UCDAVIS HEALTH | Department of Pathology and Laboratory Medicine

Interference and Point-of-Care Testing Devices

SCHOOL OF MEDICINE

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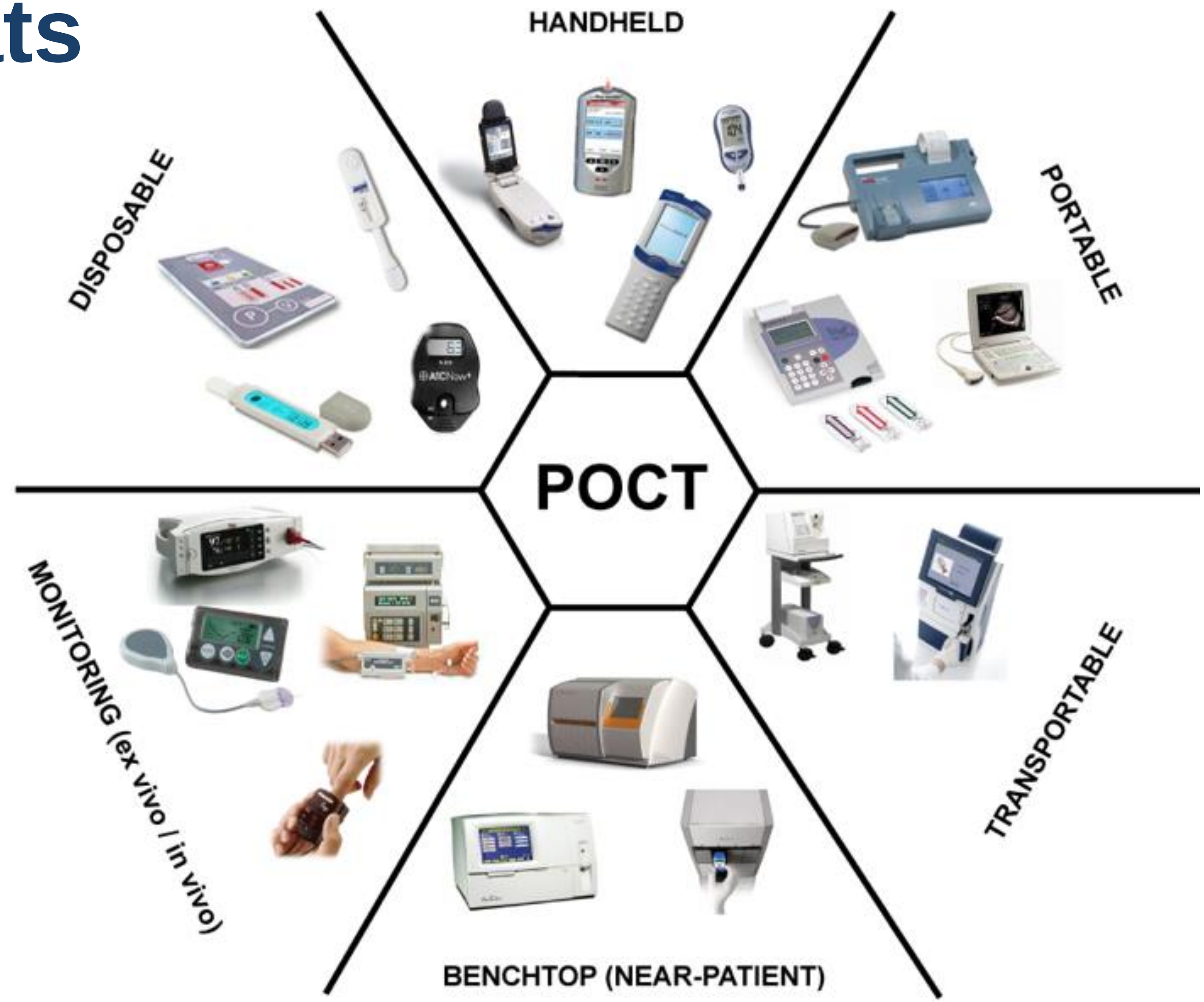
Director, Center for Diagnostic Innovation
Director, Pathology Biorepository

Learning Objectives

- Identify common interferences affecting POC testing
- Describe cases where interfering substances affected patient care.
- Describe solutions to mitigate the impact of interfering substances on POC testing.

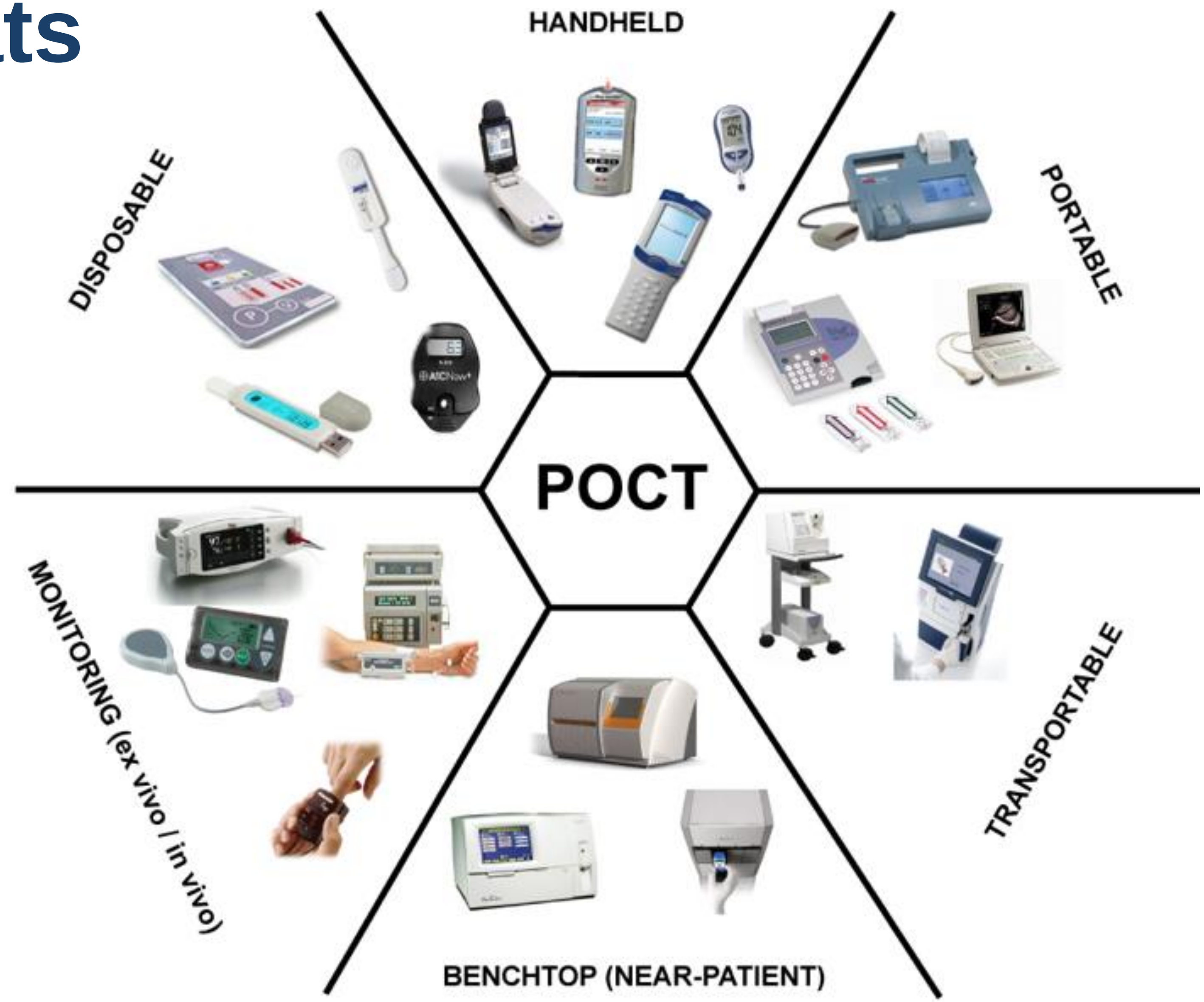
POCT Device Formats

Definition: POCT is defined as testing at or near the site of patient care



POCT Device Formats

Examples:
- Disposable
- Handheld
- Portable
- Transportable
- Benchtop
- Monitoring



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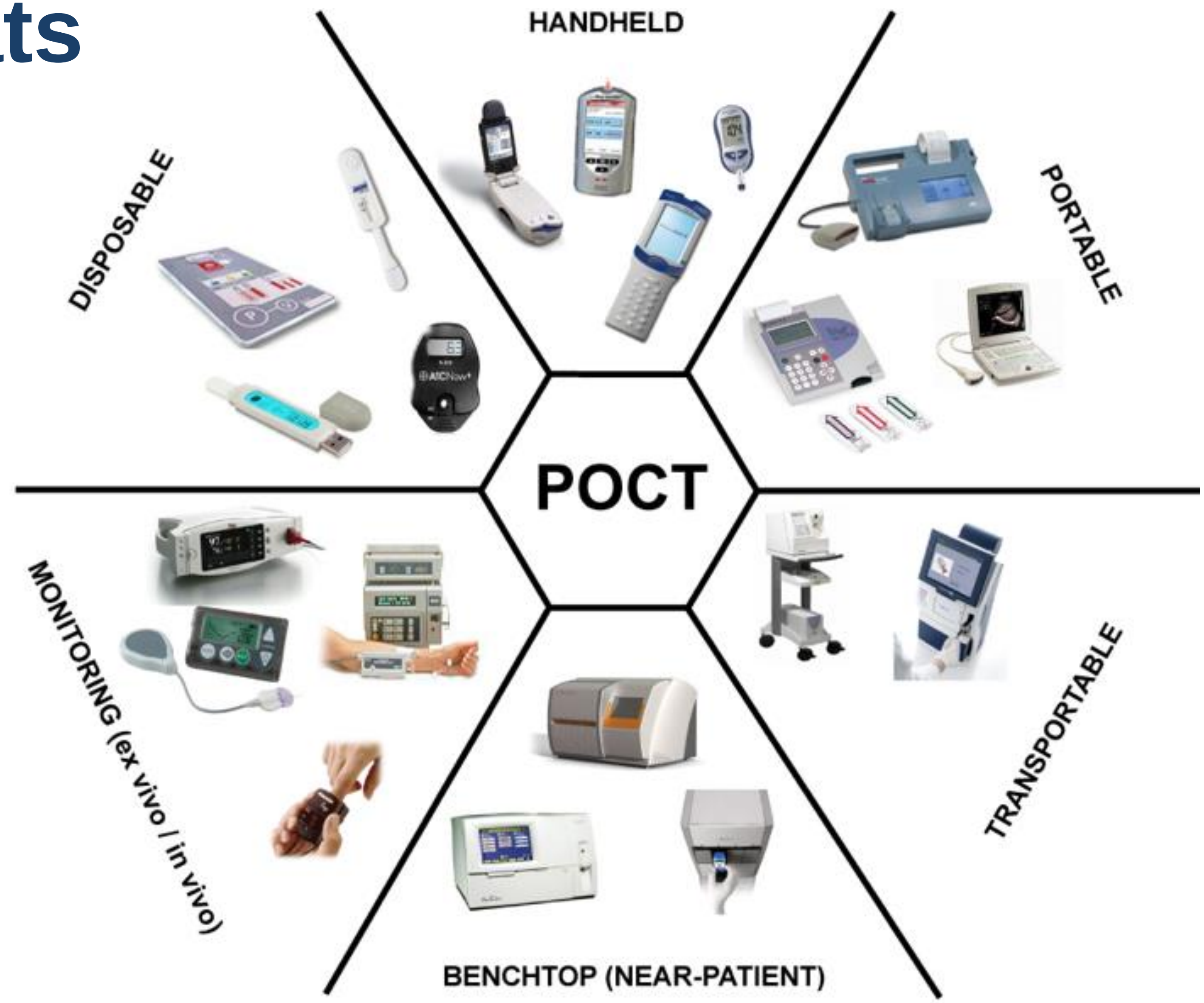
Being FDA approved as a POCT device does not mean it is not susceptible to interfering substances!!!



Total Testing Process: Difference Phases

Total Testing Process: Lab testing occurs over three critical phases:

Pre-Analytical

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Pre-Analytical	Analytical

Total Testing Process: Difference Phases

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Pre-Analytical	Analytical	Post-Analytical

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Total Testing Process: Lab testing occurs over three critical phases:

Pre-Analytical	Analytical	Post-Analytical	TREATMENT

Total Testing Process: Sources of Error

Errors in the Pre-Analytical Phase: Most frequent source of errors (up to 70%). Incorrect

Components

- Patient preparation
- Sample collection
- Transportation
- Accessioning
- Processing

Pre-Analytical	Analytical	Post-Analytical	TREATMENT

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Sources of Error

Incorrect patient ID
Mislabeling of specimens
Hemolysis
Wrong specimen type
Improper specimen collection
Interfering substances

Total Testing Process: Sources of Error

Errors in the Analytical Phase: Infrequent in laboratory tests, however may be higher in POCT due to non-lab trained personnel operating devices.

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What is the significance of testing error in POCT?

Glucose Meter Paradigm to Highlight the Role of Testing Errors

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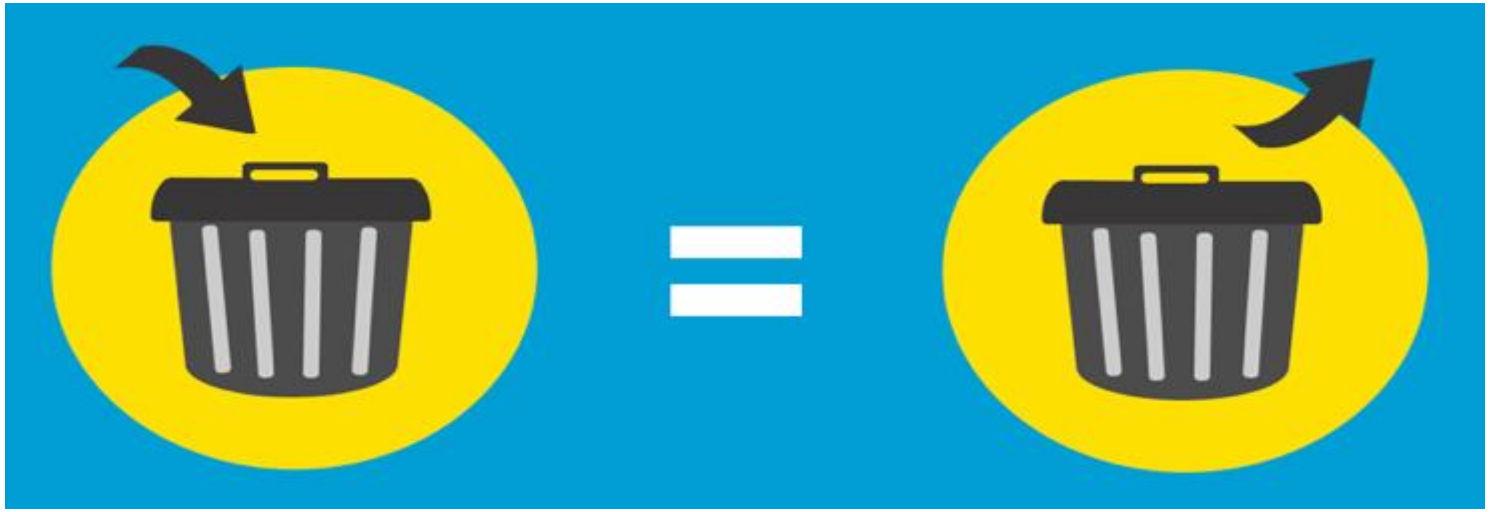
Glucose Meter Paradigm to Highlight the Role of Testing Errors



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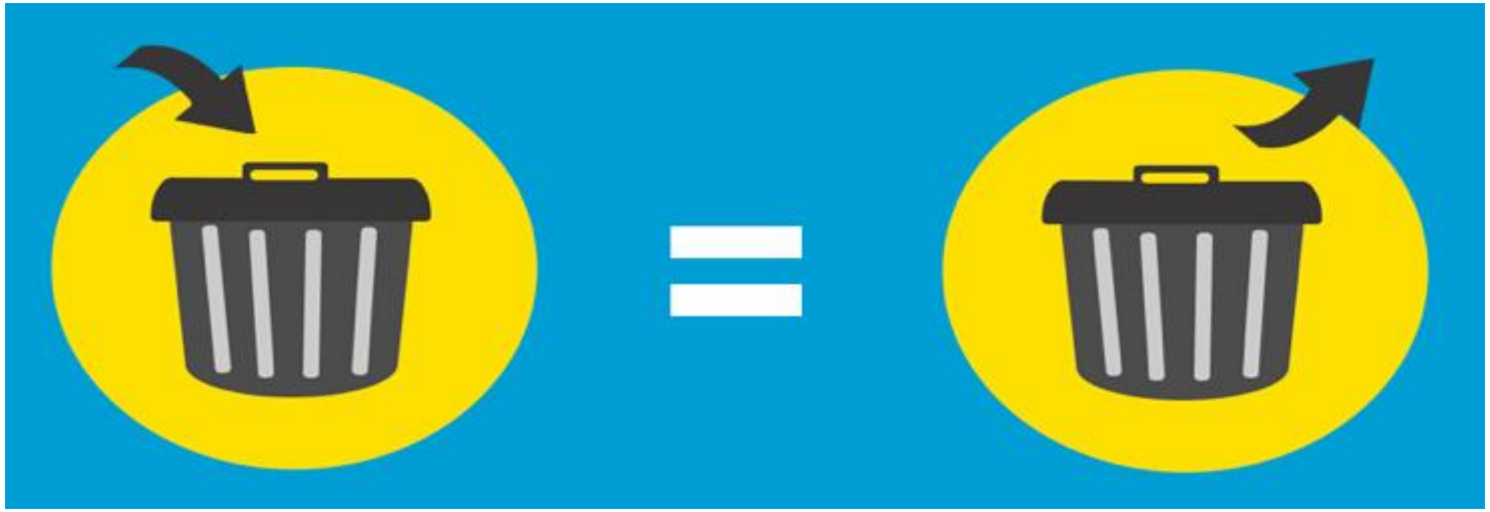

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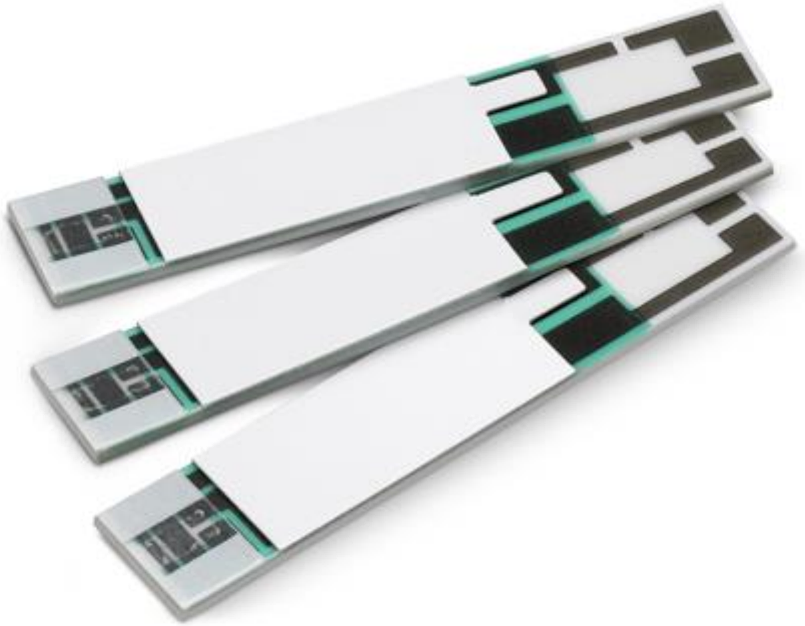
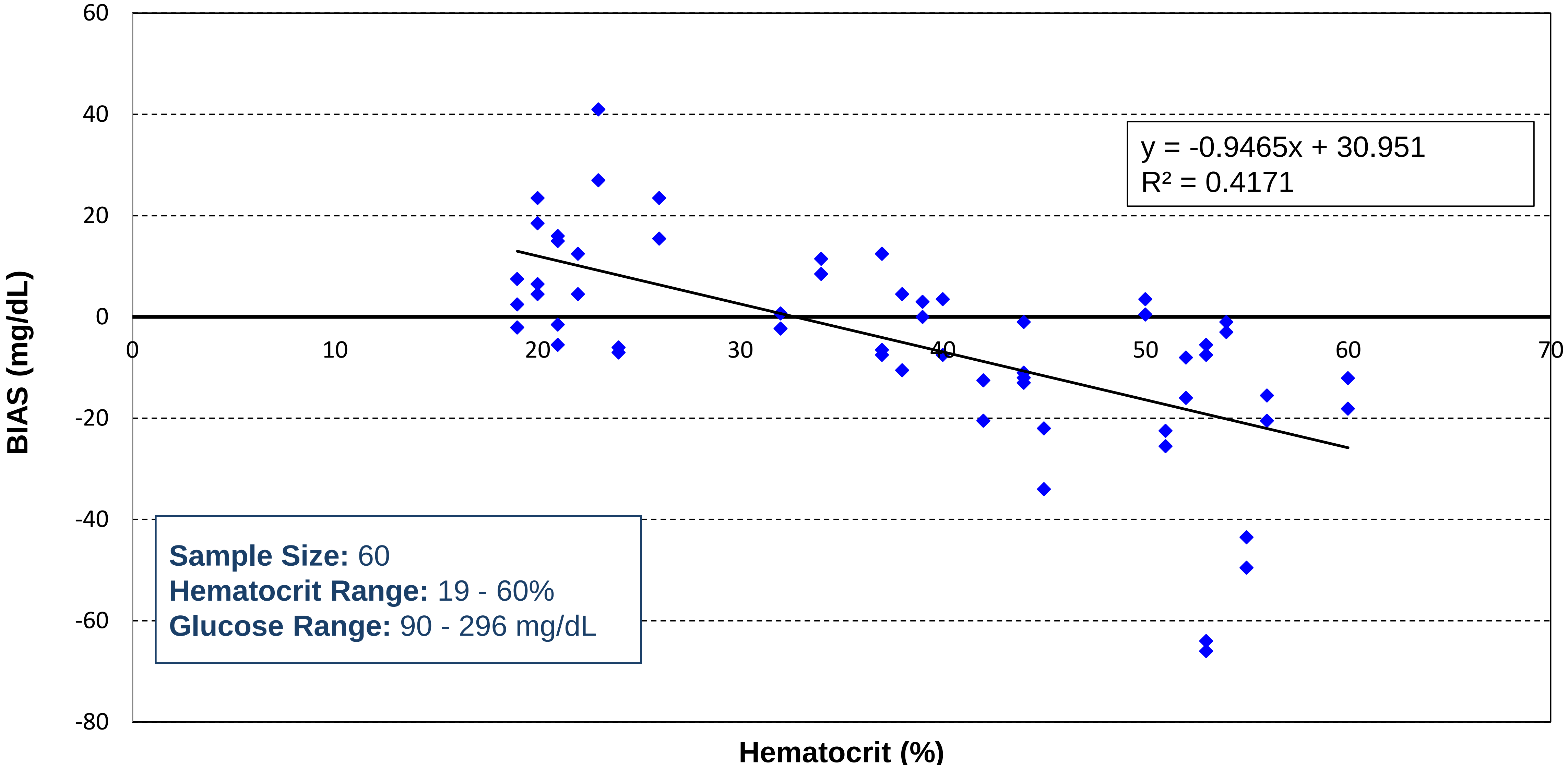
Common Confounding Factors for Glucose Meters

Anemia and polycythemia causes falsely high or falsely low results respectively.



