Measuring Blood Glucose Using Capillary Blood with Blood Glucose Meters in all Hospital Settings

Meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel
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Leslie Landree, PhD
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
Food and Drug Administration

Evaluation of Blood Glucose Monitoring System Performance

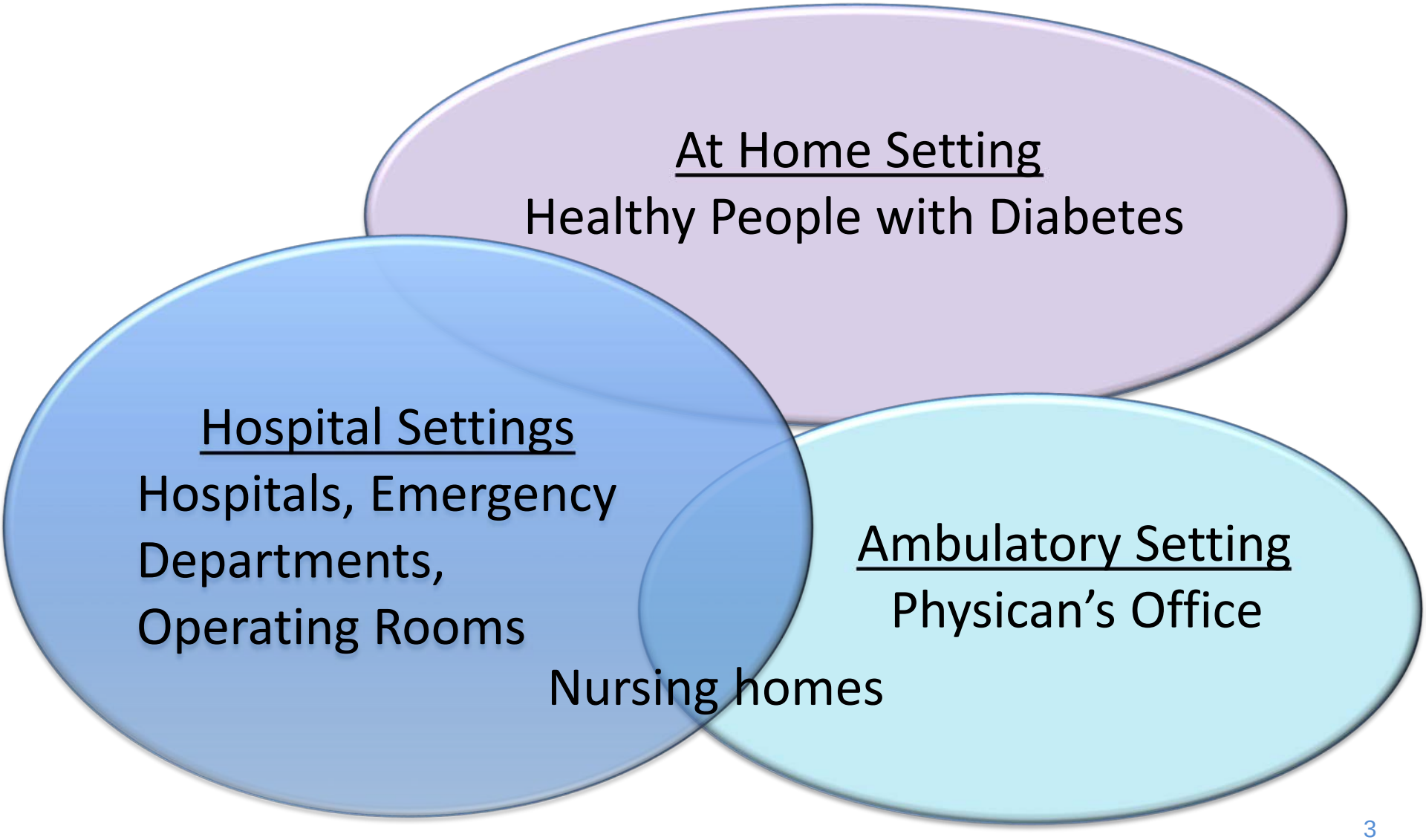
Precision - Interferences - Accuracy

✓ Precise
x Accurate

x Precise
✓ Accurate

✓ Precise
✓ Accurate

Accuracy Evaluation



Accuracy Evaluation of Blood Glucose Monitoring Systems

- In the hands of the intended user
- Environment reflective of the actual use setting
- Results of the system compared to a comparator method
  - accurate and precise laboratory method
- Evaluation of each claimed sample type (arterial, venous, capillary, neonatal heelstick etc.)

