New era in point-of-care glucose testing in the hospital: regulatory changes and clinical significance

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Disclosure

Evangelos Ntrivalas, MD, PhD, is a paid employee of Nova Biomedical, a designer and manufacturer of whole blood diagnostic technologies.

This presentation is intended to be educational and free from commercial content.

Objectives

- Discuss the new regulatory requirements for bedside glucose measuring systems (BGMS) in hospitals
  - Why FDA has new requirements for BGMS testing on critically ill
  - Glucose meter performance issues created the need for new FDA regulations
- Define the problems caused by glucose meter inaccuracy
- Describe the new FDA regulatory solution and present the clinical evidence supporting the new critical care approval
- What are the restrictions related to “off-label” use of BGMS on critically ill patients.

How are glucose meters used in the hospital?

Glucose meters are used in the detection and management of **dysglycemia** (**hypogycemia** and **hyperglycemia**) in the hospital

Specific Applications of Hospital Glucose Meter Testing

Glycemic control is the end goal

- To accomplish this goal, need to
  - 1) rapidly detect dysglycemia and
  - 2) return patient to “normoglycemia”
- Frequent measurement of glucose to detect dysglycemia
  - Frequency dependent on acuity
- Treat acute hyperglycemia with insulin
  - SQ vs. IV
- Treat hypoglycemia with oral nutrition and/or dextrose

Specific Applications of Hospital Glucose Meter Testing

Setting	Application
Emergency Department	Evaluation of unconscious patient, diagnosis of hyperglycemia, diagnosis of hypoglycemia, evaluation of acid-base disorder etiology (diabetic ketoacidosis)
General Medical Floor or Unit	Monitoring of glucose, management of diabetic patients (adjustments of anti-diabetic medications including SQ insulin)
Intensive Care Unit	Frequent monitoring as part of tight glycemic control protocol, detection of stress hyperglycemia, monitoring for hypoglycemia in critically ill non-responsive patients
Nursery	Monitoring and detection of hypoglycemia, monitoring for efficacy of nutritional management

Advantages of POCT for the Management of Dysglycemia

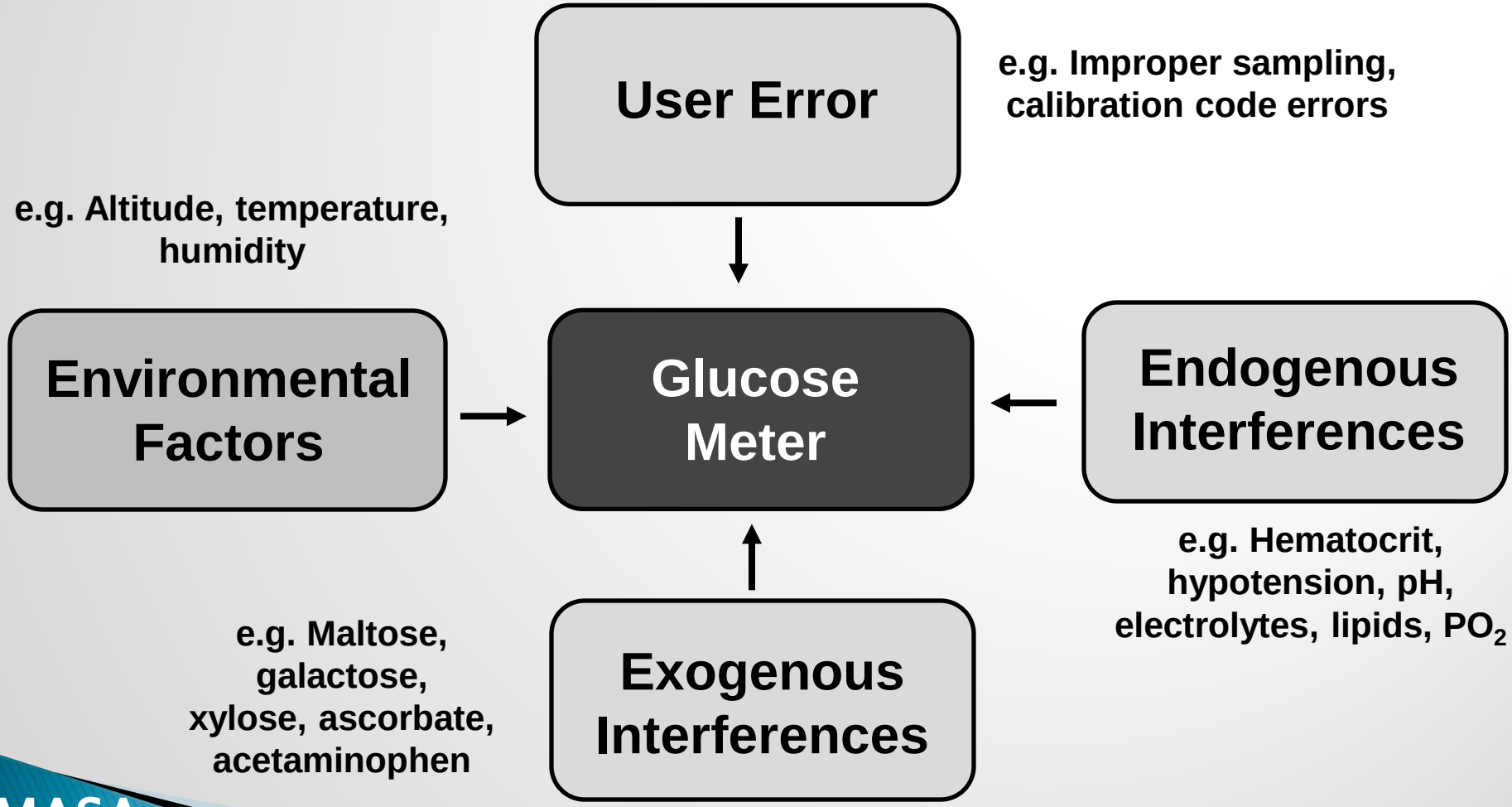
- Multiple specimen types
  - Capillary, venous, and arterial
- Low sample volume
  - Most systems require less than 5 µL of whole blood
- Rapid analysis time
  - Reduced therapeutic turn around time

Combined these features allow for frequent serial monitoring of patients with rapid therapeutic turn around time

Challenges associated with measuring glucose at the bedside

1. Pre-examination errors (pre-analytical)
2. Examination errors (analytical)
3. Post-examination errors (post-analytical)

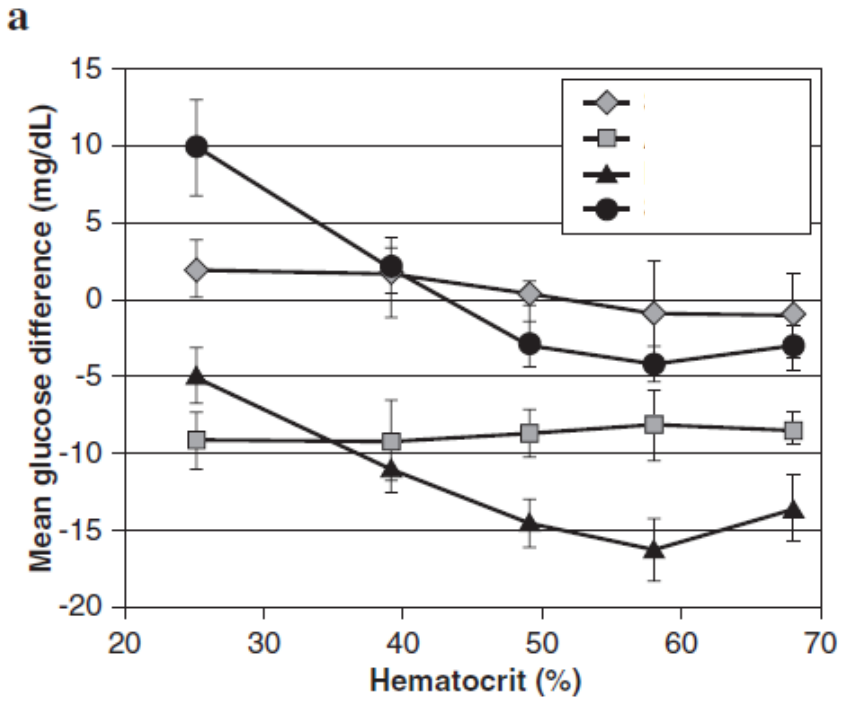
Interferences & factors reported to affect glucose POC meters



