Alere Knowing now matters.

Alere Afinion™ HbA1c Dx

July 22, 2016

Clinical Chemistry and Toxicology Panel Meeting

Introduction

Rick San George, Ph.D.

Vice President, Clinical Affairs, Alere

Agenda

1. Synopsis & Definitions
2. Overview - Alere Afinion™ HbA1c Dx
3. Clinical Considerations
4. Performance - Alere Afinion™ HbA1c Dx
5. Laboratory Director Considerations
6. Mitigation of Potential Sources of Error
7. Distinction of Moderate Complexity Test from CLIA Waived Test
8. Summary

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Synopsis & Definitions

Rick San George, Ph.D.

Vice President, Clinical Affairs, Alere

Synopsis

- Alere has submitted a 510(k) application to obtain a diagnostic claim for the Afinion HbA1c Dx product to aid in the diagnosis of diabetes and for use in clinical laboratories and moderate complexity point-of-care settings
- The potential benefits of point-of-care HbA1c for diagnostic use are significant while the potential risks of the Afinion HbA1c Dx for point-of-care diagnostic use are minimal
- The Afinion HbA1c Dx product is accurate, precise, has a low total error
- As a moderate complexity point-of-care test the Afinion HbA1c Dx test will be subject to all the same requirements for proficiency testing, quality control, and operator training as the already FDA cleared laboratory methods
- Extensive and comprehensive error mitigations have been incorporated into the design and use of the Afinion system to ensure accurate results in any setting (including CLIA waived)
- Alere's proposed approach ensures that CLIA waived laboratories cannot use the new moderate complexity test

Definitions: CLIA Test Categories

	CLIA Type		
	Waived	**Moderate-Complexity**	**High Complexity**
Types of Labs performing HbA1c Tests	• Physician office labs • Point of care facilities	• Larger physician office labs • Hospitals • Reference labs	• Large academic hospital and reference labs.
Performing Point-of-Care Testing	Yes	Yes	Yes
Proficiency Testing Required	No	Yes	Yes
Quality Control Requirements	Per manufacturer Usually every shipment or Lot or 30 days	Two levels every day of testing or establish an IQCP	Varies but at least two levels once a day
Testing Personnel Educational Requirements	None	High School	60 collegiate hours
Examples	Pregnancy, glucose meters, A1c for monitoring	Vitamin D, TSH, Troponin	Mass spectrometry, Molecular diagnostics

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Overview - Alere Afinion™ HbA1c Dx

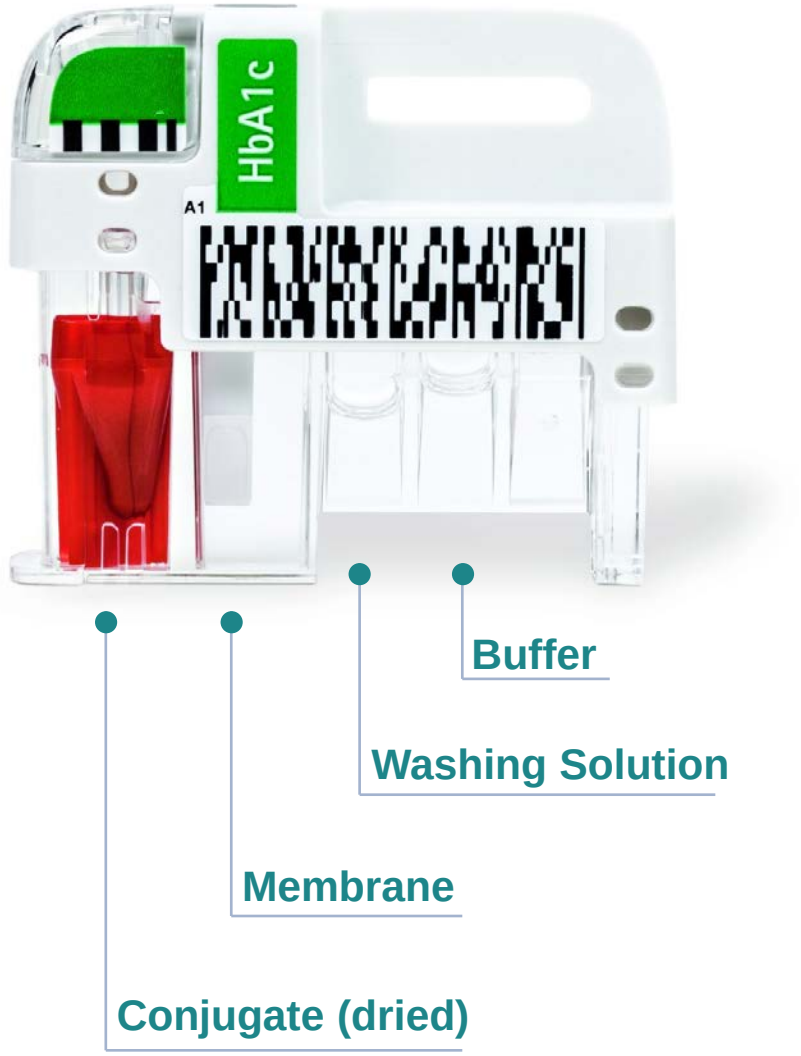
Rick San George, Ph.D.

Vice President, Clinical Affairs, Alere

Background - Alere Afinion HbA1c

- 510(k) cleared in the US as a moderate complexity test for monitoring glycemic control in people with diabetes in 2005 and CLIA waived in 2006
- In other parts of the world, Alere Afinion HbA1c is legally marketed and widely used for both monitoring and diagnosis of diabetes (ex. in Norway, Sweden, Germany etc.)
- The Alere Afinion HbA1c test offers lab quality, point-of-care, in-office results from 1.5 µL of fingerstick whole blood or venous whole blood
- It is fully automated, simple and safe to use

Alere Afinion™ HbA1c Test Cartridge



Running a test on the Alere Afinion Analyzer

New Intended Use for HbA1c in Diagnosis

- Resulting from new ADA recommendations in 2010

> *"Hemoglobin A1c measurements are used as an **aid in the diagnosis of diabetes** mellitus, as an aid to **identify patients who may be at risk** for developing diabetes mellitus, and for the **monitoring** of long-term blood glucose control in individuals with diabetes mellitus."*

- Alere has submitted a 510(k) for this intended use as a **moderate complexity** test
- This test is named Afinion HbA1c Dx

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Clinical Considerations

Richard Kahn, Ph.D.

Clinical Considerations

Richard Kahn

Clinical Professor of Medicine
University of North Carolina
Chapel Hill, NC

Disclosures

- **Consultant**

  -- Alere

- **Advisor**

  -- American Society for Nutrition

  -- America's Health Foundation

  -- Close Concerns, Inc.

Testing for Diabetes

- Millions of Americans are undiagnosed
- Hyperglycemia (diabetes or prediabetes) is a high risk CVD state
- Hyperglycemia tends to worsen over time
- Poorly controlled diabetes leads to serious chronic complications
- Ideally, we want a low-cost, rapid, convenient, easy and accurate way to diagnose diabetes.

A1c

-- Advantages

Fasting not required
Very low biological variability
Stable during acute illness
Sample stability in vial
Can be measured any time of day
Global standardization
Directly related to management

-- Disadvantages

Questionable in pts. with hemoglobinopathies, certain anemia's, advanced renal disease

Racial and ethnic differences

Most commonly used method

Ideally, we want a low-cost, rapid, convenient, easy and accurate way to diagnose diabetes.

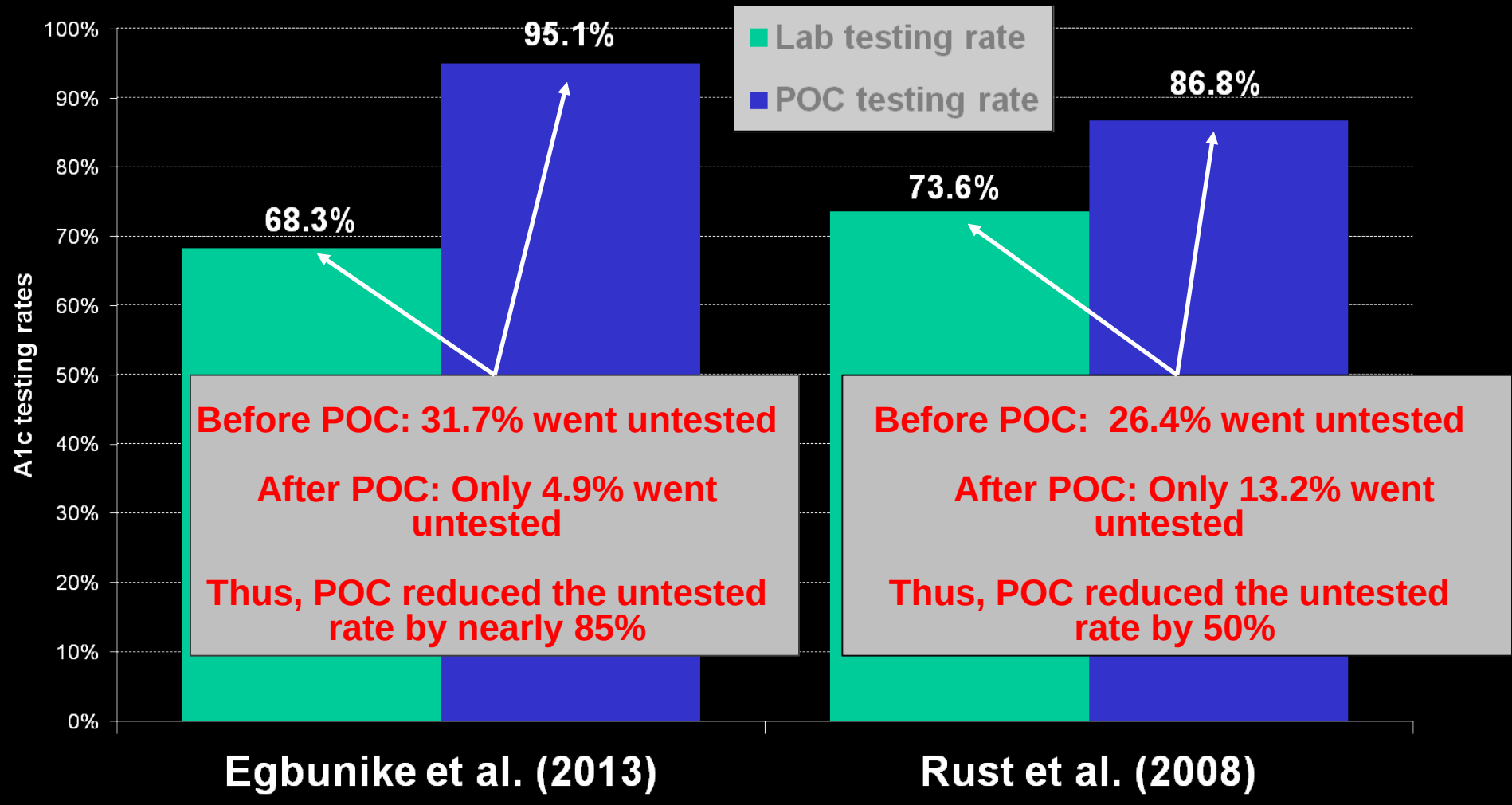
Point of care A1c testing meets these criteria

Additional Benefits of POC Diagnosis

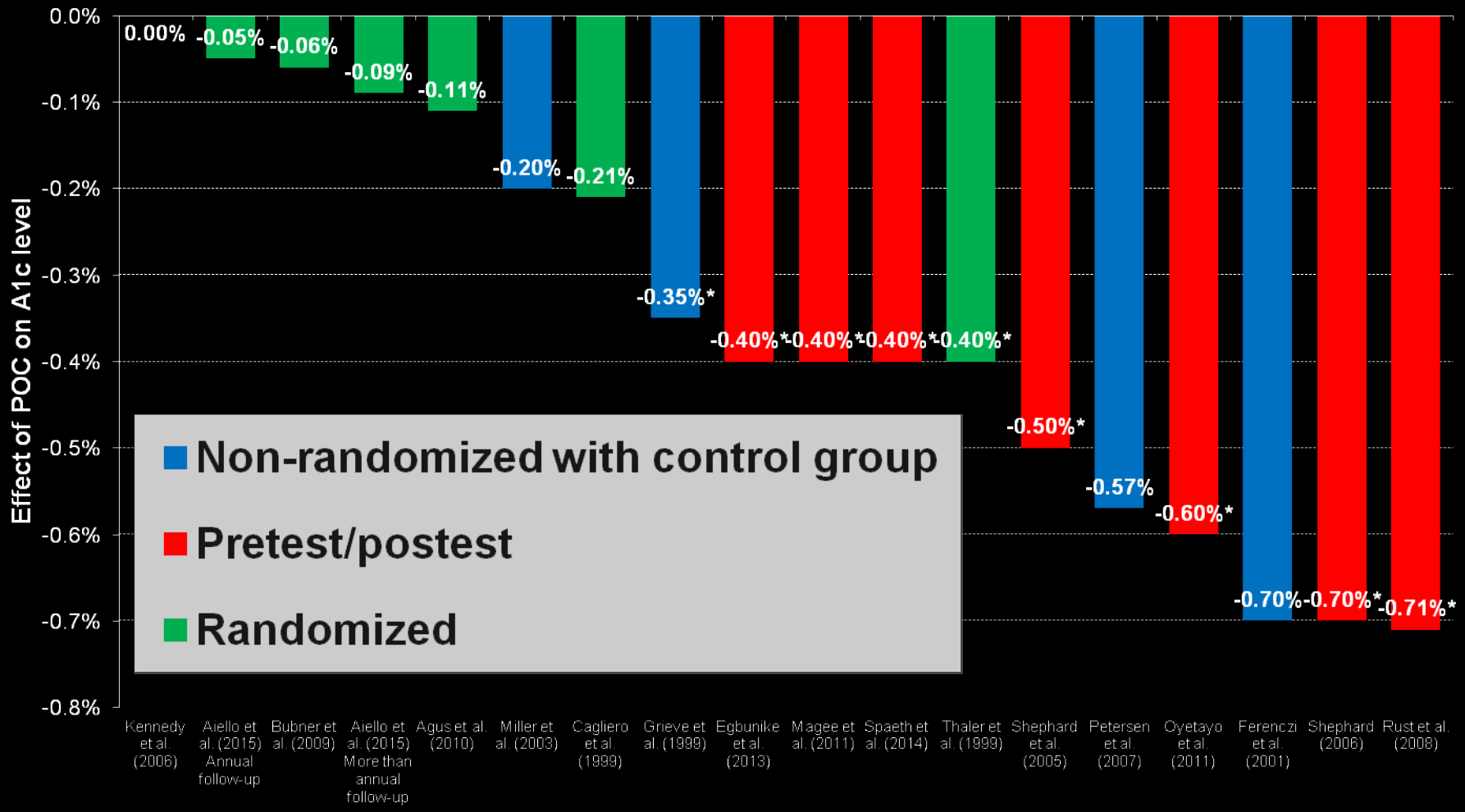
- Efficient in many ways
- Mitigates “access to care” issues
- Allows for rapid initiation of treatment
- Capitalizes on a “teachable moment”