Summary of Accuracy Results

Within ±5%	Within ±10%	Within ±12%	Within ±15%	Within ±20%	Exceeds ±20%
N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Summary of Accuracy Results

Blood Glucose Concentrations <75 mg/dL

Within ±5 mg/dL	Within ±10 mg/dL	Within ±12 mg/dL	Within ±15 mg/dL	Exceeds ±15 mg/dL
N (%)	N (%)	N (%)	N (%)	N (%)

Blood Glucose Concentrations ≥75 mg/dL

Within ±5%	Within ±10%	Within ±12%	Within ±15%	Within ±20%	Exceeds ±20%
N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

StatStrip Glucose Hospital Meter System

- FDA cleared for use throughout all hospital and professional healthcare settings with:
  - venous whole blood
  - arterial whole blood,
  - neonatal arterial and heel stick sample
- Limited against use of capillary samples in patients receiving intensive medical intervention/therapy
- Study included samples obtained from 1698 patients at 5 different hospitals

- Settings included emergency rooms, operating rooms, oncology departments, intensive care units, medical intensive care units, surgical intensive care units, cardiovascular surgical intensive care units, pediatric intensive care units, transplant departments, cardiac departments, nursing, and surgical departments

StatStrip Glucose Hospital Meter System with Arterial and Venous Samples

Glucose <75 mg/dL

Specimen Type	Within ±5 mg/dL	Within ±10 mg/dL	Within ±12 mg/dL	Within ±15 mg/dL	Exceed ±15 mg/dL
Arterial	163/201 (81.1%)	189/201 (94.0%)	195/201 (97.0%)	197/201 (98.0%)	4/201 (2.0%)
Venous	68/79 (86.1%)	77/79 (97.5%)	78/79 (98.7%)	79/79 (100%)	0/79 (0.0%)

Glucose ≥75 mg/dL

Specimen Type	Within ±5%	Within ±10%	Within ±12%	Within ±15%	Within ±20%	Exceeds ±20%
Arterial	844/1267 (66.6%)	1175/1267 (92.7%)	1220/1267 (96.3%)	1244/1267 (98.2%)	1258/1267 (99.3%)	9/1267 (0.7%)
Venous	171/268 (63.8%)	246/268 (91.8%)	260/268 (97.0%)	267/268 (99.6%)	268/268 (100%)	0/268 (0.0%)

StatStrip

Glucose <75 mg/dL

Specimen Type	Within ±12 mg/dL
Arterial	195/201 ***(97.0%)***
Venous	78/79 ***(98.7%)***

Glucose ≥75 mg/dL

Specimen Type	Within ±12%
Arterial	1220/1267 ***(96.3%)***
Venous	260/268 ***(97.0%)***

POCT12

95% of the results within +/- 12 mg/dL for values <100 mg/dL

95% of the results within +/- 12.5% for values >100 mg/dL

StatStrip	POCT12	FDA BGMS Guidance

Glucose <75 mg/dL

Specimen Type	Within ±12 mg/dL
Arterial	195/201 ***(97.0%)***
Venous	78/79 ***(98.7%)***

95% within +/- 12 mg/dL < 100 mg/dL

95% within +/- 12 mg/dL < 75 mg/dL

Glucose ≥75 mg/dL

Specimen Type	Within ±12%
Arterial	1220/1267 ***(96.3%)***
Venous	260/268 ***(97.0%)***

95% within +/- 12.5% > 100 mg/dL

95% within +/- 12.0% ≥ 75 mg/dL

Capillary Limitation

- No information provided on the performance of these meters with capillary samples from intensively treated patients
- All hospital meters are labeled with limitations against using the devices for capillary blood in certain populations, including patients receiving intensive medical intervention/therapy.