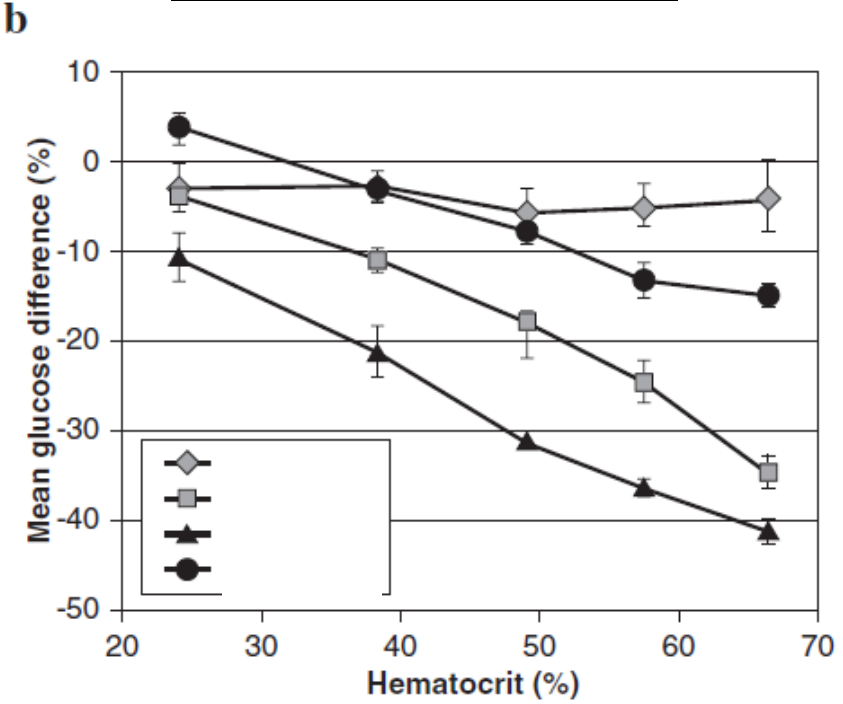
Isbell and Lyon. Glucose meters. Where are we now? Where are we heading? MLO. 2012

Interferences & factors reported to affect glucose POC meters – Hematocrit

Glucose = 54 mg/dL

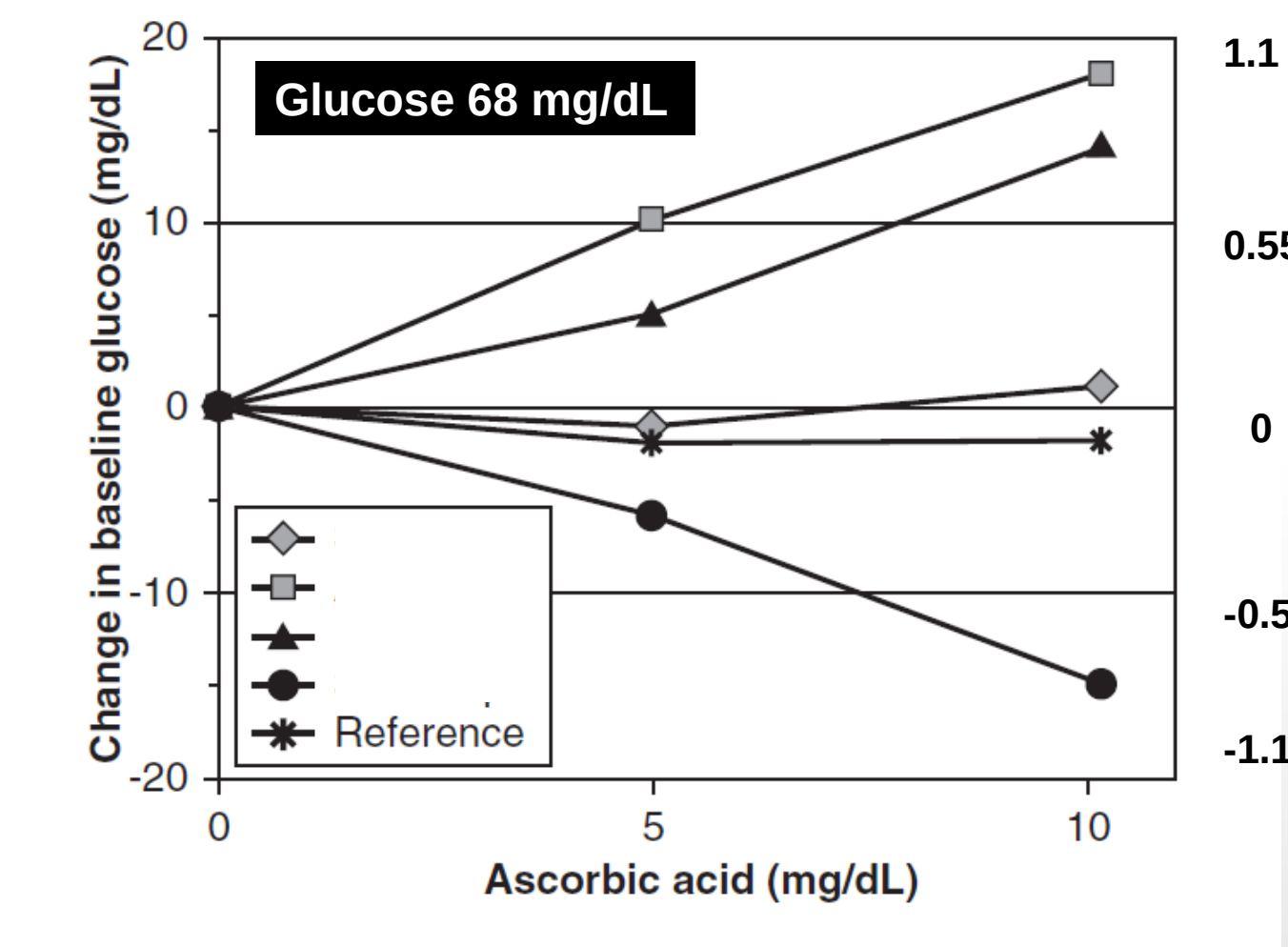


Glucose = 247mg/dL



Karon BS et al. Evaluation of the Impact of Hematocrit and Other Interference on the Accuracy of Hospital-Based Glucose Meters. Diabetes Technology & Therapeutics, Vol 10, No 2, 2008.

Interferences & factors reported to affect glucose POC meters – Ascorbic Acid



Karon BS et al. Evaluation of the Impact of Hematocrit and Other Interference on the Accuracy of Hospital-Based Glucose Meters. Diabetes Technology & Therapeutics, Vol 10, No 2, 2008.