The same benefits as point of care monitoring

Impact of POC A1c on Testing Frequency



Impact of POC A1c Monitoring



A1c Diagnostic Thresholds

Prediabetes --- 5.7-6.4 %

Diabetes --- ≥ 6.5%

No clinically significant event takes place at the diabetes diagnostic cutpoint.

But… false positive or false negatives occur as with all diagnostic methods.

Adverse Impact of a False Positive (A1c reads ≥6.5% but really <6.5%)

- Requires confirmation testing

Adverse Impact of a False Positive (A1c reads ≥6.5% but really <6.5%)

- Requires confirmation testing
- Patient actually has high-risk prediabetes

Adverse Impact of a False Positive (A1c reads ≥6.5% but really <6.5%)

- Requires confirmation testing
- Patient actually has high-risk prediabetes

HRs for 15-year incidence of type 2 diabetes according to HbA_{1c}

	Model 0	Model 1	Model 2	Model 3
HbA_{1c} category				
<5.00%	2.31 (0.39–13.92)	2.55 (0.42–15.39)	2.55 (0.42–15.58)	2.43 (0.40–14.97)
5.00–5.49% (reference)	1.00	1.00	1.00	1.00
5.50–5.99	12.58 (3.83–41.30)	11.62 (3.52–38.36)	10.97 (3.30–36.47)	11.43 (3.43–38.07)
6.00–6.49%	61.05 (18.23–204.4)	52.82 (15.57–179.3)	45.52 (13.1–158.0)	46.72 (13.4–163.3)

Adverse Impact of a False Positive (A1c reads ≥6.5% but really <6.5%)

- Requires confirmation testing
- Patient actually has high-risk prediabetes
- Patient subject to consequences of treatment (e.g. visits, testing, drug therapy)

ADA Guidelines 2016

Prediabetes	Diabetes
Intensive lifestyle counseling	Intensive lifestyle counseling
More frequent follow-up	More frequent follow-up
Consider metformin	Consider metformin
Screen and treat CVD risk factors	Screen and treat CVD risk factors

Diabetes Care 2016 39; (Suppl.1)

Adverse Impact of a False Positive (A1c reads ≥6.5% but really <6.5%)

- Requires confirmation testing
- Patient actually has high-risk prediabetes
- Patient subject to consequences of treatment (e.g. visits, testing, drug therapy)
- Possible employment and insurance issues

Americans With Disabilities Act

Cannot deny or discriminate in employment

Americans With Disabilities Act

Cannot deny or discriminate in employment

Affordable Care Act

Cannot deny coverage for people with diabetes

Cannot charge higher rates

Cannot discriminate for pre-existing condition

No dollar limits on coverage

Covers essential health benefits

Adverse Impact of a False Positive (A1c reads ≥6.5% but really <6.5%)

- Requires confirmation testing
- Patient actually has high-risk prediabetes
- Patient subject to consequences of treatment (e.g. visits, testing, drug therapy)
- Possible employment and insurance issues
- Psychological impact of diagnosis

Adverse Impact of a False Positive (A1c reads ≥6.5% but really <6.5%)

- Requires confirmation testing
- Patient actually has high-risk prediabetes
- Patient subject to consequences of treatment (e.g. visits, testing, drug therapy)
- Possible employment and insurance issues
- Psychological impact of diagnosis

(no data on impact)

Adverse Impact of a False Positive (A1c reads ≥6.5% but really <6.5%)

- Requires confirmation testing
- Patient actually has high-risk prediabetes
- Patient subject to consequences of treatment (e.g. visits, testing, drug therapy)
- Possible employment and insurance issues
- Psychological impact of diagnosis

The very same likelihood as a false positive laboratory result

Adverse Impact of a False Negative (A1c reads <6.5% but really ≥6.5%)

- False reassurance about health status

Adverse Impact of a False Negative (A1c reads <6.5% but really ≥6.5%)

- False reassurance about health status

(Repeat testing annually will mitigate)

Adverse Impact of a False Negative (A1c reads <6.5% but really ≥6.5%)

- False reassurance about health status

- Patient receives treatment for high-risk prediabetes

(Repeat testing at least annually)

ADA Guidelines 2016

Prediabetes	Diabetes
Intensive lifestyle counseling	Intensive lifestyle counseling
More frequent follow-up	More frequent follow-up
Consider metformin	Consider metformin
Screen and treat CVD risk factors	Screen and treat CVD risk factors

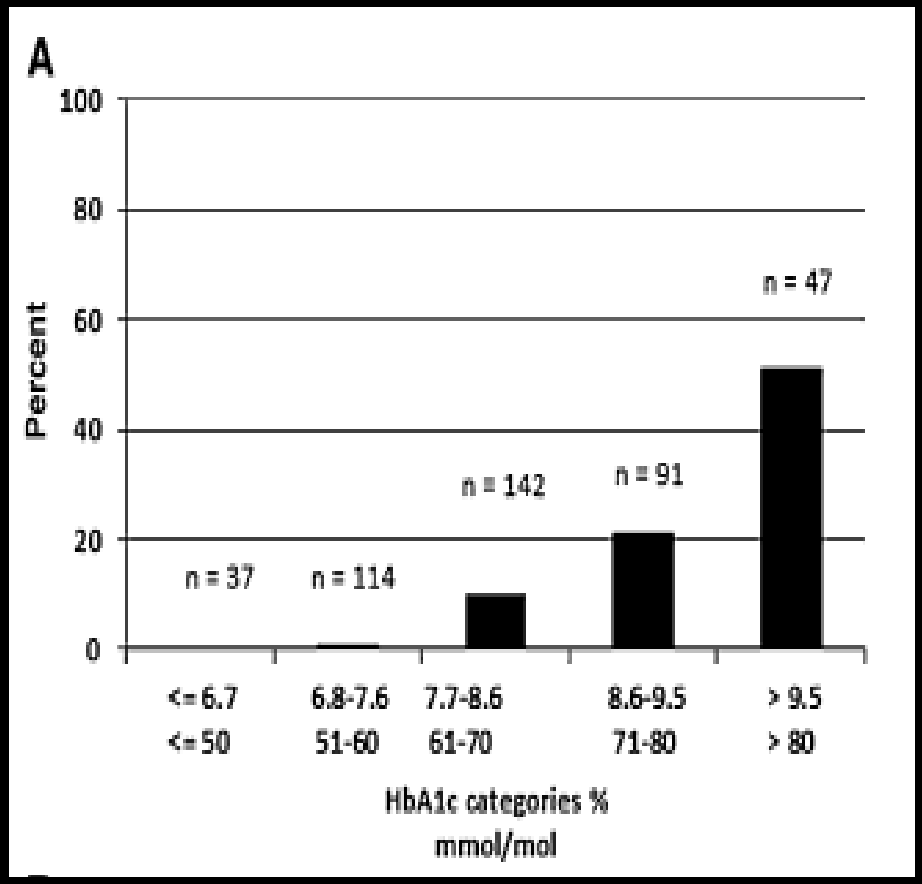
Diabetes Care 2016 39; (Suppl.1)

Adverse Impact of a False Negative (A1c reads <6.5% but really ≥6.5%)

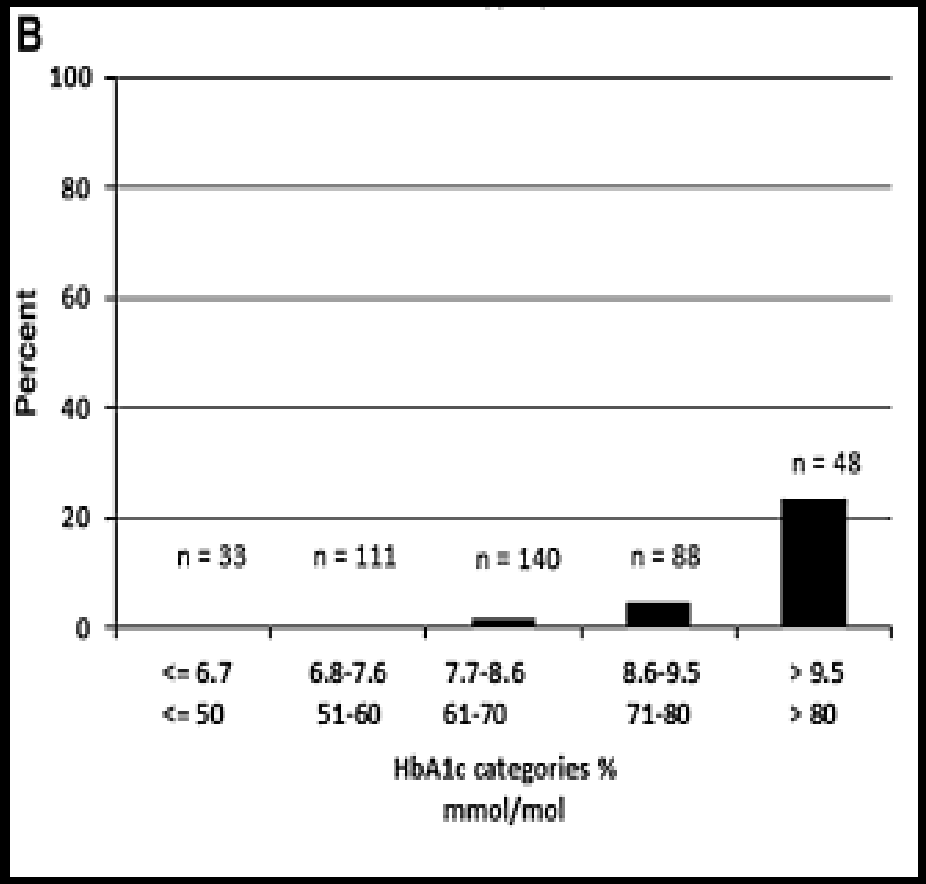
- False reassurance about health status
- Patient receives treatment for high-risk prediabetes
- Chronic complications more likely (?)