New Studies on Capillary Measurement Using BGMS in Critical Care

- 3 large studies of BGMS devices using capillary blood in these settings
- We have obtained permission from the sponsors of these studies to share this data in the context of this Advisory Panel Meeting
- Goal = increase transparency on accuracy of BGMS in patients receiving intensive medical intervention/therapy
  - Hear from the clinical community and the public
  - Receive advice from our Advisory Panel

New Studies on Capillary Measurement Using BGMS in Critical Care

- Three new studies
  - Study 1: Prospective trial using meter A
  - Study 2: Retrospective trial using meter A
  - Study 3: Prospective trial using meter B

- These 3 studies compared capillary test results obtained from a glucose meter to matched measurements obtained using a laboratory method.

Study 1 - Meter A

- Capillary whole blood samples (N=567) critical care units
  - cardiovascular intensive care unit (CVICU)
  - medical intensive care unit (MICU)
  - operating room (OR)
- Meter results were compared to a laboratory method
- Arterial and venous data was also collected and results compared to the laboratory method
- Meter results obtained by intended use operators

Study 1 - Meter A

Accuracy for glucose ≥75 mg/dL

Study 1	**Within ±5%**	**Within ±10%**	**Within ±12%**	**Within ±15%**	**Within ±20%**	**Exceeds ±20%**
Arterial and Venous	135/200 (67.5%)	186/200 (93.0%)	191/200 (95.5%)	196/200 (98.0%)	200/200 (100%)	0/200 (0.0%)

Study sites had implemented glycemic control protocols, therefore no glucose results below 75 mg/dL were collected in this study

Study 1 - Meter A vs. StatStrip

Study 1 – Meter A

Study 1	Within ±5%	Within ±10%	Within ±12%	Within ±15%	Within ±20%	Exceeds ±20%
Arterial and Venous	135/200 (67.5%)	186/200 (93.0%)	191/200 (95.5%)	196/200 (98.0%)	200/200 (100%)	0/200 (0.0%)

Cleared Nova Biomedical StatStrip Study

Specimen Type	Within ±5%	Within ±10%	Within ±12%	Within ±15%	Within ±20%	Exceeds ±20%
Arterial	844/1267 (66.6%)	1175/1267 (92.7%)	1220/1267 (96.3%)	1244/1267 (98.2%)	1258/1267 (99.3%)	9/1267 (0.7%)
Venous	171/268 (63.8%)	246/268 (91.8%)	260/268 (97.0%)	267/268 (99.6%)	268/268 (100%)	0/268 (0.0%)

Study 1 - Meter A
Capillary

Specimen Type	Within ±5 %	Within ±10 %	Within ±12 %	Within ±15 %	Within ±20 %	Exceeds ±20 %
Capillary	277/567 (48.9%)	450/567 (79.4%)	484/567 (85.4%)	516/567 (91.0%)	549/567 (96.8%)	18/567 (3.2%)

Study 1 - Meter A
Capillary vs. Venous and Arterial

Capillary

Specimen Type	Within ±5 %	Within ±10 %	Within ±12 %	Within ±15 %	Within ±20 %	Exceeds ±20 %
Capillary	277/567 (48.9%)	450/567 (79.4%)	484/567 (85.4%)	516/567 (91.0%)	549/567 (96.8%)	18/567 (3.2%)

Arterial and Venous

Study 1	Within ±5%	Within ±10%	Within ±12%	Within ±15%	Within ±20%	Exceeds ±20%
Arterial and Venous	135/200 (67.5%)	186/200 (93.0%)	191/200 (95.5%)	196/200 (98.0%)	200/200 (100%)	0/200 (0.0%)

Study 2 - Meter A

- Retrospective study of 14,000 paired critical care capillary samples
- Capillary results on the BGMS were compared to the matched laboratory plasma results
- Criteria used to identify samples:
  - Patients in critical care departments
  - Capillary result obtained by the intended operator using the meter
  - Plasma glucose result obtained from the same subject on the laboratory method within 15 minutes.