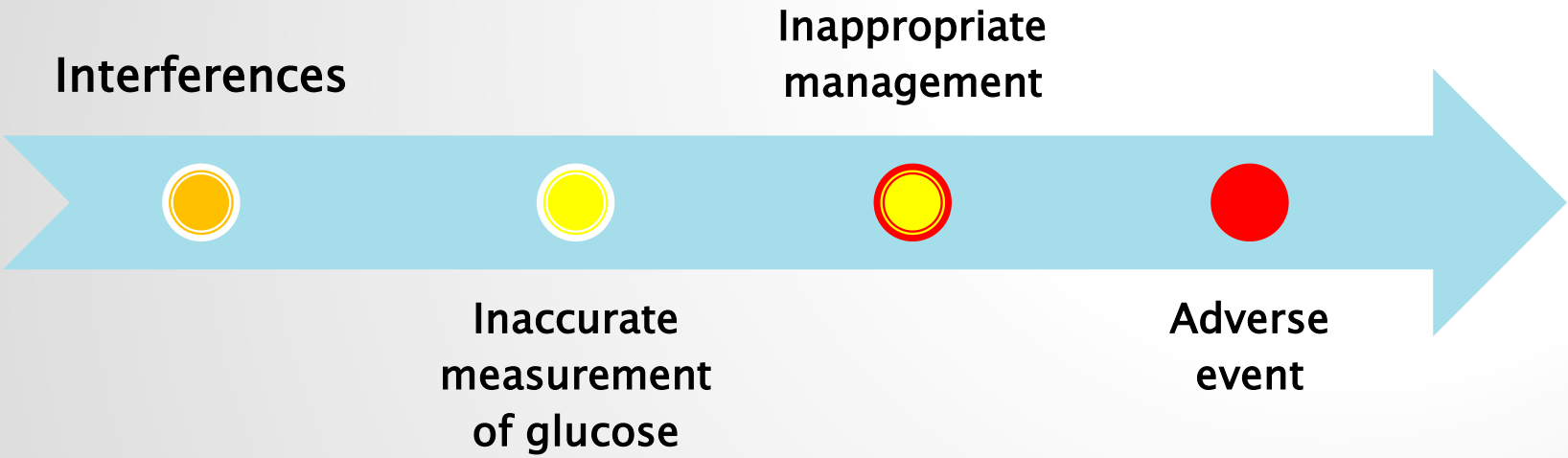
Point-of-care glucose testing in the hospital

What led to the change in regulatory requirements?

Chronology of Awareness of BGMS Performance Problems

- Implementation of intensive insulin therapy (IIT) and tight glycemic control (TGC) protocols
- Erroneous glucose results led to adverse events and deaths
- FDA holds open forum: "Public Meeting: Blood Glucose Meters" (Mar 16,17 2010)
- FDA issues warning letters about PQQ enzyme POCT systems, maltose interferences, etc.
- Community of patients, providers, manufacturers, and regulators identify the need for improved performance criteria for all glucose meters

Clinical Consequences of Bad Measurements



For example a falsely high result could lead to over-treatment with insulin or missed detection of hypoglycemia

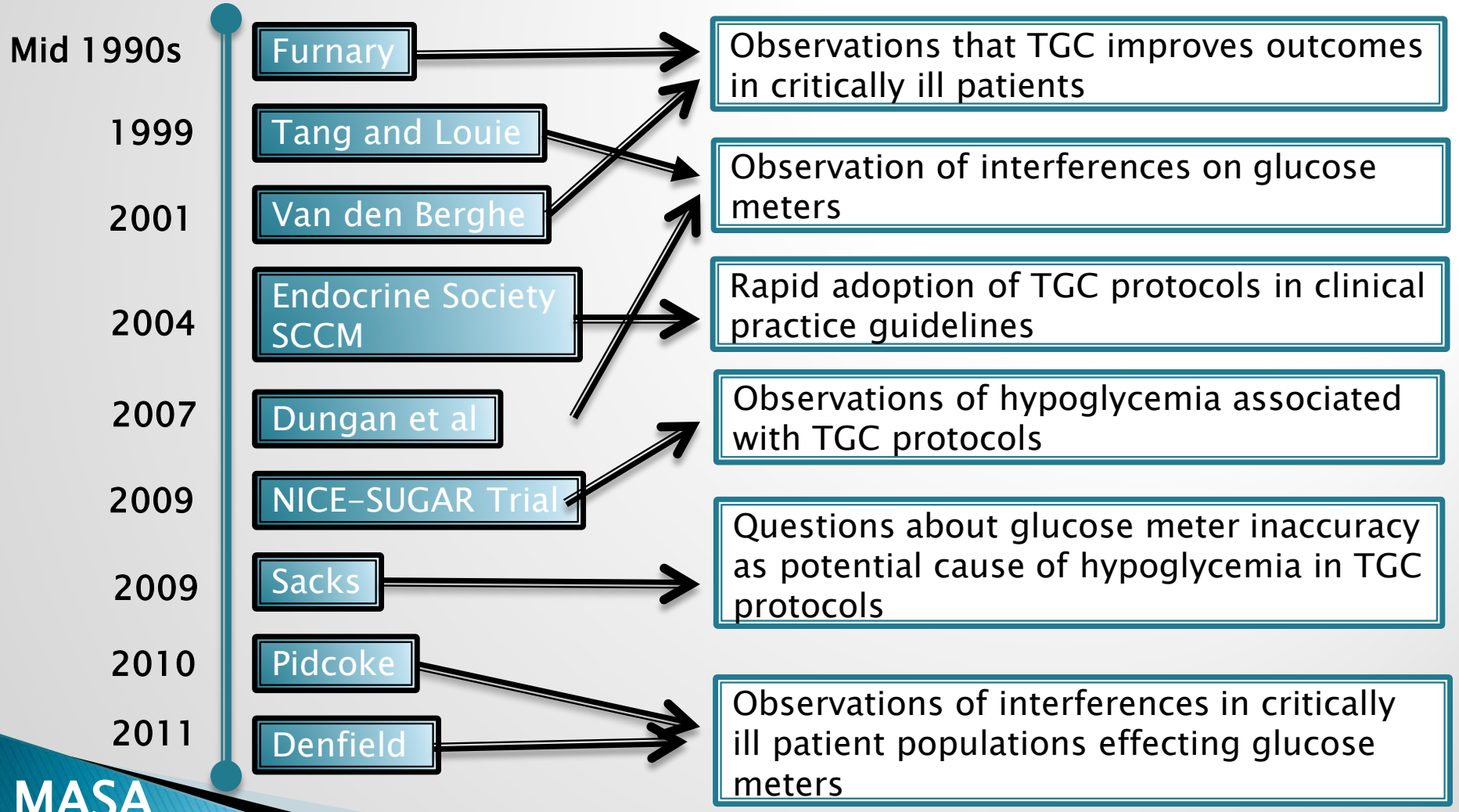
Avoidance of analytical errors requires technology designed specifically to eliminate interferences seen on hospitalized patients

Chronology of Awareness of BGMS Performance Problems

- Serious injuries and deaths reported due to whole blood glucose meters:
  - 100 deaths associated with whole blood glucose monitoring reported to the FDA (1992-2009) including hospital deaths attributed to maltose, galactose and ascorbic acid among others
  - 12,672 serious injuries to hospitalized patients (2004-2008)
  - Interferences were the primary root cause of deaths and adverse events.