Impact of A1c from Onset of Diabetes to Development of Retinopathy & Nephropathy (20-25 yrs Follow-up)

Proliferative Retinopathy



Persistent Macroalbuminuria



Diabetes Care. 2015; 38:308-315

Adverse Outcomes Associated with Long-Term A1c Levels

Endpoints	HR (95% CI) per 1% higher mean HbA_{1c} level						
	Knots	Overall population				Intensive glucose control	Standard glucose control	*p* value (intensive vs standard)
		Unadjusted	*p* value	Adjusted[a]	*p* value	Adjusted[a]	Adjusted[a]	
Macrovascular events	Below 7.0	1.07 (0.91, 1.26)	0.4117	1.02 (0.86, 1.21)	0.8310	1.13 (0.89, 1.43)	0.82 (0.65, 1.04)	0.7362
	Above 7.0	1.43 (1.35, 1.51)	<0.0001	1.38 (1.30, 1.47)	<0.0001	1.58 (1.43, 1.75)	1.31 (1.21, 1.42)	0.0974
Microvascular events	Below 6.5	1.06 (0.79, 1.42)	0.7012	1.02 (0.76, 1.39)	0.8744	1.06 (0.69, 1.63)	0.82 (0.54, 1.25)	0.9016
	Above 6.5	1.58 (1.51, 1.65)	<0.0001	1.40 (1.33, 1.47)	<0.0001	1.72 (1.59, 1.87)	1.26 (1.18, 1.35)	<0.0001
All-cause death	Below 7.0	1.04 (0.88, 1.23)	0.6246	1.01 (0.85, 1.21)	0.9158	1.12 (0.87, 1.44)	0.81 (0.64, 1.04)	0.9008
	Above 7.0	1.42 (1.34, 1.51)	<0.0001	1.38 (1.29, 1.48)	<0.0001	1.67 (1.50, 1.86)	1.29 (1.18, 1.41)	0.0080

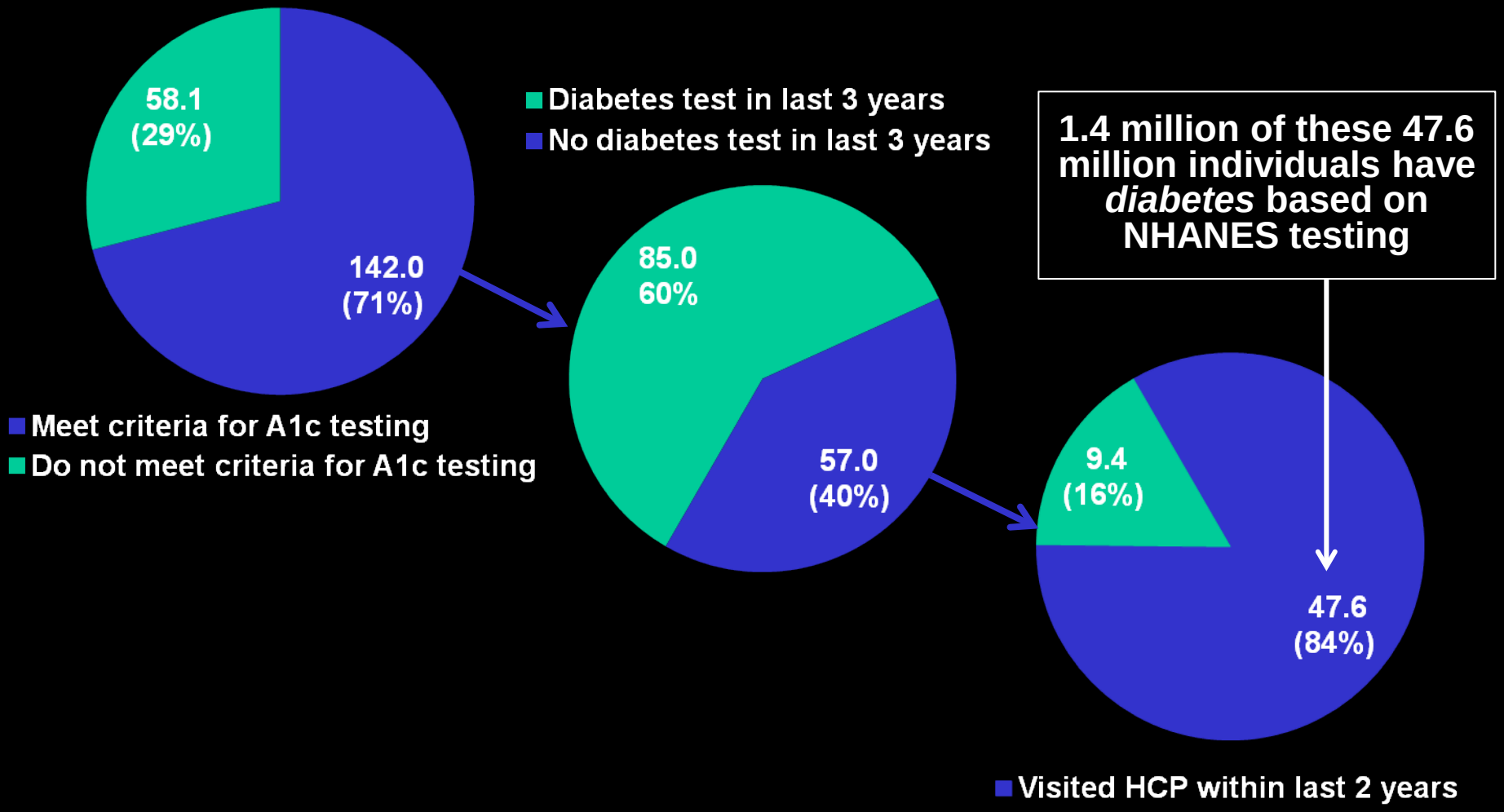
ADVANCE Study. Diabetologia 2012;55:636-643

Adverse Impact of a False Negative (A1c reads <6.5% but really ≥6.5%)

- False reassurance about health status
- Patient receives treatment for high-risk prediabetes
- Chronic complications are very unlikely

The very same likelihood as a false negative laboratory result

Potential Impact of Increased Testing for Diagnosis



NHANES 2013 and 2014 data.

Conclusion

The potential benefits of point of care A1c for diagnosis are significant while the potential risks are minimal.

Performance - Alere Afinion™ HbA1c Dx

Rick San George, Ph.D.

Vice President, Clinical Affairs, Alere

General Concerns About POC HbA1c for Diagnosis

- Not accurate enough
- Not precise enough/lack of reproducibility
- Lack of mandated proficiency testing (PT)
- Lot-to-lot variations in reagents/calibration
- Lack of on-going quality assurance of results
- Unknown performance in CLIA waived settings

These concerns do not apply to the Alere Afinion HbA1c Dx

HbA1c Tests for Diagnosis

FDA states in its Executive Summary:

> *"The discussion at this panel meeting should focus on the questions related to POC use and CLIA waiver. FDA therefore requests that, for the purposes of this discussion, the panel assume that the Afinion HbA1c Dx assay has equivalent analytical performance to other cleared diagnostic HbA1c tests."*

Alere concurs with the focus of today's meeting. However, because many of the questions about POC use and CLIA waiver arise from concerns about analytical performance, Alere will briefly summarize the performance data for the Afinion HbA1c Dx assay.

FDA Special Controls for a HbA1c Test System for Diagnosis of Diabetes

PART 862 - CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES Subpart B--Clinical Chemistry Test Systems Sec. 862.1373 Hemoglobin A1c test system	
(1) The device must have initial and annual standardization verification by a certifying glycohemoglobin standardization organization deemed acceptable by FDA.	
(2) The premarket notification submission must include performance testing to evaluate precision, accuracy, linearity, and interference, including the following:	
	(i) Performance testing of device **precision** must, at a minimum, use blood samples with concentrations near 5.0 percent, 6.5 percent, 8.0 percent, and 12 percent hemoglobin A1c. This testing must evaluate precision over a minimum of 20 days using at least three lots of the device and three instruments, as applicable.
	(ii) Performance testing of device **accuracy** must include a minimum of 120 blood samples that span the measuring interval of the device and compare results of the new device to results of a standardized test method. Results must demonstrate little or no bias versus the standardized method.
	(iii) Total error of the new device must be evaluated using single measurements by the new device compared to results of the standardized test method, and this evaluation must demonstrate a **total error less than or equal to 6 percent**.
(3) When assay interference from Hemoglobin F or interference with other hemoglobin variants with low frequency in the population is observed, a warning statement must be placed in a black box and must appear in all labeling material for these devices describing the interference and any affected populations.	

Key Studies to Demonstrate < 6% Total Error

Total Error combines accuracy and precision

$$\%\mathrm{TE} = |\%\ \mathrm{Bias}| + 1.96 \times \%\mathrm{CV} \times (1 + \%\mathrm{Bias}/100)$$

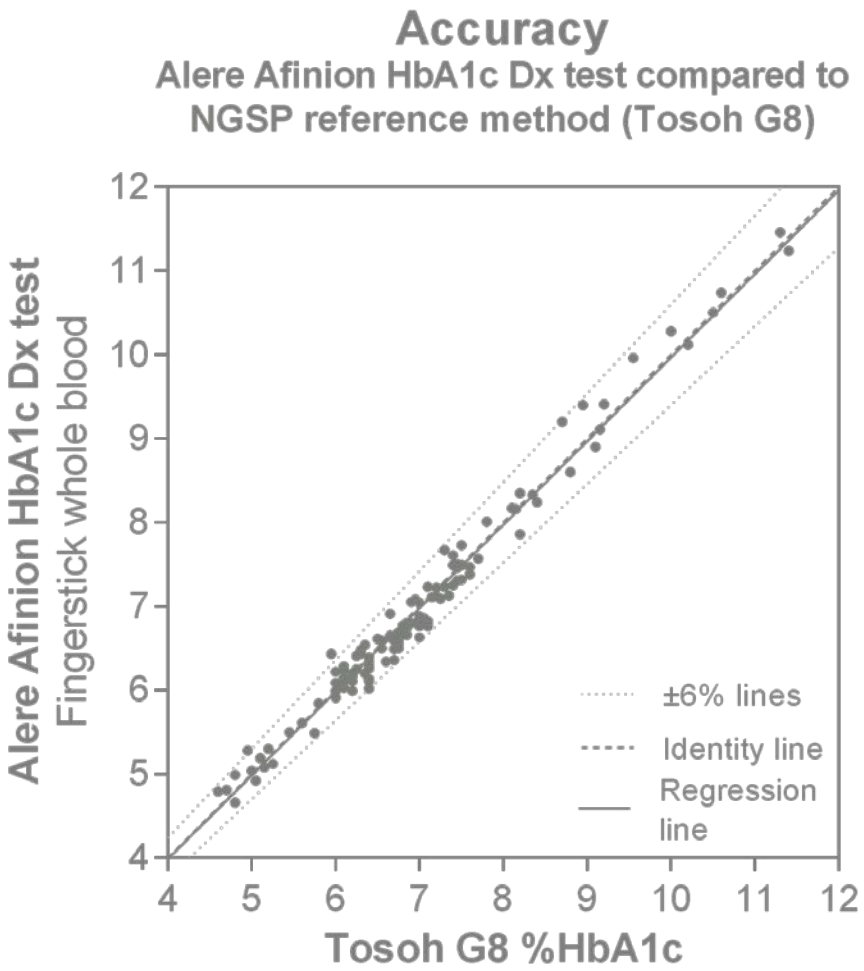
Accuracy Study (%Bias)

Precision Study (%CV)

Total Error (%TE) Calculation

Accuracy Study Results: Fingerstick Samples

y = 0.997x + 0.000, r = 0.991, n = 120		
97.5% of results within ±6%		
Decision level (%HbA1c)	Absolute Bias (units of %HbA1c)	**%Bias**
5.0	-0.017	**-0.335**
6.5	**-0.022**	**-0.334**
8.0	-0.027	**-0.334**
12.0	-0.040	**-0.333**

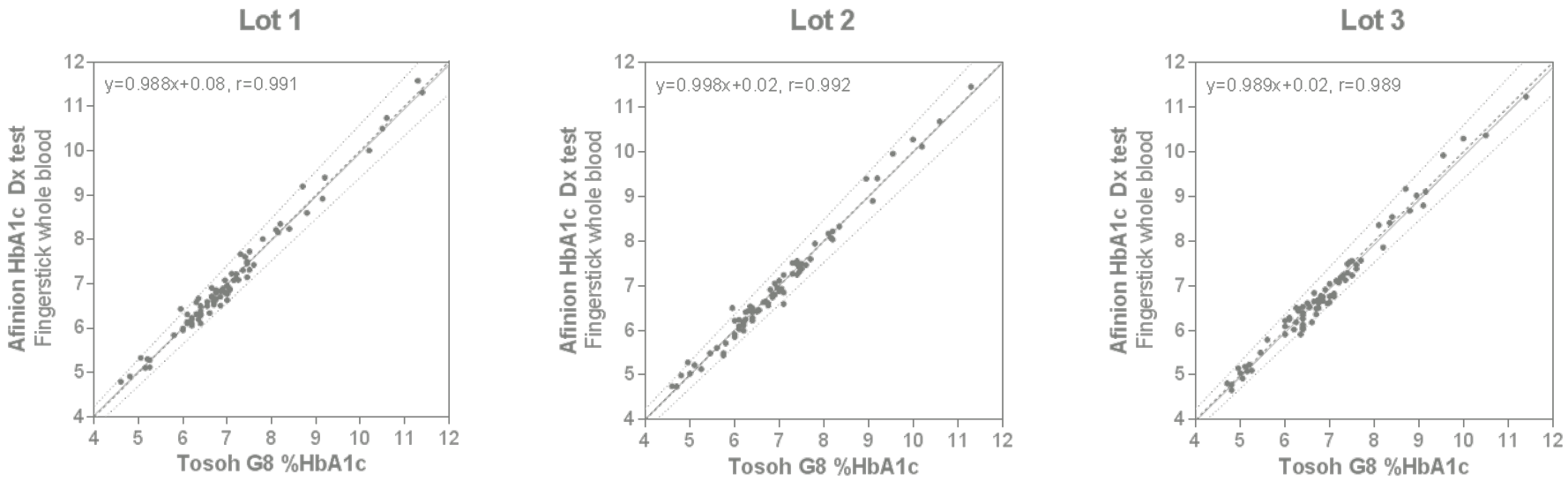


The Afinion HbA1c Dx is accurate

Accuracy Study Results: Fingerstick Samples

Accuracy - results per lot

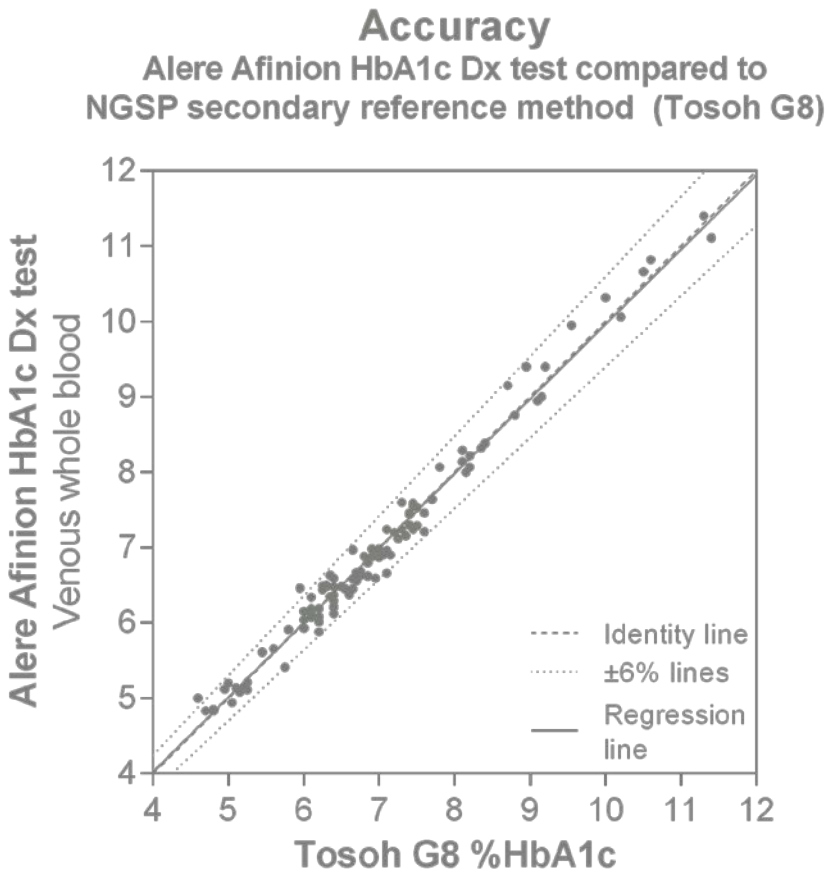
Alere Afinion HbA1c Dx test compared to NGSP secondary reference method (Tosoh G8)