Hematocrit Effects on BGMS Measurements



Note: Bias = BGMS – Plasma Glucose

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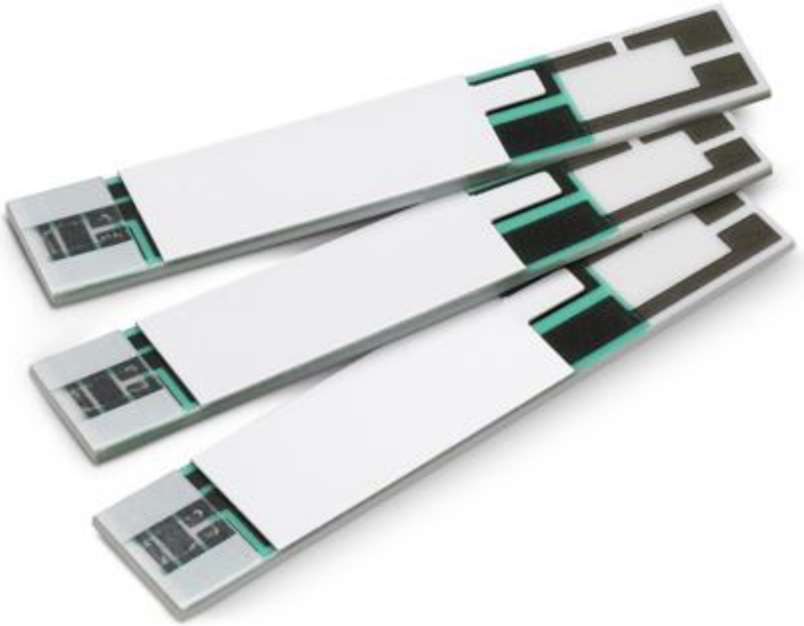
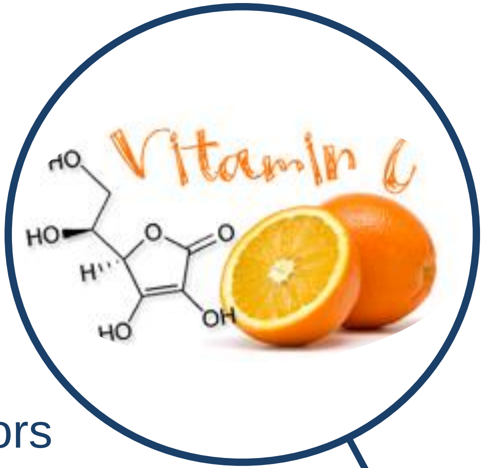
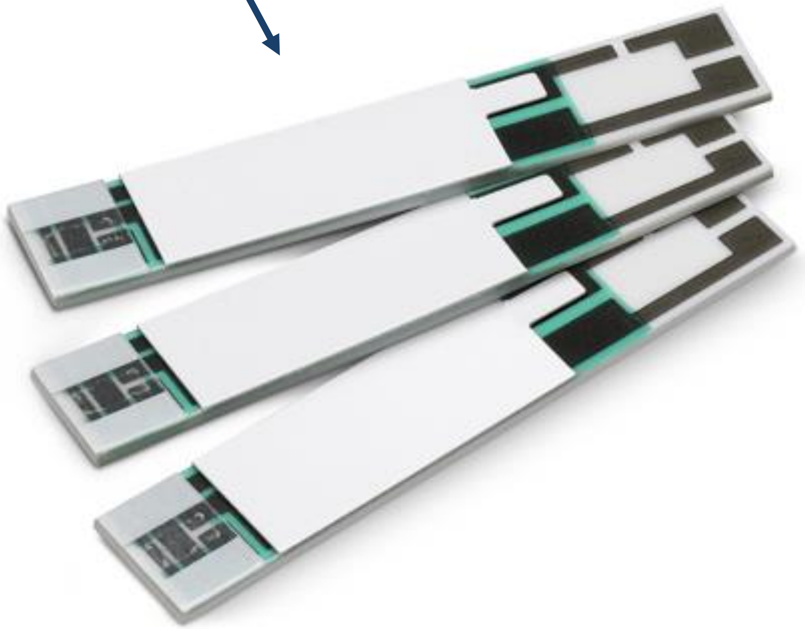
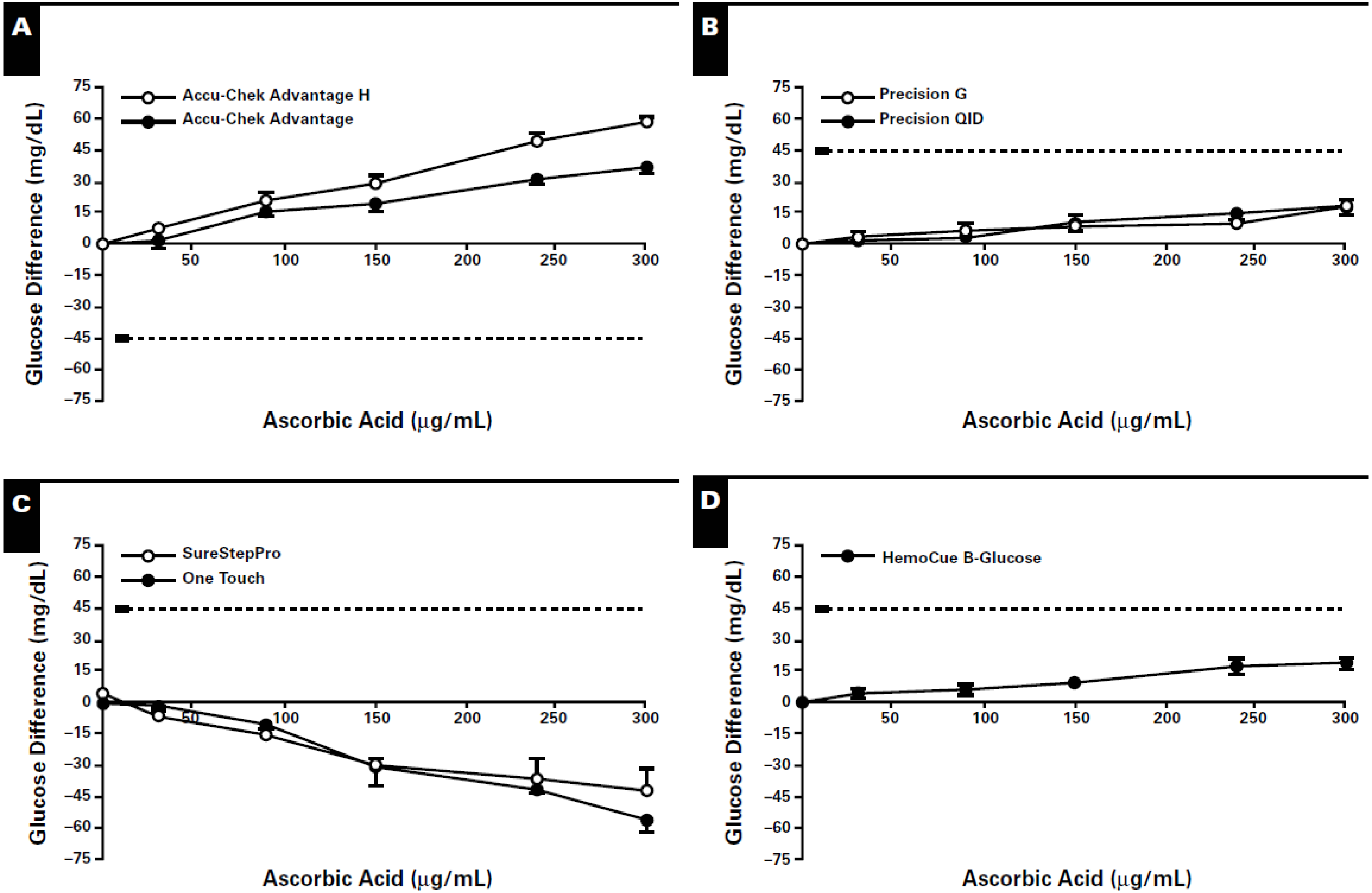


Common Confounding Factors for Glucose Meters

Oxidizing and reducing substances interfere with electrochemical sensors causing falsely high or low results.





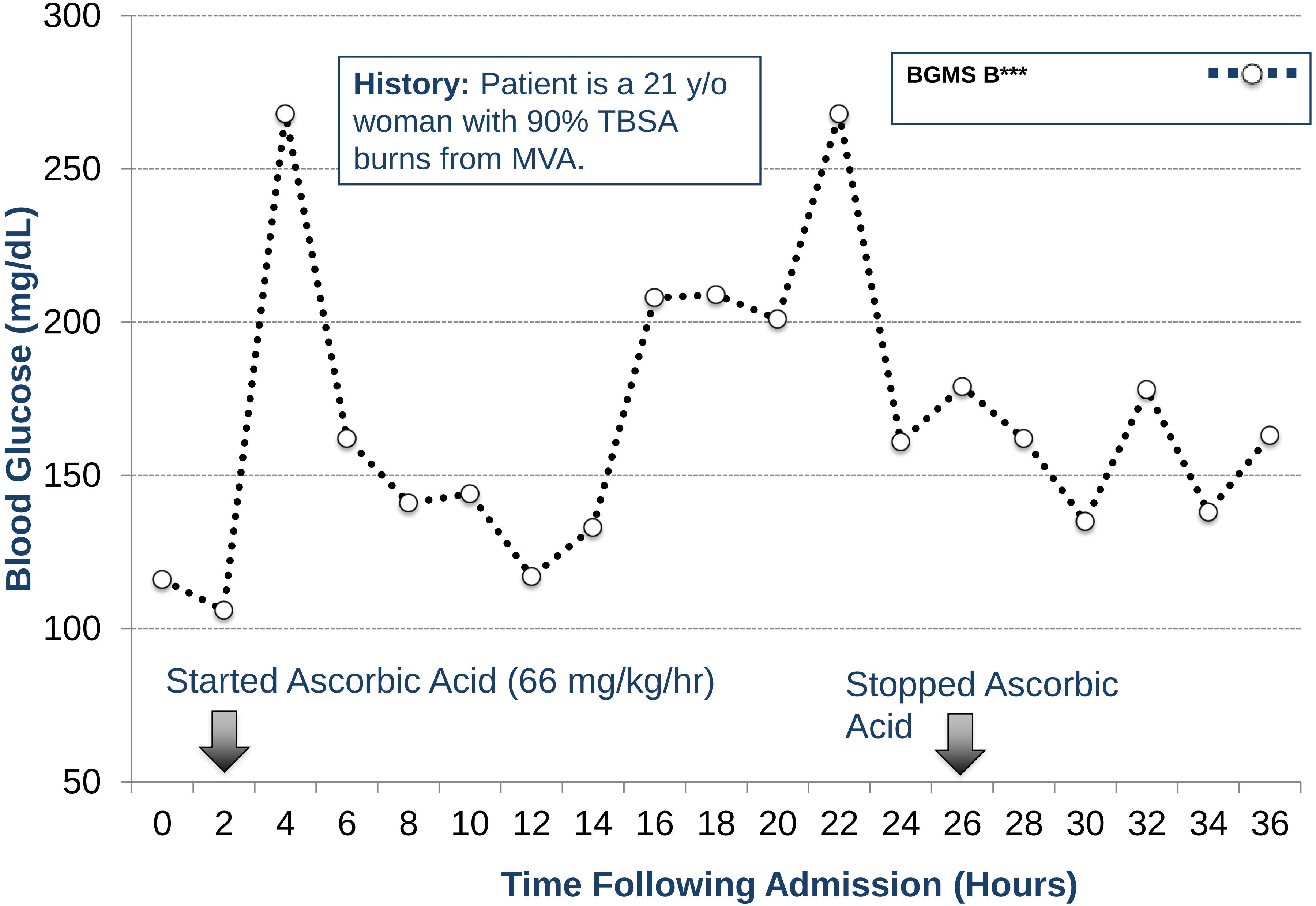


Tang Z, et al. *Am J Clin Pathol* 2000;113:75-86

The role of drug interferences in critical care BGMS accuracy

Tran NK, et al. *J Burn Care Res* 2014;35:72-79

CASE EXAMPLE: ASCORBIC ACID INTERFERENCE



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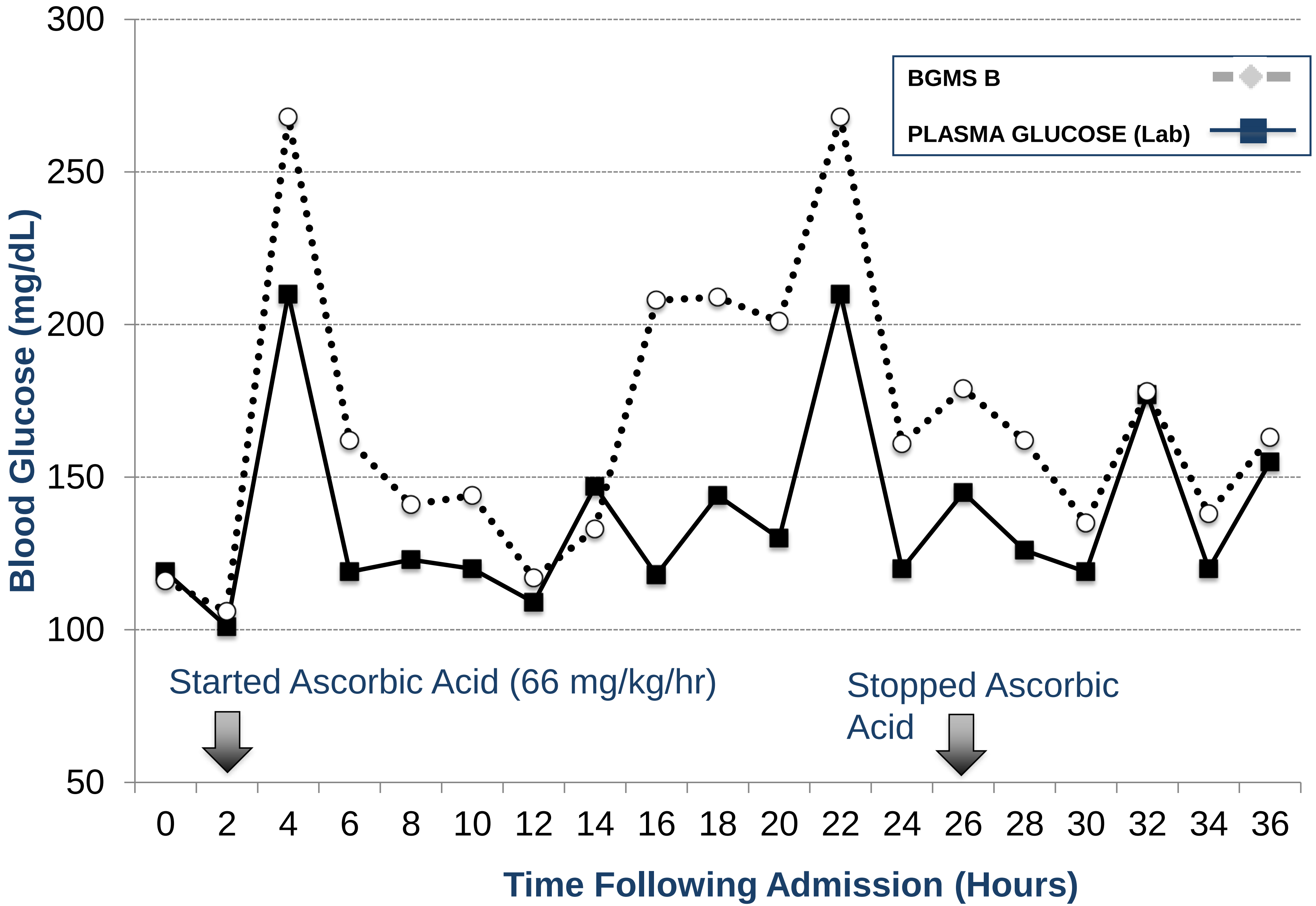

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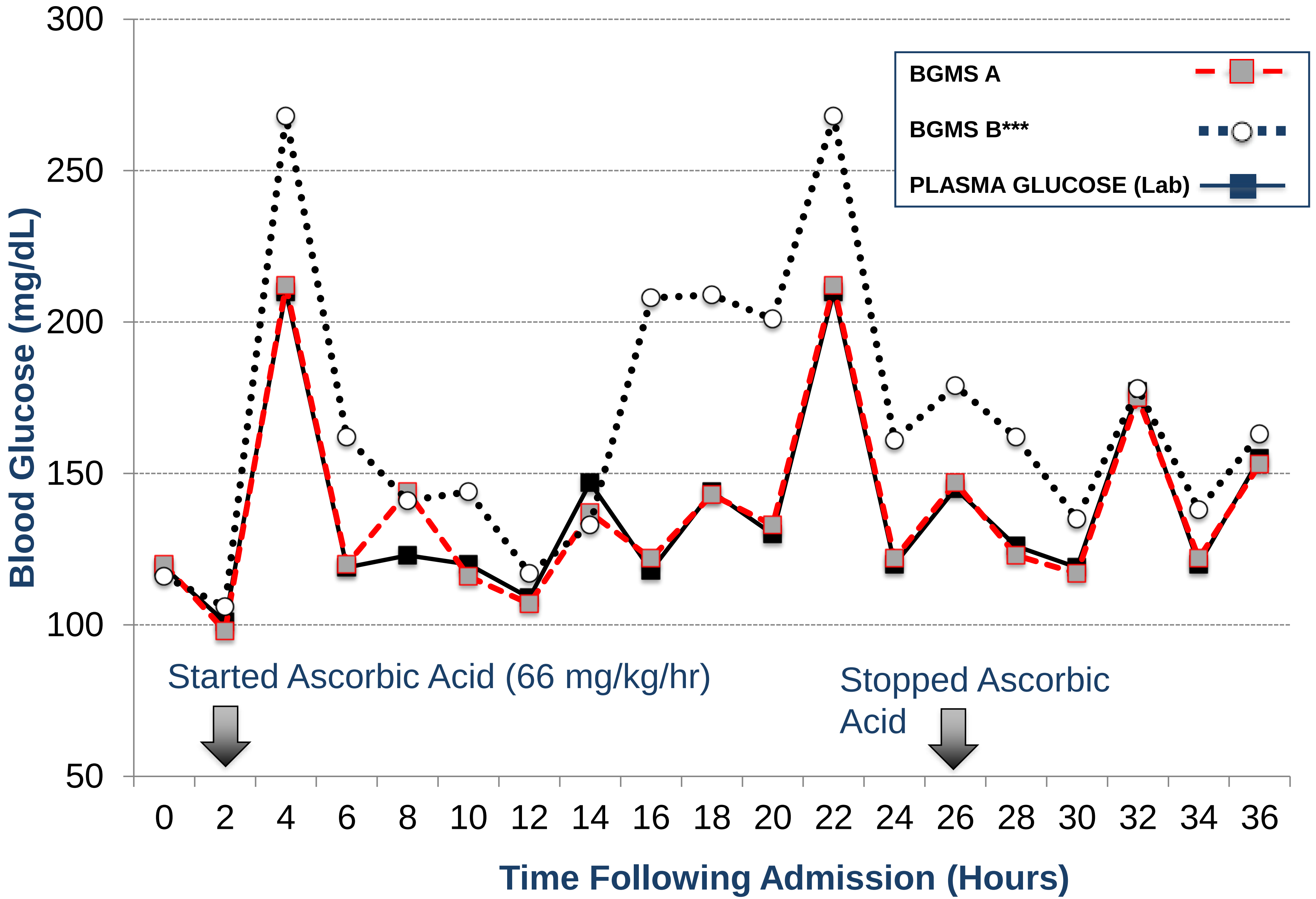

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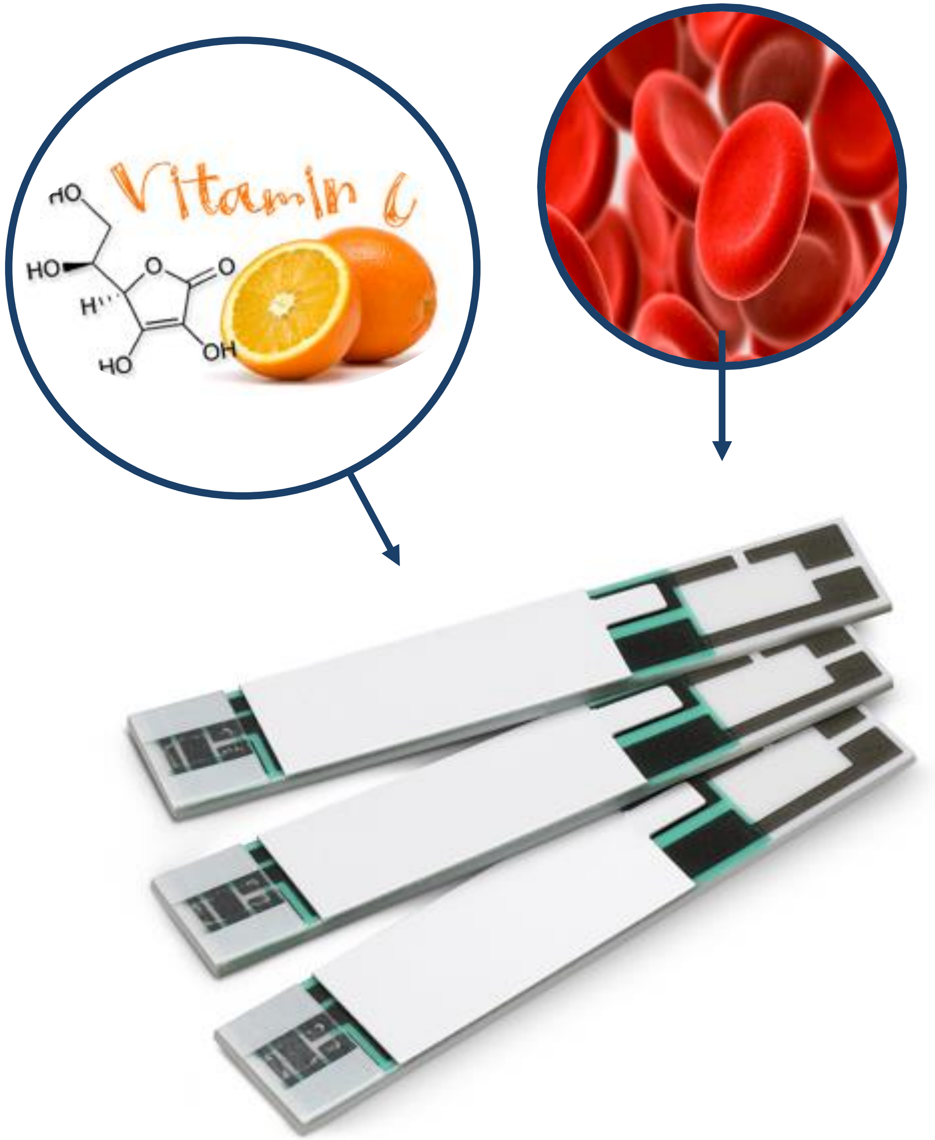
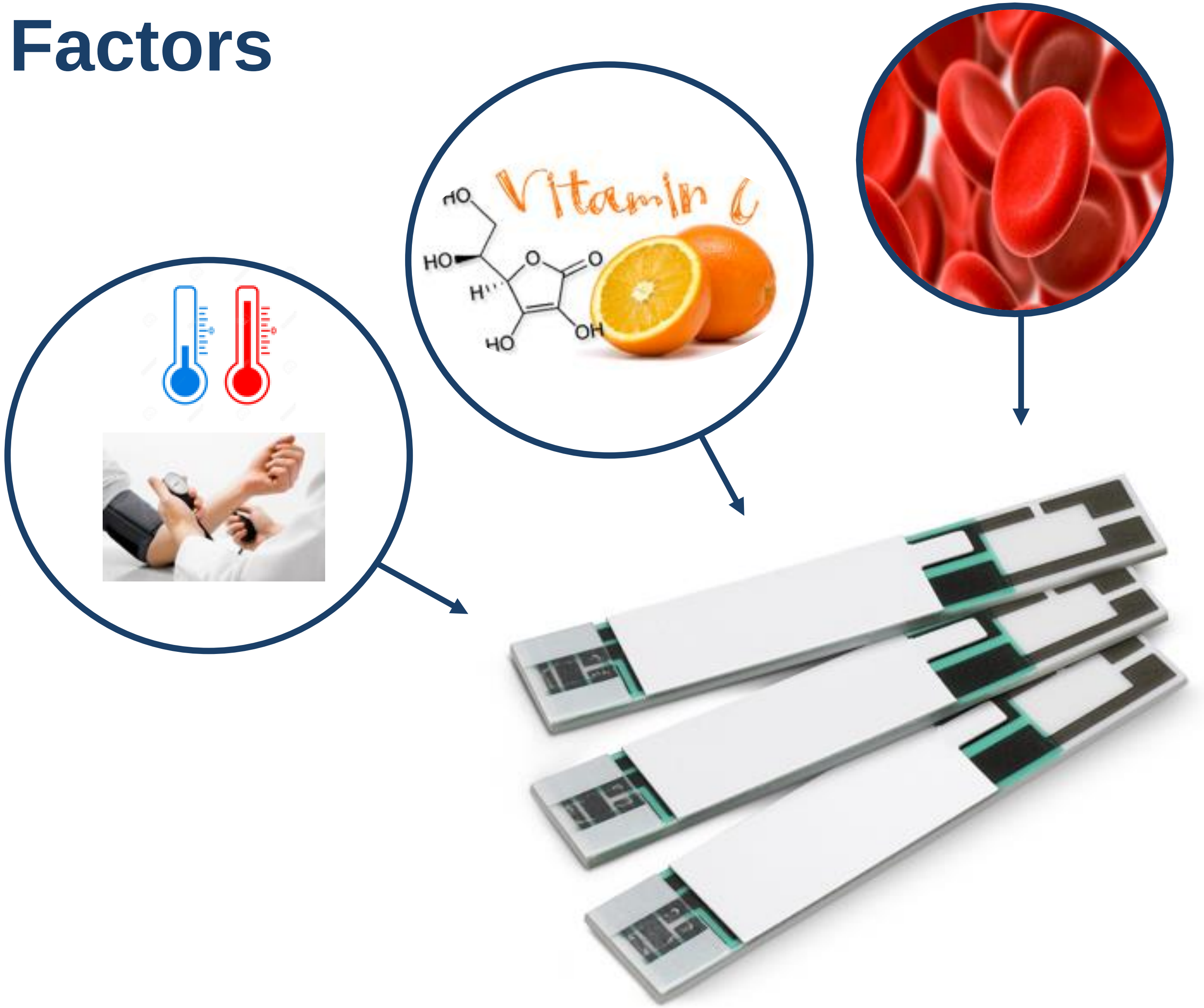


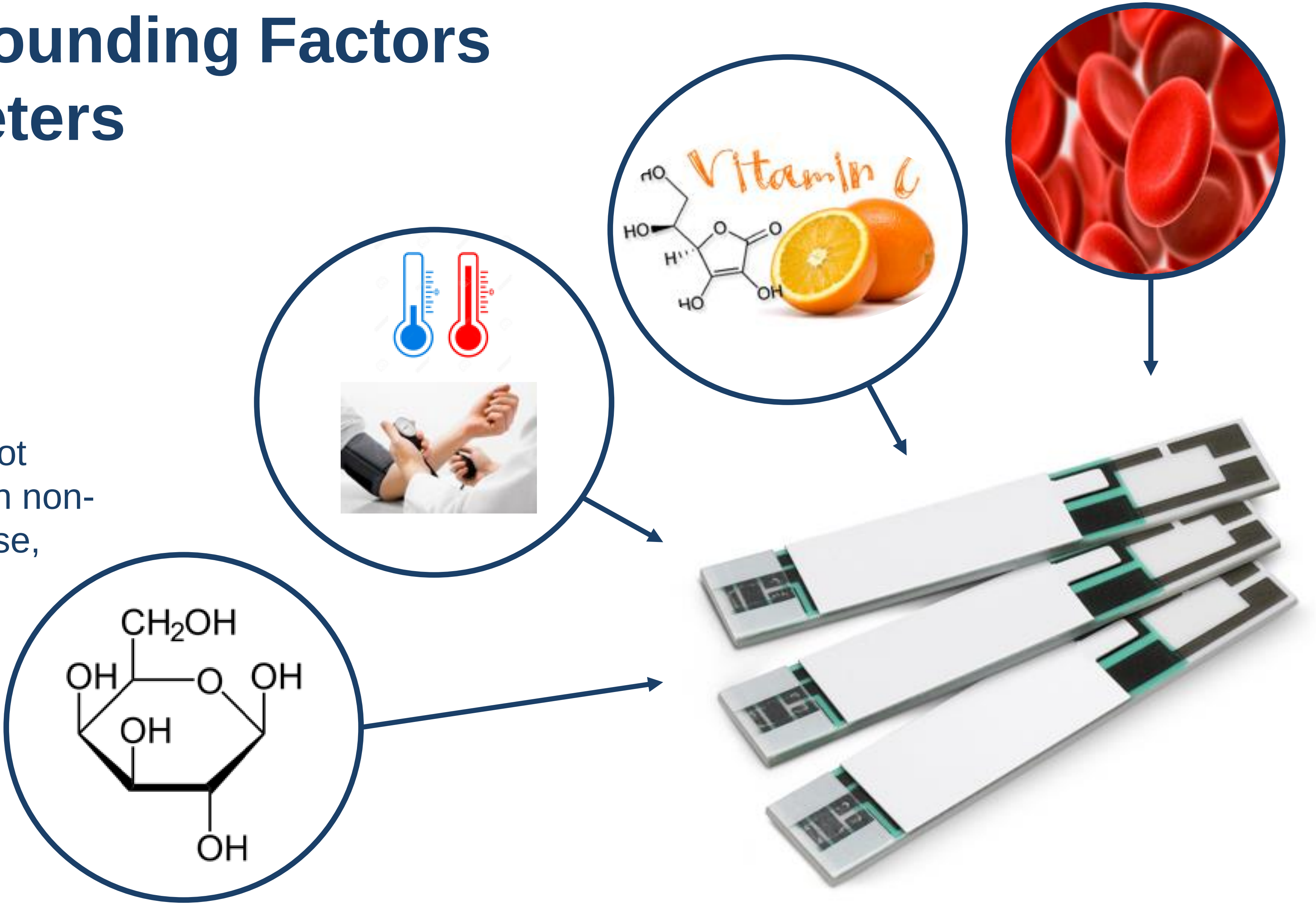
Common Confounding Factors for Glucose Meters

Specimen temp alters biosensor enzyme kinetics. Hypotension/shock affect capillary specimens.



