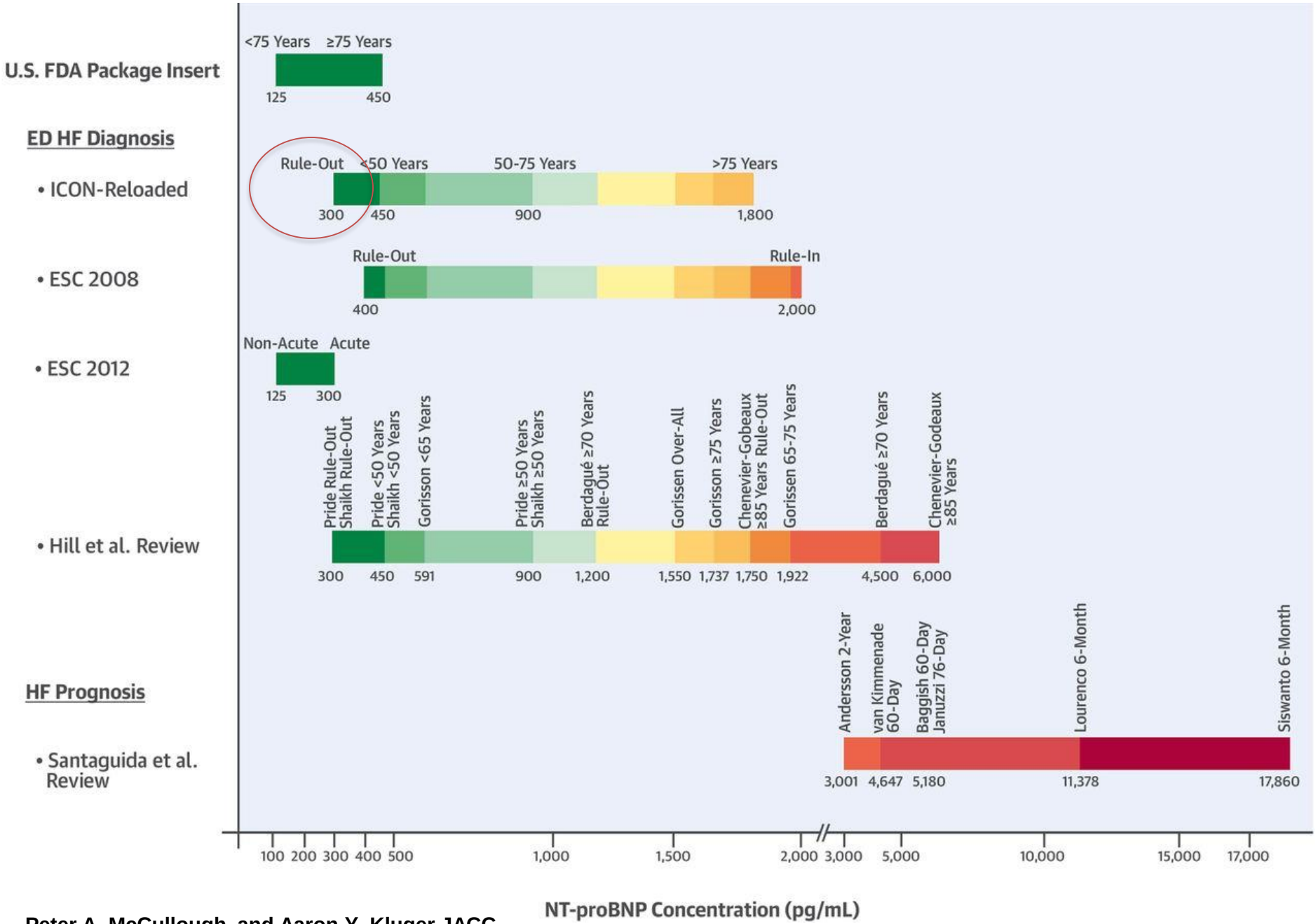
Maisel, et al
NEJM 2002;
347:161-7.



Januzzi, JL, et al
AJC 2005;
95:948.