No significant lot-to-lot variability

Accuracy Study Results: Venous Whole Blood

y = 0.991x + 0.053, r = 0.990, n = 120		
97.1% of results within ±6%		
Decision level (%HbA1c)	Absolute Bias (units of %HbA1c)	**%Bias**
5.0	0.010	**0.195**
6.5	**-0.003**	**-0.052**
8.0	-0.017	**-0.206**
12.0	-0.051	**-0.429**

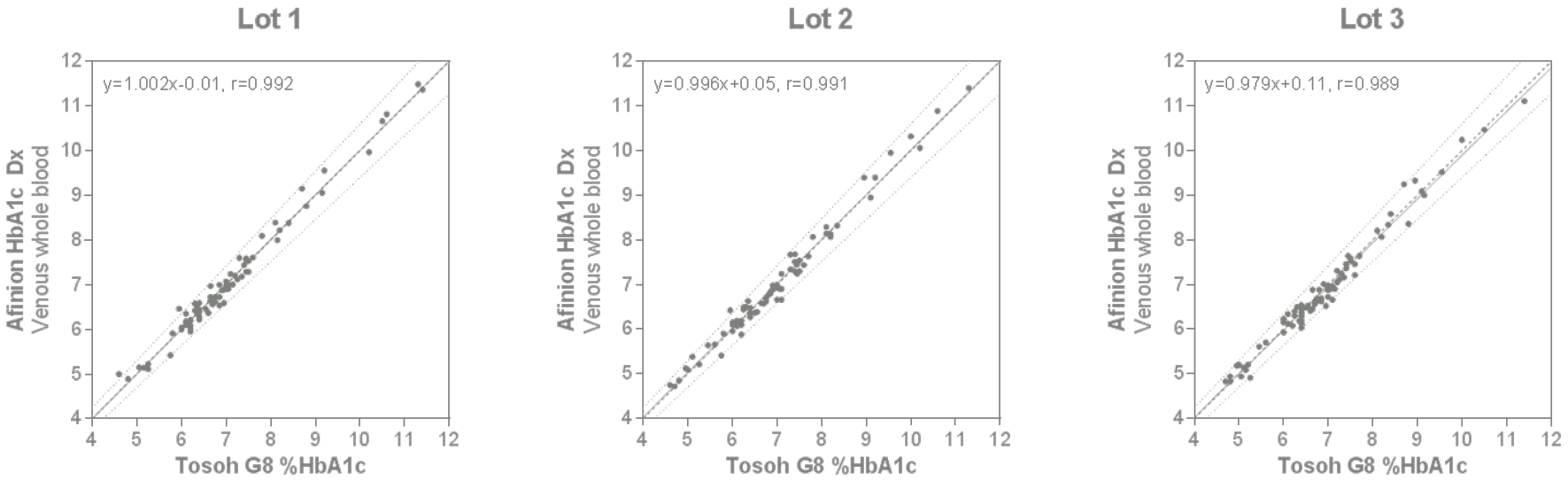


Afinion HbA1c Dx is accurate

Accuracy Study Results: Venous Whole Blood

Accuracy - results per lot

Alere Afinion HbA1c Dx test compared to NGSP secondary reference method (Tosoh G8)



No significant lot-to-lot variability

Precision: Fingerstick Samples

Interval %HbA1c	No. of samples, N	Minimum %HbA1c	Maximum %HbA1c	Mean %HbA1c	S_r	Duplicate %CV
4.00-5.99	47	4.77	5.99	5.41	0.103	**1.90**
6.00-6.99	**68**	**6.00**	**6.98**	**6.46**	**0.090**	**1.40**
7.00-9.99	51	7.02	9.94	7.93	0.106	**1.33**
≥10	6	10.07	11.52	10.72	0.059	**0.55**

S_r estimated per interval: $$S_r = \sqrt{\frac{\sum_i \left(X_{i1} - X_{i2}\right)^2}{2N}}$$

Duplicate %CV = (S_r /Interval Mean)*100%

Afinion HbA1c Dx is precise: <2% CV on fingerstick samples

Precision Results: Venous Whole Blood

Results are root mean square pooled results for each sample type and level across all sites and all lots

HbA1c Level	%HbA1c Range (mean)	Repeat-ability %CV (within run)	%CV between run	%CV between day	%CV between lot	%CV total
Low	4.74-5.24	1.21	0.20	0.13	0.75	1.45
Threshold	**6.18-6.62**	**1.12**	**0.12**	**0.10**	**0.58**	**1.27**
Medium	7.90-8.48	1.11	0.00	0.04	0.36	1.16
High	11.81-12.36	0.97	0.14	0.00	0.00	0.98
Control C I	6.32	0.89	0.00	0.16	0.27	0.94
Control C II	8.48	0.79	0.00	0.07	0.00	0.79

Afinion HbA1c Dx is precise:
<1.5% CV on venous whole blood samples

Total Error Results

Fingerstick Whole Blood:

%HbA1c Level	%Bias	%CV	%TE
5.0	-0.335	1.90	4.05
6.5	-0.334	1.40	3.07
8.0	-0.334	1.33	2.94
12.0	-0.333	0.55	1.41

Venous Whole Blood:

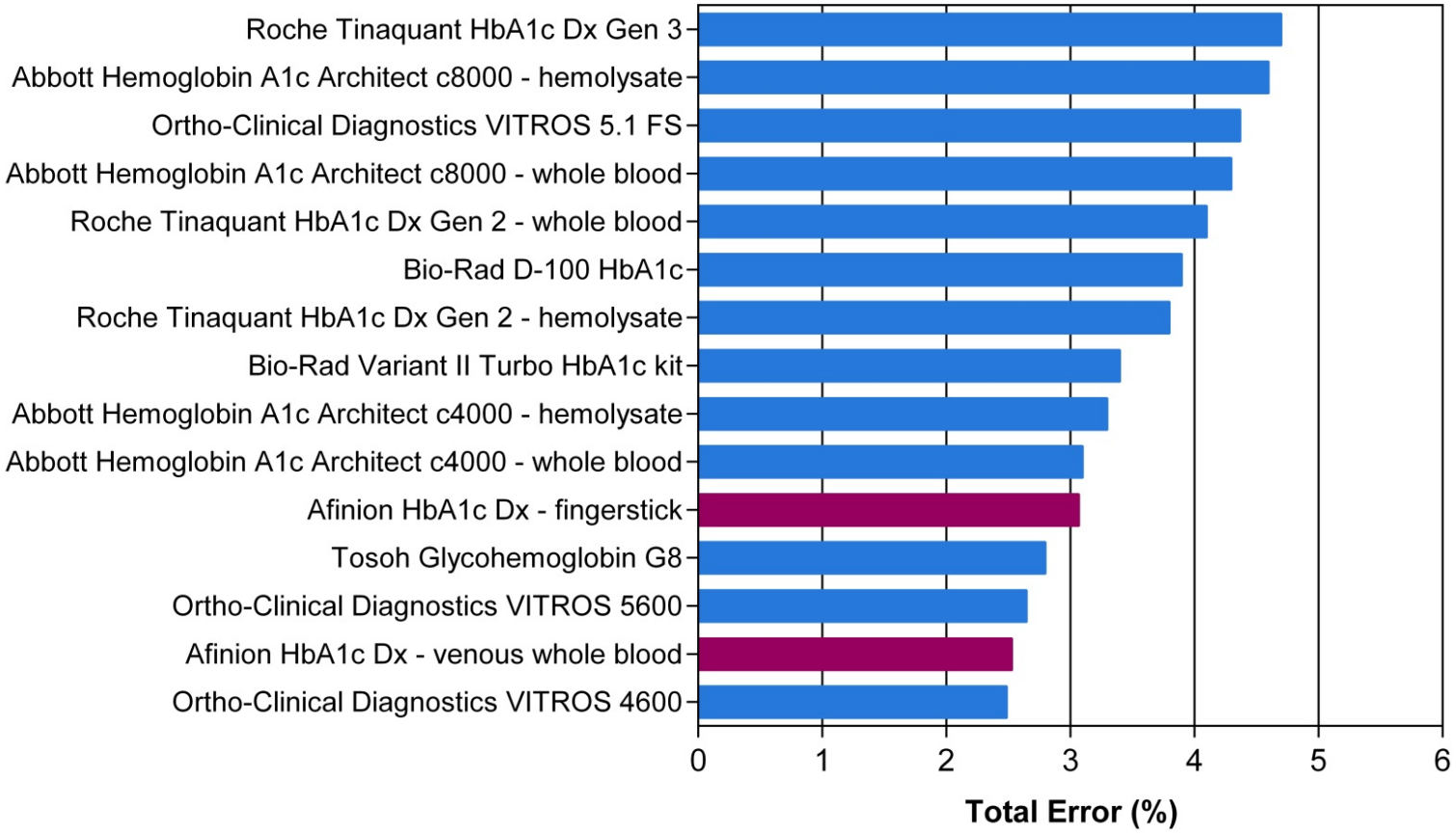
%HbA1c Level	%Bias	%CV	%TE
5.0	0.195	1.45	3.04
6.5	-0.052	1.27	2.53
8.0	-0.206	1.16	2.48
12.0	-0.429	0.98	2.35

Total Error: <4.1% for both sample types and all levels

$$\%\mathrm{TE} = |\%\ \mathrm{Bias}| + 1.96 \times \%\mathrm{CV} \times (1 + \%\mathrm{Bias}/100)$$

Alere Afinion™ HbA1c Dx Total Error at Diagnostic Cutoff of 6.5% vs. Cleared Central Laboratory Systems*

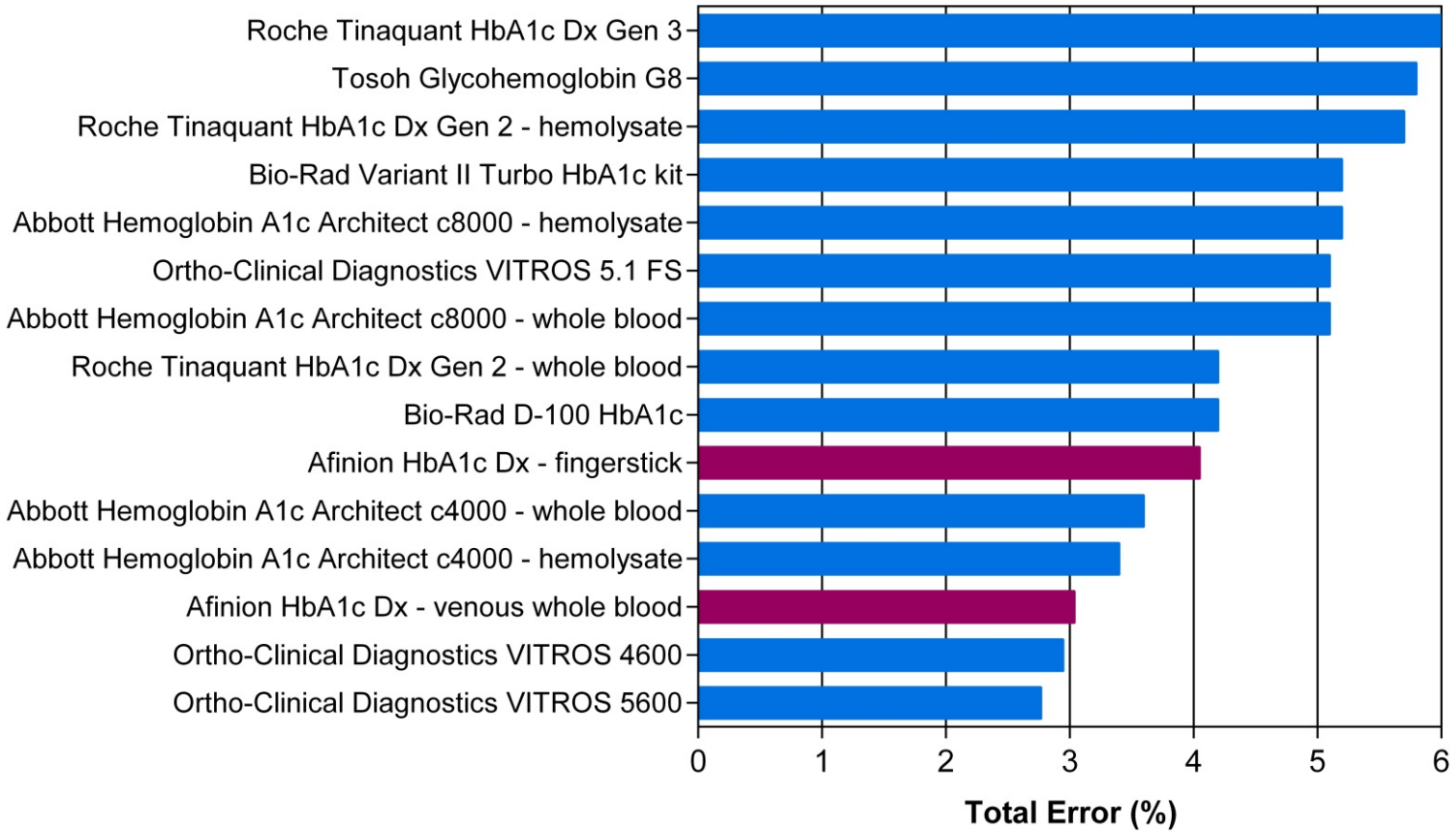
Data from 510(k) decision summaries http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?IVDProducts=on