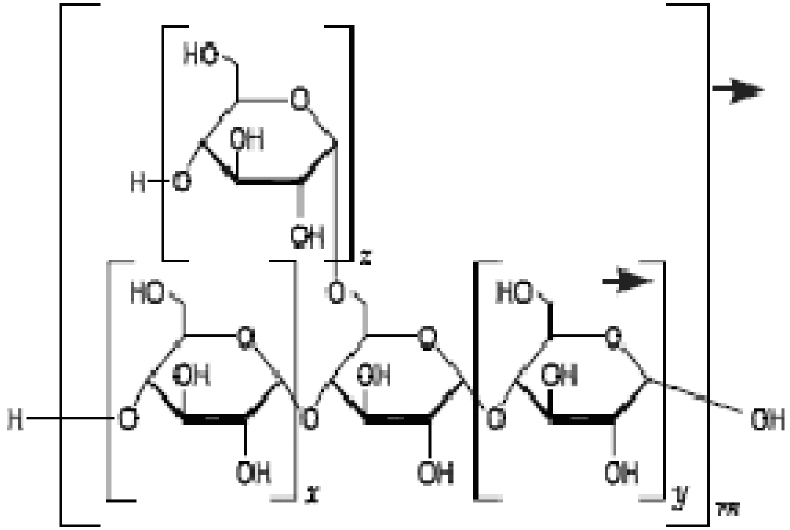
Common Confounding Factors for Glucose Meters

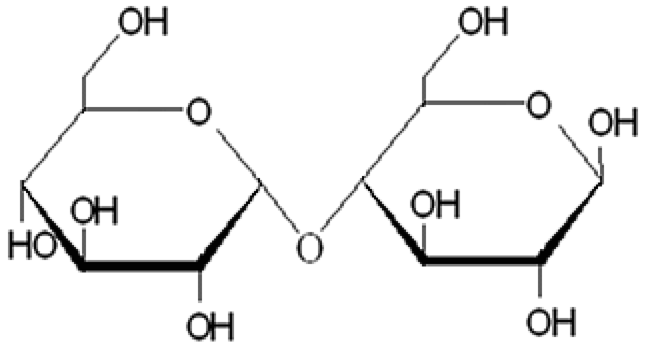
Some glucose meters cannot differentiate between certain non-glucose sugars (e.g., maltose, galactose)



Non-Glucose Sugar Interferences

- Icodextrin is a dialysis drug. It is metabolized by the body to maltose. In some glucose biosensors, maltose is indistinguishable from glucose.





From Pharmacotherapy

Interference of Maltose, Icodextrin, Galactose, or Xylose with Some Blood Glucose Monitoring Systems

Thomas G. Schleis, M.S.

Authors and Disclosures

Posted: 10/04/2007; Pharmacotherapy. 2007;27(9):1313-1321.

Abstract and Introduction

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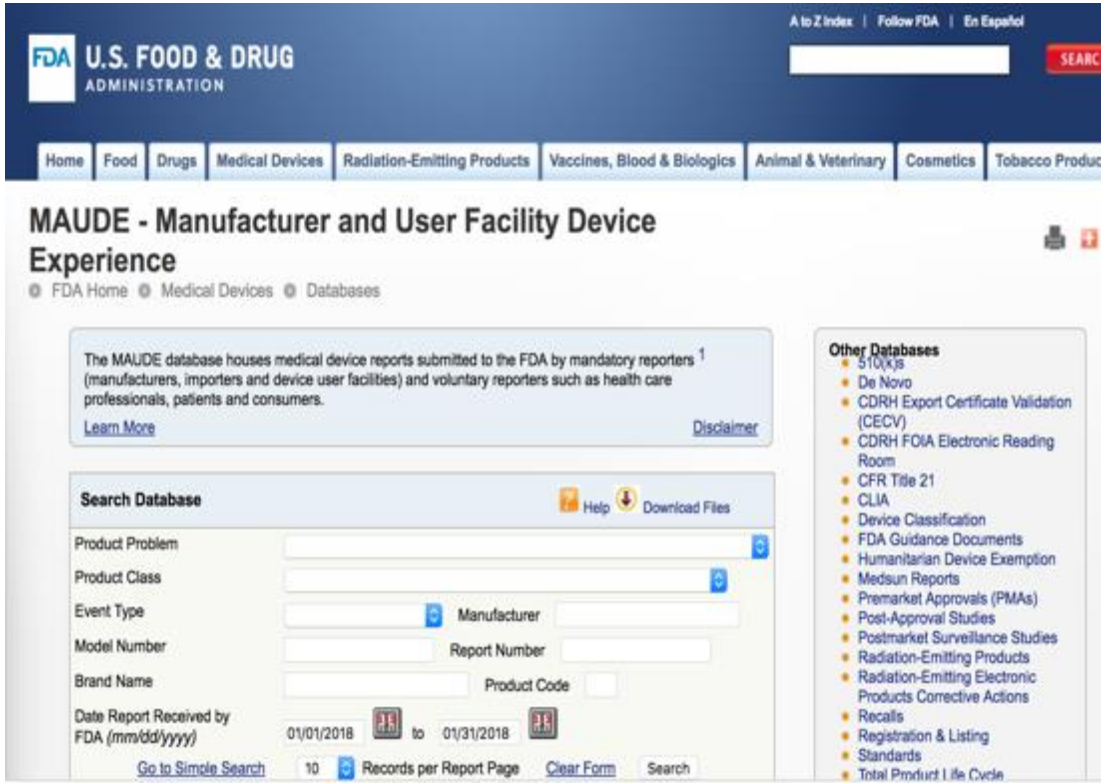
Labeling Requirements for Maltose-Containing Products
Galactose and Xylose
Pharmacology and Pharmacokinetics of Maltose
Discussion
Conclusion
References

Abstract

Maltose, a disaccharide composed of two glucose molecules, is used in a number of biological preparations as a stabilizing agent or osmolality regulator. Icodextrin, which is converted to maltose, is present in a peritoneal dialysis solution. Galactose and xylose are found in some foods, herbs, and dietary supplements; they are also used in diagnostic tests. When some blood glucose monitoring systems are used—specifically, those that use test strips

Maltose Related Deaths



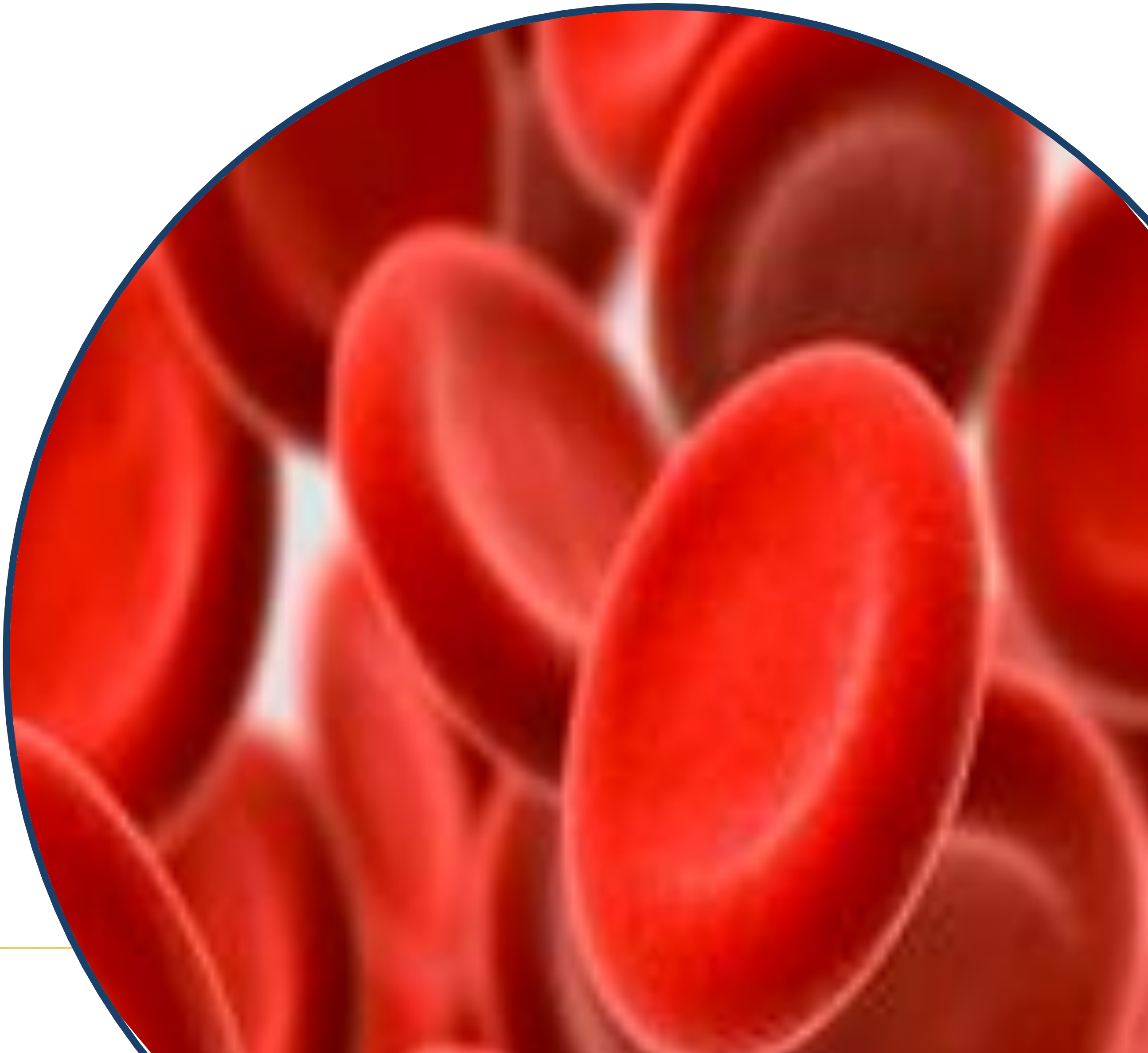
	BGMS A	BGMS B	BGMS C
Timeframe	1997-14	2013-14	2007-11
Adverse Events (Deaths)	28 (13)	5 (0)	0 (0)
Erroneous Results	557	168	15
Non-Clinical Event	387	59	21
TOTAL	1094	232	36

FDA MAUDE Database website: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/ search.cfm, Accessed on August 20, 2014

Continuous Glucose Monitors?

- Similar sensor designs so susceptible to similar interferences (will vary based on manufacturer).
- CGM based on interstitial fluid measurements and not plasma or whole blood.
- Potential for many other sources of interferences.
- CGM does not fall under CLIA and most devices compared against obsolete or poor reference methods such as the YSI.
- **Use WITH caution!**

INTERFERENCES IN WHOLE BLOOD ANALYSIS



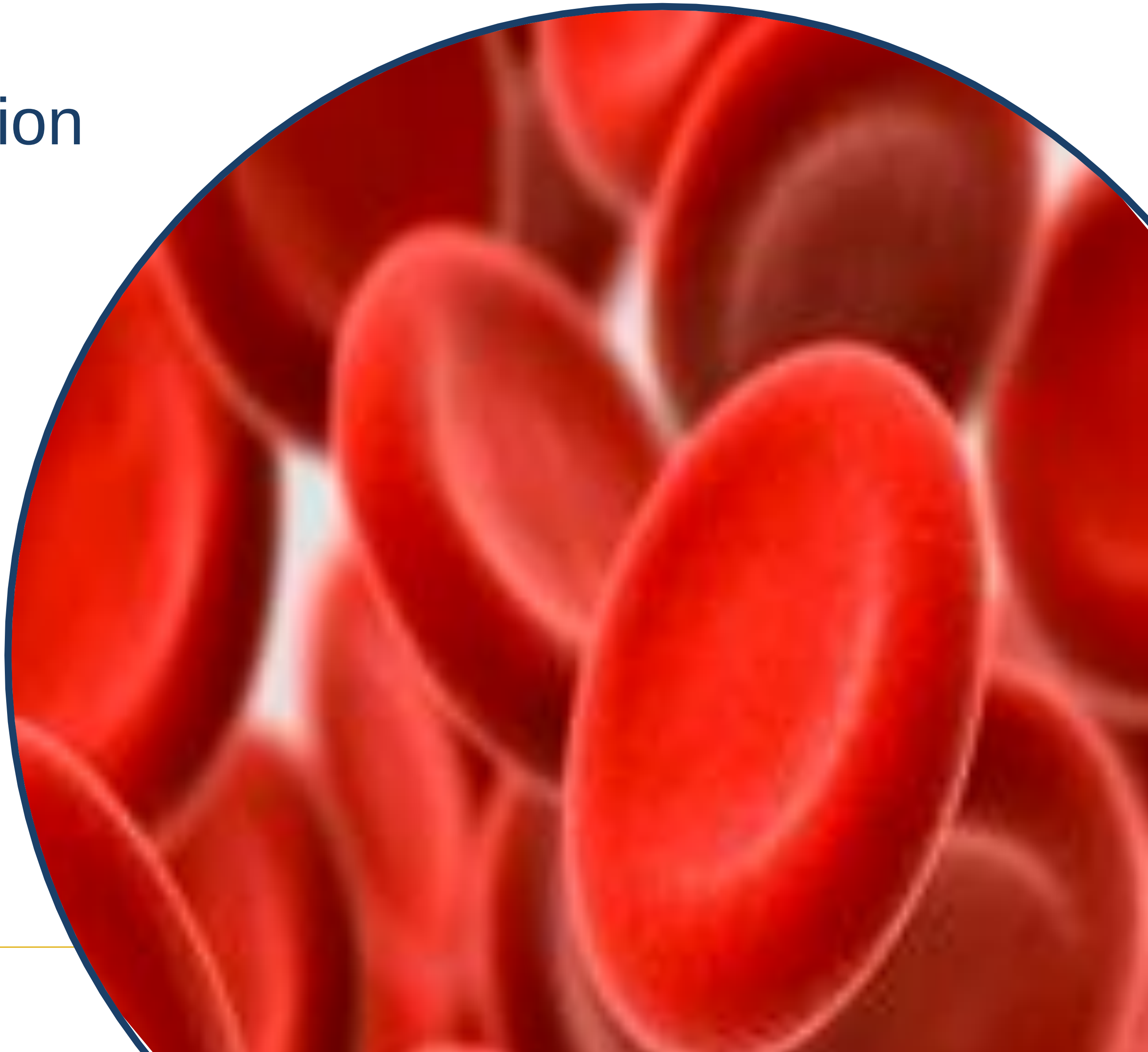
INTERFERENCES IN WHOLE BLOOD ANALYSIS

Air Contamination

Delayed Testing

Hemodilution/Hemoconcentration

Hemolysis



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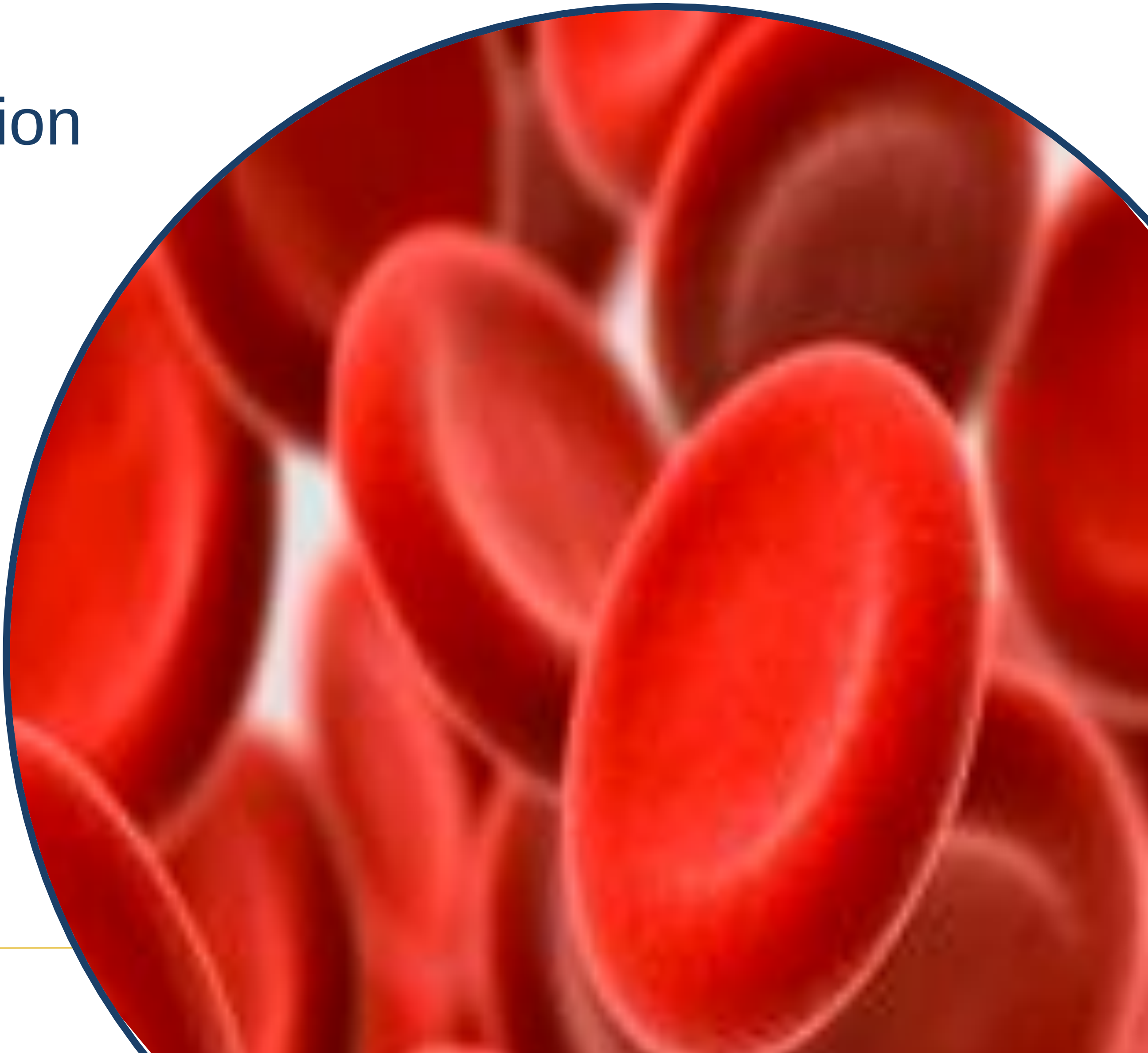

Air Contamination of Blood Specimens

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- POC VBG#2: pH = 7.56, pCO_2 = 12.7, pO_2 = **<u>165.9</u>**
- End tidal CO_2 = 28

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Blood Gas Laboratory identified “air bubbles” in syringe

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- End tidal CO2 = 28
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- **Air bubbles can quickly (<5 mins) cause the specimen to equilibrate atmospheric air (1 atm = 760 mmHg = 0.21 x 760 = 150 mmHg for pO2!!!)**

INTERFERENCES IN BLOOD GAS ANALYSIS

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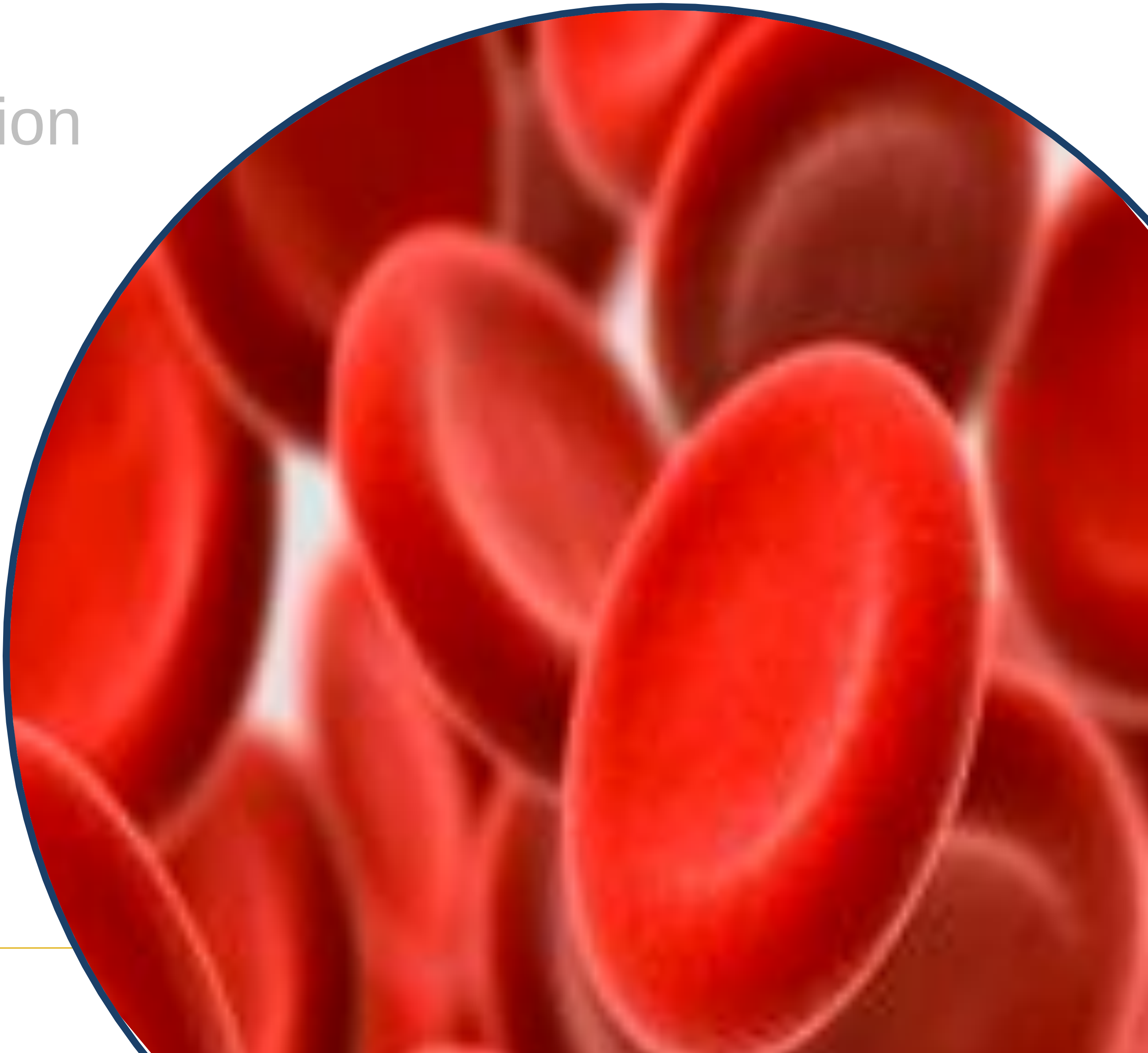
Hemodilution/Hemoconcentration

Hemolysis



Specimen Processing Delays and Lactate

<u>Pre-Analytical</u>

- Transportation delays

Analysis should be performed within 20 to 30 minutes—Faster is better!

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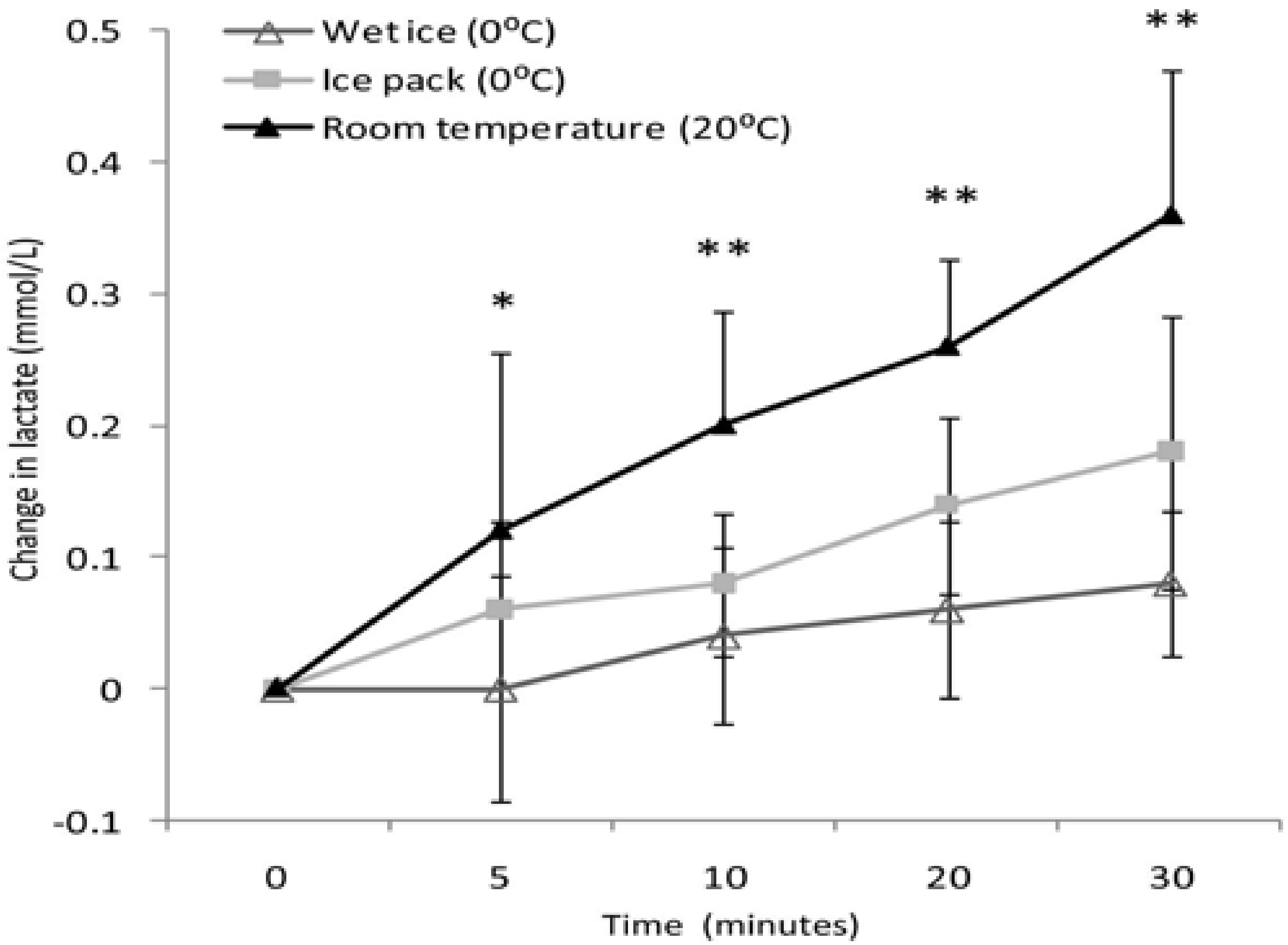


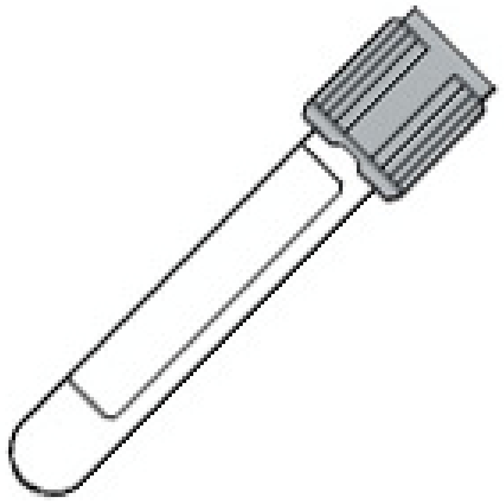
Seymour CW, et al. BMC Research Notes 2011;4:169

Specimen Processing Delays and Lactate

<u>Pre-Analytical</u>

- Transportation delays
- Inadequate inhibition of glycolysis

If delays are expected, using a grey top tube may be appropriate, however it may take up to 15 minutes to achieve inhibition!