Roche assay
450 pg/ml (age<50)
LR (+)=4.08
LR(-)=0.03
50-75 yrs: >900
>75 yrs: >1800

Cut Point	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
300 pg/ml	99%	68%	62%	99%	79%
450 pg/ml	98%	76%	68%	99%	83%
600 pg/ml	96%	81%	73%	97%	86%
900 pg/ml	90%	85%	76%	94%	87%
1000 pg/ml	87%	86%	78%	91%	87%

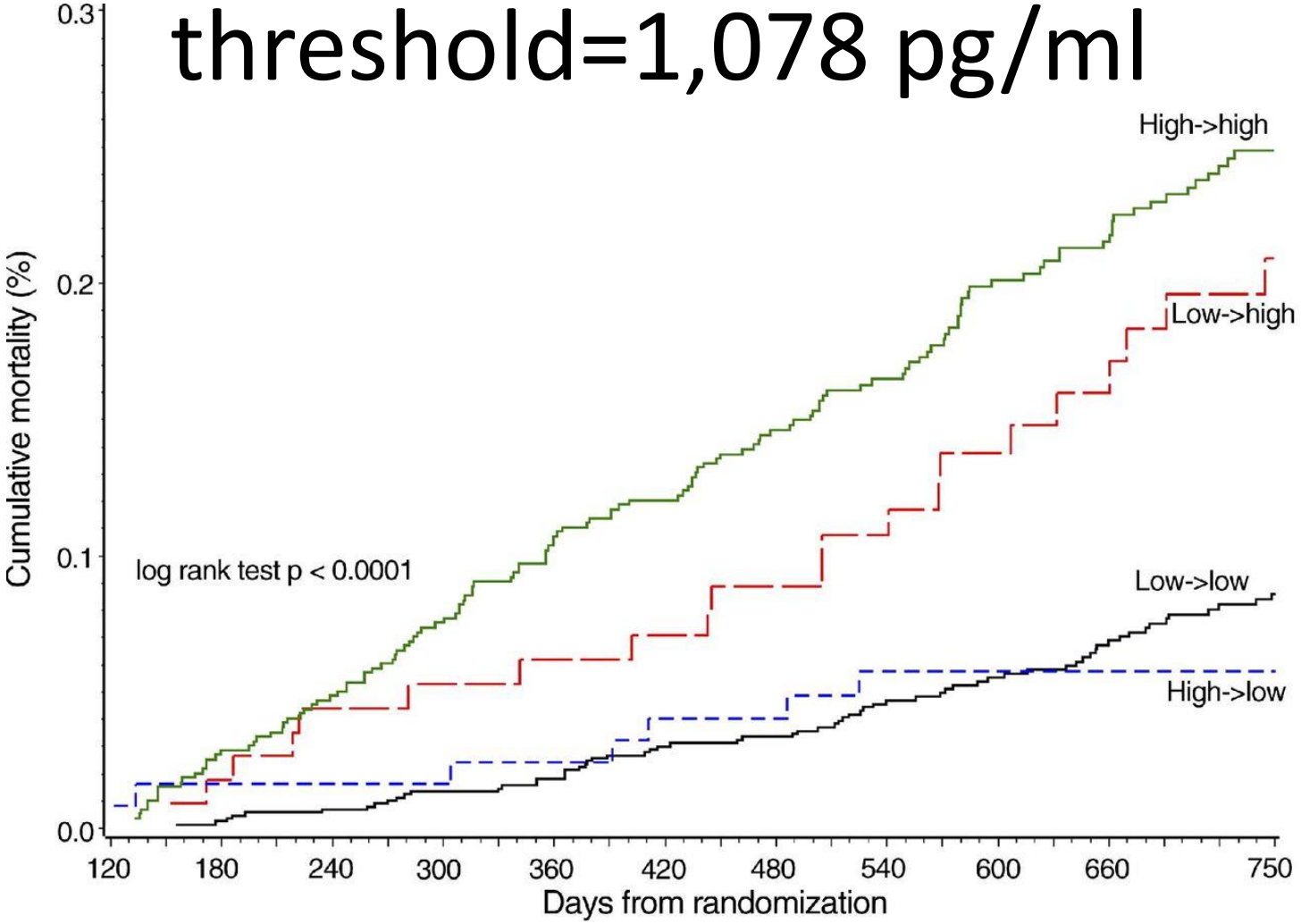


Peter A. McCullough, and Aaron Y. Kluger JACC 2018;71:1201-1203

Exclusionary “rule out” cut-point

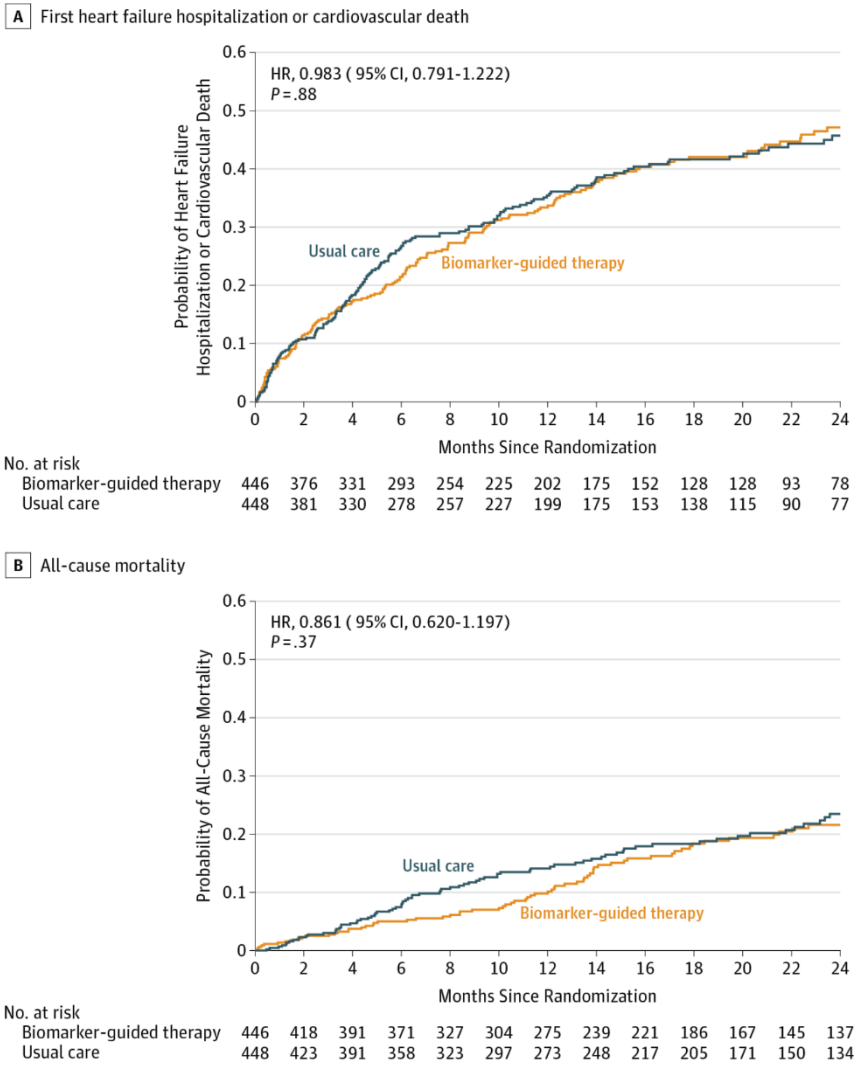
- <300 pg/ml
- Sensitivity=93.9
- Specificity=71.7
- LR(+)=3.36
- LR(-)=0.1