**Afinion data not yet reviewed by FDA. Performance characteristics for the Afinion HbA1c Dx assay have not yet been established. Data presented are not from head-to-head studies and are not intended to imply superiority.*

Alere Afinion™ HbA1c Dx Total Error at 5.0% HbA1c vs. Cleared Central Laboratory Systems*

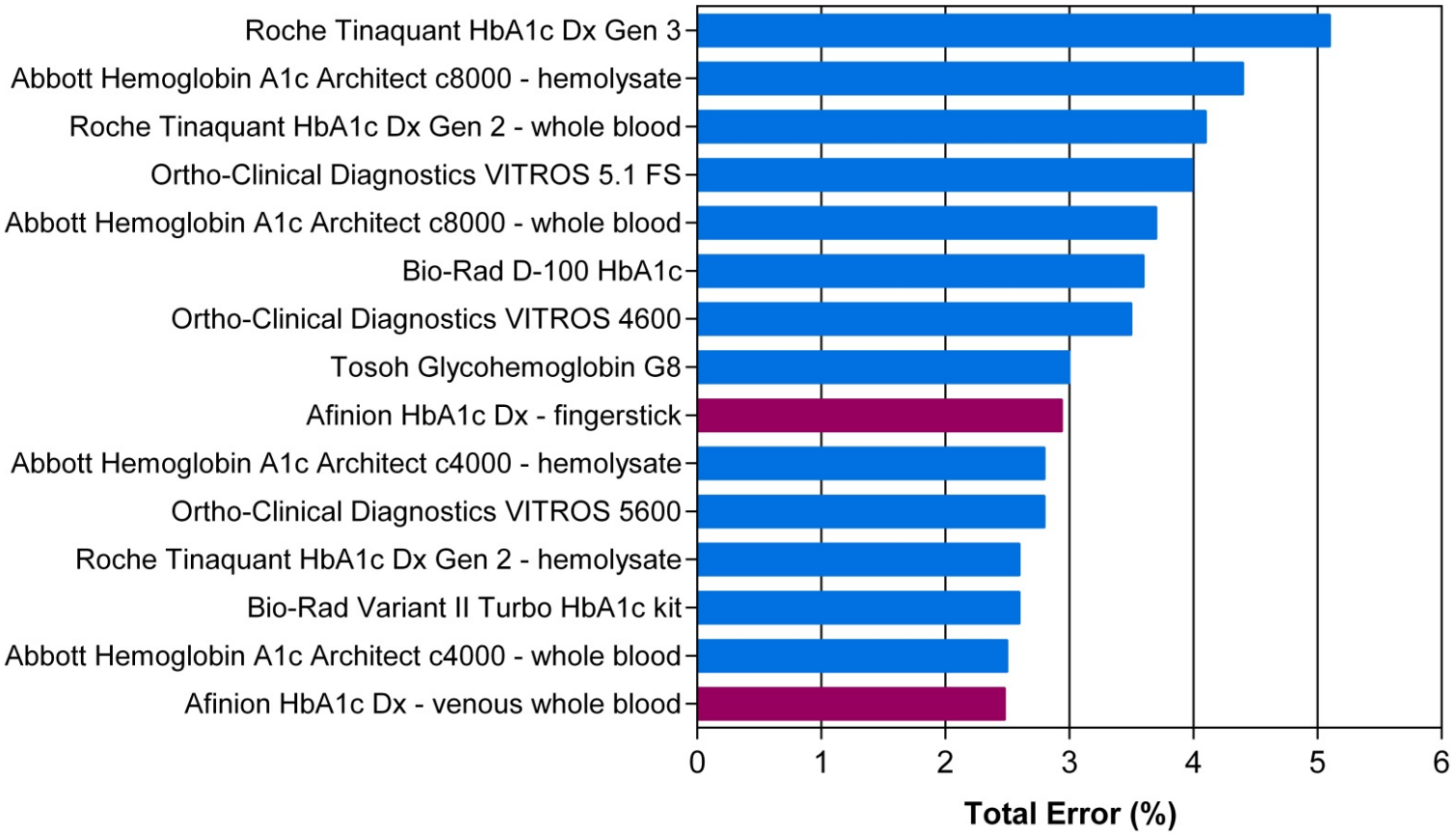
Data from 510(k) decision summaries http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?IVDProducts=on



**Afinion data not yet reviewed by FDA. Performance characteristics for the Afinion HbA1c Dx assay have not yet been established. Data presented are not from head-to-head studies and are not intended to imply superiority.*

Alere Afinion™ HbA1c Dx Total Error at 8.0% HbA1c vs. Cleared Central Laboratory Systems*

Data from 510(k) decision summaries http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?IVDProducts=on



**Afinion data not yet reviewed by FDA. Performance characteristics for the Afinion HbA1c Dx assay have not yet been established. Data presented are not from head-to-head studies and are not intended to imply superiority.*

Assurance of Ongoing Quality

Two levels of Alere Afinion™ HbA1c quality control (QC) material are available

CLIA regulations for moderate complexity tests require two levels of QC material to be run daily or an alternative implemented under an Individualized Quality Control Plan (IQCP)

This is true for all moderate complexity tests whether POC or central laboratory

Proficiency Testing

- CLIA regulations for moderate complexity tests require participation in CMS accredited proficiency testing (PT) programs
- PT involves purchasing of value assigned samples
  - 3-5 fresh whole blood samples
  - 2-3 times per year
- Assigned value is unknown to the lab
- Laboratory will run samples and report results to the program provider
- Laboratory receives results

This is true for all moderate complexity tests whether POC or central laboratory

Afinion HbA1c Dx Performance Summary

The Alere Afinion™ HbA1c Dx test is:

- Accurate
- Precise
- Exhibits insignificant lot-to-lot variation
- Exhibits total error of <6% as required by FDA special controls

Afinion Moderate Complexity HbA1c Dx Performance Summary

Each HbA1c test should be evaluated on the merits of its own performance and not where the test is performed

The requirements for a moderate complexity POC HbA1c or laboratory HbA1c test are the same

- Proficiency testing is required
- The same QC is required
- The same operator training is required

Performance Concerns Addressed

In Alere's opinion, the following concerns have been addressed for the Alere Afinion™ HbA1c Dx for testing in labs running tests of moderate complexity:

Not accurate enough	✓
Not precise enough / lack of reproducibility	✓
Lot-to-lot variations in reagents / calibration	✓
Lack of mandated proficiency testing (PT)	✓
Lack of ongoing quality assurance of results	✓
Unknown performance in CLIA-waived settings	

Remaining Content

Will Address:

- The concern regarding unknown performance in CLIA waived settings
- Mitigation of potential sources of error
- The distinction of the moderate complexity Afinion HbA1c Dx testing system from the existing CLIA waived Afinion HbA1c test for monitoring use

Alere™ Knowing now matters.

Laboratory Director Considerations

Mitchell G. Scott, Ph.D., DABCC

Laboratory Director Perspective and Concerns

Mitchell G. Scott, Ph.D., DABCC
Professor of Pathology and Immunology
Co-Medical Director, Clinical Chemistry
Medical Director, Point of Care Testing
Barnes-Jewish Hospital
Washington University School of Medicine
St. Louis, MO

Disclosures

- Consultant
  - Alere
  - IL
  - Becton-Dickinson
- Research Support
  - Siemens
  - Abbott
  - IL

Concerns

A. Analytic Performance

1. Proficiency Testing and NGSP Performance
2. Peer Reviewed External Studies
3. Physician Office Setting
4. Alere Afinion HbA1c Dx 510(k) data

B. Probability of False Positive or False Negative

C. What Could Go Wrong?

Moderate Complexity Requires Proficiency Testing

- Alere is currently seeking clearance for diagnostic use with Moderate Complexity CLIA categorization