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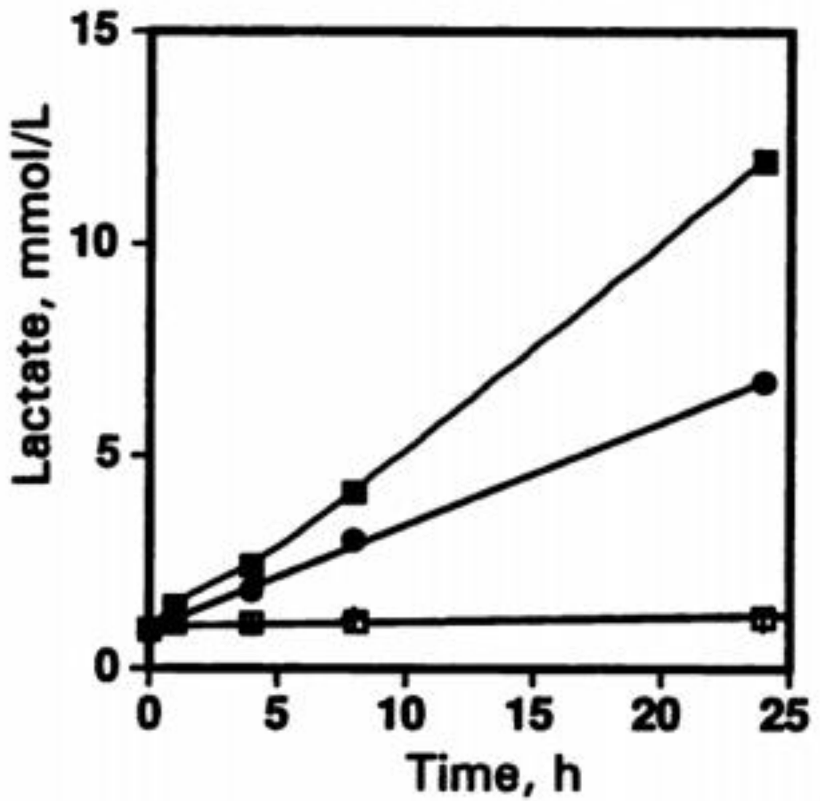

Fig. 2. Lactate stability in whole blood at room temperature with F vs OX. Heparinized blood was obtained from a normal volunteer and then split into aliquots that received 60 mmol/L F (□), 12 mmol/L OX (●), both additives (+), or neither (■).

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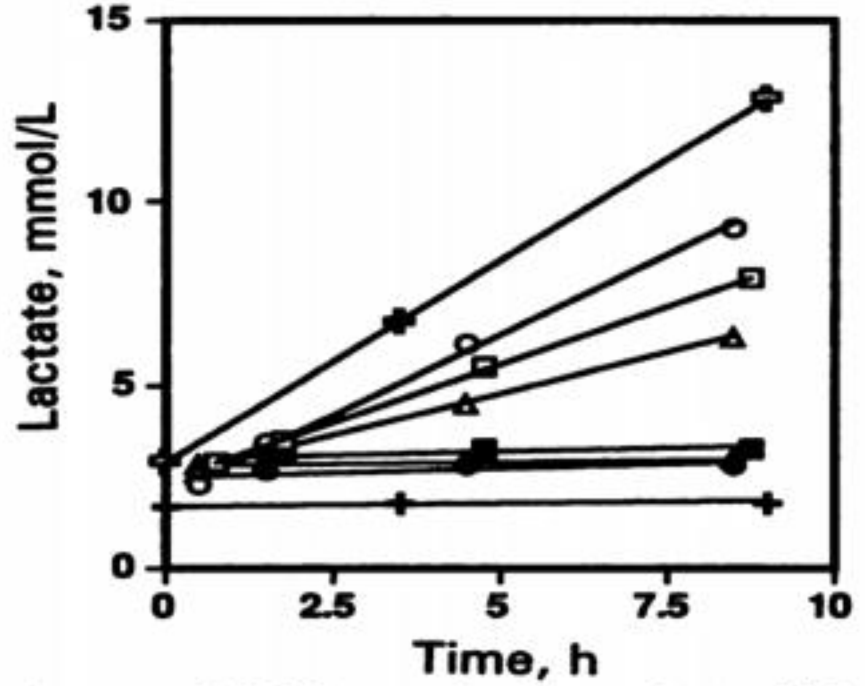

Fig. 1. Effectiveness of F/OX in samples from patients with leukocytosis. Samples were evaluated from three patients with increased neutrophil counts due to granulocyte colony-stimulating factor, and a fourth patient with a carcinoma-associated leukemoid reaction. EDTA-anticoagulated whole blood was stored at room temperature with (*closed symbols*) and without F/OX (*open symbols*). Neutrophil counts were 51.7 (⊕), 52.5 (○), 27.1 (□), and 23(△) × 10^9/L.

Specimen Processing Delays and Lactate

<u>Pre-Analytical</u>

- Transportation delays
- Inadequate inhibition of glycolysis
- Specimens not placed on ice

False elevations of lactate could be mitigated by placing samples on ice. Iced samples exhibit similar results to those tested immediately at up to 6 hours.

Specimen Processing Delays and Lactate

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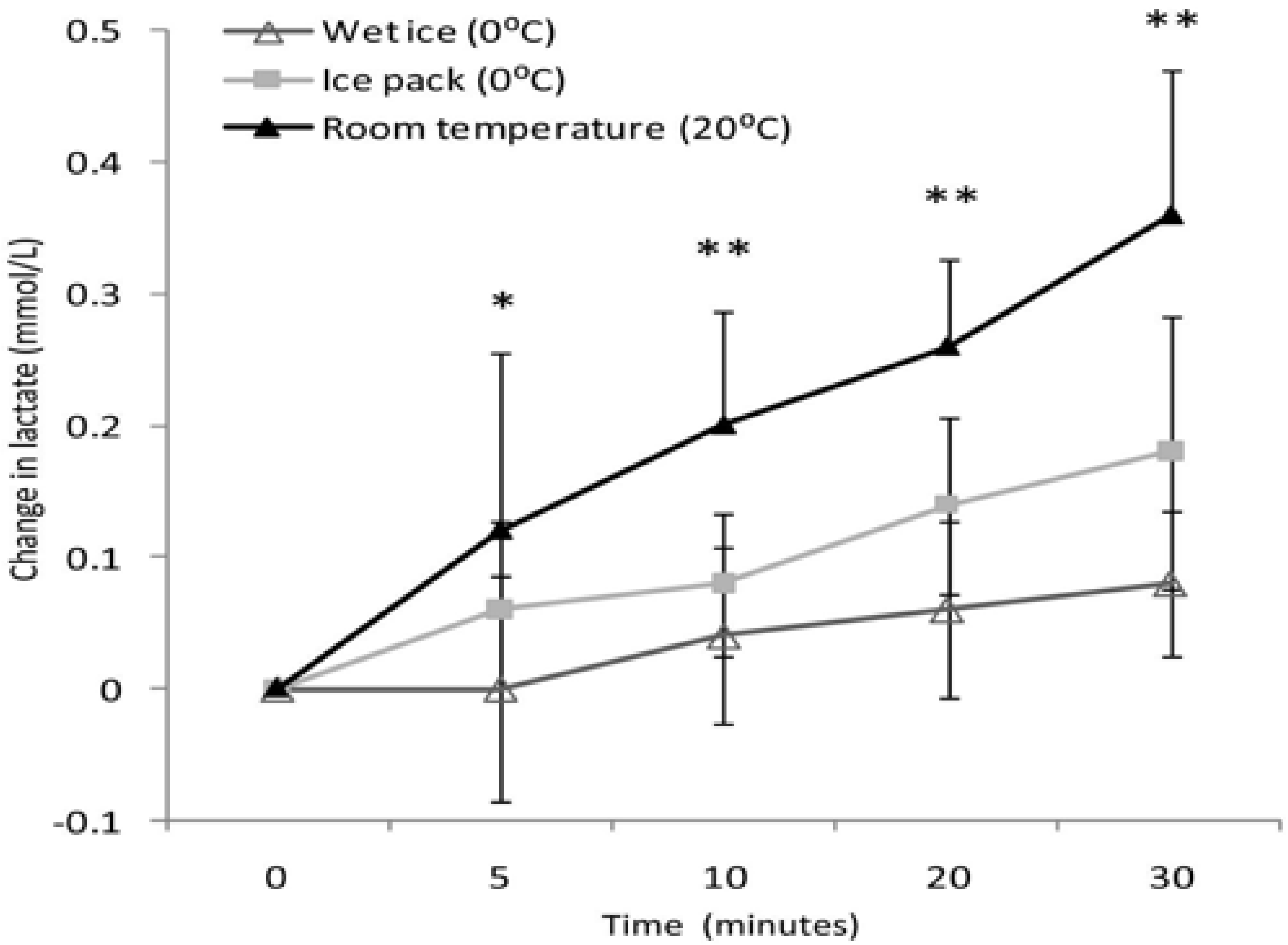

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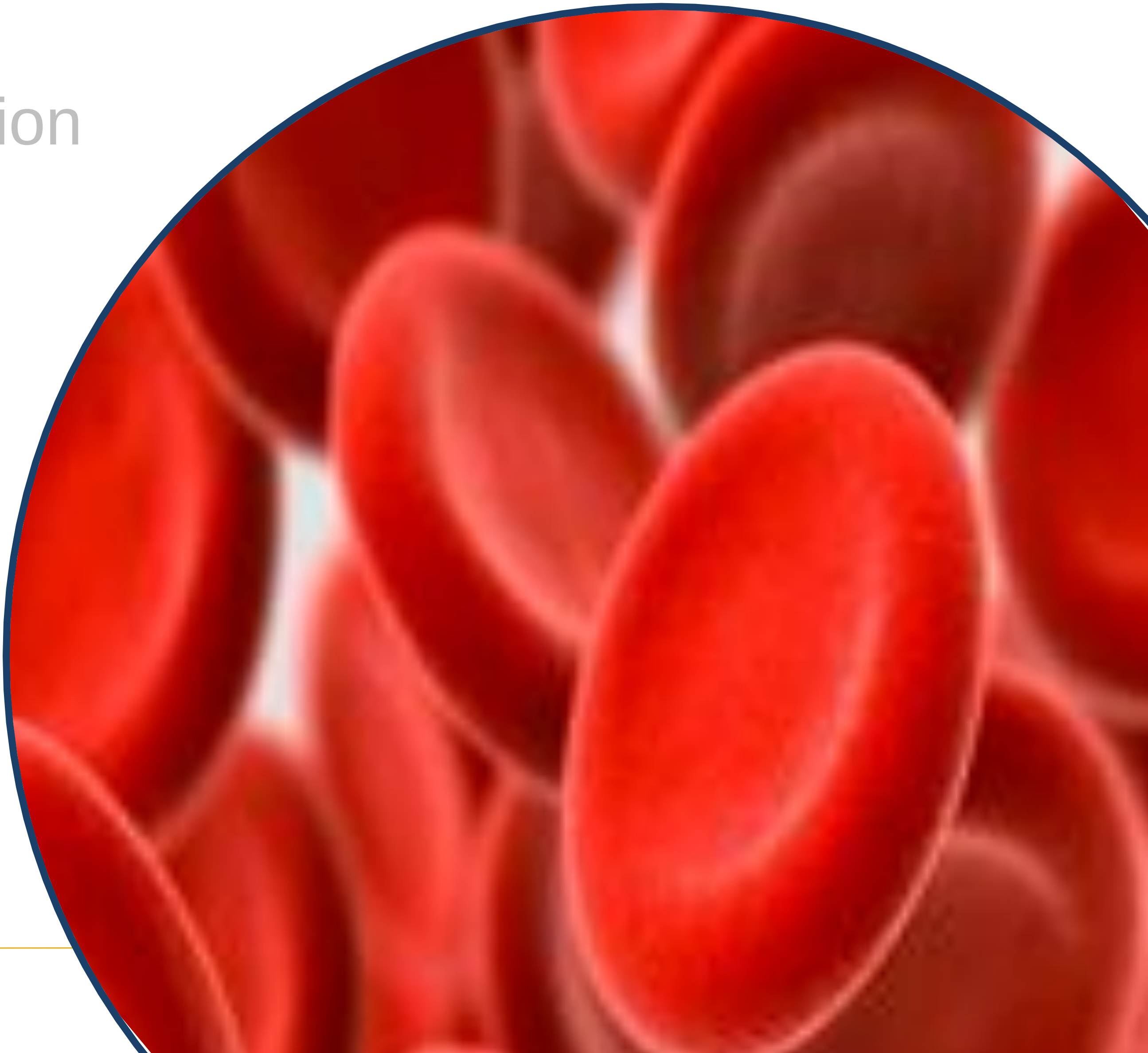
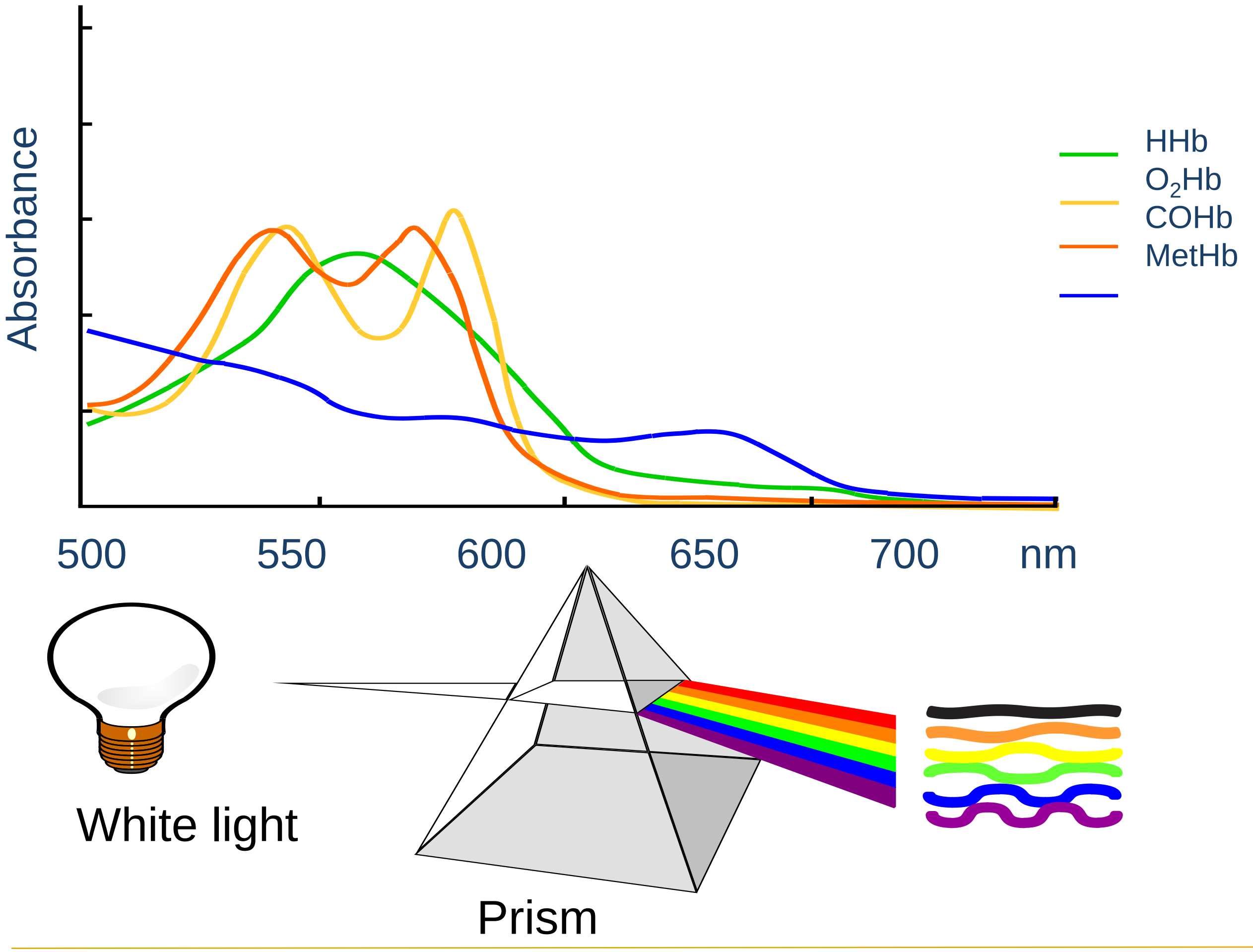


Contemporary Hemoglobinometric Techniques

- **Spectrophotometric (Non-Cyanohemoglobin)**



- Measurement of hemoglobin is based on the absorption spectra
- Oxy- and deoxyhemoglobin exhibit different absorption in the red to IR wavelengths.
- Measurement based on Beer's Law ($A = elc$).
- Some methods require lysis and reacting with non-cyanide-based reagents.

Contemporary Hemoglobinometric Techniques

Conductance (Impendance)

- Red blood cell membranes are not conductive.

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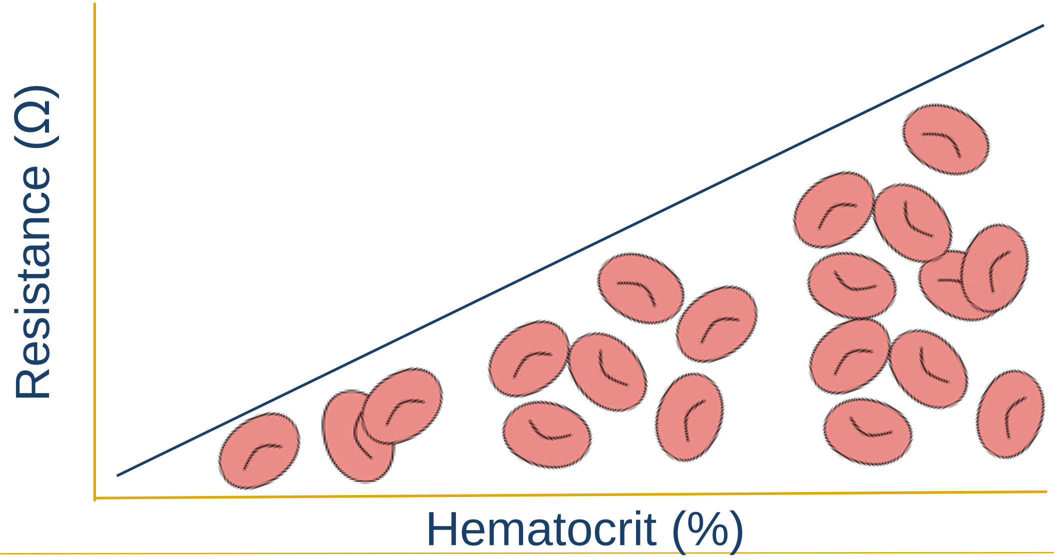
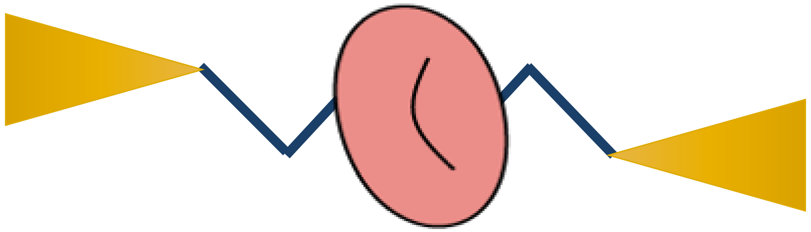


Contemporary Hemoglobinometric Techniques

Conductance (Impendance)

Electrode



VS.

- Red blood cell membranes are not conductive.
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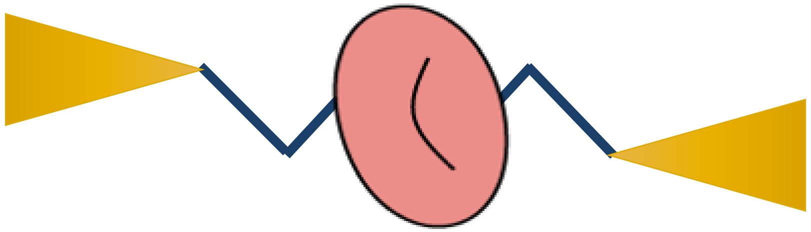

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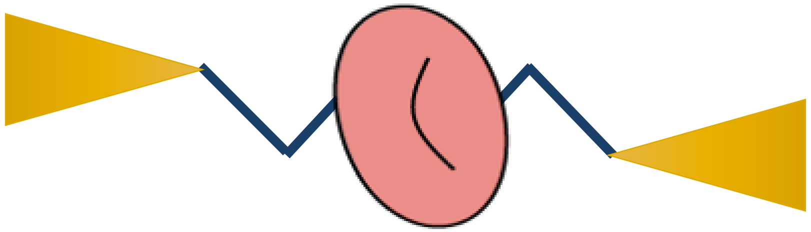
- Red blood cell membranes are not conductive.
- The number of red blood cells is proportional to the change in conductance and conforms to Ohm's Law (V = IR)
- Conductance-based methods measure hematocrit. The hematocrit can then be used to calculate hemoglobin based on a conversion factor (estimated hemoglobin = hematocrit / 3.4)*

Contemporary Hemoglobinometric Techniques

Conductance (Impendance)

Electrode



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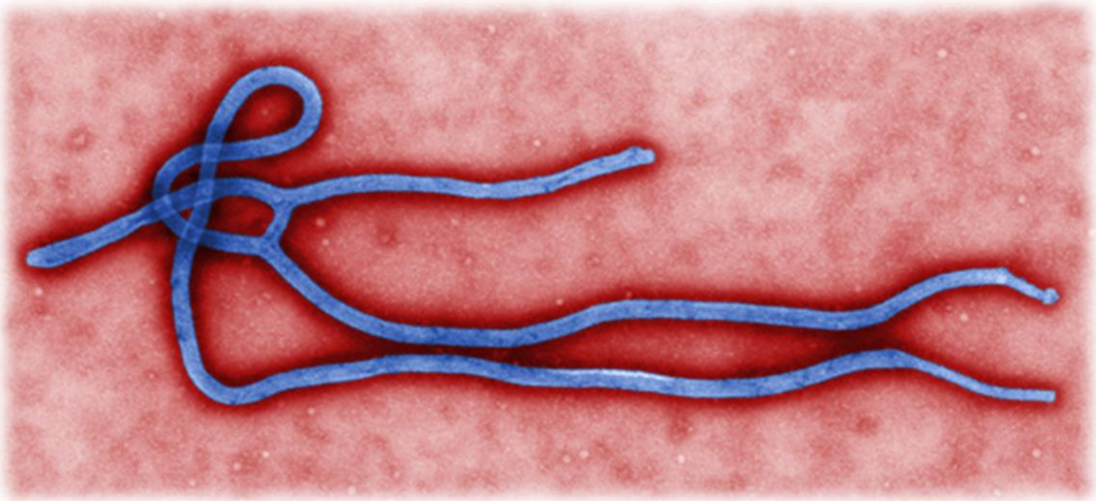
Case Study 2: Hemoconcentration

Background: Patient with suspected Ebola Virus symptoms admitted for evaluation. Isolation protocols were in effect.



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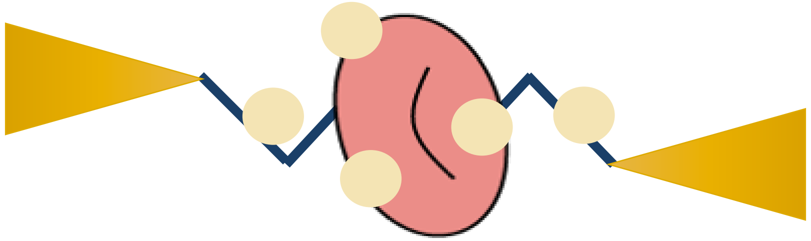
Inadequate mixing may result in artificial changes in total hemoglobin measurements.

Contemporary Hemoglobinometric Techniques

Conductance (Impendence)

= Plasma Protein

Electrode



High Resistance

- Plasma protein content contributes to hematocrit measurements for conductance-based systems.

Contemporary Hemoglobinometric Techniques

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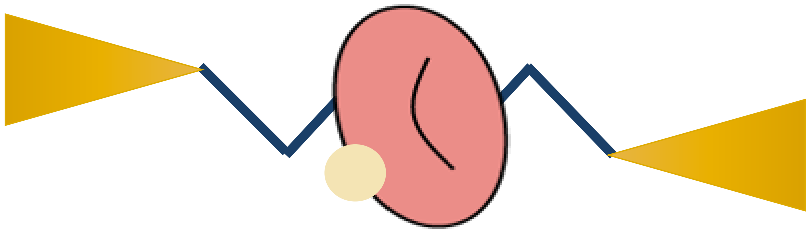

Low Resistance from low plasma protein concentration!

- Plasma protein content contributes to hematocrit measurements for conductance-based systems.
- Conductance-based systems assumes a relatively fixed protein concentration. Therefore, during hemodilution, hematocrit may be falsely lower and causing an underestimation of total hemoglobin.