FDA/CDRH Public Meeting, 2010

Chronology of Awareness of BGMS Performance Problems



Chronology of Awareness of BGMS Performance Problems

29th Annual Arnold O. Beckman Conference
San Diego, CA (April 12-13, 2011)
"Glycemic Control in the Hospital: Evidence, Issues, and Future Directions"

- Major point of discussion at this conference was the safety of TGC protocols with a focus on hypoglycemic events

- Concerns that inaccurate meters may be contributing to hypoglycemic events were discussed

Continued call for more accurate meters

Awareness of BGMS Performance Problems

Increased number of clinical glucose meter performance studies 2004 to 2011

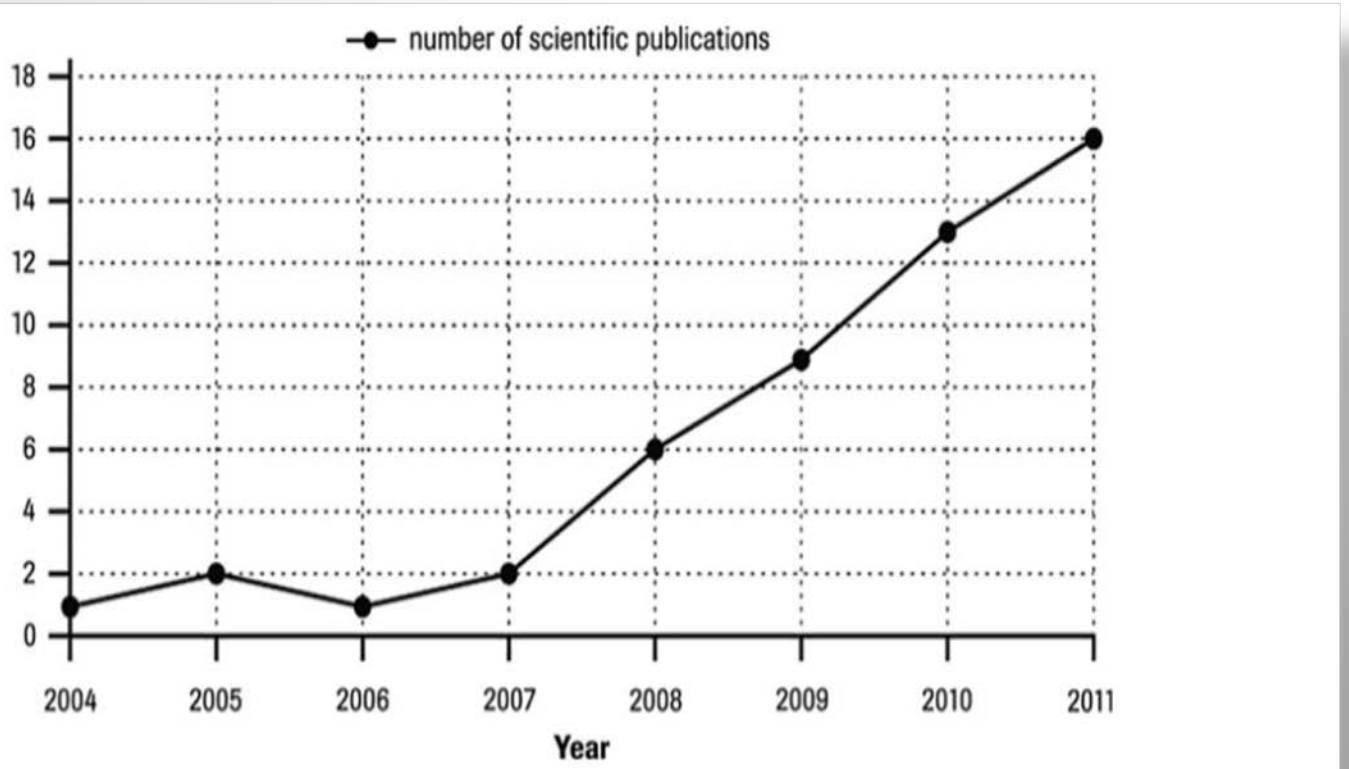


FIG. 1. Number of publications assessing the performance of several blood glucose systems between 2004 and 2011.

Thorpe, G., Diabetes Technology & Therapeutics Volume 15, Number 3, 2013

Conflicting Performance Requirements for BGMS

In 2010 which standard was clinically acceptable for glucose bedside monitoring?

- ADA
- ISO 15197:2003 (SMBG only-not hospital meters)
- CLSI C30-A2
- FDA CLIA Waived requirements

SMBG performance problems were allowed by inadequate standards

- Prior to 2013 ISO, CLSI, and FDA allowed for 5% of all results to be erroneous
  - 6.2 billion glucose measurements/year globally including self test and hospital
    - 310 million erroneous glucose results were allowable
    - 1 billion hospital bedside tests globally. 500 million in US which = potential ~25 million erroneous results
  - No risk assessment was required in any of these standards & there was no limit to error on any individual sample

SMBG performance problems were allowed by inadequate standards

- ADA was the only professional organization to request more stringent performance requirements in published practice guidelines
  - 2004 –10% Total allowable error (TAE) (*bias + imprecision*)
  - 2006 – 5% Total allowable error (TAE) (*bias + imprecision*)
  - Meter result must be equivalent to central lab result

The ADA request was never adopted

How was this serious analytical performance problem hidden?

- Guidelines were developed using SMBG (non-hospital) glucose meters tested on otherwise healthy, non hospitalized people with diabetes
  - Use of a non-clinical laboratory reference analyzer – YSI
  - Comparative data using a predicate glucose meter did not identify interferences
  - **No clinical studies of potential interferences such as drugs, hematocrit, non-glucose sugars, oxygen and other electrochemical interferences**
  - Performance data represented as bias only, not total error
- Laboratory practice only required simple verification of manufacturer stated claims for linearity and imprecision

Awareness that led to change

- Introduction of the 1st hospital glucose meter designed for hospitalized patients in 2007, that corrected for all interferences such as hematocrit, electrochemical, & non-glucose sugar interferences
- Proof of methodology was to:
  - Have many hospital labs independently verify the product's labeling claims, particularly interferences
  - Validate the product's performance in all clinical settings, including critical care

Awareness that led to change

- 138 publications evaluating analytical performance
  - 42 peer reviewed journal articles
  - 87 posters presented at national and international meetings
  - 9 other

- Results:
  - No clinical interferences have been found
  - Proven performance independent of geography, institution, operator, or patient condition/therapy