- If cleared, end users would be required to perform proficiency testing

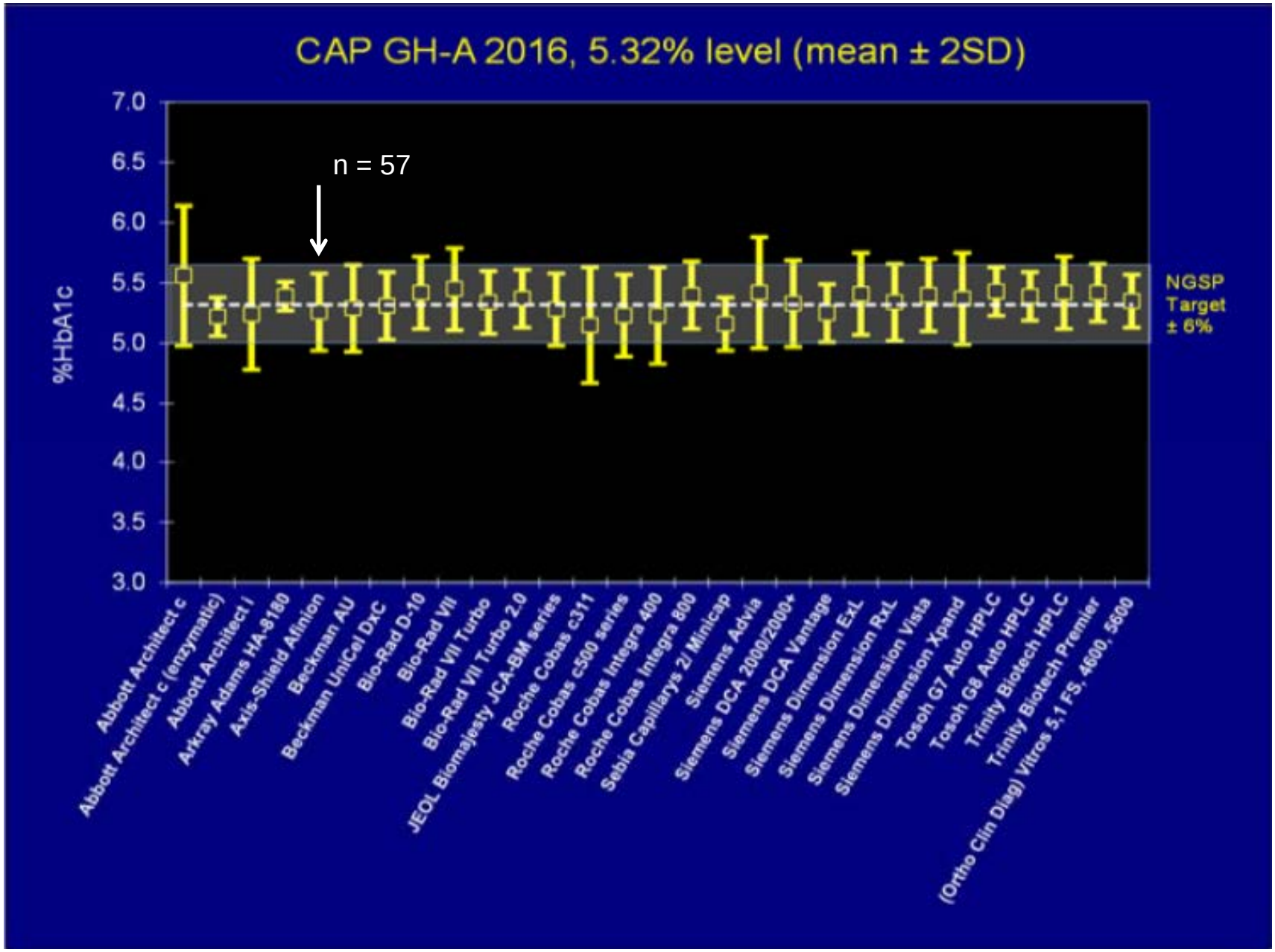
A. Analytical Performance

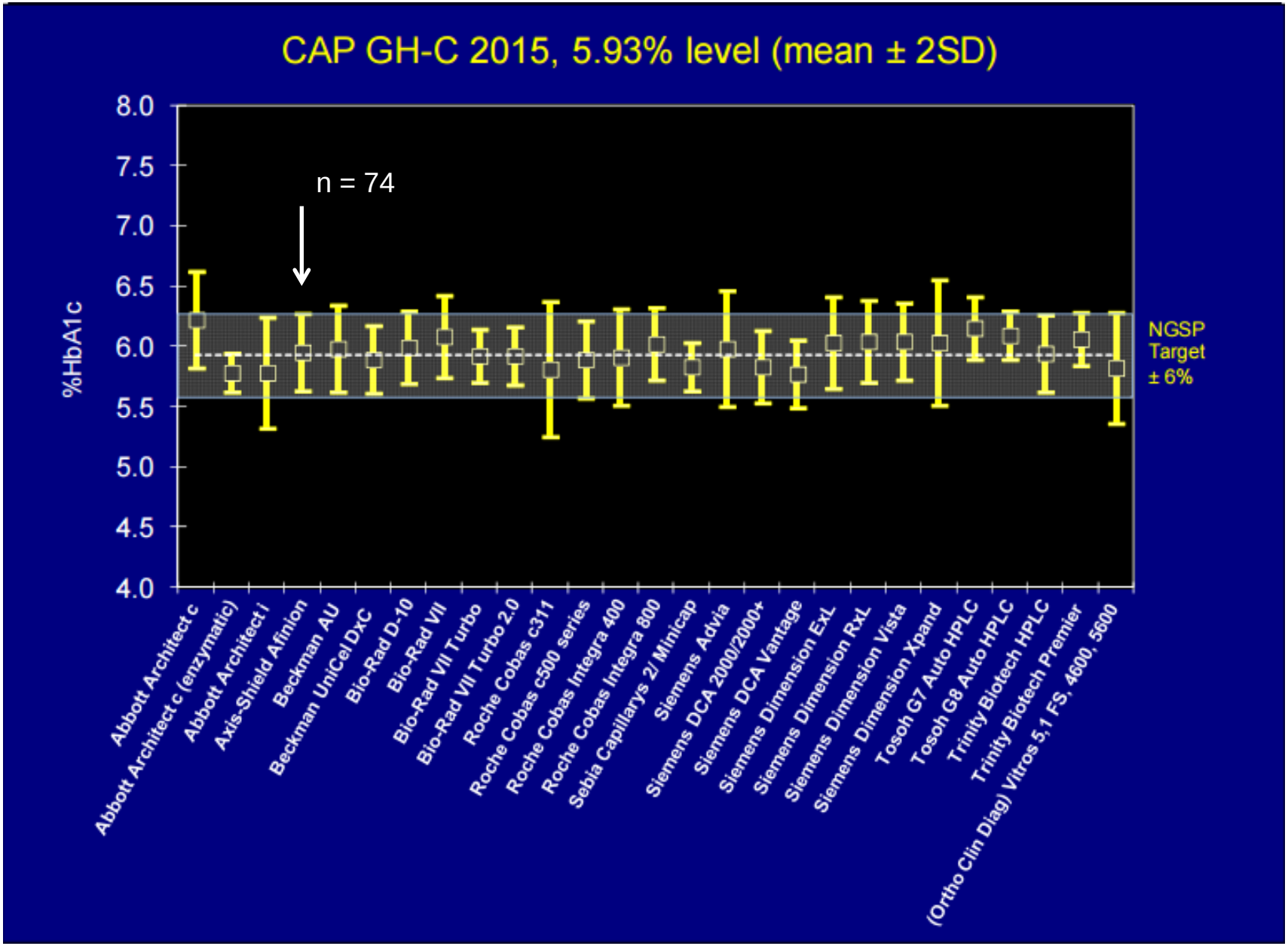
1. CAP/NGSP
2. Peer-reviewed studies
3. GP Office Setting
4. FDA Submission Data

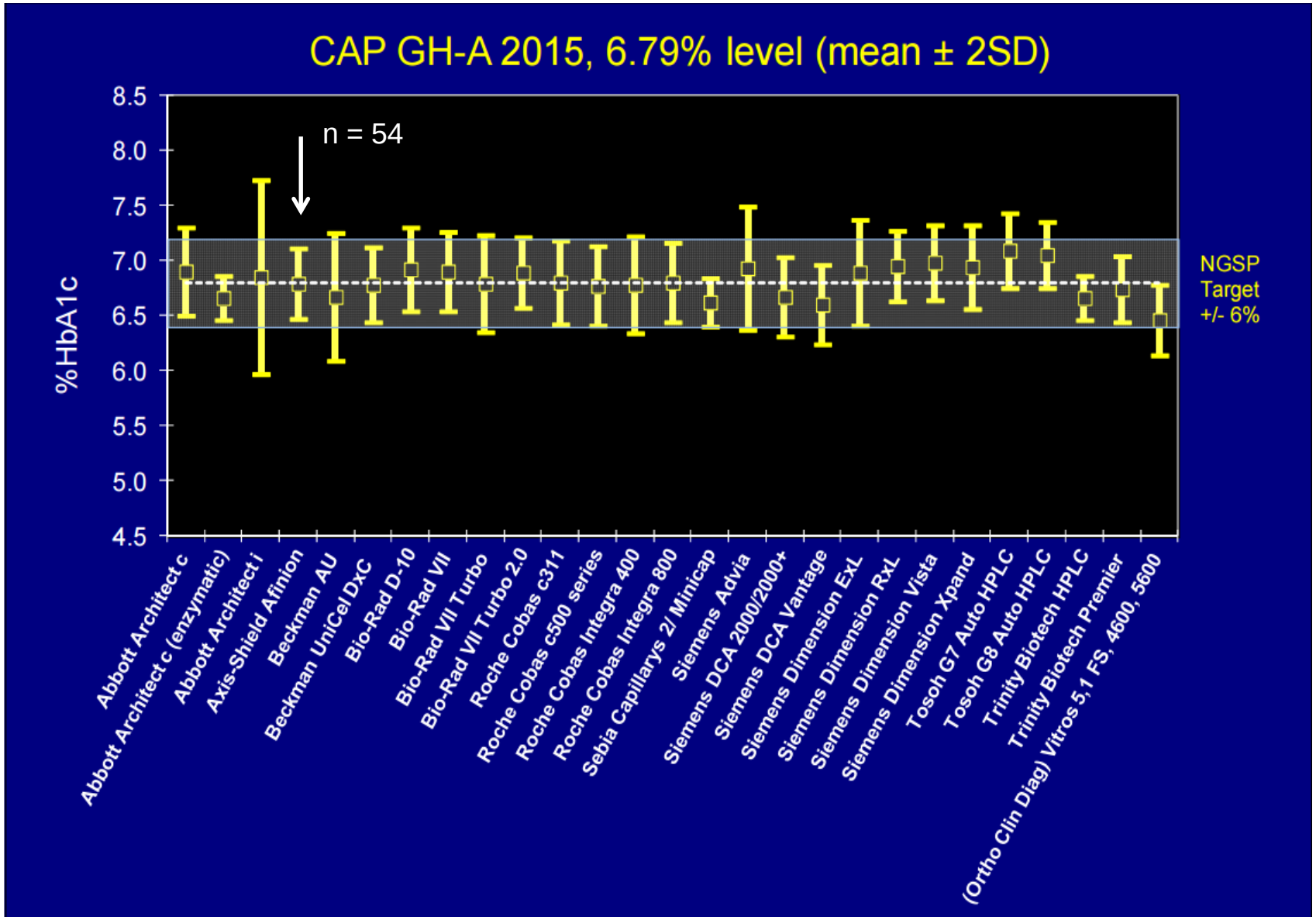
1. Proficiency Testing and NGSP Data

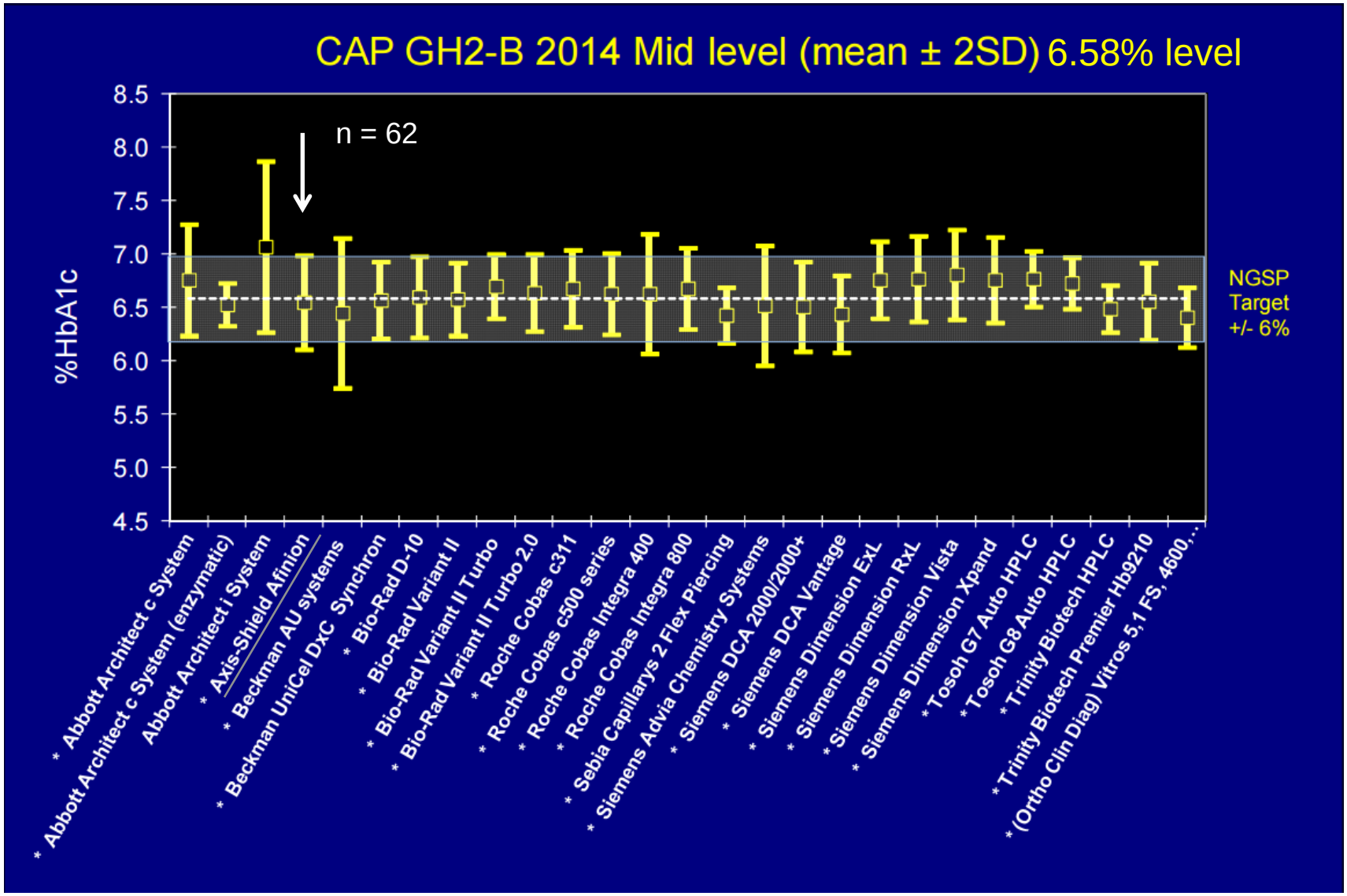
- 50 – 80 Alere Afinion HbA1c sites participate in CAP GH proficiency testing
  - Few small physician offices
  - Large centers with POC A1c in clinics running under CAP certification which requires PT for waived tests

- Alere Afinion HbA1c has been NGSP Certified since 2005
  - Current criteria: ± 6% relative error for 37 of 40 samples


CAP GH-A 2016, 5.32% level (mean ± 2SD)
%HbA1c
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
n = 57
NGSP Target ± 6%
Abbott Architect c
Abbott Architect c (enzymatic)
Abbott Architect i
Arkray Adams HA-8180
Axis-Shield Afinion
Beckman AU
Beckman UniCel DxC
Bio-Rad D-10
Bio-Rad Vll
Bio-Rad Vll Turbo
Bio-Rad Vll Turbo 2.0
JEOL BiomajestY JCA-BM series
Roche Cobas c311
Roche Cobas c500 series
Roche Cobas Integra 400
Roche Cobas Integra 800
Sebia Capillarys 2/ Minicap
Siemens Advia
Siemens DCA 2000/2000+
Siemens DCA Vantage
Siemens Dimension ExL
Siemens Dimension RxL
Siemens Dimension Vista
Siemens Dimension Xpand
Tosoh G7 Auto HPLC
Tosoh G8 Auto HPLC
Trinity Biotech HPLC
Trinity Biotech Premier
(Ortho Clin Diag) Vitros 5,1 FS, 4600, 5600