Contemporary Hemoglobinometric Techniques

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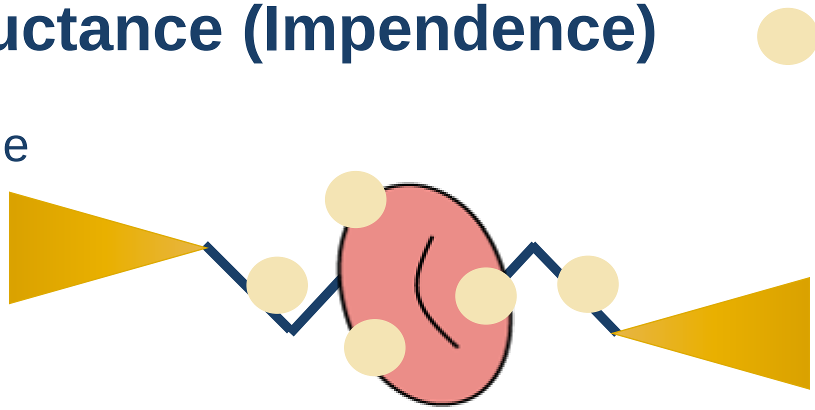

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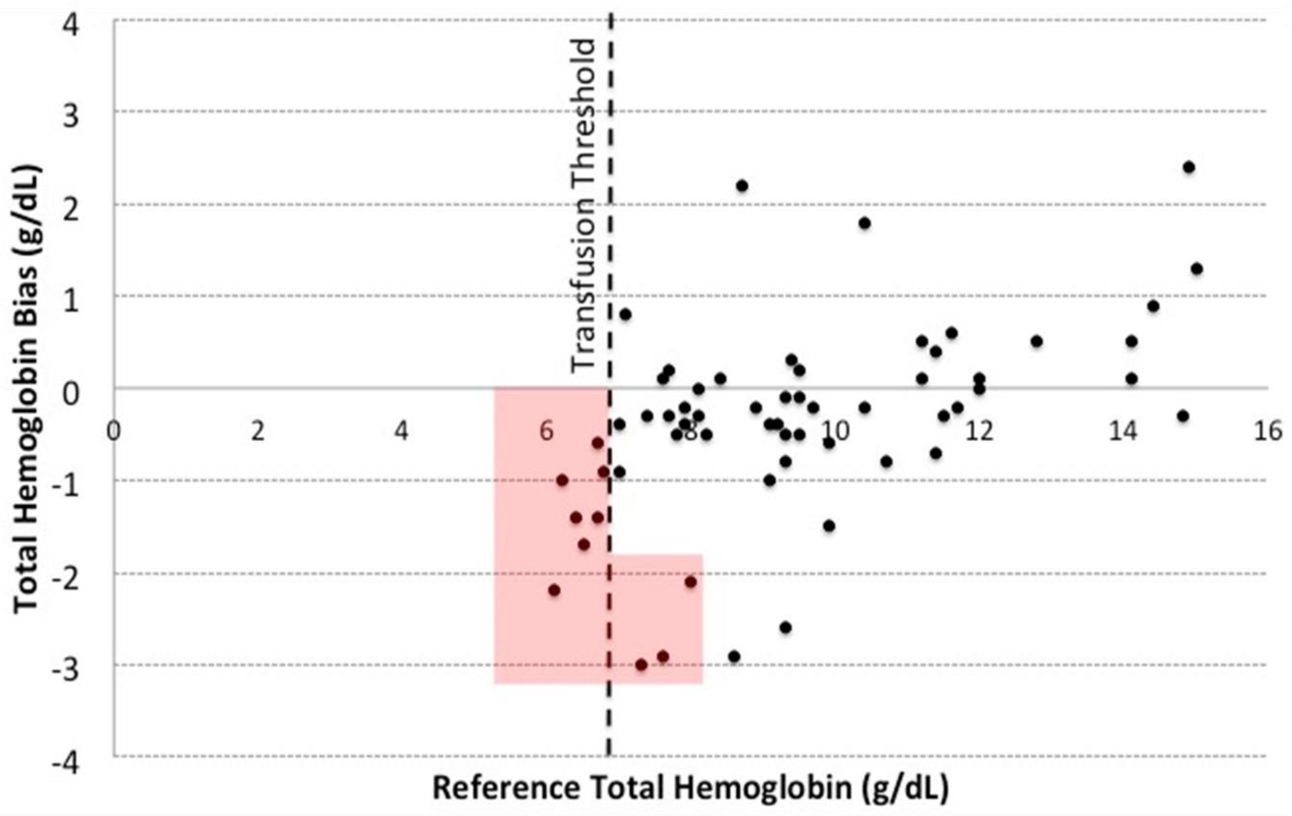
- **UCDMC Study:** Comparison of a handheld blood gas analyzer using conductance-based measurement of hemoglobin versus a benchtop blood gas analyzer using a spectrophotometric-based method for hemoglobinometry.

Clinical Impact of Hemodilution for Point-of-Care Hemoglobin Measurements

- Sixty patients requiring cardiac surgery were evaluated.
- Paired specimens were tested using a handheld POC analyzer and spectrophotometric methods through the core laboratory.
- Mean (SD) bias was -1.4 (1.1) g/dL, P = 0.011.
- Based on core laboratory results 12 patients would have received unnecessary transfusions.



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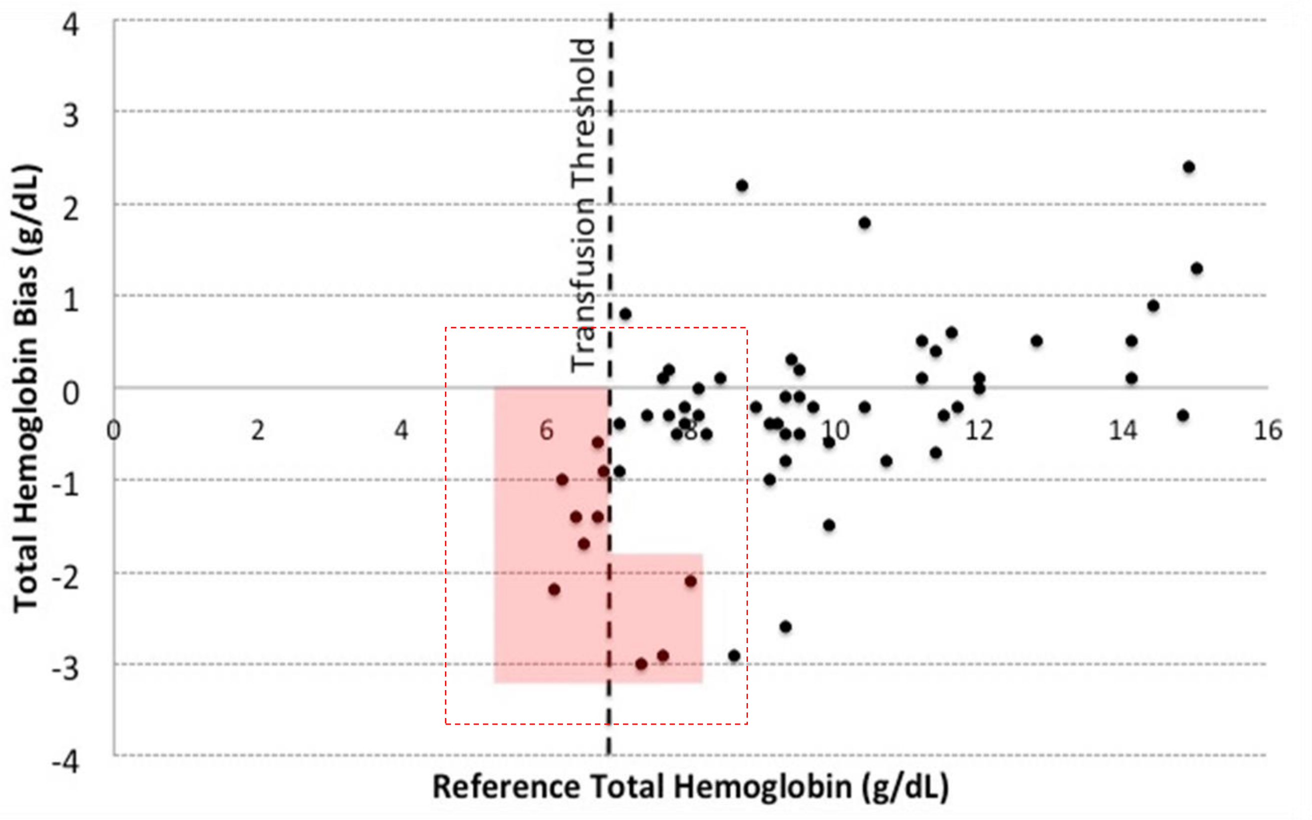

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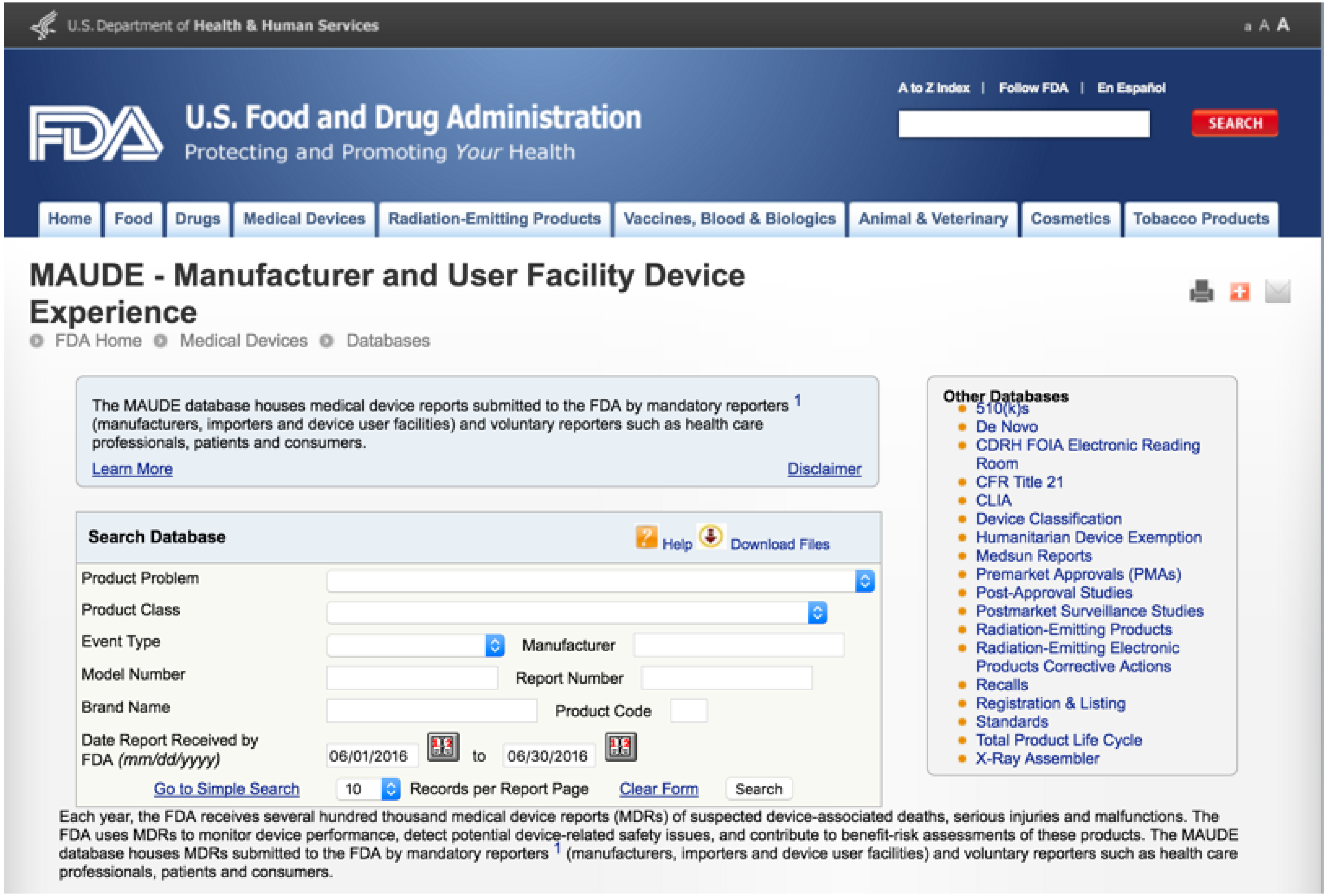
= $219

$219 x 12 = $2,628
POTENTIALLY WASTED

Toner RW, et al. Appl Health Econ Health Policy 2011;9:29-37

Case Study 3: Hemodilution



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Background: FDA MAUDE database reports a case (03P76-25) of a neonatal patient with discrepant point-of-care (POC) hemoglobin values compared to the laboratory. The POC device used a conductance-based method of hemoglobin measurement, while the laboratory used a spectrophotometric method.

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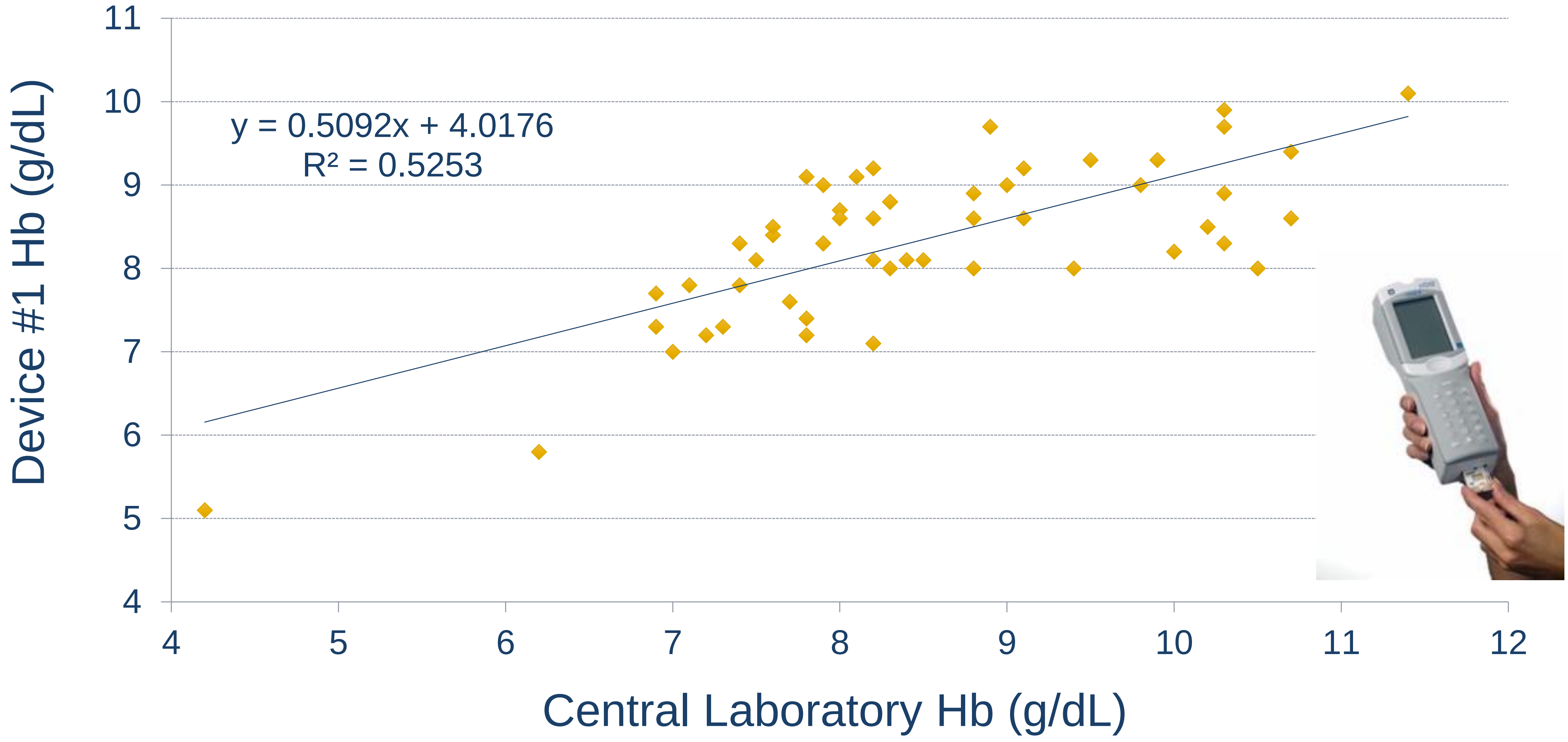
- Transfusion was stopped halfway after the laboratory reported a hematocrit of 40% and hemoglobin of 11.7 g/dL.
- Post-transfusion POC and lab hematocrit values were 45 and 50% respectively.

Analytical Performance of Optical vs. Conductance-Based Hemoglobinometry



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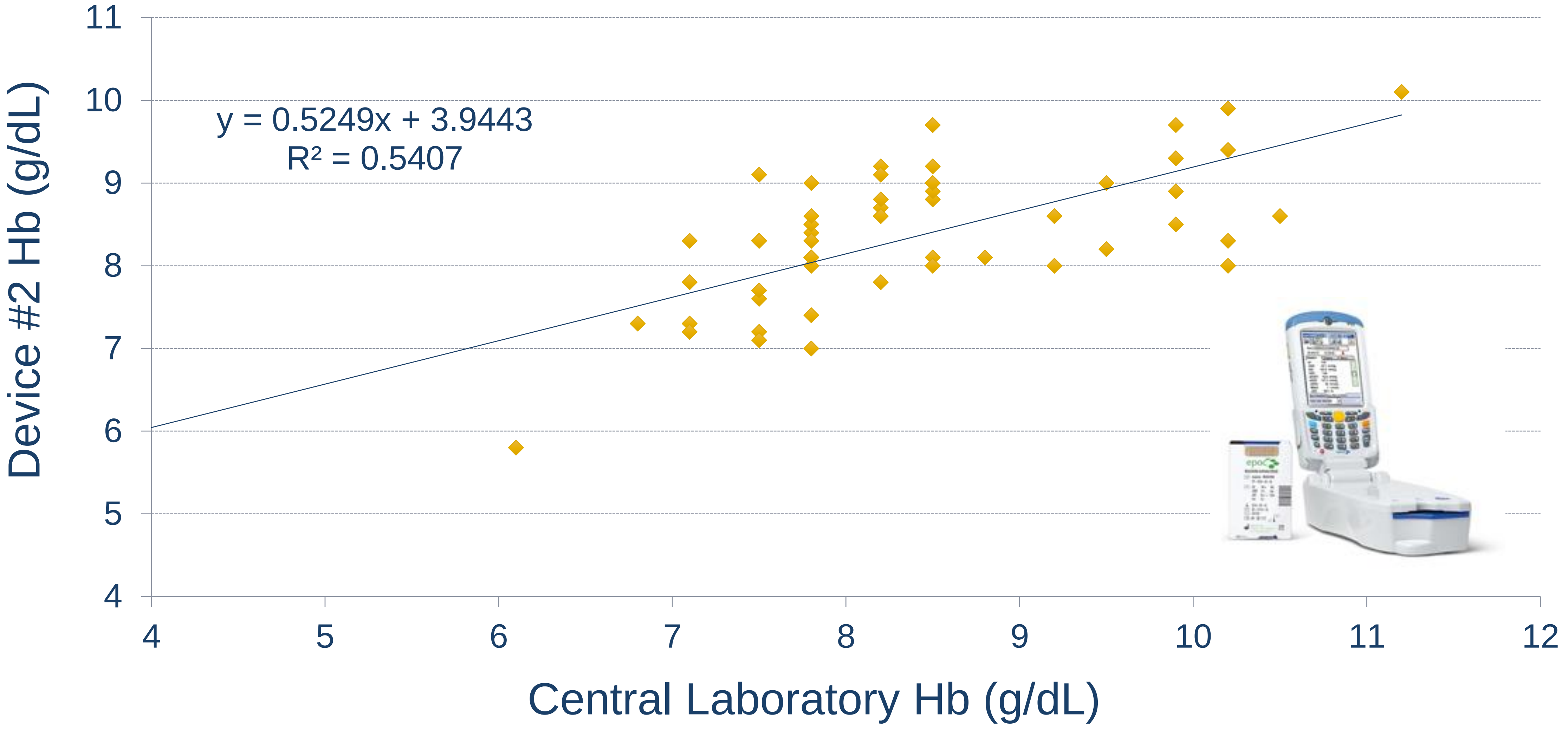

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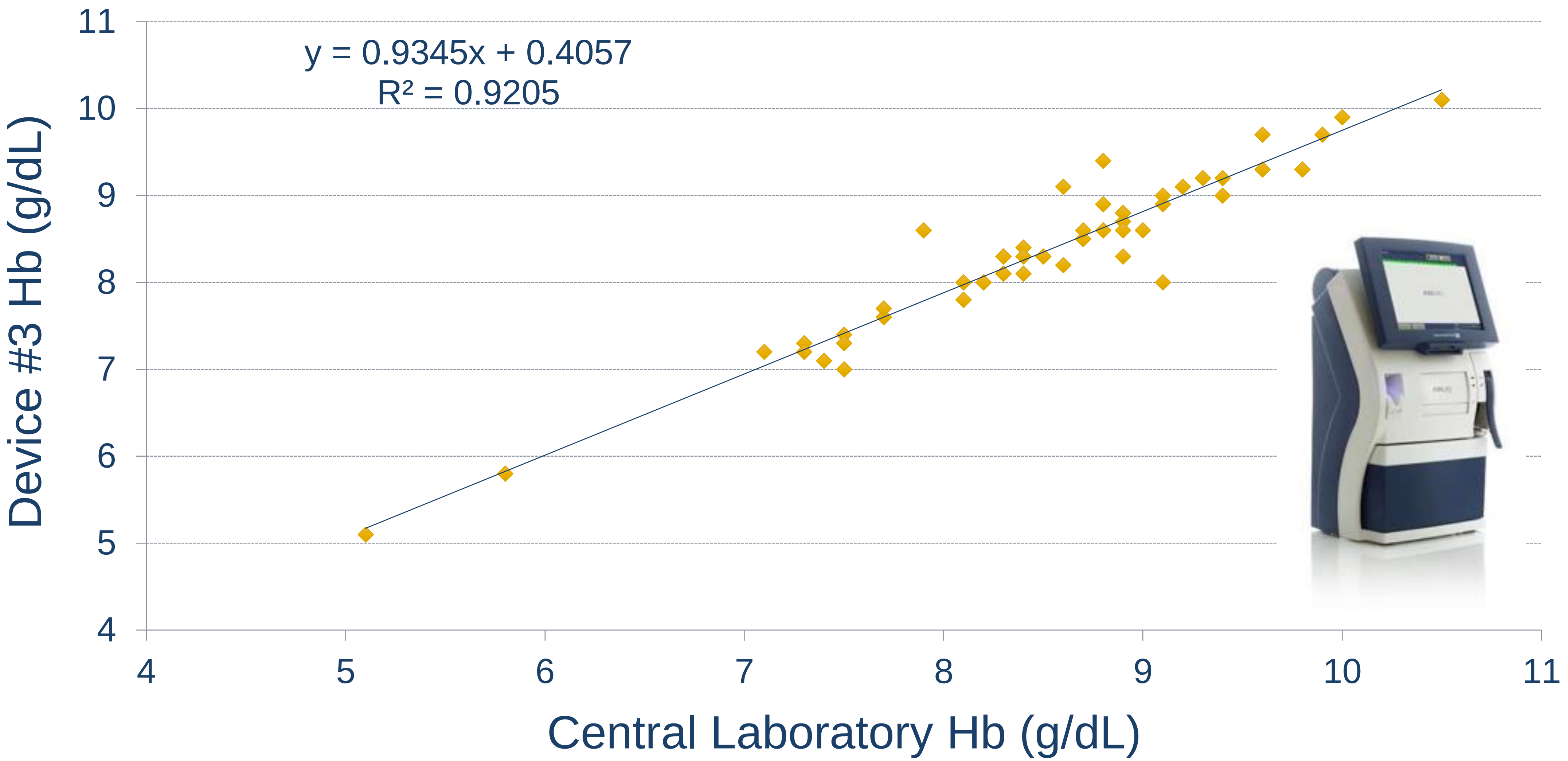

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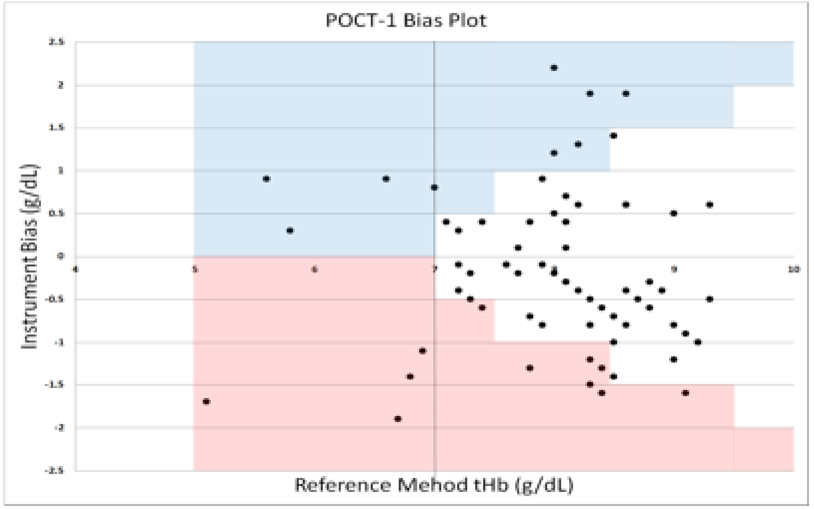

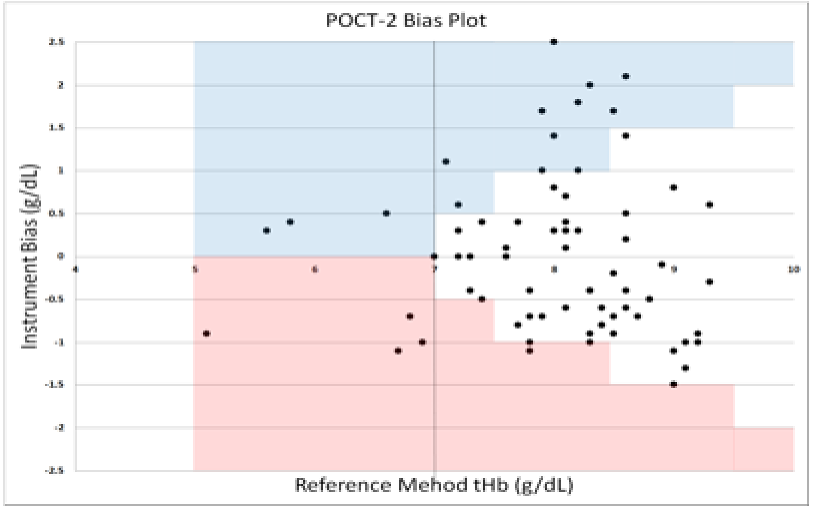

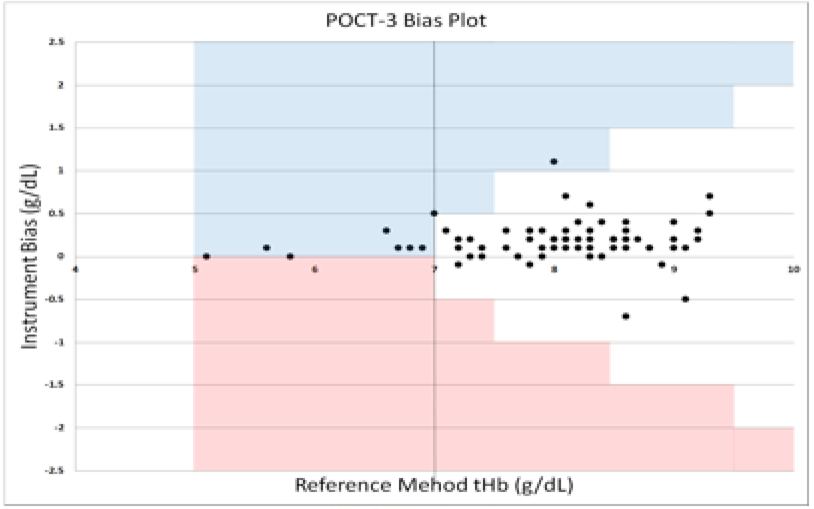

Notes: Reference Method = Beckman LH hematology analyzer

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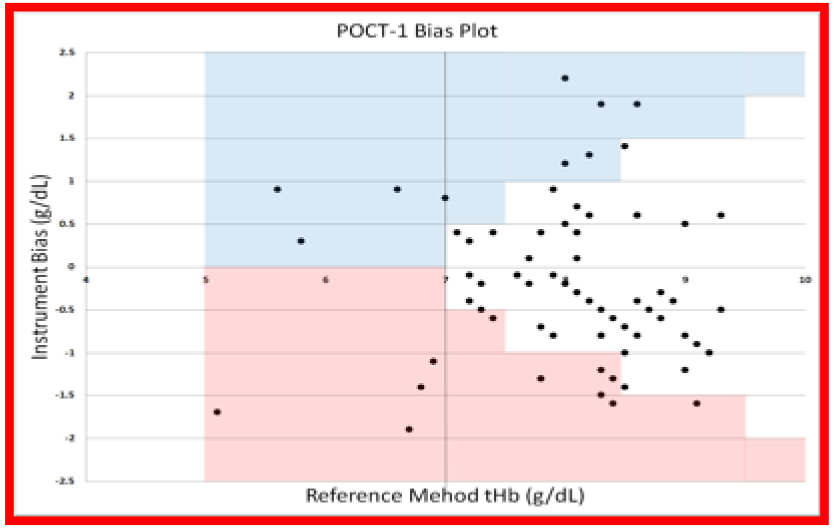