BNP and Prognosis Baseline and 4 months: threshold=1,078 pg/ml



Serge Masson et al. JACC 2008;52:997-1003

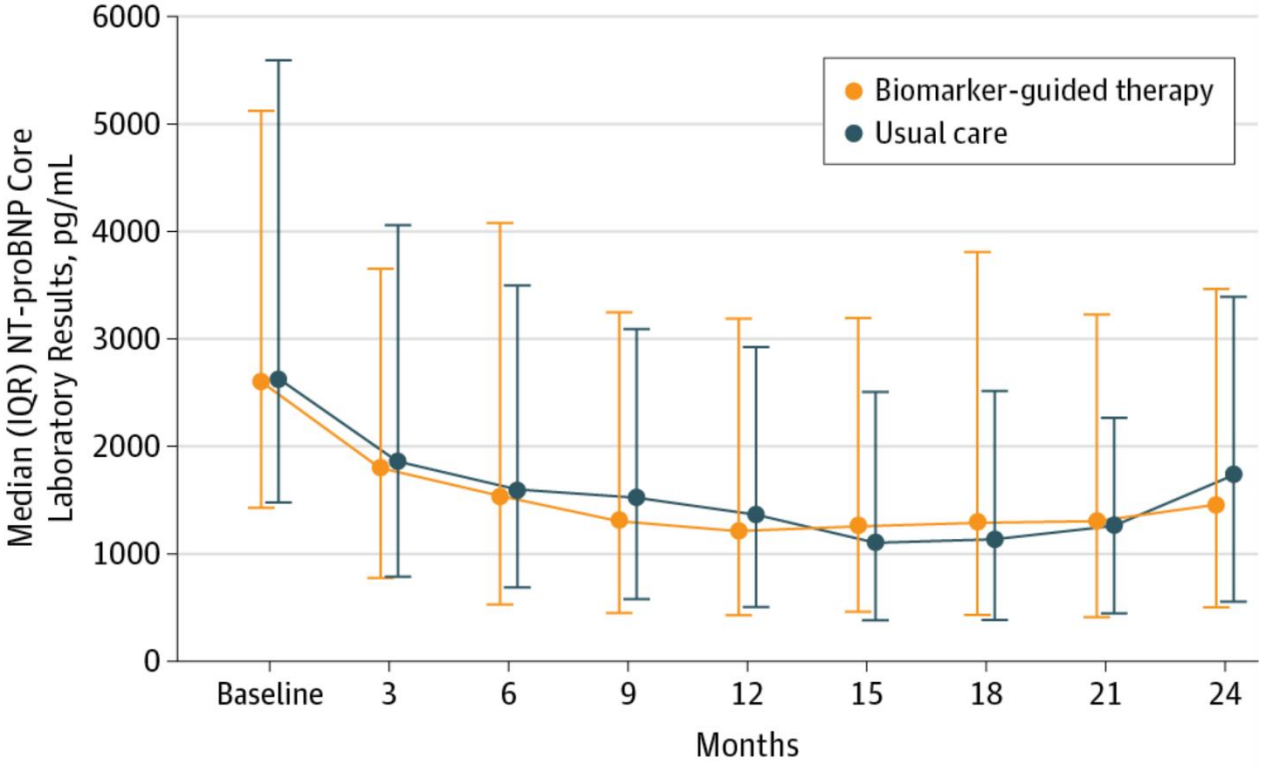
BNP Guided Therapy



From: **Effect of Natriuretic Peptide–Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients With Heart Failure and Reduced Ejection Fraction A Randomized Clinical Trial**

JAMA. 2017;318(8):713-720.

BNP levels with BNP guided Rx



No. of participants									
Biomarker-guided therapy	426	355	305	263	228	180	153	123	105
Usual care	430	347	307	244	225	183	141	116	110

From: **Effect of Natriuretic Peptide–Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients With Heart Failure and Reduced Ejection FractionA Randomized Clinical Trial**

JAMA. 2017;318(8):713-720. doi:10.1001/jama.2017.10565

Cardiovascular Biomarkers

- Are useful for diagnosis if used properly.
- Are surrogate markers for prognosis.
  - Unlike LDL, BP, glucose
- Other factors may be better to monitor treatment:
  - weight, symptoms.

2018 MID-ATLANTIC
CONFERENCE

8th ANNUAL CURRENT CONCEPTS IN
VASCULAR THERAPIES

2018

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SMG and EVMS
April 27, 2018

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