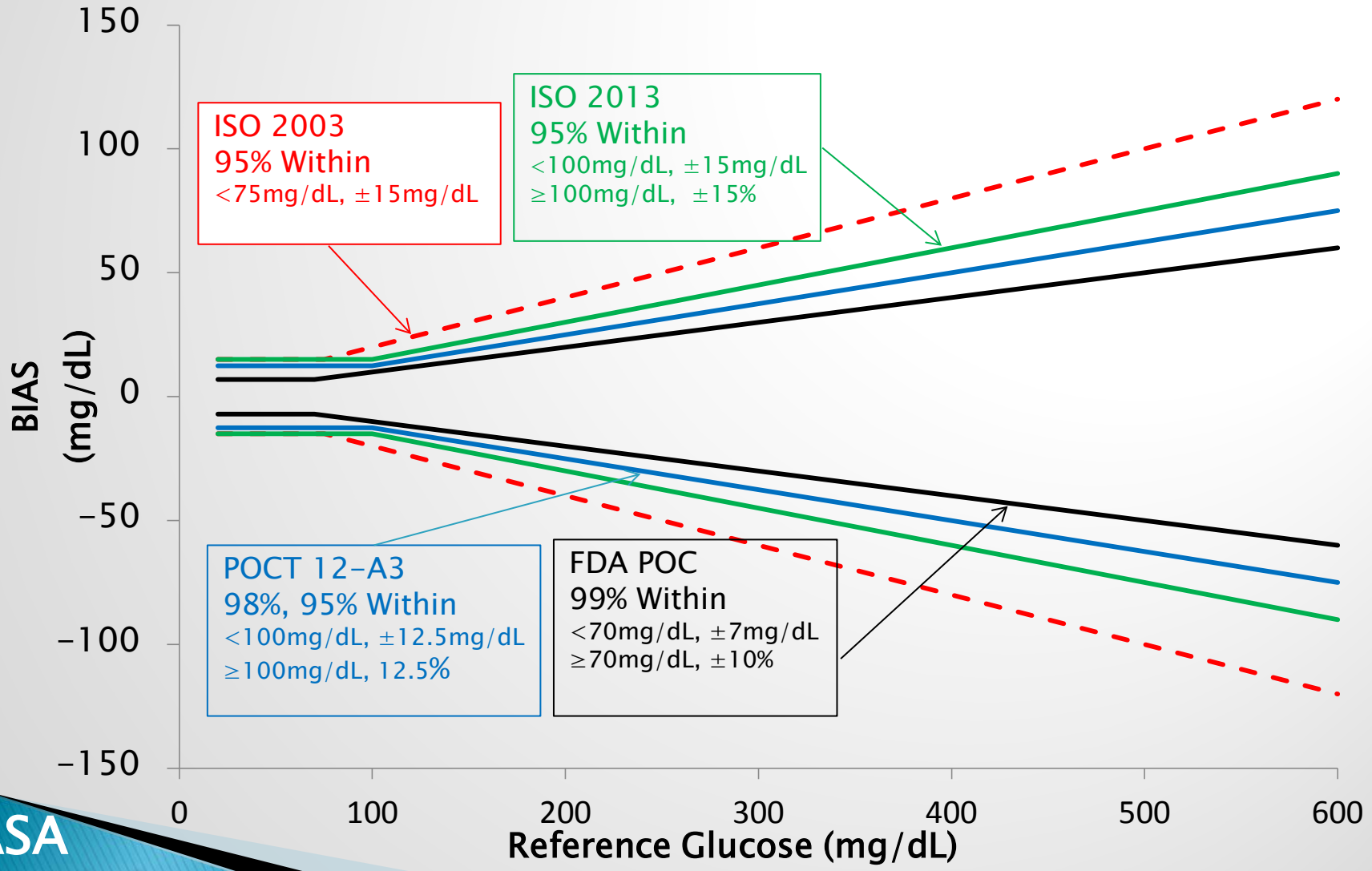
Awareness that led to change

- Open meetings were held by FDA, SCCM, AACE, ADA, Diabetes Science & Technology Societies regarding new standards
- New Performance Guidelines in 2013
  - CLSI POCT12-A3 (Acute and Chronic Care facilities – Laboratory Guideline)
    - FDA does not recognize POCT12-A3 for manufacturer's submissions
  - ISO 15197:2013 (SMBG only)
    - **FDA did not vote in favor of ISO 15197:2013**

Awareness that led to change

- FDA Draft Guidance for Manufacturers in 2014
  - New draft guidance documents define 2 device classifications
    - BGMS (Blood Glucose Monitor System) for hospitalized patients
    - SMBG (Self-Monitoring Blood Glucose) for non-hospitalized patients
  - FDA defined new performance criteria for new devices in these 2 categories plus increased the number of patients to be studied
    - Minimum 350 subjects for each specimen type, more if necessary
    - Subjects should accurately reflect the “Intended Use” population

New FDA Draft Guidelines Tightens Glucose Meter Expectations



Awareness that led to change

- Up until this point, the awareness did not lead to any changes
- Continued reporting through 2014 of sentinel events that resulted in adverse events and deaths using SMBG glucose meters on hospitalized patients
- New York State Health Department issued a directive in 2014 that glucose meters were considered highly-complex if used on critically ill patients and could not be used by non-laboratory personnel
- CMS followed NY State's lead, as well as, other accrediting agencies, CAP, Joint Commission, & ECRI

The Result: Confusion for hospitals!!!

- What applies to us – FDA or CMS?
- How are we supposed to validate these devices based on these new criteria? (time and resources)
- What are the validation standards for hospital use?
- Who can and where can bedside testing be performed in the US hospitals?

The Change – FDA Resolved the Problem in September, 2014

NEW FDA requirements for BGMS include:

- Hospital glucose meters should be designed for and tested on all hospitalized patients and all drug categories
- Testing must include all patients including critically ill, all medical conditions, all drug therapies, and include a risk assessment
- Results must be substantially equivalent to central laboratory methods

The Change – FDA Resolved the Problem in September, 2014

- NEW FDA requirements for BGMS include:
  - CLIA-Waived status based on studies demonstrating tighter performance characteristics with POC users
    - This ended the process of testing SMBG on non-hospitalized patients
  - In September 2014, the FDA announced that one POCT glucose system had met these requirements and was approved for use on all patients including critically ill
  - All other POCT glucose testing systems are categorized as off label if used on intensive care patients

Surgery and Recovery

Inpatient

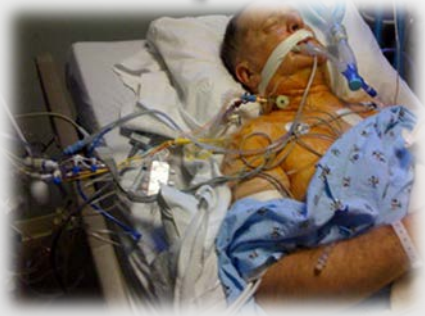
Emergency and Trauma

ALL

Oncology and Dialysis

Labor & Delivery

NICU and Nursery



Intensive Care

Specialty Clinics

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Understand · Prove · Communicate · Grow

Pathway to the New Approval

- 2006-present
  - Lab and clinical evaluations published that verified and validated the product's performance in all patient settings and conditions/therapies
- 2010
  - Engaged FDA to determine acceptable clinical study protocols
  - Initiated a multi-center, university hospital-based study to investigate the performance of the product in critically ill patients
- 2013 – 2014
  - Data submitted to FDA for labeling change consideration
  - Multiple review sessions with FDA to evaluate performance and determine if the product was safe and effective in critically ill patients resulting in approval issued on September 24, 2014

How was the claim achieved?

Multisite study involving 5 prestigious university hospital medical centers in the United States and Europe:

- Patient data includes:
  - N = 1,698 critically ill patients (1,815 glucose measurements)
- 19 different complex critical care condition categories as defined by World Health Organization (WHO)
  - 257 different specific critical care conditions including severity of illness scores were included
- >8,000 administered compounds in complex treatment regimens
  - 33 different parent drug classes as defined by US Pharmacopeia (USP)
  - 134 drug class subcategories

How was the claim achieved?

- Comparative analysis of 1,815 point-of-care glucose measurements to a laboratory reference method and severity of illness scores
- Extreme patient clinical ranges of hematocrit, electrolytes, blood gases, pH, and other endogenous biochemical parameters were specifically included
- Data was analyzed by multiple models for assessing the safety and efficacy of the device for use in intensive insulin therapy including:
  - Parkes Error grid analysis
  - Karon, Boyd, and Klee insulin dosing error risk model analysis
  - POCT12-A3 and ISO15197:2013 performance criteria analysis
  - Stratified sensitivity & specificity analysis

How was the claim achieved?

Results:

- Glucose POCT testing demonstrated substantial clinical equivalence to plasma hexokinase IDMS laboratory reference methods

- Total analytical error (bias + imprecision) was substantially equivalent to central laboratory plasma hexokinase and IDMS definitive methods

How was the claim achieved?