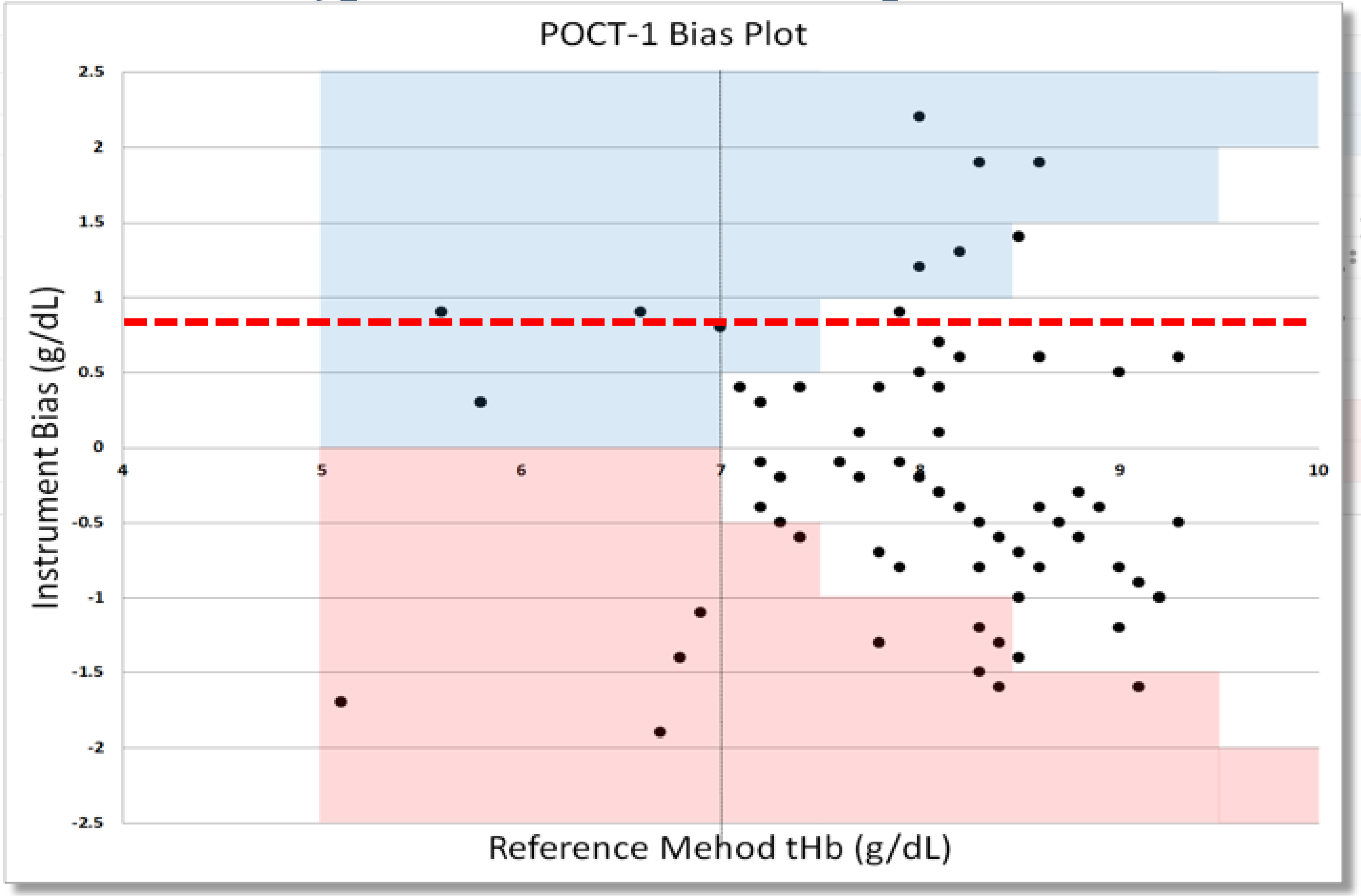

Median (IQR) Bias: 0.78 (0.78) g/dL
$P < 0.001$
N = 50

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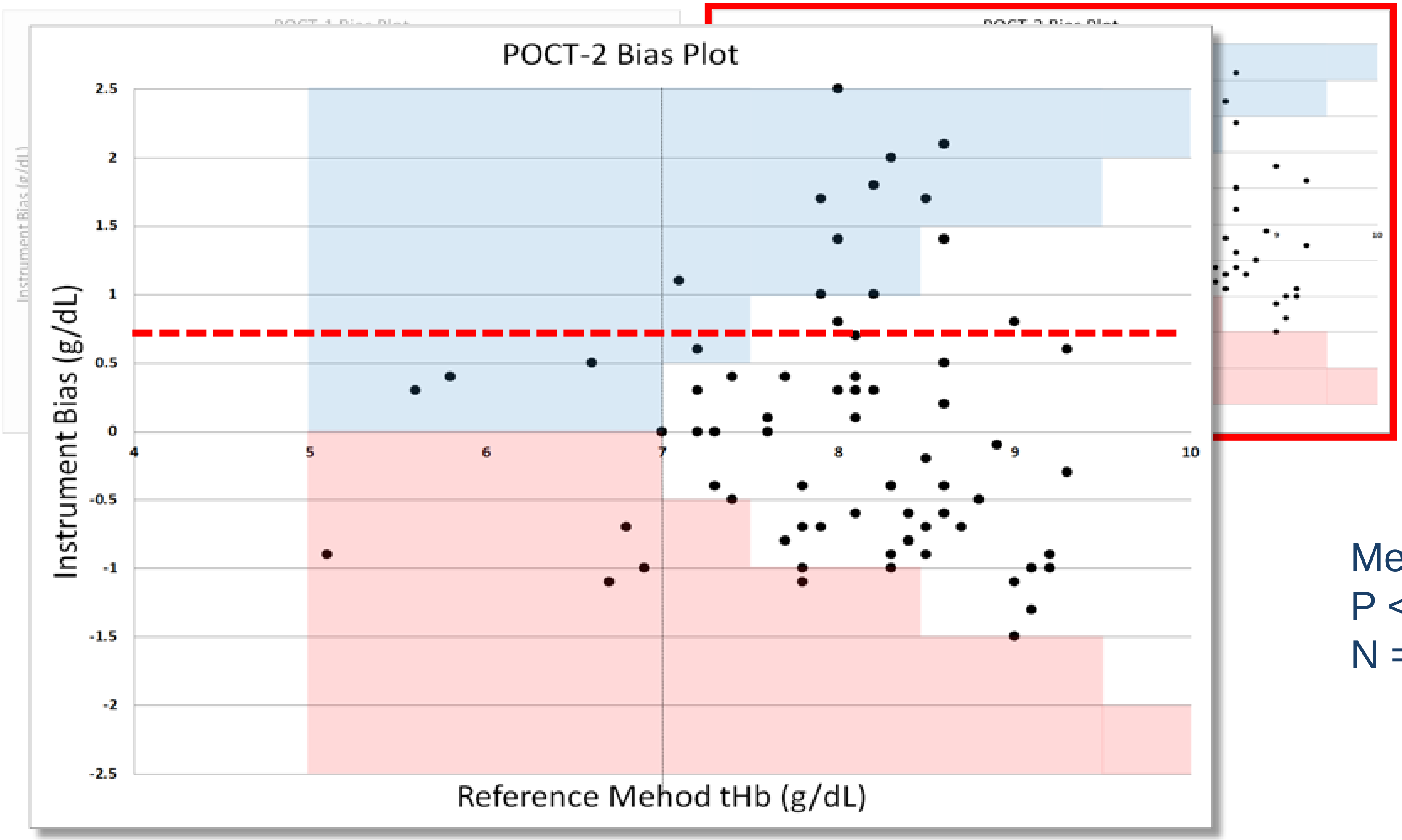

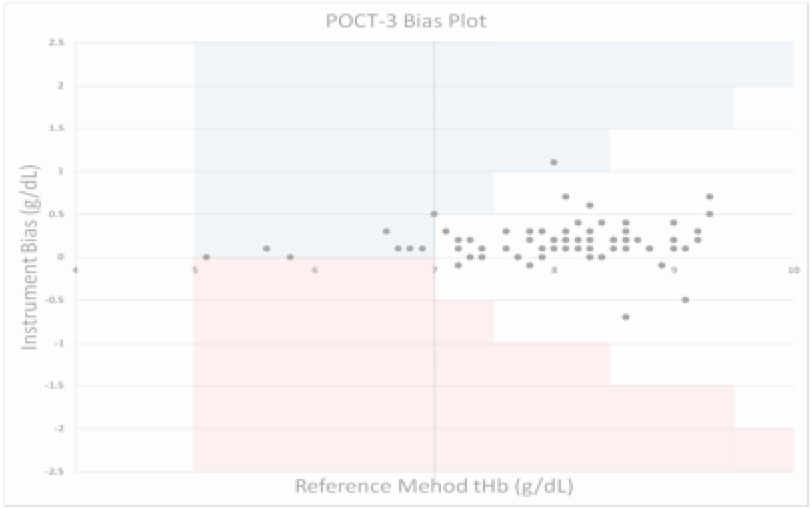

Median (IQR) Bias: 0.73 (0.60) g/dL
P < 0.001
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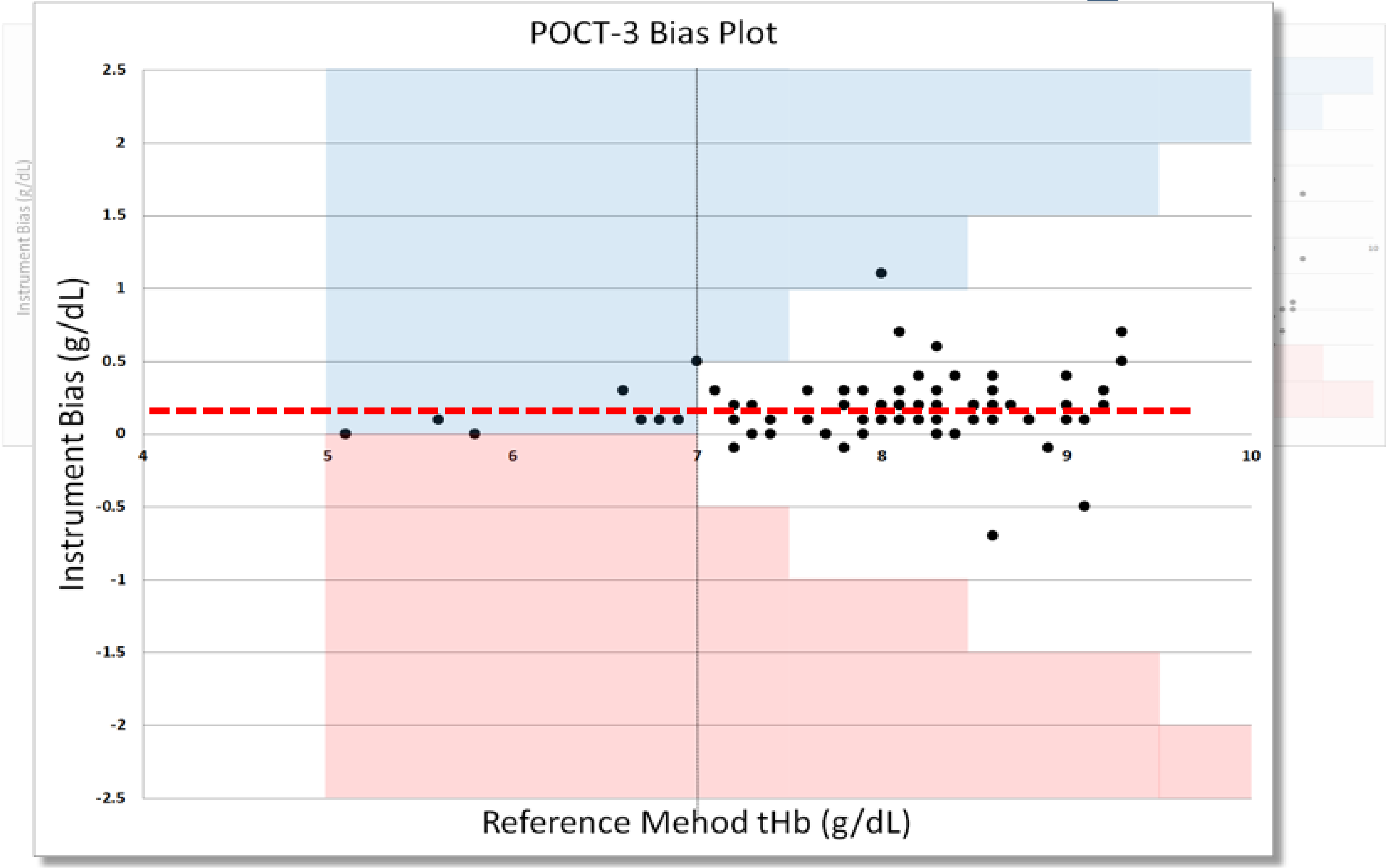

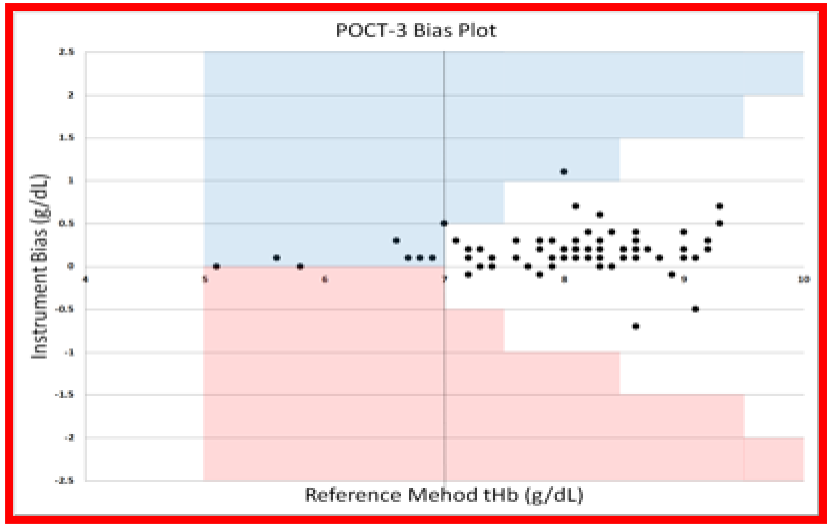

Median (IQR) Bias: 0.22 (0.20) g/dL
P = 0.510
N = 50

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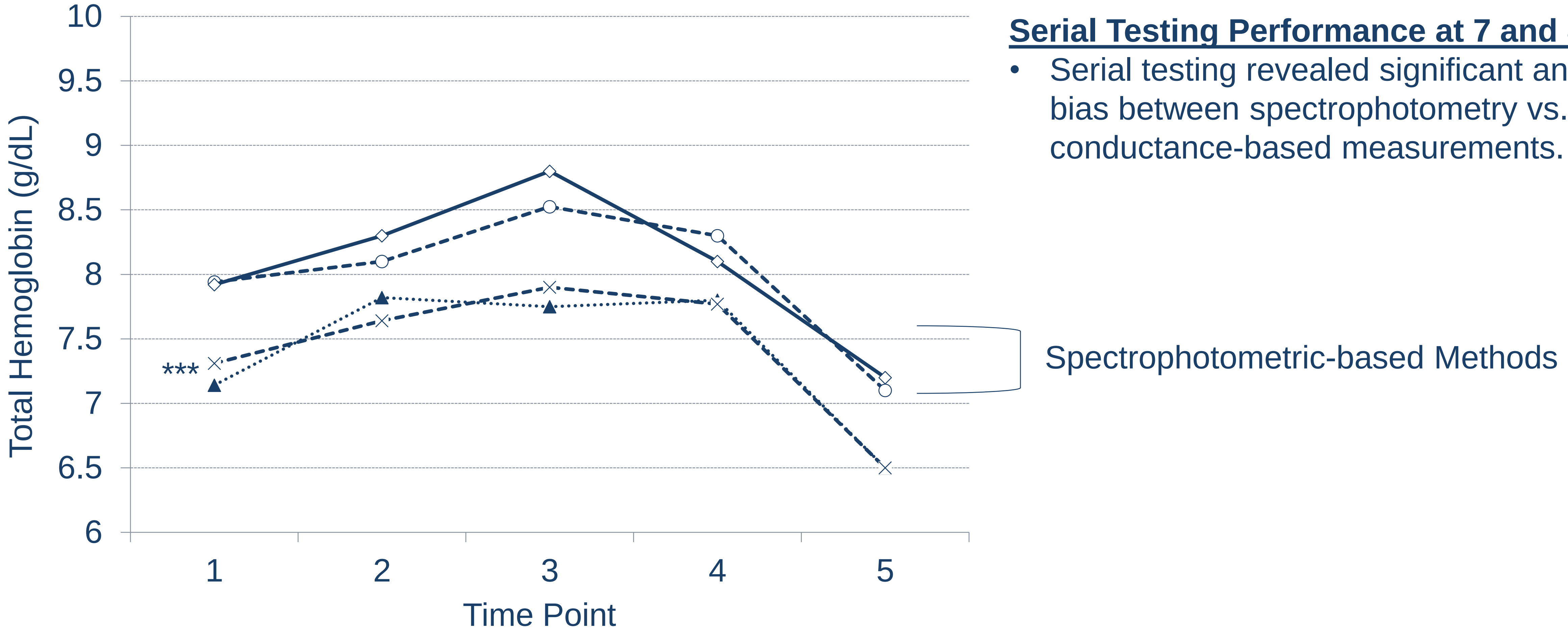
Analytical Performance of Optical vs. Conductance-Based Hemoglobinometry



Serial Testing Performance at 7 and 8 g/dL

- Serial testing revealed significant analytical bias between spectrophotometry vs. conductance-based measurements.

Notes: *** P<0.001, Central Lab = Spectrophotometric Method, n = 20 patients

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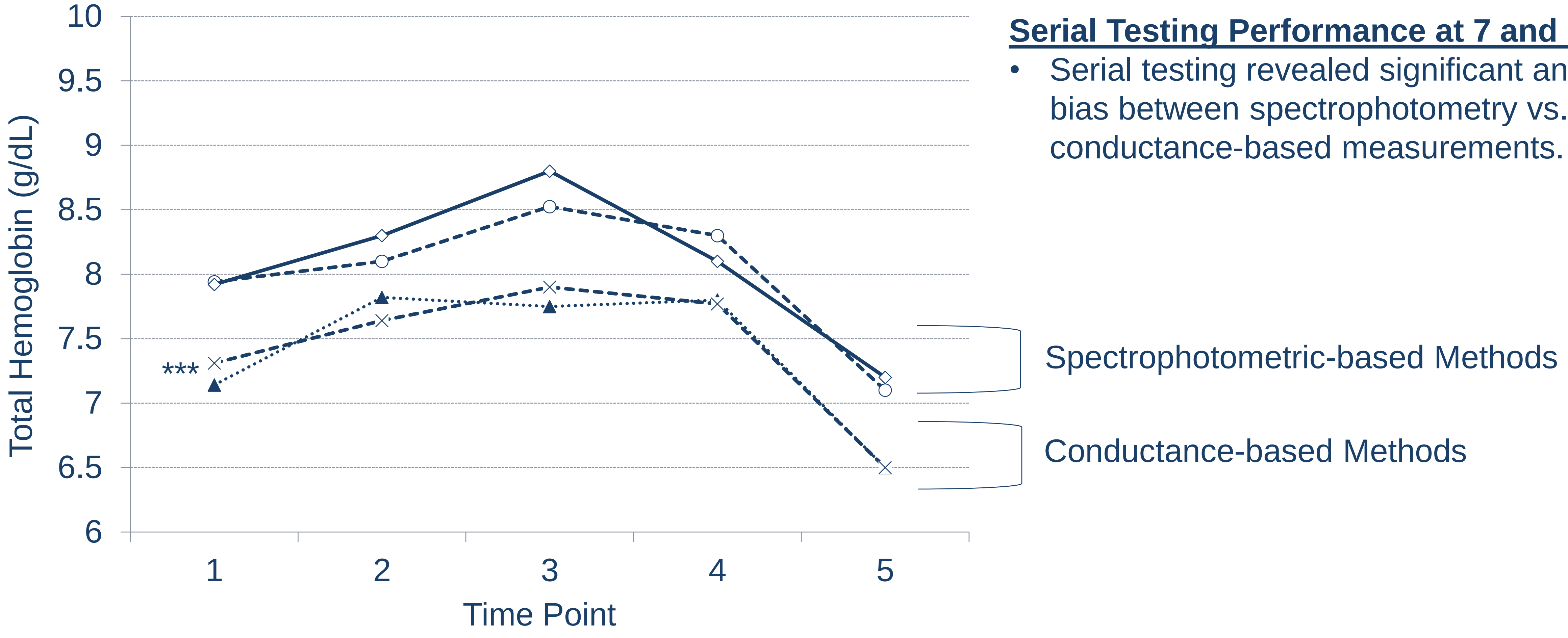

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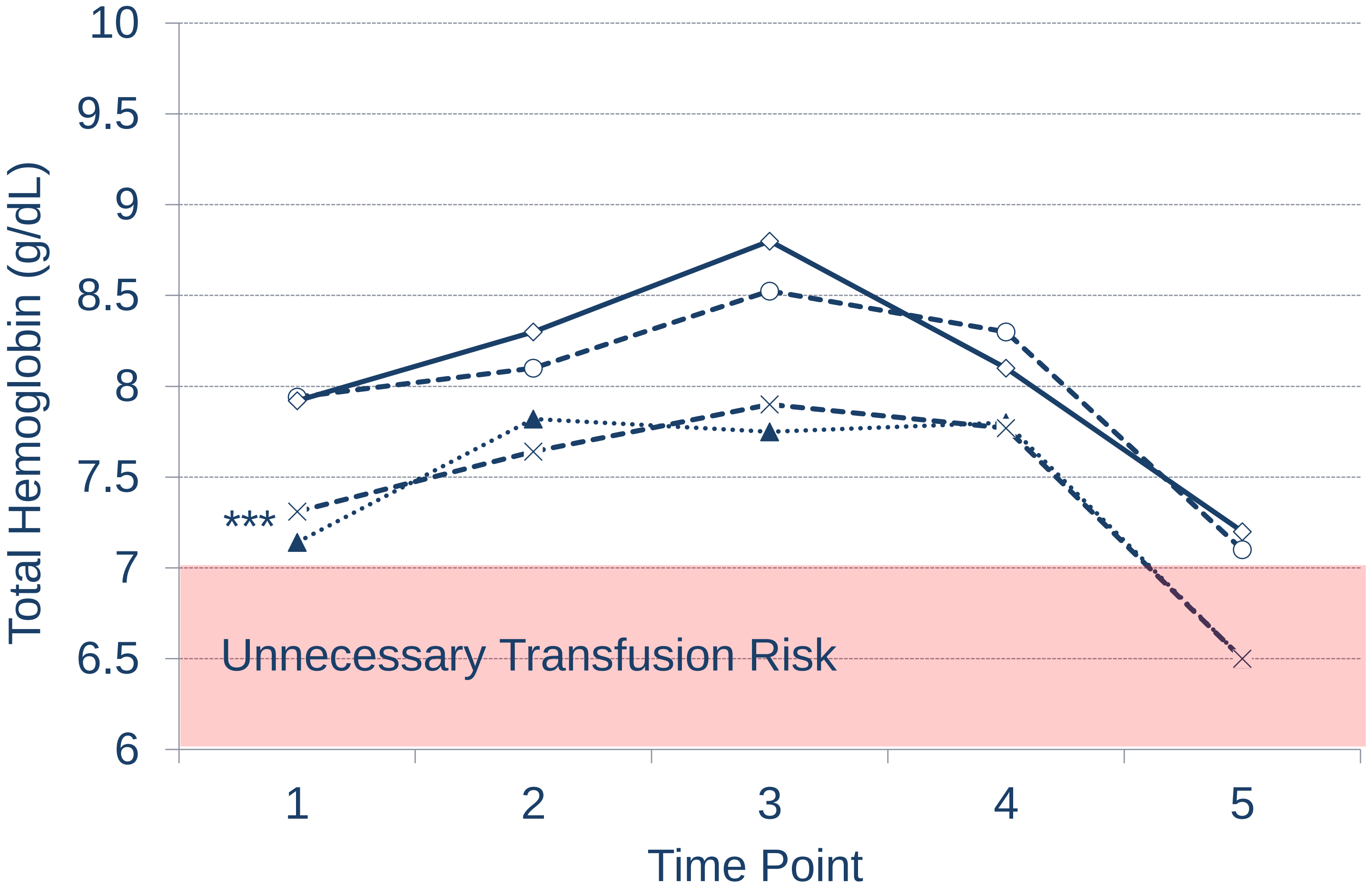