Study 2 - Meter A
Capillary

Glucose <75 mg/dL

Specimen Type	Within ±5 mg/dL	Within ±10 mg/dL	Within ±12 mg/dL	Within ±15 mg/dL	Exceed ±15 mg/dL
Capillary	907/1894 (47.9%)	1470/1894 (77.6%)	1614/1894 (85.2%)	1737/1894 (91.7%)	157/1894 (8.3%)

Glucose ≥75 mg/dL

Specimen Type	Within ±5%	Within ±10%	Within ±12%	Within ±15%	Within ±20%	Exceeds ±20%
Capillary	7473/ 14884 (50.2%)	11087/ 14884 (74.5%)	12799/ 14884 (86.0%)	13712/ 14884 (92.1%)	14350/ 14884 (96.4%)	534/ 14884 (3.6%)

Study 3 - Meter B

- Capillary whole blood specimens (N=345) were obtained from patients within critical care units
- Meter testing was performed by intended operators
- Capillary meter results were compared to matched plasma results on a laboratory method

Study 3 Meter B Capillary

Glucose <75 mg/dL

Specimen Type	Within ±5 mg/dL	Within ±10 mg/dL	Within ±12 md/dL	Within ±15 mg/dL	Exceed ±15 mg/dL
Capillary	7/12 (58.3%)	11/12 (91.7%)	11/12 (91.7%)	12/12 (100%)	0/12 (0%)

Glucose ≥75 mg/dL

Specimen Type	Within ±5%	Within ±10%	Within ±12%	Within ±15%	Within ±20%	Exceeds ±20%
Capillary	169/333 (50.8%)	272/333 (81.7%)	288/333 (86.5%)	308/333 (92.5%)	324/333 (97.3%)	9/333 (2.7%)

Study 3 Meter B
Healthy Population
Capillary

Glucose <75 mg/dL

Specimen Type	Within ±5 mg/dL	Within ±10 mg/dL	Within ±12 mg/dL	Within ±15 mg/dL	Exceed ±15 mg/dL
Healthy Population	13/18 (72.2%)	18/18 (100.0 %)	18/18 (100.0%)	18/18 (100.0 %)	0/18 (0.0%)

Glucose ≥75 mg/dL

Specimen Type	Within ±5%	Within ±10%	Within ±12%	Within ±15%	Within ±20%	Exceeds ±20%
Healthy Population	104 / 145 (71.7 %)	137 / 145 (94.5 %)	140 / 145 (96.6%)	145 / 145 (100.0 %)	145 / 145 (100.0 %)	0 / 145 (0.0%)

Combined Data for Glucose Concentrations <75 mg/dL

Study	N	Within ±5 mg/dL	Within ±10 mg/dL	Within ±12 mg/dL	Within ±15 mg/dL	Exceeds ±15 mg/dL
Study 1 (meter A)	-	-	-	-	-	-
Study 2 (meter A)	1894	(47.9%)	(77.6%)	(85.2%)	(91.7%)	(8.3%)
Study 3 (meter B)	12	(58.3%)	(91.7%)	(91.7%)	(100%)	(0%)
Meter B: healthy population	18	(72.2%)	(100.0 %)	(100.0%)	(100.0 %)	(0.0%)
Statstrip: venous	79	(86.1%)	(97.5%)	(98.7%)	(100%)	(0.0%)
Statstrip: arterial	201	(81.1%)	(94.0%)	(97.0%)	(98.0%)	(2.0%)

Combined Data for Glucose Concentration ≥75 mg/dL

Study	N	Within ±5%	Within ±10%	Within ±12%	Within ±15%	Within ±20%	Exceeds ±20%
Study 1 – meter A	567	(48.9%)	(79.4%)	(85.4%)	(91.0%)	(96.8%)	(3.2%)
Study 2 – meter A	14884	(50.2%)	(74.5%)	(86.0%)	(92.1%)	(96.4%)	(3.6%)
Study 3 - meter B	333	(50.8%)	(81.7%)	(86.5%)	(92.5%)	(97.3%)	(2.7%)
Meter A: Venous / Arterial	200	(67.5%)	(93.0%)	(95.5%)	(98.0%)	(100%)	(0.0%)
Meter B: healthy population	145	(71.7 %)	(94.5 %)	(96.6%)	(100.0 %)	(100.0 %)	(0.0%)
Statstrip: venous	268	(63.8%)	(91.8%)	(97.0%)	(99.6%)	(100%)	(0.0%)
Statstrip: arterial	1267	(66.6%)	(92.7%)	(96.3%)	(98.2%)	(99.3%)	(0.7%)

- The community may not be aware of this difference in meter performance
- Many recent opportunities for discussion of appropriate accuracy criteria in this patient population
- No criteria proposed so far would allows for the capillary data just presented