Results:

- The device met all FDA performance criteria for multiple analysis models
- No known clinically significant interferences were observed following analysis of extensive range of medication, biochemical, and pathophysiological interference factors

The most comprehensive dataset ever submitted to the FDA for a BGMS

Insulin dosing risk assessment models

Comparison of Four Models for Assessing Insulin Dosing Error when a Blood Glucose Monitoring System is used in Various Patient Populations

Jeffrey A DuBois[1], Martha E Lyon[2], Andrew W Lyon[2], Robbert J Slingerland[3], Marion Fokkert[3],
Alain Roman[4], Nam Tran[5], William Clarke[6], David Sartori[6]

[1] Medical and Scientific Affairs, Nova Biomedical, Waltham, MA; [2]Department of Pathology and Laboratory Medicine, Saskatoon Health Region, Saskatoon, Saskatchewan, Canada; [3]Department of Pathology and Laboratory Medicine, ISALA Clinics, Zwolle, Netherlands; [4]Department of Surgical Intensive Care, St. Pierre University Hôpital, Brussels, Belgium; [5]Department of Pathology and Laboratory Medicine & Burn ICU, UC Davis Medical Center, Sacramento, CA; [6]Department of Pathology and Laboratory Medicine, Johns Hopkins Medical Center, Baltimore, MD

Awarded Best Abstract and Best Poster
AACC, San Diego
CPOCT 2014

Effect of new FDA approval on hospital POC glucose testing

- Only glucose meter cleared for use with all patients in all clinical settings including intensive care
- CLIA-Waived status also earned through the new FDA submission
- New labeling eliminates “off-label”, high complexity classification. All other meters are “off-label” and high complexity testing when used in intensive care settings
- Analytical performance substantially equivalent to central laboratory IDMS traceable reference methods

Effect of new FDA approval on hospital POC glucose testing

- Internationally compliant with all standards, regulatory and accreditation agencies
- Labeling and comprehensive bibliography helps each hospital satisfy requirements from CAP, ECRI, TJC, JCI, NY State Health Department, or other regulatory or accrediting agencies

Effect of new FDA approval on hospital POC glucose testing

- **What does off-label and highly complex use mean to hospitals**
- Before beginning off-label testing, extensive validation of the safety and effectiveness of the off-label device on critically ill patients is required.

- Studies performed for glucose meter clearance:
  - 1815 individual critical care patient samples were paired with an IDMS traceable laboratory glucose reference method.
  - Critical care patients (19 critical care condition categories and 257 subcategories)
  - Interference testing was performed on 8000 medications (33 parent drug classes and 134 drug subclasses)

  - Completing a validation requirement for off-label use still does not remove the high complexity user requirements

Effect of new FDA approval on hospital POC glucose testing

- **What does off-label and highly complex use mean to hospitals**
  - Only high complexity operators can use products off-label. High complexity operators must either be licensed to run high complexity tests or individuals degreed in clinical laboratory technology, *i.e. nurses cannot run off label tests*
  - Glycemic management programs are at risk if nursing staff cannot perform POCT testing
  - Accreditation & reimbursement are at risk if off label restrictions are not followed
  - Off-label use increases patient safety risk and hospital liability

Four Years after FDA Open Meeting

Proper Management Depends on Quality Glucose Meter Results

1. Good specimen
2. Properly trained operators
3. **Accurate measuring device**

The benefit of hospital glycemic management programs that use well defined protocols and a hospital meter that meets the new standard of performance cleared by the FDA

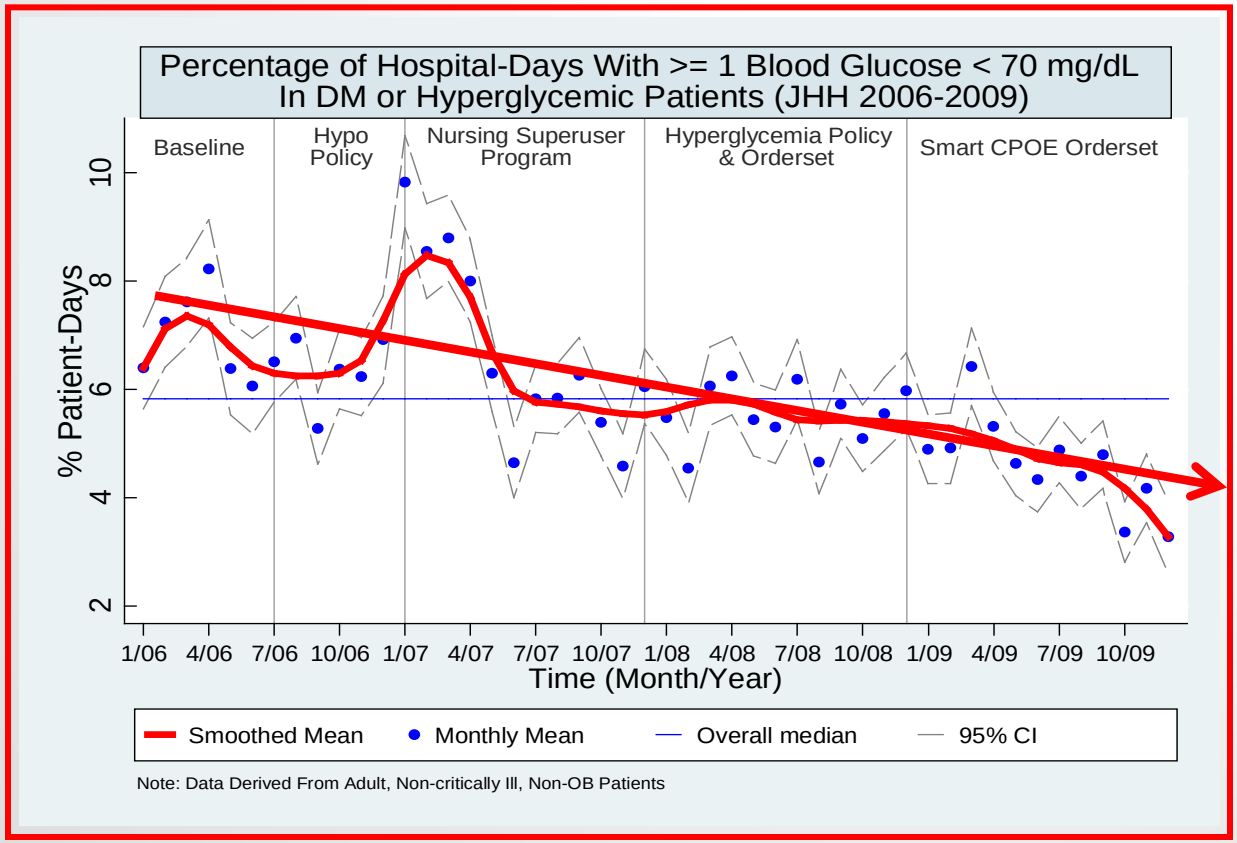
The benefits to hospitals include improved outcomes and lower costs

Improved analytical & clinical performance required by the new regulations enables optimal management of dysglycemia with improved clinical outcomes, including:

- Reduced time to reach the target glycemic control range
- Increased time within the glycemic control range
- Reduction in glycemic variability
- Reduction of hypoglycemic events
- Reduction of insulin dosing errors and quantity of insulin administered
- Reduction in comorbidities resulting in decreased LOS in the ICU
- Reduction in overall costs of care
- Reduction in mortality