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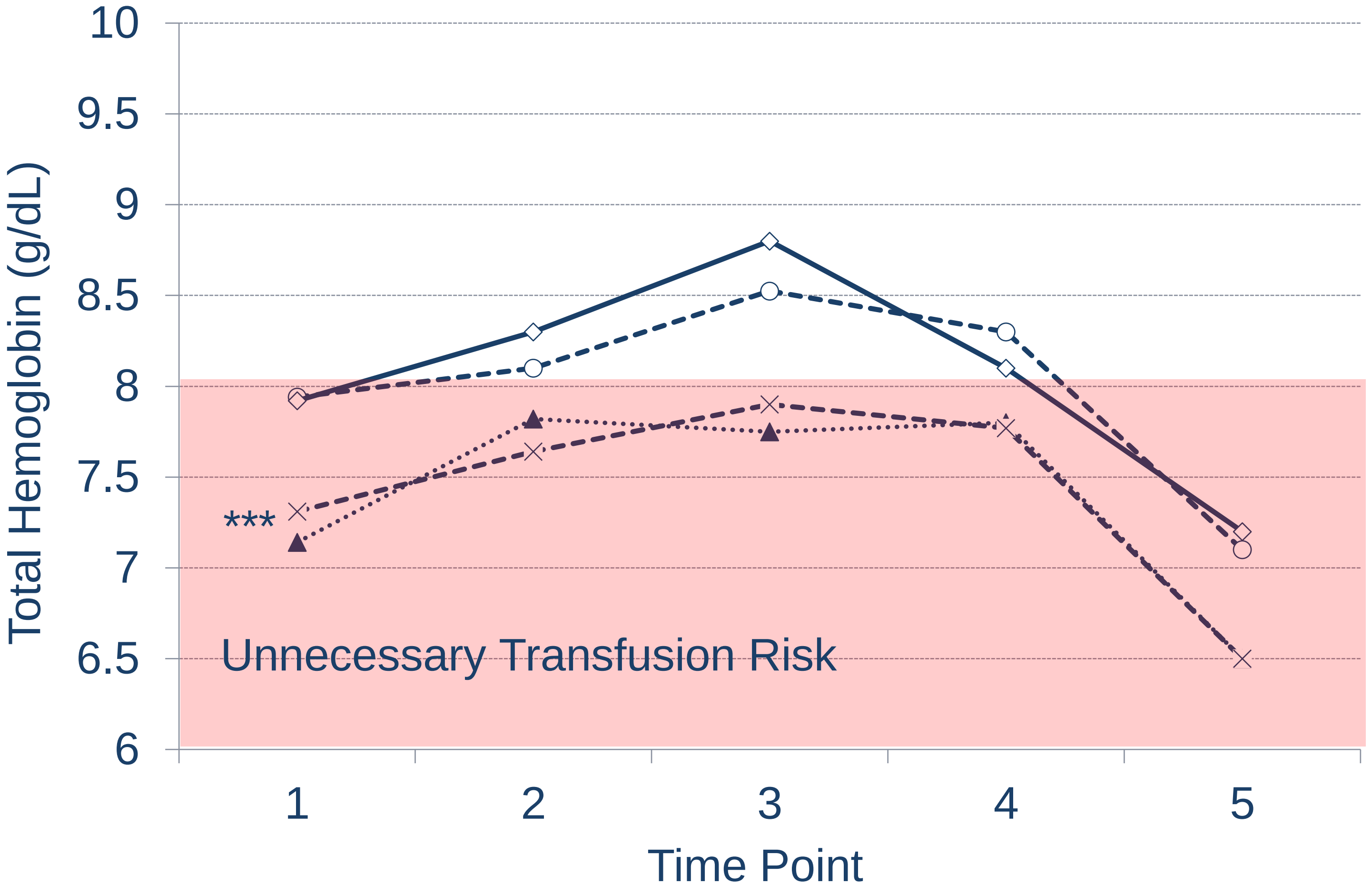

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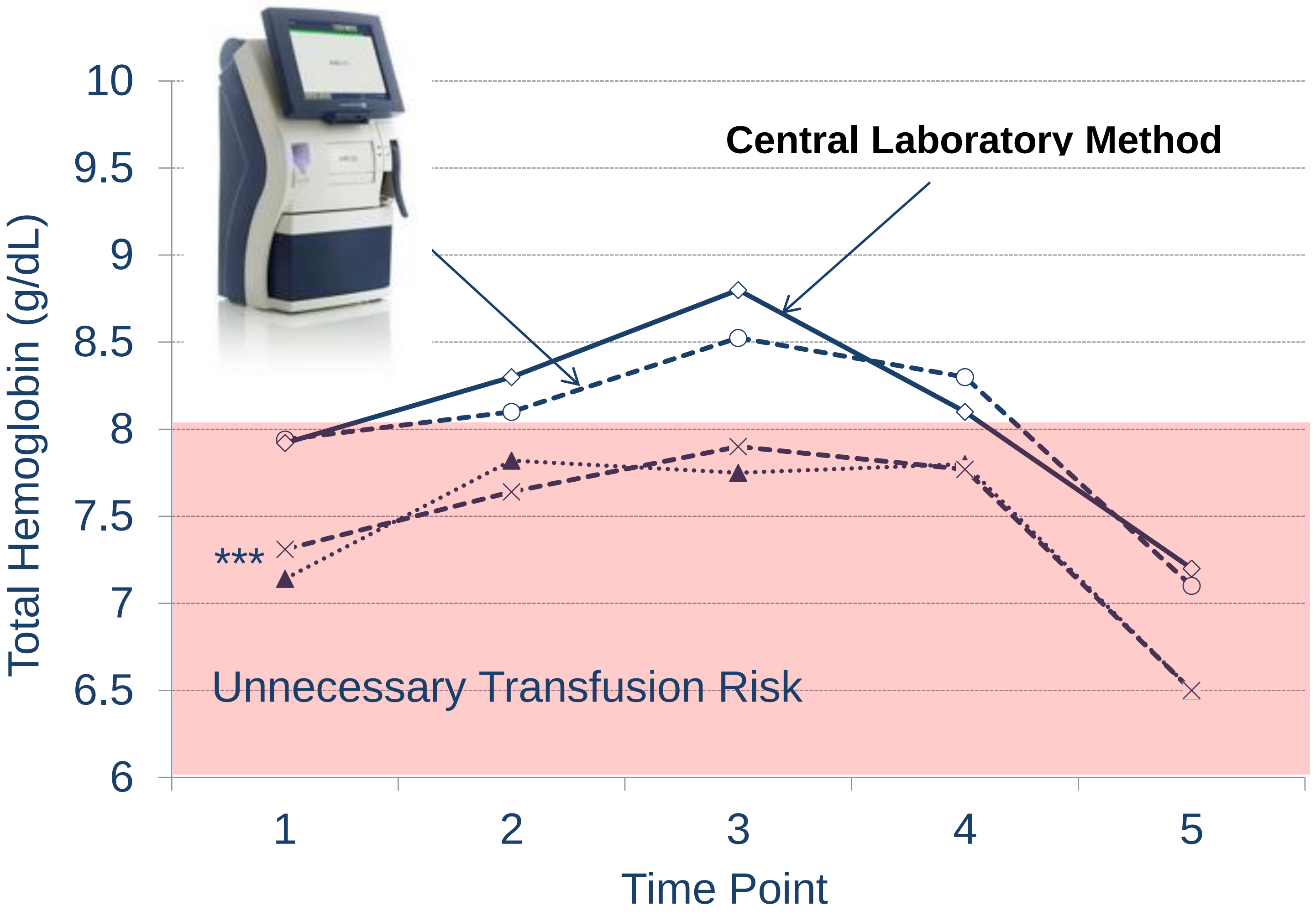

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Manufacturer and User Facility Device Experience (MAUDE) Database Summary


	Device 1	Device 2	Device 3
Timeframe	2011-2016	2011-2016	2014-2016*
Erroneous Results	8	0	0
Improper Transfusions	5	0	0

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/results.cfm, Accessed on July 19, 2016

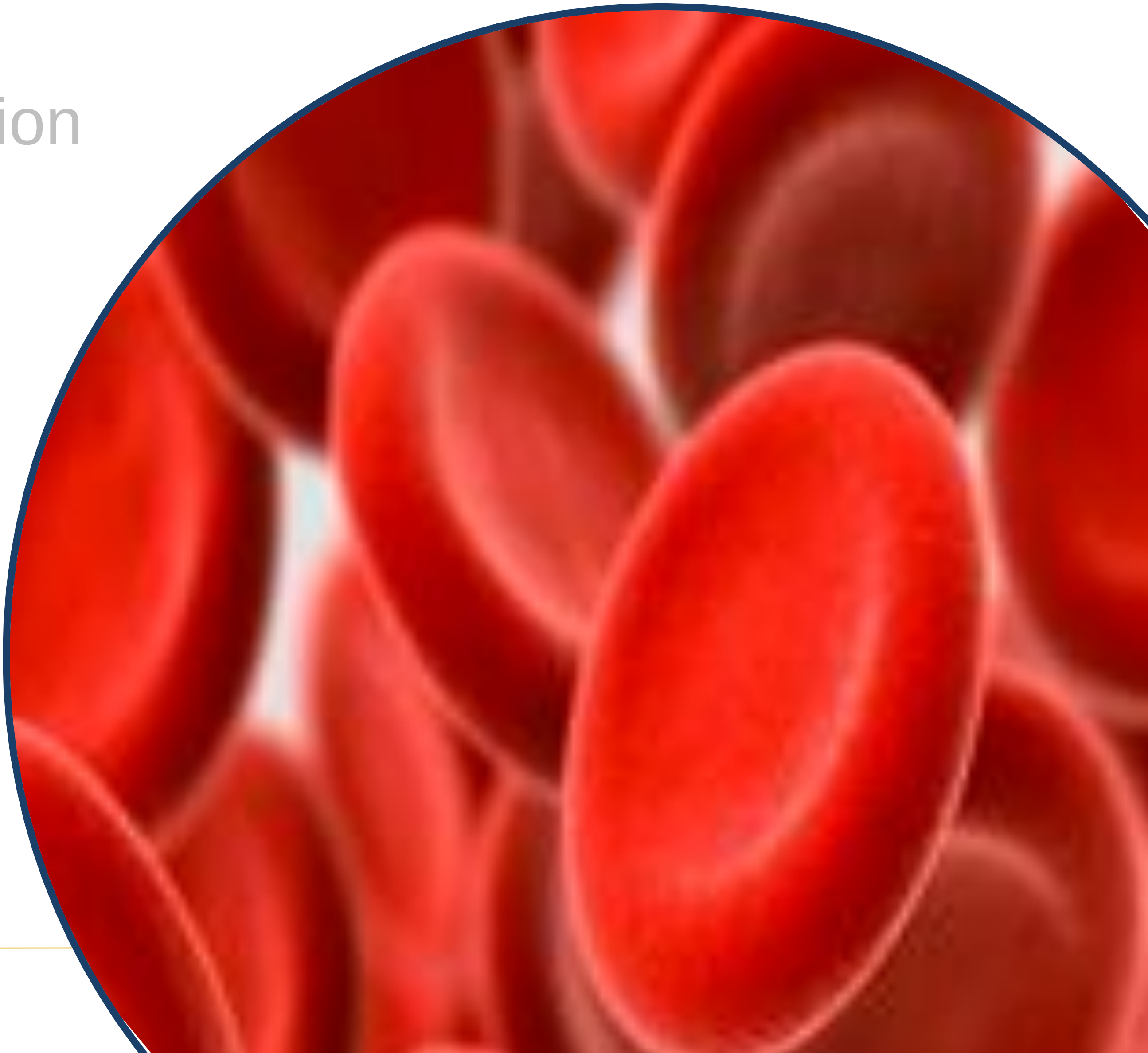
INTERFERENCES IN WHOLE BLOOD ANALYSIS

Air Contamination

Delayed Testing

Hemodilution/Hemoconcentration

Hemolysis



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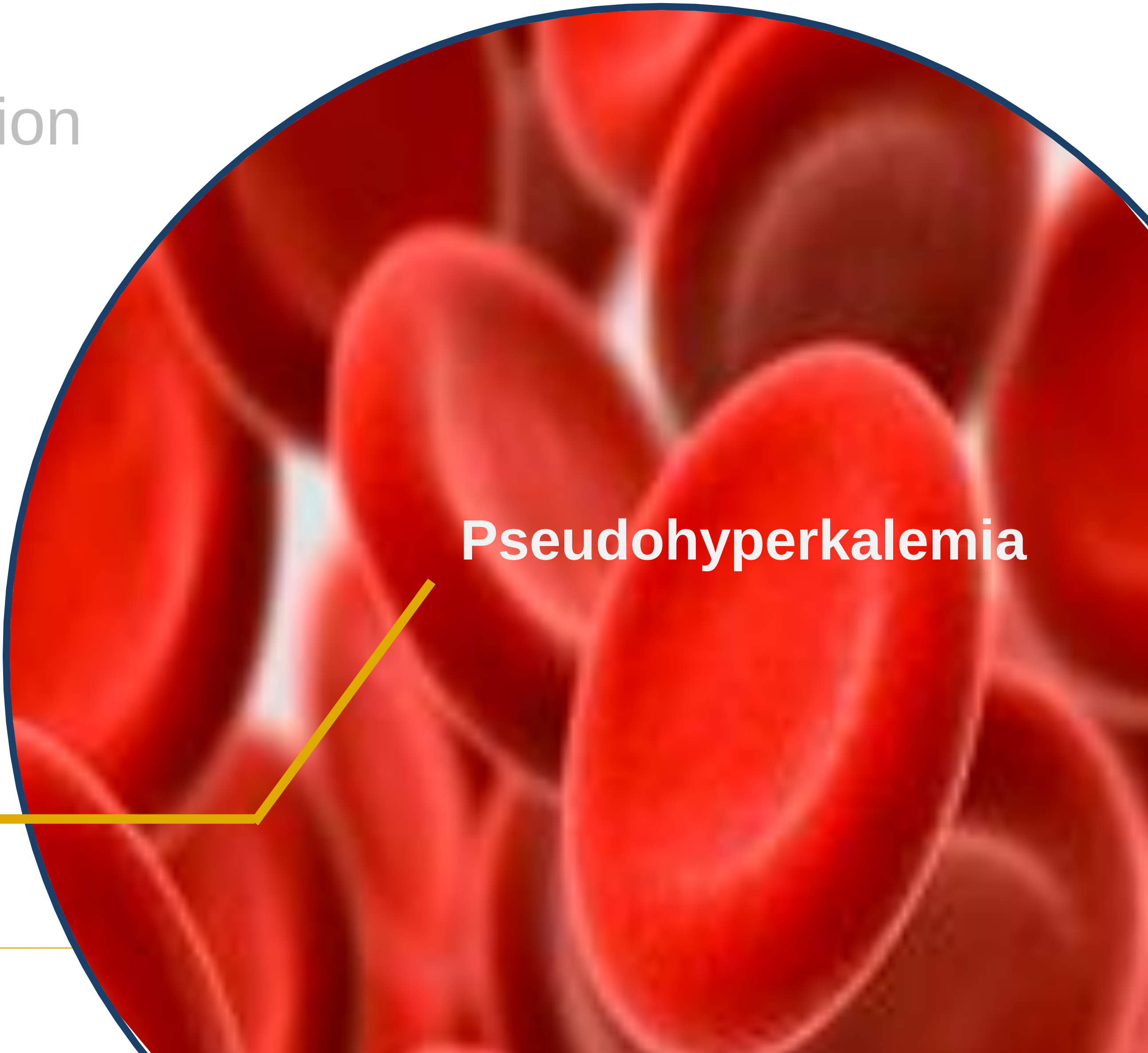

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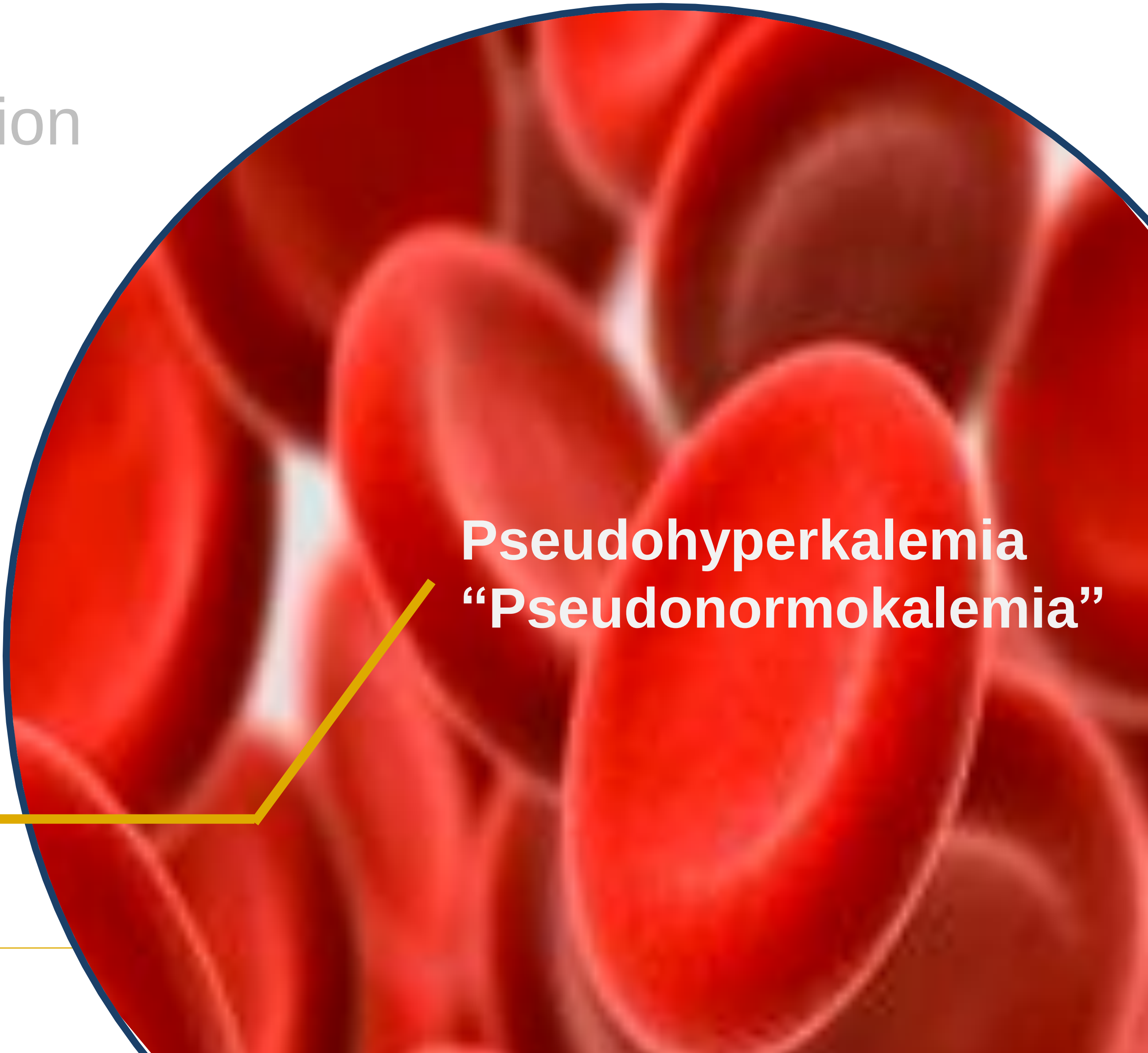

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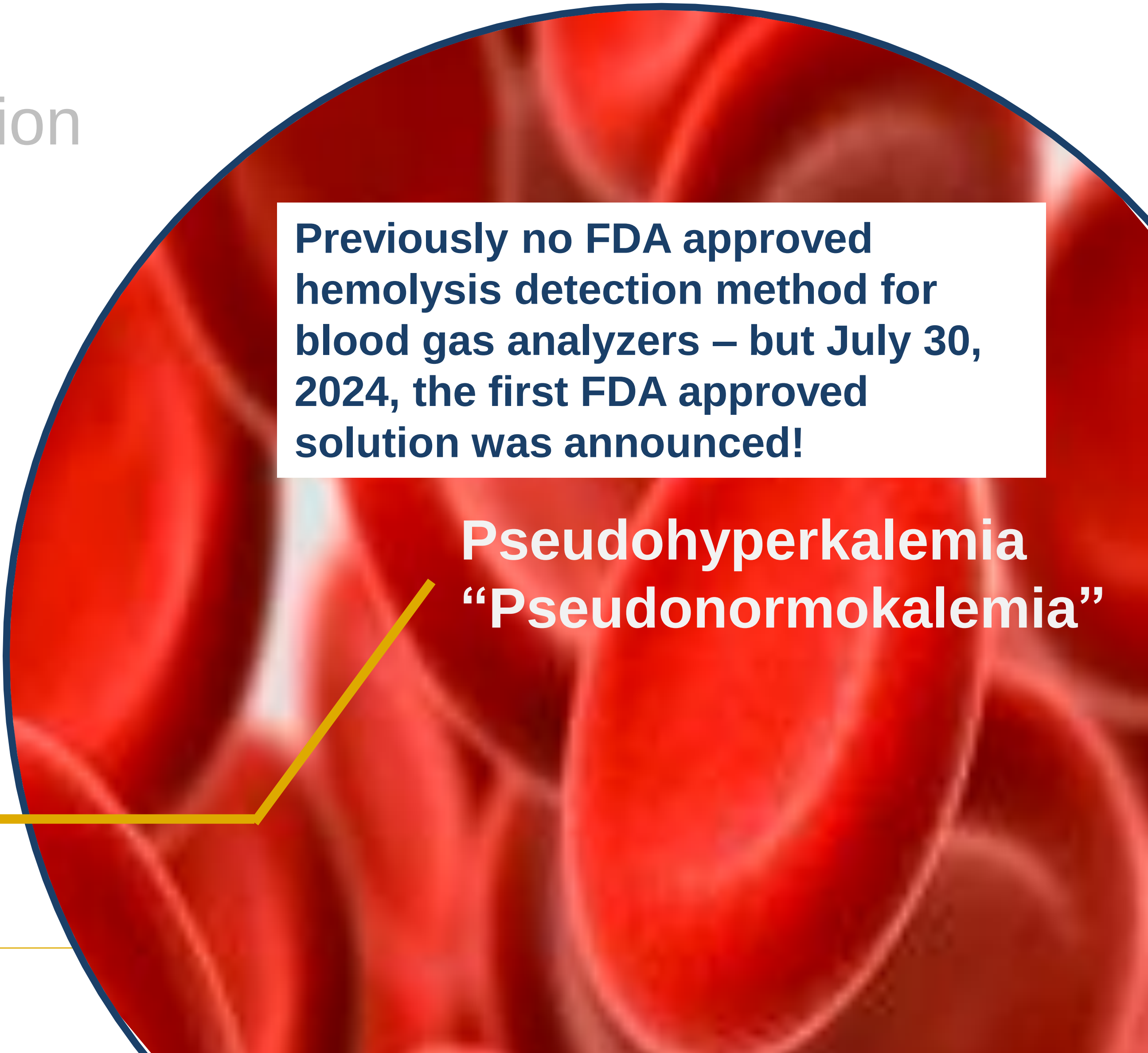
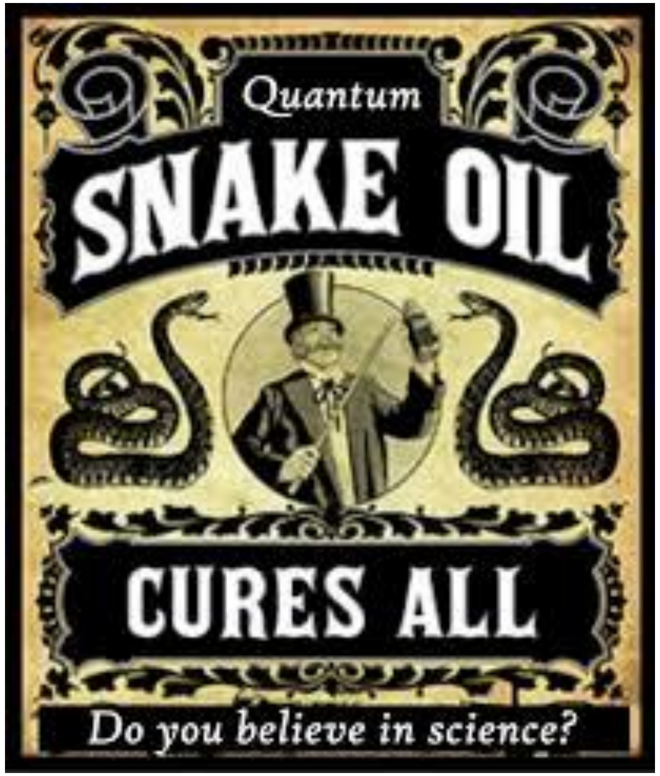


Previously no FDA approved hemolysis detection method for blood gas analyzers – but July 30, 2024, the first FDA approved solution was announced!

Pseudohyperkalemia
“Pseudonormokalemia”

Biotin: The “Snake Oil” of 2018?