CAP GH-C 2015, 5.93% level (mean ± 2SD)
%HbA1c
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
n = 74
NGSP Target ± 6%
Abbott Architect c
Abbott Architect c (enzymatic)
Abbott Architect i
Axis-Shield Afinion
Beckman AU
Beckman UniCel DxC
Bio-Rad D-10
Bio-Rad VII
Bio-Rad VII Turbo
Bio-Rad VII Turbo 2.0
Roche Cobas c311
Roche Cobas c500 series
Roche Cobas Integra 400
Roche Cobas Integra 800
Sebia Capillarys 2/ Minicap
Siemens Advia
Siemens DCA 2000/2000+
Siemens DCA Vantage
Siemens Dimension ExL
Siemens Dimension RxL
Siemens Dimension Vista
Siemens Dimension Xpand
Tosoh G7 Auto HPLC
Tosoh G8 Auto HPLC
Trinity Biotech HPLC
Trinity Biotech Premier
(Ortho Clin Diag) Vitros 5,1 FS, 4600, 5600


CAP GH-A 2015, 6.79% level (mean ± 2SD)
n = 54
%HbA1c
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
NGSP Target +/- 6%
Abbott Architect c
Abbott Architect c (enzymatic)
Abbott Architect i
Axis-Shield Afinion
Beckman AU
Beckman UniCel DxC
Bio-Rad D-10
Bio-Rad VII
Bio-Rad VII Turbo
Bio-Rad VII Turbo 2.0
Roche Cobas c311
Roche Cobas c500 series
Roche Cobas Integra 400
Roche Cobas Integra 800
Sebia Capillarys 2/ Minicap
Siemens Advia
Siemens DCA 2000/2000+
Siemens DCA Vantage
Siemens Dimension ExL
Siemens Dimension RxL
Siemens Dimension Vista
Siemens Dimension Xpand
Tosoh G7 Auto HPLC
Tosoh G8 Auto HPLC
Trinity Biotech HPLC
Trinity Biotech Premier
(Ortho Clin Diag) Vitros 5,1 FS, 4600, 5600


CAP GH2-B 2014 Mid level (mean ± 2SD) 6.58% level
n = 62
%HbA1c
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
NGSP Target +/- 6%
* Abbott Architect c System
* Abbott Architect c System (enzymatic)
Abbott Architect i System
* Axis-Shield Afinion
* Beckman AU systems
* Beckman UniCel DxC Synchron
* Bio-Rad D-10
* Bio-Rad Variant II
* Bio-Rad Variant II Turbo
* Bio-Rad Variant II Turbo 2.0
* Roche Cobas c311
* Roche Cobas c500 series
* Roche Cobas Integra 400
* Roche Cobas Integra 800
* Sebia Capillarys 2 Flex Piercing
* Siemens Advia Chemistry Systems
* Siemens DCA 2000/2000+
* Siemens DCA Vantage
* Siemens Dimension ExL
* Siemens Dimension RxL
* Siemens Dimension Vista
* Siemens Dimension Xpand
* Tosoh G7 Auto HPLC
* Tosoh G8 Auto HPLC
* Trinity Biotech HPLC
* Trinity Biotech Premier Hb9210
* (Ortho Clin Diag) Vitros 5,1 FS, 4600,...

2. Peer-Reviewed External Studies

Clinical Chemistry 56:1
44–52 (2010)

Six of Eight Hemoglobin A_{1c} Point-of-Care Instruments Do Not Meet the General Accepted Analytical Performance Criteria

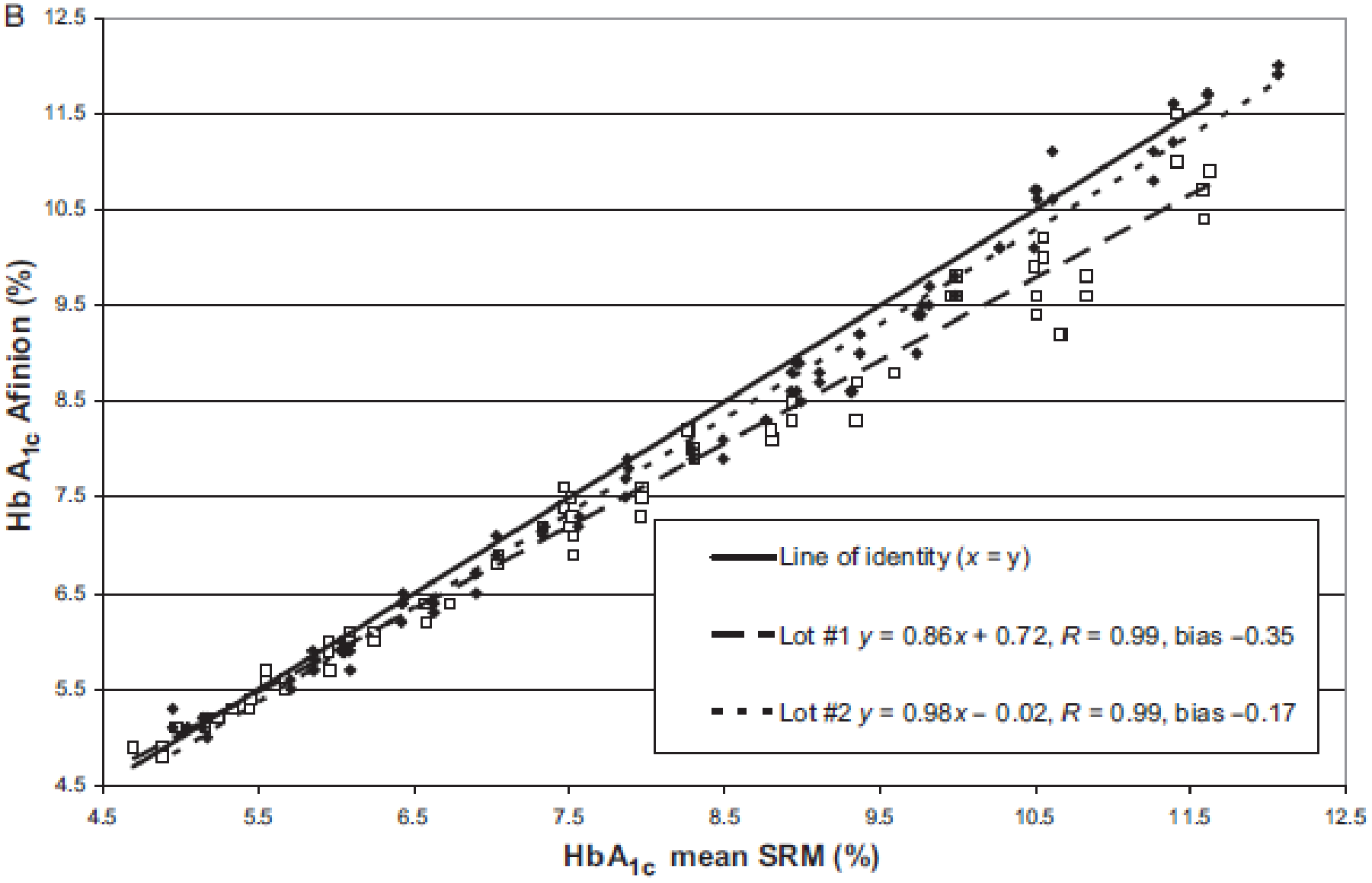
Erna Lenters-Westra[1,2*] and Robbert J. Slingerland[1,2]

- Full CLSI EP 9 and 10 protocols for precision, accuracy and bias
- Eight POC HbA1c methods
- The comparator was the mean of 3 reference methods (Roche, Primus, Tosoh)
- NGSP criteria at the time used to determine acceptability

Table 1. EP-5 total CV imprecision results from the different POC instruments.

	In2it	DCA Vantage	Clover	InnovaStar	Nycocard	Afinion
Patient sample 1	4.9% (5.1%)[a]	1.8% (5.1%)	4.0% (5.0%)	3.2% (5.2%)	4.8% (4.8%)	2.4% (4.7%)
Patient sample 2	3.3% (11.2%)	3.7% (11.2%)	3.5% (11.9%)	3.9% (11.5%)		
Nycocard normal control					5.3% (6.1%)	
Nycocard abnormal control					5.2% (11.6%)	
Afinion control CI						1.4% (6.3%)
Afinion control CII						1.8% (8.2%)

[a] Hb A_{1c} value of the sample/control are in parentheses.


B
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
Hb A1c Afinion (%)
4.5
5.5
6.5
7.5
8.5
9.5
10.5
11.5
12.5
HbA1c mean SRM (%)
Line of identity (x = y)
Lot #1 y = 0.86x + 0.72, R = 0.99, bias –0.35
Lot #2 y = 0.98x – 0.02, R = 0.99, bias –0.17

Conclusion

- Only the DCA Vantage and Alere Afinion methods met the current NGSP accuracy and precision criteria
  - Note: This and similar studies are likely to be the origins of some of the concerns that led to the original 2010 ADA statement regarding POC HbA1c

Clinical Chemistry 60:8
1062–1072 (2014)

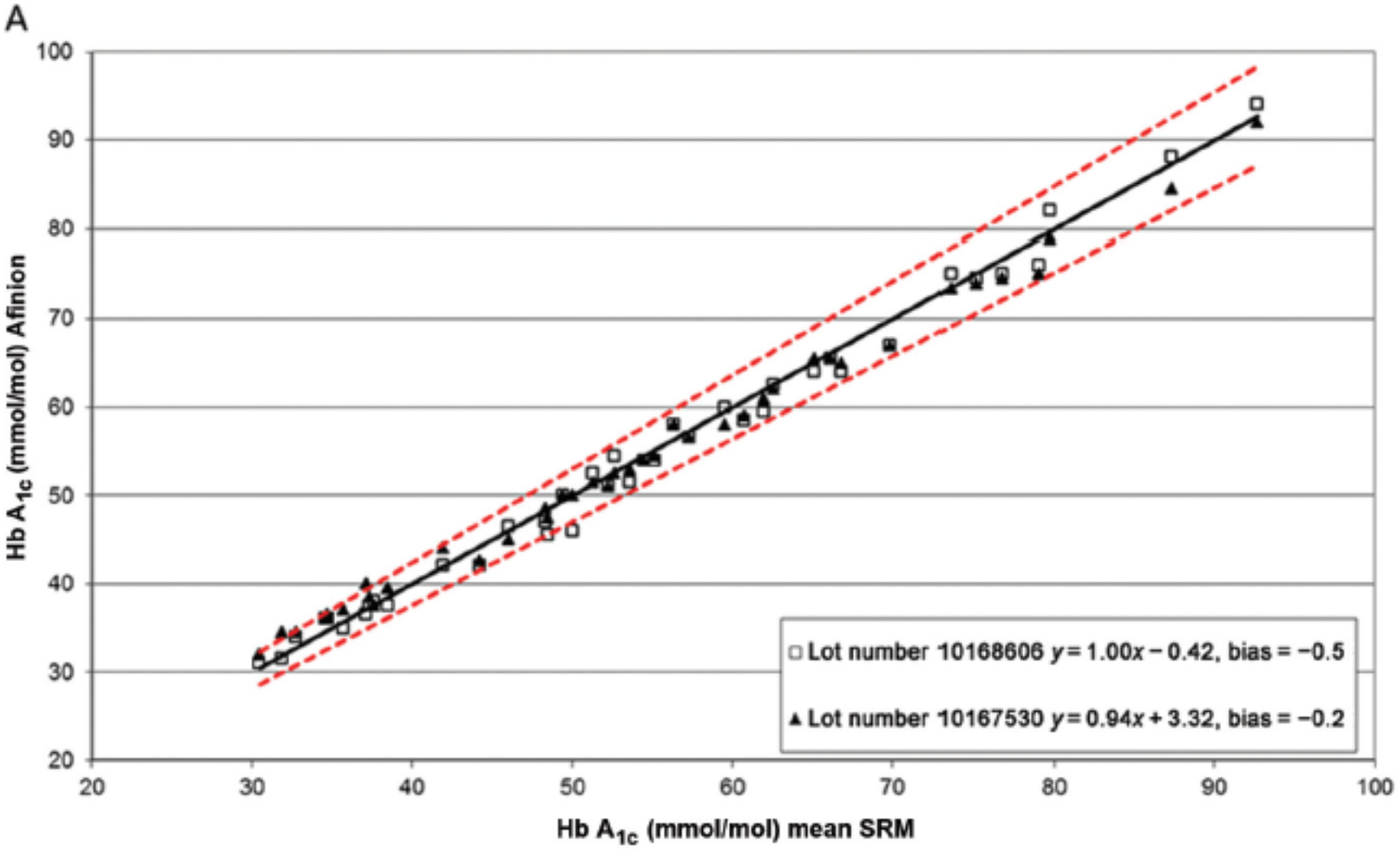
Three of 7 Hemoglobin A_{1c} Point-of-Care Instruments Do Not Meet Generally Accepted Analytical Performance Criteria

Erna Lenters-Westra[1,2*] and Robbert J. Slingerland[1,2]

- Repeated study in 2014 (same comparator)
- New, tighter NGSP criteria
  - 6% relative total error and 2% CV (NGSP units)

Table 1. Imprecision results based on EP-5 and the duplicates in EP-9.