Hypoglycemia

- 25,160 admissions
- 19% reduction in hypoglycemia frequency



Munoz and Golden, *Joint Commission Journal of Quality and Patient Safety*, 2012

The benefits to hospitals include improved outcomes and lower costs

Economic outcomes resulting from improved glucose meter analytical performance

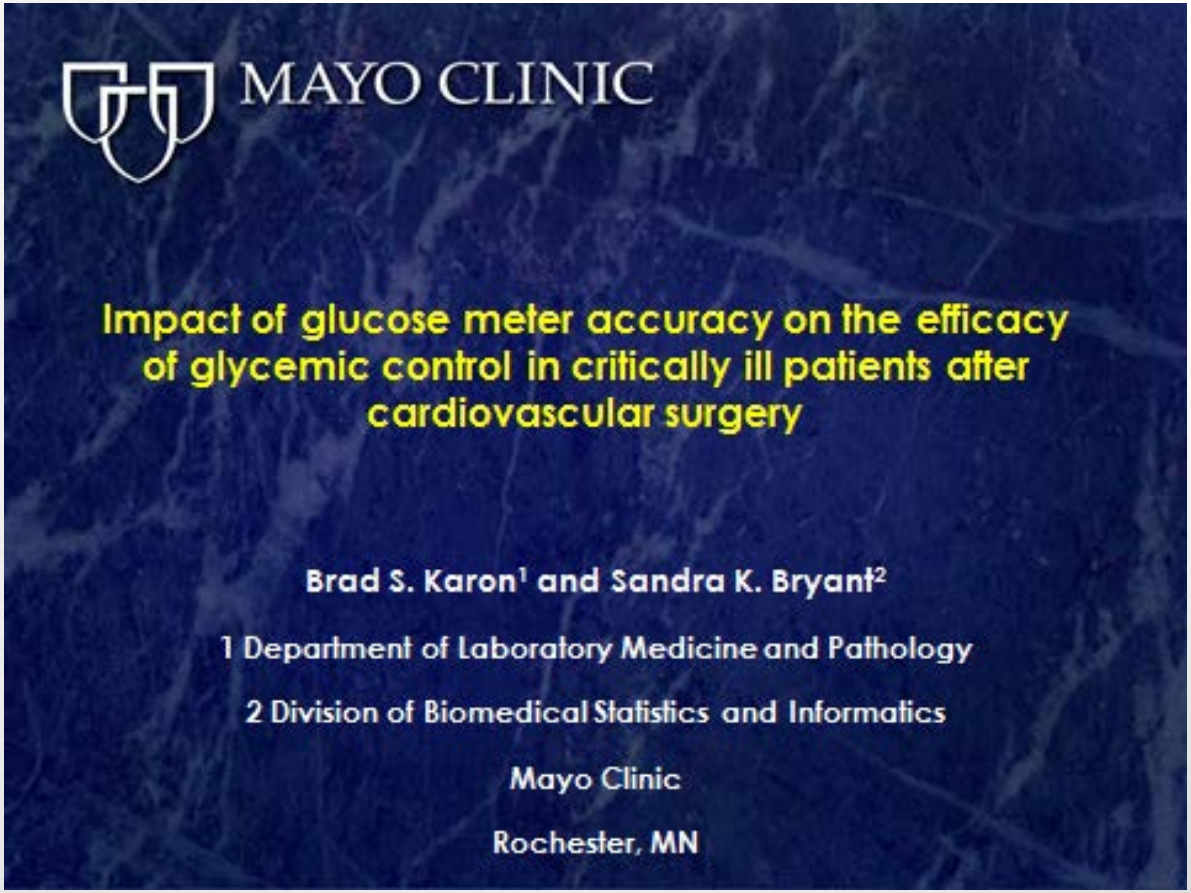
Pre- & Post glycemic management program implementation results

- 25,603 admissions
- In-hospital mortality
  - **36% reduction**
- Length of stay
  - **2.7 days lower length of stay/admission**
- Hospital costs
  - **$3,900 decrease in hospital costs/admission**

Spanakis and Golden, Diabetes, 2013; 62(suppl. 1):A67

Results of improved glucose meter accuracy in ICU patients

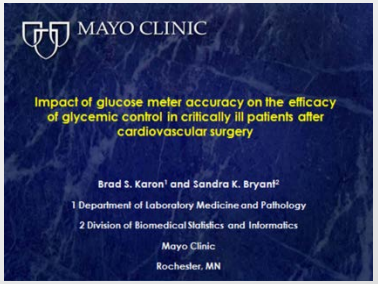
Mayo Clinic
Podium Presentation
AACC, San Diego
CPOCT 2014



Results of improved glucose meter accuracy in ICU patients

	Period 1 (Meter 1)	Period 2 (Meter 2)
Median (IQR) bias (mg/dL)	11 (6 – 18) mg/dL	1 (–5 – 5) mg/dL
% within 20%/15 mg/dL serum	92%	98%
% within 15%/15 mg/dL (NACB) serum	80%	97%
% within 12.5%/12.5 mg/dL (CLSI POCT12-A3) serum	69%	95%

Mayo Clinic
Podium Presentation
AACC, San Diego
CPOCT 2014



Results of improved glucose meter accuracy in ICU patients

Conclusions

- Glucose meter bias decreased between Period 1 (Meter 1) and Period 2 (Meter 2) in ICU patients
- Reduced glucose meter bias likely improved efficacy of glycemic control after cardiovascular surgery
  - Reduced time to achieve target levels
  - Glycemic variability decreased (SD and CONGA)
  - Time within target range (110–150 mg/dL) increased
  - Fewer episodes hyperglycemia (> 200 mg/dL) observed

Mayo Clinic
Podium Presentation
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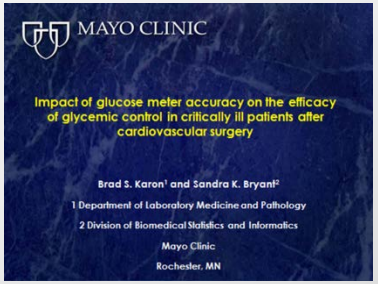


BGM Performance Can Affect Patient Safety and Outcomes

Automatic hematocrit correcting meters improves glycemic control and reduces hypoglycemic risk in severely burned adult patients

Z. Godwin, BS, J. Brockhold, BS, N.K. Tran, PhD
University of California-Davis

- Pilot RCT to evaluate glycemic control outcomes associated with two different glucose meters used in a burn unit where confounding factors (anemia) have been shown to affect glucose meters
- GMS-1 automatically corrects for effects of Hematocrit and GMS-2 does not

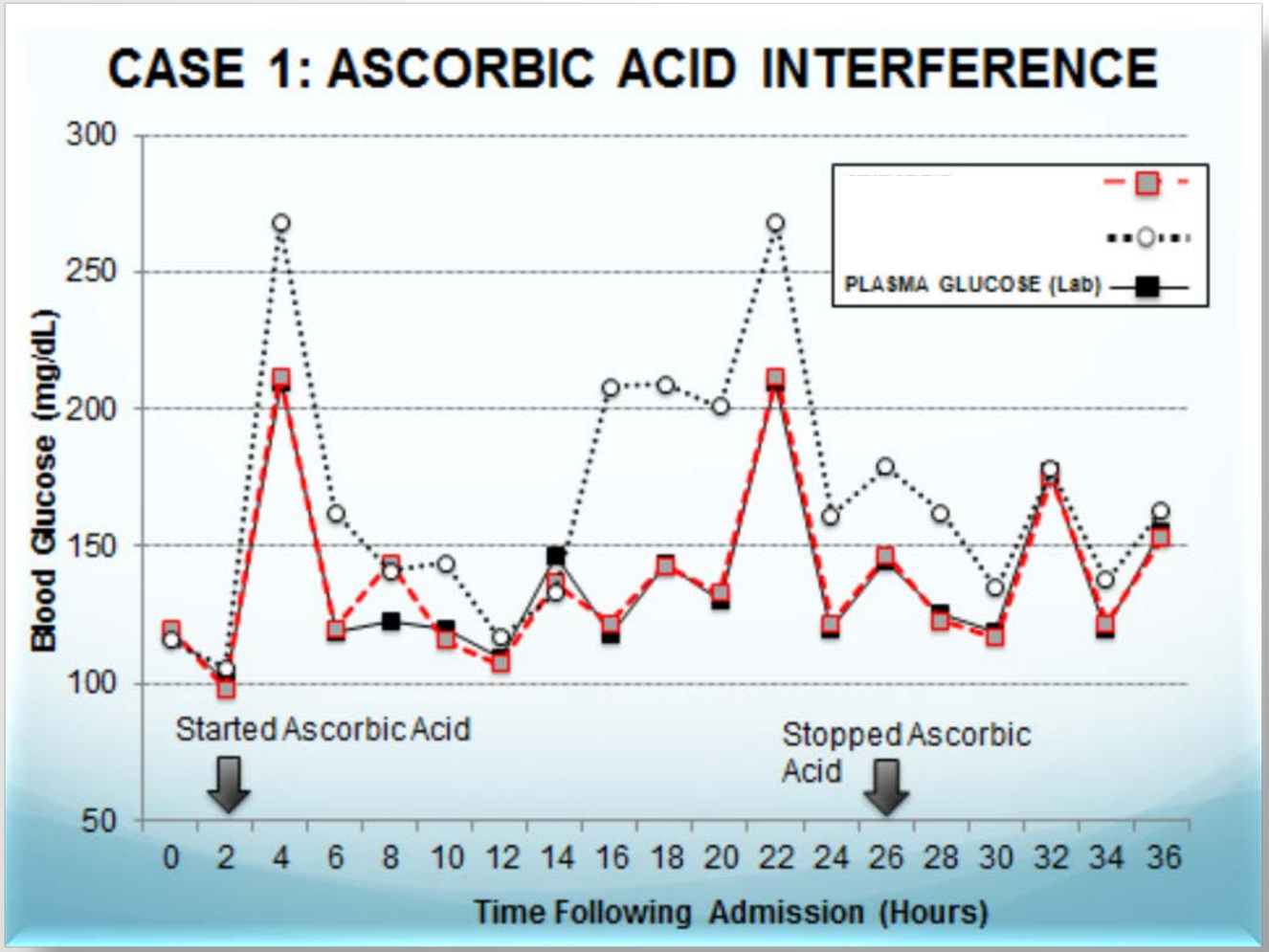
American Burn Association 45th Annual Meeting.
April 23-26, 2013. Palm Springs, CA