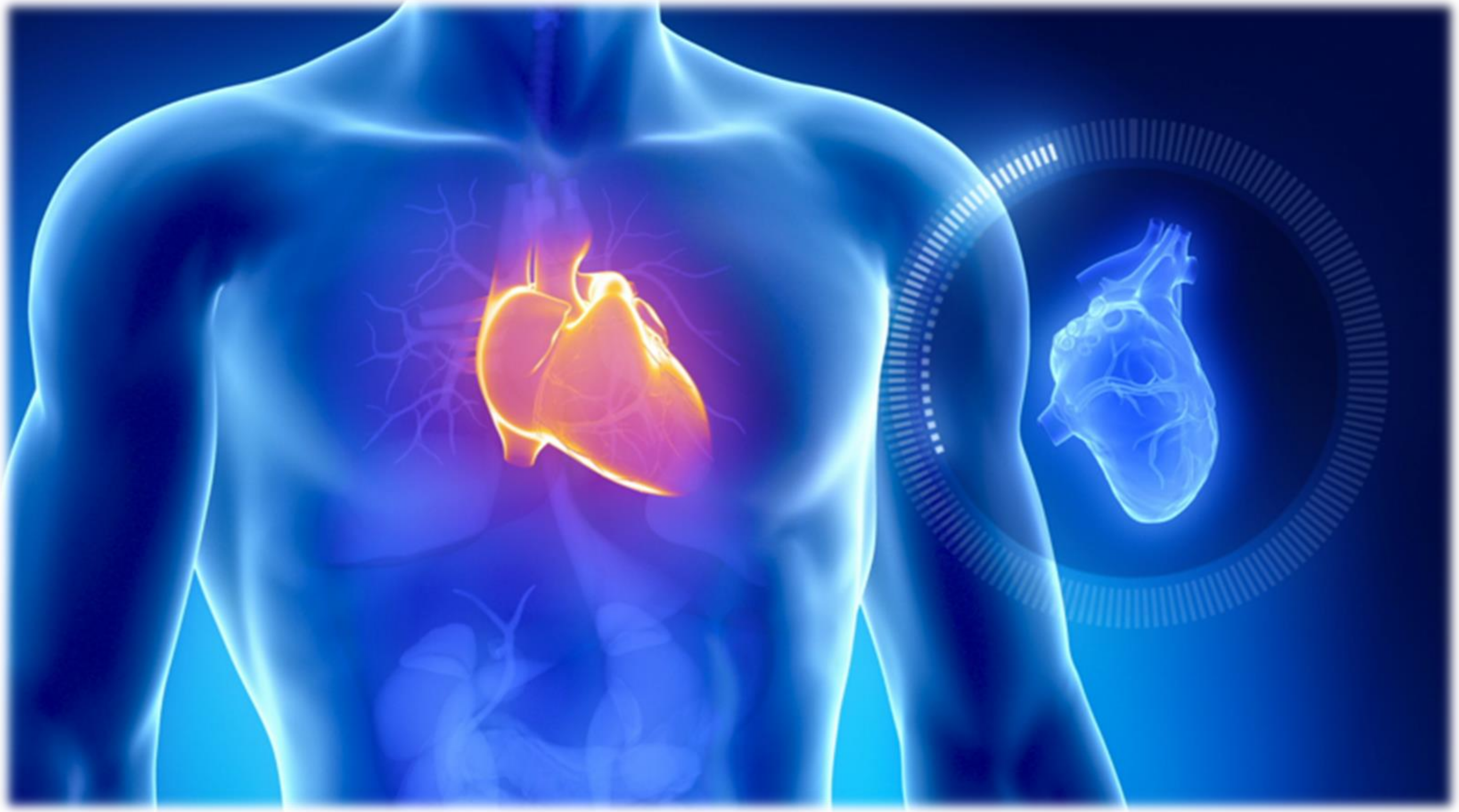
The FDA Warns that Biotin May Interfere with Lab Tests: FDA Safety Communication

Date Issued: November 28, 2017

Product:

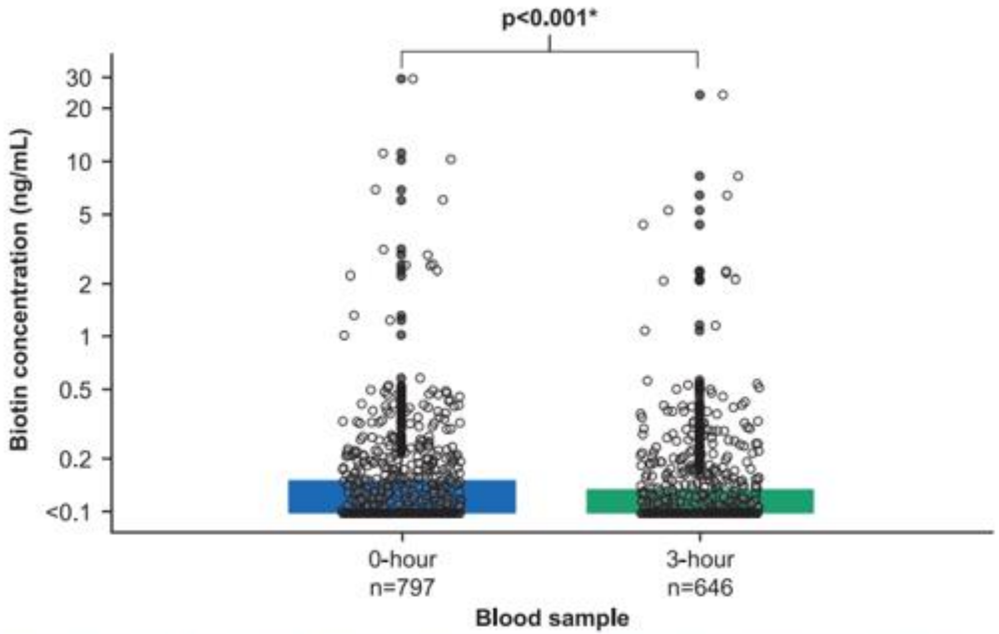
Many lab tests use biotin technology due to its ability to bond with specific proteins which can be measured to detect certain health conditions. For example, biotin is used in hormone tests and tests for markers of cardiac health like troponin. Biotin, also known as vitamin B7, is a water-soluble vitamin often found in multi-vitamins, prenatal vitamins, and dietary supplements marketed for hair, skin, and nail growth.

Biotin and Cardiac Troponin Testing



Estimating the Probability of Biotin Interference

- 1,443 Gen 5 troponin T samples tested (0-hour, n = 797; 3-hour, n=646) from 850 patients.



*There was a statistically significant difference between 0-hour and 3-hour biotin concentrations ($p<0.001$; paired Wilcoxon rank sum test).

Mumma B, et al. AACC Poster Presentation 2018

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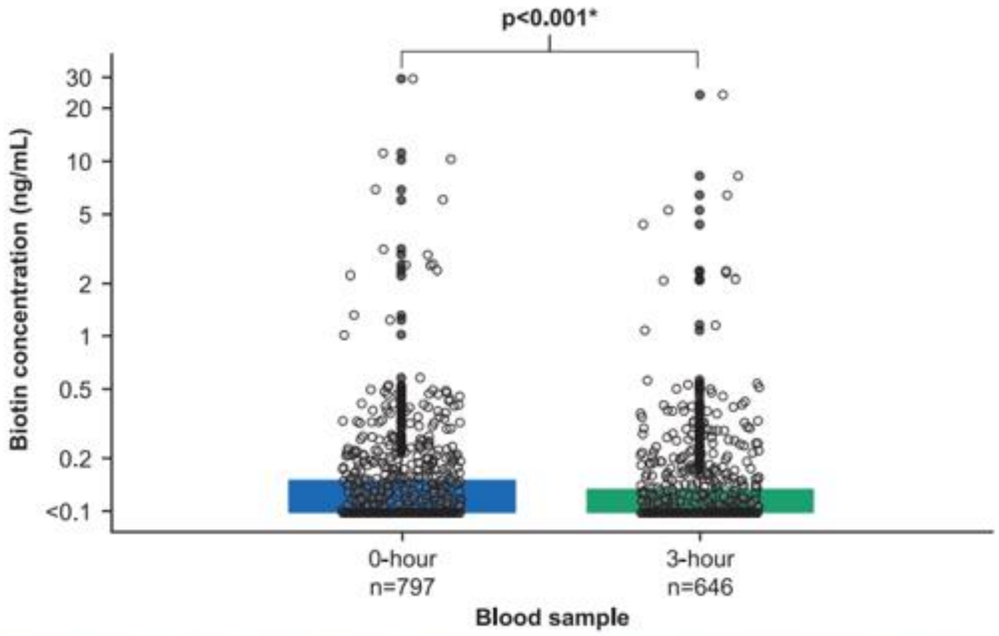

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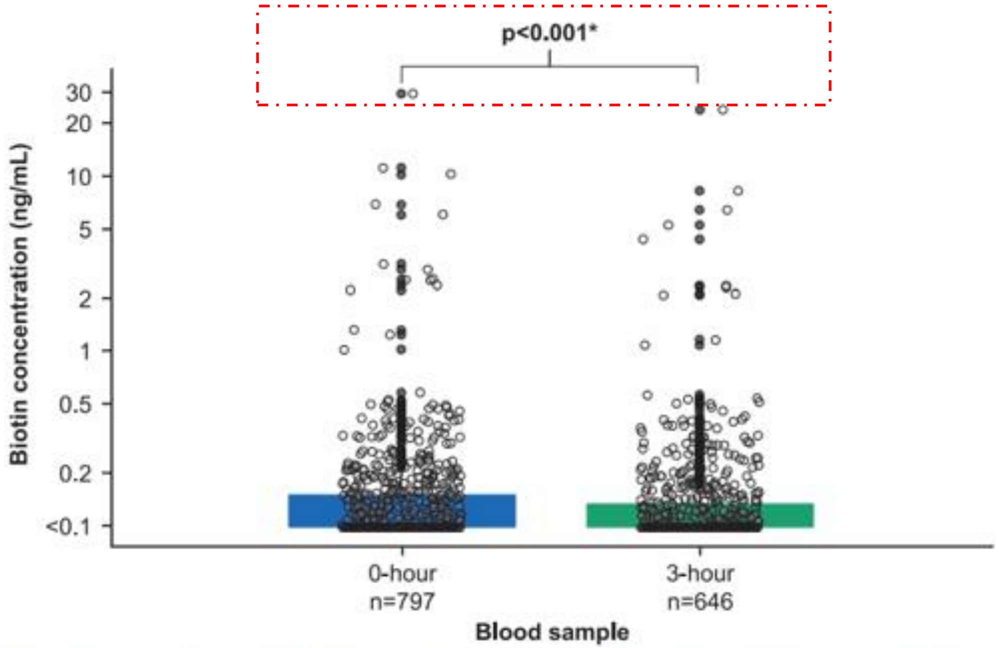
- Biotin not detectable in 471 (59%) and 399 (62%) 3-hour samples.
- Only one 0-hour sample and one 3-hour sample had biotin >20 ng/mL (0.13% [95% CI: 0-0.7%]).



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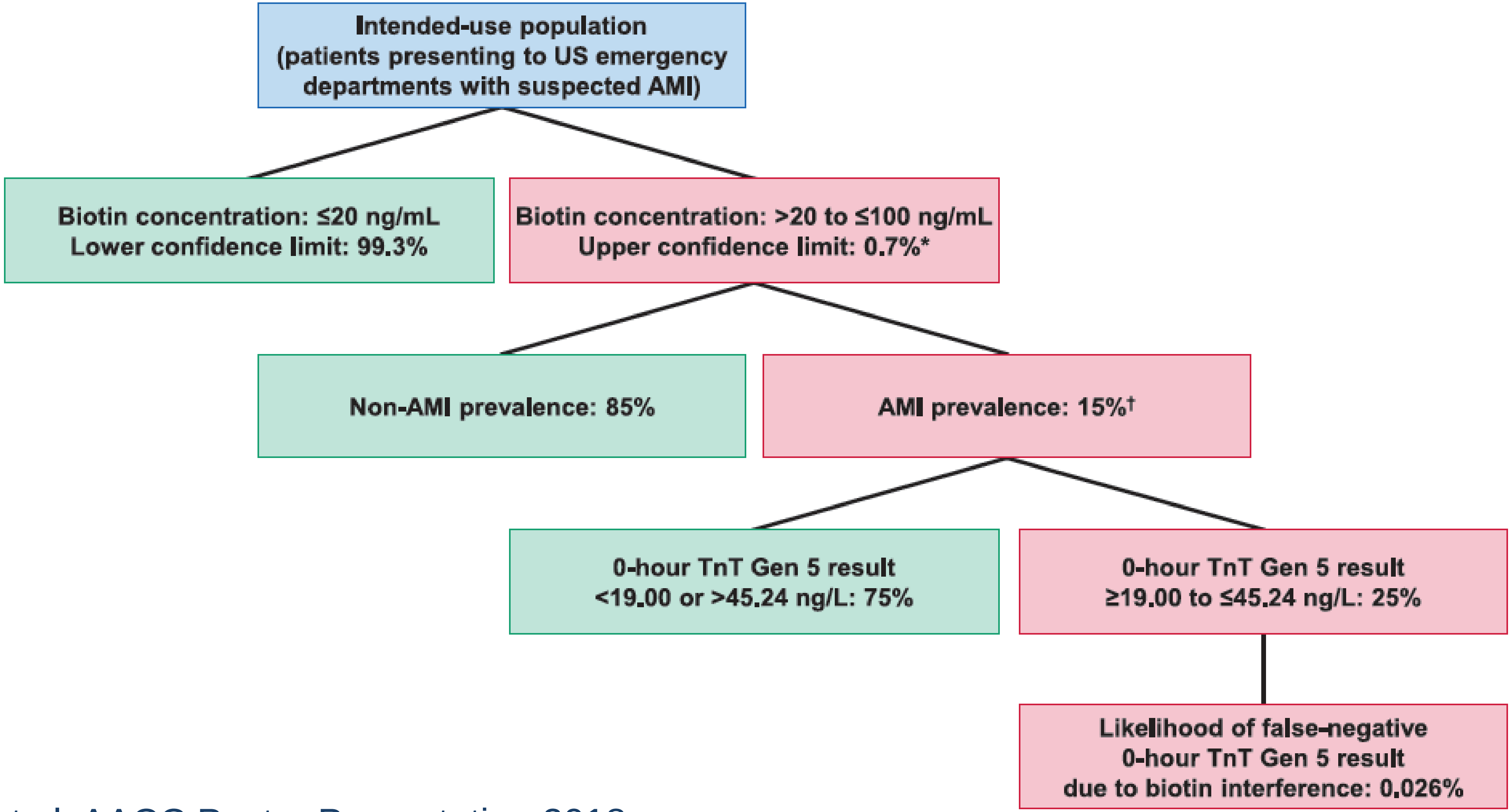

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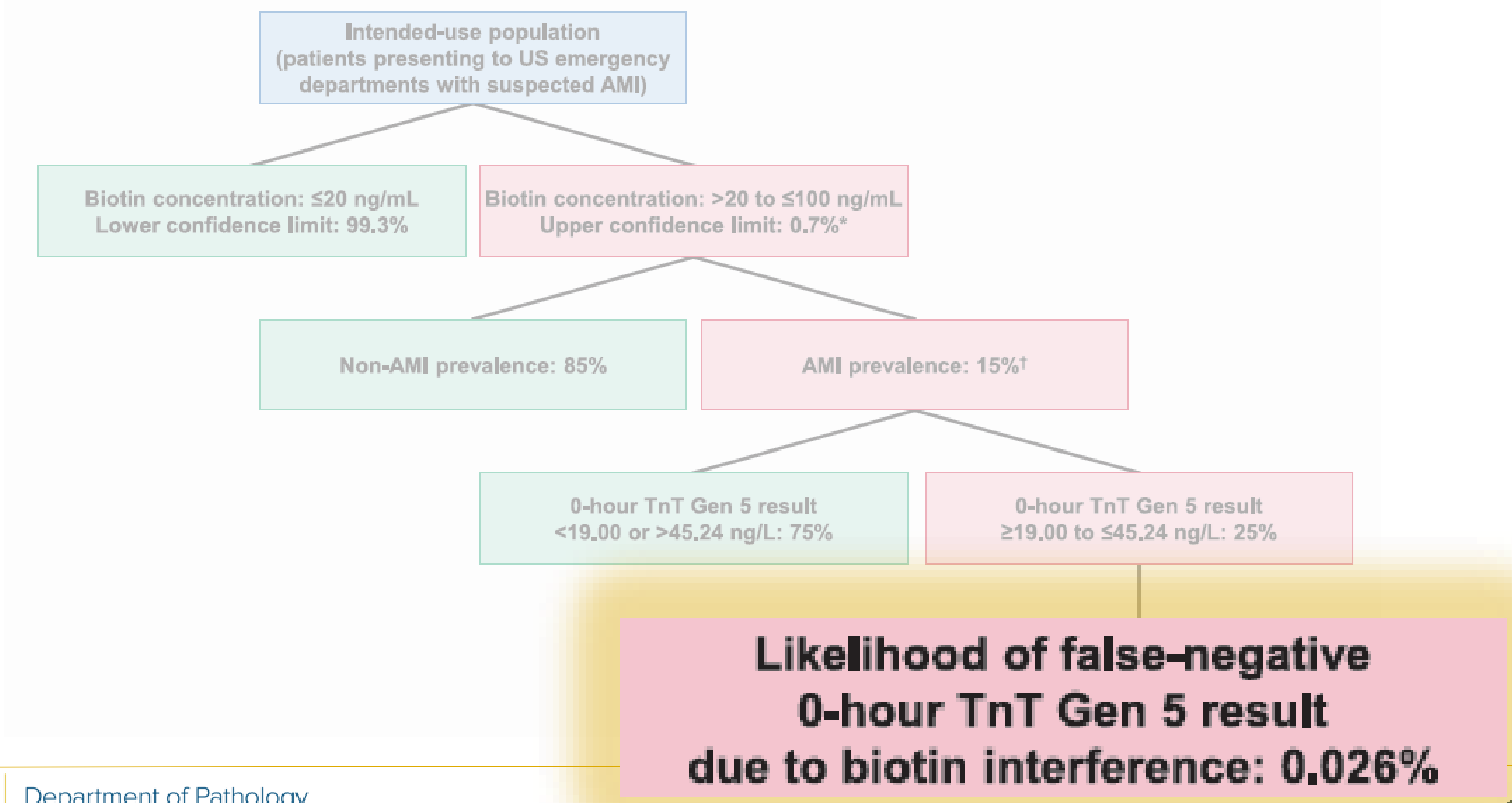

UC Davis Cardiac Troponin Patients

Adult ED Patients with Unknown Biotin Status: **540**

Average Plasma Biotin: 1.15 (0.97) ng/mL

Specimens collected as part of clinical validation

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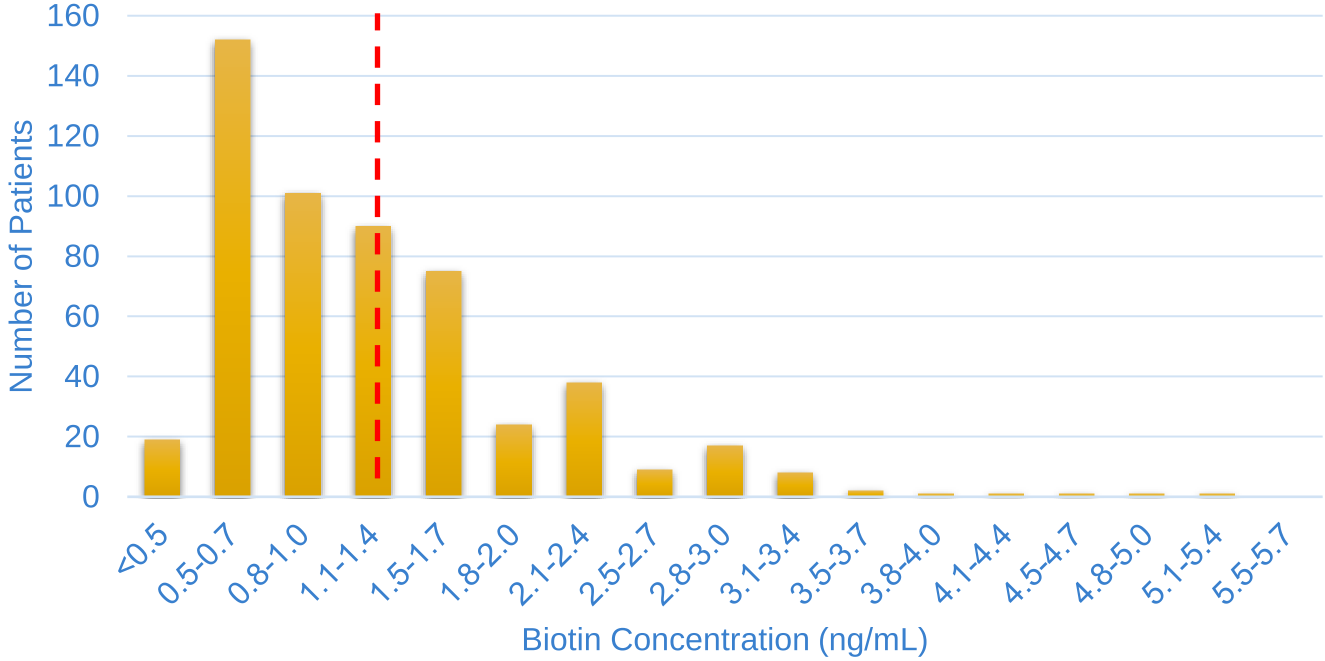

Gen 5 TnT Biotin Interference Threshold is 20 ng/mL

Biotin quantified by GC-TOF-MS

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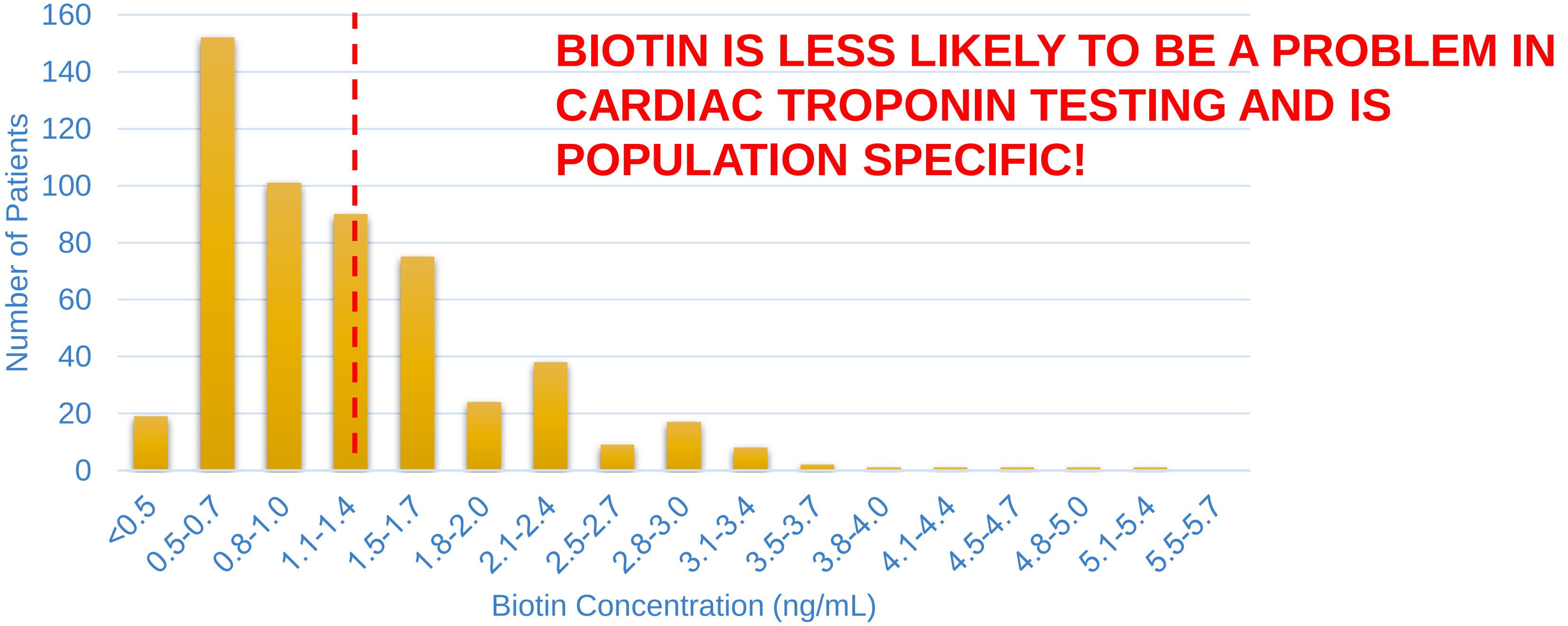

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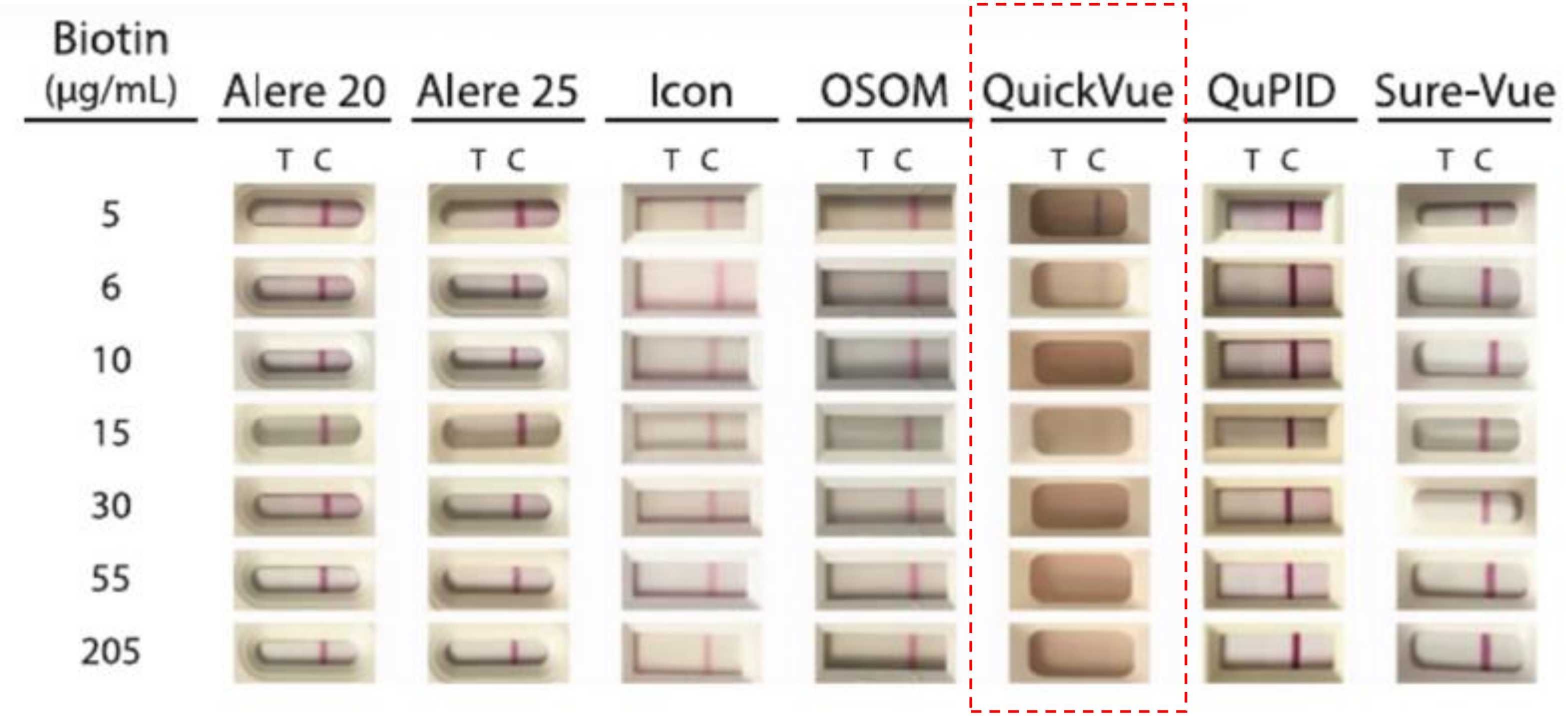
Biotin and Urine Pregnancy Testing

Biotin Interference with Urine Pregnancy Tests



- Recent studies show some point-of-care urine pregnancy tests were affected by biotin.
- Biotin is cleared by the kidneys.
- In this study, the QuickVue urine pregnancy test exhibited interference as low as 6 microgram/mL of urine biotin!

Williams G, et al. Clin Biochem 2018;53:168-170

Best POCT Practices for Mitigating Interfering Substances

POCT Best Practices for Interferences

- **Education:** The laboratory must be the leader in educating providers **and patients** of potential test interferences. Go to grand rounds, build partnerships, and provide multi-modality means to disseminate knowledge.

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- **Electronic Early-Warning Systems:** Leverage electronic solutions. Ordering of susceptible tests could flag both on the provider and laboratory side certain substances are identified.

Conclusions

- Interfering substances are out there and impact POC testing as much as traditional lab testing!
- Interferences in common POC devices such as glucose meters have resulted in injury and death.
- Interferences in whole blood analysis have resulted in inappropriate treatment decisions.
- Medications and supplements may also affect POC immunoassays such as urine pregnancy tests.
- Education and awareness is critical to minimizing errors associated with interfering substances.

Questions?