Accuracy Criteria Proposed by External Committees

	Recommended Criteria	Study 2
POCT12	***95%*** within ±12 mg/dL <100 mg/dL and ±12% >100 mg/dL.	***85.2%*** <75 mg/dL ***86%*** >75 mg/dL
ISO 15197:2013 (for OTC blood glucose meters)	***95%*** within ±15 mg/dL <100 mg/dL and ±15% >100 mg/dL	***91.7%*** <75 mg/dL ***92.1%*** > 75 mg/dL

Accuracy Criteria Proposed During the POC BGMS Guidance Development

	Criteria Used/Proposed	Study 2 Capillary
FDA Final BGMS Guidance	***95%*** within ±12 mg/dL <75 mg/dL and ±12% >75 mg/dL	***85%*** <75mg/dL ***86%*** ≥75mg/dL
FDA draft BGMS Guidance	***99%*** within ±7 mg/dL <70 mg/dL and ±10% >70mg/dL	***77.6%*** <75mg/dL ***74.5%*** ≥75mg/dL
Most Stringent Comment to FDA's Draft BGMS Guidance	***95%*** within ±7mg/dL <70 mg/dL and ±10% >70 mg/dL	***77.6%*** <75mg/dL ***74.5%*** ≥75mg/dL
Most Permissive Comment to FDA's Draft BGMS Guidance	***95%*** within ±12 mg/dL <100 mg/dL and ±12% >100 mg/dL	***85%*** <75mg/dL ***86%*** ≥75mg/dL

Potential Factors Influencing Accuracy

- Investigators have been unable to identify specific subpopulations within this hospitalized patient population that would explain the difference in performance

- Possible factors:
  - Compromised capillary blood flow
  - Sample collection factors
  - Unidentified patient conditions

Question 1 for the Panel

1. Given the data presented, please discuss any factors that should be considered in assessing the benefits and risks of glucose meters intended for measuring blood glucose in capillary blood in patients receiving intensive medical intervention/therapy.
   a) Please discuss the benefits of such testing.
   b) Please discuss whether there are unique risks when capillary blood is tested in patients receiving intensive medical intervention/therapy.
   c) If there are unique risks, please discuss potential mitigations for each risk.
   d) Please discuss the benefit to risk balance for this intended use.

Clinical Laboratory Improvement Amendments (CLIA) of 1988

- Ensures quality laboratory testing
- Any laboratory that performs testing on human specimens (e.g. blood, urine, tissue) for the purpose of diagnosis, prevention, or treatment of disease, or assessment of health, must be certified under the CLIA regulations

CLIA Complexity - Tests

	High Complexity	Moderate Complexity	Waived
Definition	Complex tests with manual steps or extensive troubleshooting Any tests not categorized or cleared tests modified by lab	Tests with several steps (i.e., sample separation into serum/plasma)	Simple tests with low likelihood of erroneous result Over-the-counter, CLIA waiver by application
Example	 Mass spectrometry	 Automated immunoassay to detect vitamin D in serum	 Urine pregnancy test

For a device to be waived:

- Automatically waived (e.g., urine pregnancy tests, visually read urine dipsticks)

- Intended for home use, such as over-the-counter (OTC) tests

- Other tests can apply for waived status:
  - simple to use in the hands of the intended operators, and
  - according to the statute, waived tests are **"simple laboratory examinations and procedures that have an insignificant risk of an erroneous result"**[1]

[1]42 U.S. Code § 263(d)(3)

CLIA Regulation of BGMS

- Most glucose meters used in hospitals were settings have been cleared for over-the-counter use and are therefore waived
- Importance of having CLIA waived BGMS in point-of-care professional healthcare settings
- FDA has been encouraging manufacturers of hospital use glucose meters to seek FDA clearance and CLIA waiver for use in all hospital patient populations

Question 2 for the Panel

Given the data presented, what are the relevant factors FDA should weigh in considering whether capillary blood glucose meter testing in intensively treated population would meet the criteria for CLIA waiver (i.e., “simple” and with “an insignificant risk of an erroneous result”)?

FDA Goals

- Increase transparency on the accuracy of BGMS when capillary blood is tested in CLIA waived settings on patients receiving intensive medical intervention/therapy,
- Obtain advice from our Advisory Panel on this topic, and
- Hear public comment on this use.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