BGM Performance Can Affect Patient Safety and Outcomes

Table 1. GMS-1 vs. -2 Results			
	GMS-1 Group (n = 6 patients)	GMS-2 Group (n = 6 patients)	P-Value
Mean Age (Years, SD, n patients)	35.7 (6.2, 6)	40 (15.1, 6)	0.585
Mean TBSA (%, SD, n patients)	44.5 (6.5, 6)	57.8 (12.4, 6)	0.273
Mean Multiple Organ Dysfunction Score (SD, n measurements)	5.4 (4.3, 413)	5.4 (12.4, 251)	0.985
Mean Hematocrit (%, SD, n = measurements)	26.1 (4.9, 263)	25.3 (5.2, 424)	0.777
Mean Glucose Bias (mg/dL, SD, n measurements)	-1.9 (9, 113)	5.48 (11.1, 419	<0.001
Hypoglycemic Events	2	14	<0.001
% Hypoglycemic Events	11% (119/1,088)	23% (1,846/8,027)	<0.001
Mean Glycemic Variability (SD, n patients)	20.3 (5.89, 6)	23.7 (2.49, 6)	0.310
Mean Insulin Rate (U/hr, SD, n measurements)	2.66 (1.8, 2,312)	4.02 (3.68, 4,641)	<0.001

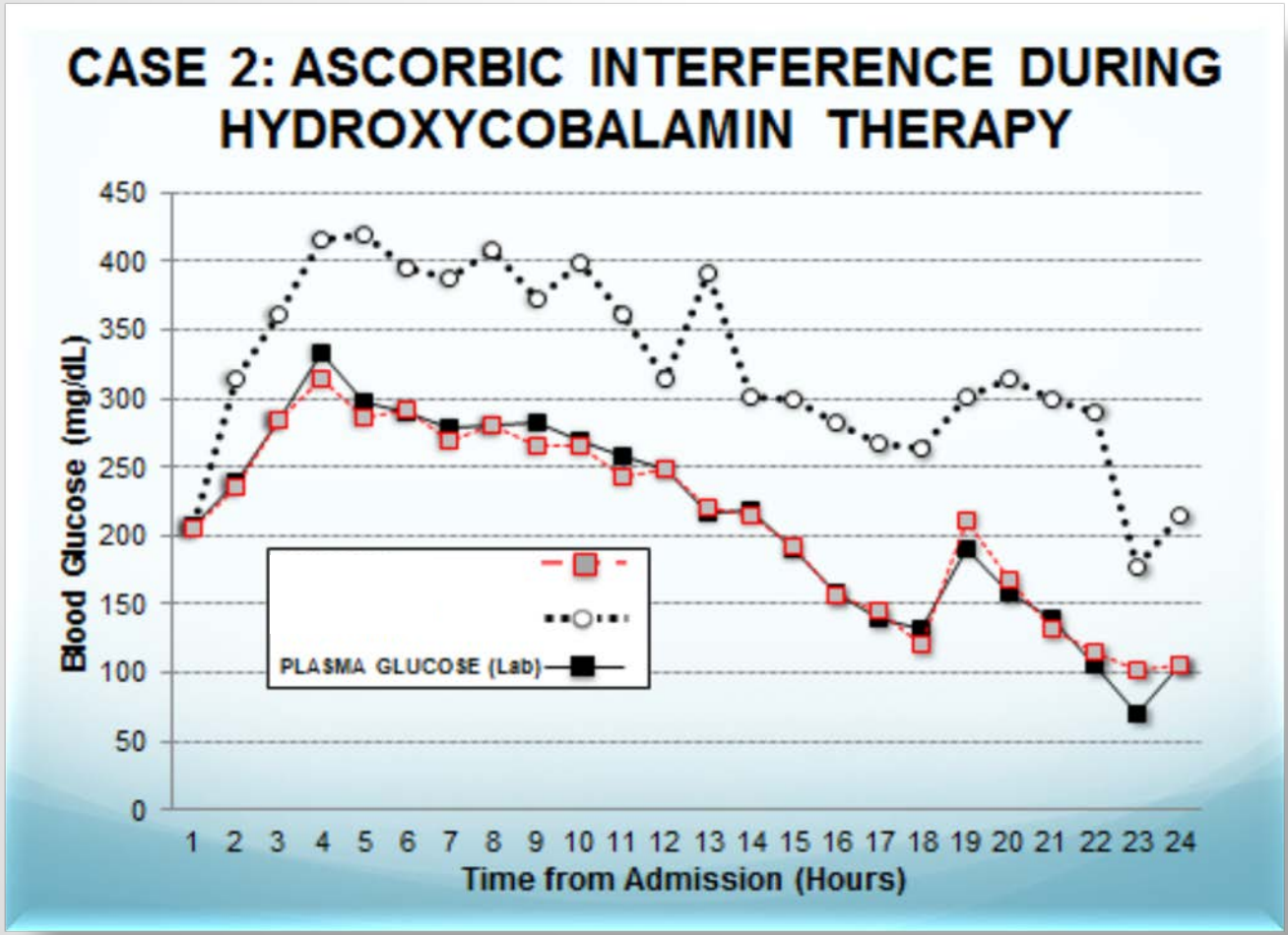
American Burn Association 45th Annual Meeting. April 23–26, 2013. Palm Springs, CA

BGM Performance Can Affect Patient Safety and Outcomes



University of California Davis Medical Center
Presented at IFCC and CPOCT, 2014

BGM Performance Can Affect Patient Safety and Outcomes



University of California Davis Medical Center
Presented at IFCC and CPOCT, 2014

New FDA POCT glucose clearance summary

- The new intensive care FDA regulatory approval is all about RISK REDUCTION to obtain improved patient safety & outcomes
- Glucose meter demonstrated laboratory equivalent accuracy independent of strip lot, meter, operator, lab, location, or patient condition
- **Did not** show any clinically significant interferences including hematocrit abnormalities, non-glucose sugars, or electrochemically active substances e.g., ascorbate

New FDA POCT glucose clearance summary

- Performance has been extensively **verified** and **validated** in virtually all intensive care patient populations
- Satisfied all national & international regulatory & accrediting criteria
- Improved patient outcomes and lowered hospital costs

Thank you

entrivalas@novabio.com