Instrument	Hb A_{1c} value sample/control			
	SI units (mmol/mol)	CV (%)	DCCT units (%)	CV (%)
B-analyst	29[a]	3.0	4.7[a]	2.1
	61[b]	1.6	8.0[b]	1.2
	92[b]	1.3	10.9[b]	1.1
Lot number 1[c]		1.7		1.3
Lot number 2[c]		1.8		1.7
Afinion	44[b]	2.1	6.2[b]	1.3
	66[b]	1.9	8.2[b]	1.4
Lot number 1[c]		3.0		2.1
Lot number 2[c]		2.8		1.7
DCA Vantage	47	3.1	6.5	1.9
	73	4.2	8.8	3.2
Lot number 1[c]		3.2		2.6
Lot number 2[c]		3.2		2.4


A
100
90
80
70
60
50
40
30
20
20
30
40
50
60
70
80
90
100
Hb A1c (mmol/mol) Afinion
Hb A1c (mmol/mol) mean SRM
Lot number 10168606 y = 1.00x − 0.42, bias = −0.5
Lot number 10167530 y = 0.94x + 3.32, bias = −0.2

Conclusions

- Alere Afinion, DCA Vantage and Cobas B101 met NGSP criteria for accuracy and precision

- Performed in a well-respected laboratory setting

3. Physician Office Setting

- Previous studies were in laboratory settings
- Those participating in Proficiency Testing are primarily larger diabetes clinics operating in moderate complexity mode
- But what about POC testing in a general practitioner setting???

Journal of Diabetes Science and Technology
Volume 6, Issue 2, March 2012

TECHNOLOGY REPORT

Accuracy and Precision of the Axis-Shield Afinion Hemoglobin A1c Measurement Device

Jamie R. Wood, M.D.,[1] Brett M. Kaminski, B.S.,[2] Craig Kollman, Ph.D.,[2] Roy W. Beck, M.D., Ph.D.,[2] Callyn A. Hall, B.S.,[2] Jason P. Yun, B.A.,[1] Eda Cengiz, M.D.,[3] Michael J. Haller M.D., M.S.C.I.,[4] Krishna Hassan, M.D.,[5] Georgeanna J. Klingensmith, M.D.,[6] and William V. Tamborlane, M.D.[3]

- Fingerstick testing of 700 subjects in 7 pediatric diabetes clinics
- Comparator was TOSOH HPLC at U of Minnesota
- Precision using 6 NGSP samples performed at 3 sites

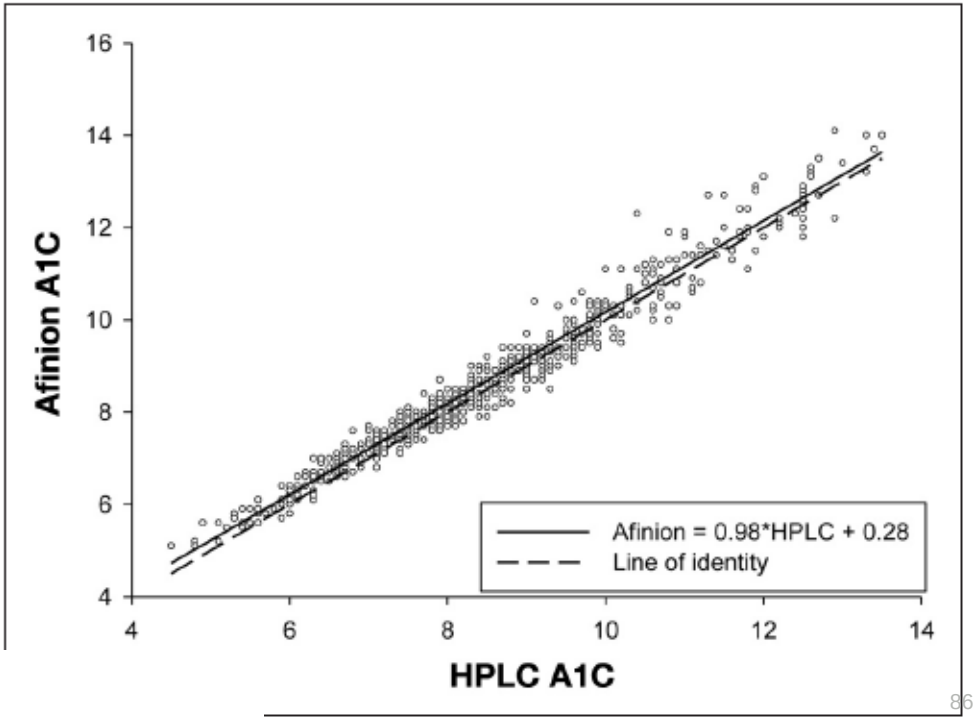
Table 1.
Precision Analysis of Repeated Measurements of Whole Blood Samples

Whole blood samples[a]	Mean A1C[b]	Afinion			DCA			HPLC		
		N	SD_{ws}[c]	CV[d] (%)	N	SD_{ws}[c]	CV[d] (%)	N	SD_{ws}[c]	CV[d] (%)
All samples	7.48	108	0.18	2	108	0.23	3	36	0.06	1
Sample A	5.60	18	0.15	3	18	0.19	3	6	0.00	0
Sample B	5.66	18	0.12	2	18	0.24	4	6	0.05	1
Sample C	6.61	18	0.15	2	18	0.11	2	6	0.04	1
Sample D	8.09	18	0.15	2	18	0.15	2	6	0.08	1
Sample E	9.46	18	0.26	3	18	0.24	3	6	0.05	1
Sample F	9.47	18	0.19	2	18	0.36	4	6	0.08	1

[a] Samples were provided by the NGSP.
[b] Mean A1C is the average of six repeated HPLC measurements per sample measured at the central laboratory at the University of Minnesota.
[c] Within-sample standard deviation (SD_{ws}) was estimated by repeated measures regression model.
[d] Coefficient of variation (CV) is SD_{ws} divided by mean A1C.

Table 3.
Accuracy Compared with HPLC by A1C and Center

	N	Mean difference[a]		Mean relative difference[b]	
		Afinion	DCA	Afinion (%)	DCA (%)
Overall	688	+0.15	−0.19	+1.9	−2.1
By HPLC A1C					
<7.0%	122	+0.24	−0.02	+3.9	−0.2
7.0–<8.0%	182	+0.18	−0.10	+2.4	−1.4
8.0–<9.0%	157	+0.08	−0.19	+1.0	−2.3
9.0–<10.0%	107	+0.05	−0.35	+0.5	−3.7
≥10.0%	120	+0.18	−0.37	+1.6	−3.3



Conclusions

- Both the DCA and Alere Afinion have acceptable performance for routine use in pediatric clinic settings

- Differences to HPLC are clinically insignificant

Clinical Chemistry 59:12
1790–1801 (2013)

Diagnosing Diabetes Mellitus: Performance of Hemoglobin A_{1c} Point-of-Care Instruments in General Practice Offices

Una Ørvim Sølvik,[1*] Thomas Røraas,[2] Nina Gade Christensen,[2] and Sverre Sandberg[1,2,3]

- 6 years of Norwegian NOKLUS EQA data
- %CV determined from duplicate analysis of samples
- 1288 GP offices
- 52 hospital laboratories
- Acceptable criteria = relative 6% total error and CV < 2%
- SS is internationally respected EQA and POC expert

Percentage of Testing Sites Meeting Both Accuracy and Precision Targets

Conclusions

- A large percentage of GP offices using Alere Afinion and DCA POC HbA1c testing meet acceptable performance criteria

- GP offices are similar to central labs in meeting criteria

Other External Quality Surveillance Results

- Switzerland
  - Legally required for all sites
  - For Alere Afinion™ HbA1c users most are GP offices
    - 1227 Alere Afinion™ HbA1c participants in the latest 2016 report

- Sweden
  - June 2016 Equalis Survey, n = 754 sites
  - Afinion = 268, DCA = 430, all others < 20

Switzerland

Sample A

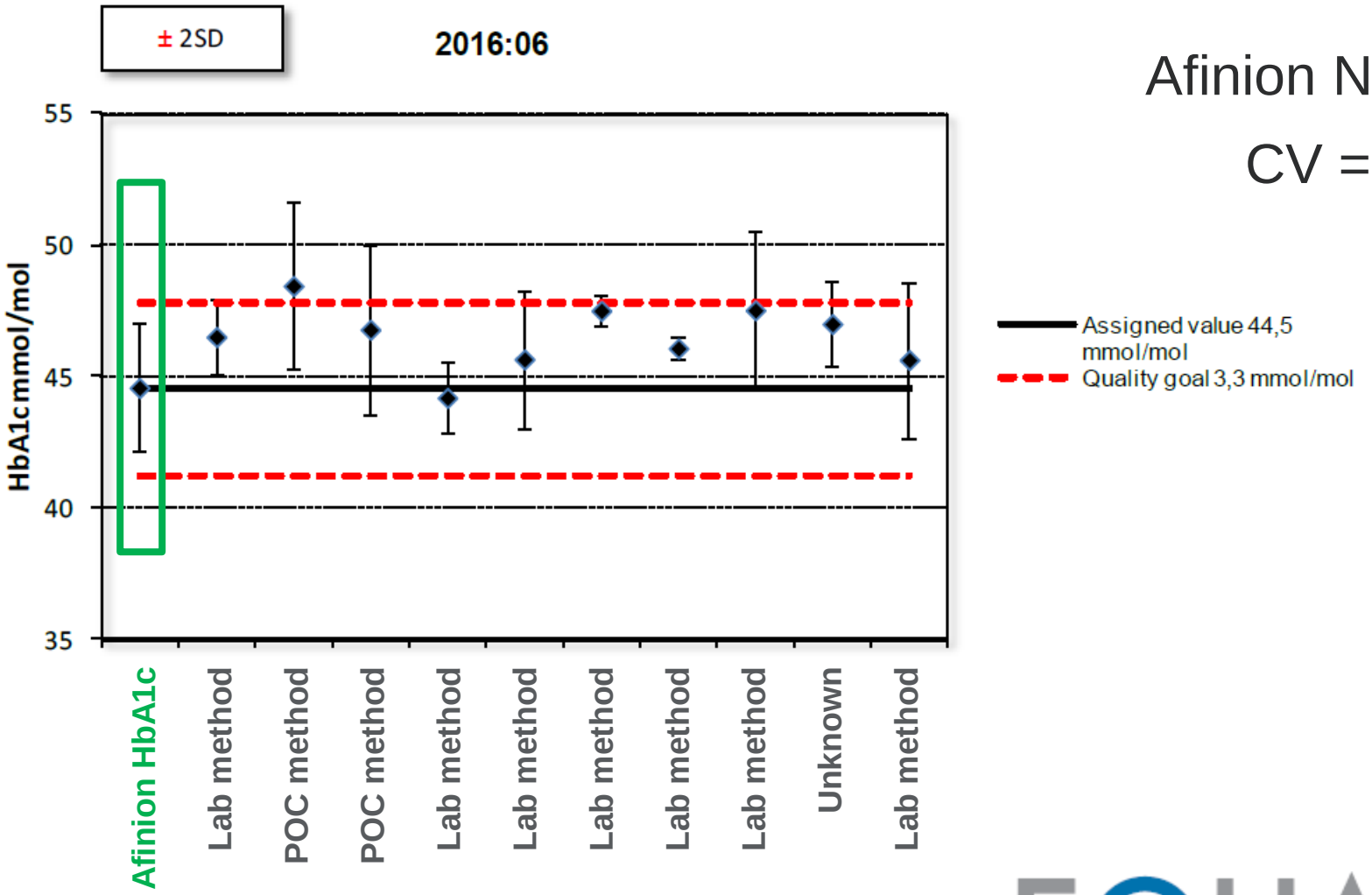
No.	Methode	Total	% good	% insuff.	% outlier	Target value	CV%
1	Cobas b101	30	100.0	0.0	0.0	7.9	3.4
2	Afinion	653	99.4	0.6	0.0	7.9	2.5
3	Eurolyser	15	93.3	6.7	0.0	8.1	4.3
4	Hemocue HbA1c 501	12	91.7	0.0	8.3	7.9	3.8
5	NycoCard	93	80.7	11.8	7.5	7.8	5.8
6	DCA2000/Vantage	205	98.5	1.0	0.5	7.8	3.2
7	Others	9	88.9	11.1	0.0	8.1	4.0
8	HPLC	6	100.0	0.0	0.0	8.0	4.2
9	Roche, Cobas	17	100.0	0.0	0.0	7.9	2.8

Sample B

No.	Methode	Total	% good	% insuff.	% outlier	Target value	CV%
1	Cobas b101	34	100.0	0.0	0.0	9.0	3.0
2	Afinion	574	99.4	0.3	0.3	9.2	2.3
3	Eurolyser	11	81.8	0.0	18.2	9.1	4.2
4	A1c Now	4	75.0	0.0	25.0	9.3	2.8
5	Hemocue HbA1c 501	6	83.3	0.0	16.7	9.1	1.3
6	NycoCard	70	84.3	7.1	8.6	8.9	5.3
7	DCA2000/Vantage	222	96.4	1.8	1.8	9.0	3.3
8	Others	6	100.0	0.0	0.0	8.9	3.6
9	HPLC	4	75.0	25.0	0.0	9.0	5.6
10	Roche, Cobas	14	100.0	0.0	0.0	8.8	2.7

% good acceptance criteria is 9% relative of target value

Sweden



Afinion N= 268

CV = 2.6%

EQUALIS

4. Alere Afinion HbA1c Dx 510(k) Submission Data

B. Probability of False Positive with a 6% relative total error

What is the chance that I will be diagnosed with diabetes when my true HbA1c is 6.1% when the method has a total error of 6%?

- 6.1 %HbA1c x 0.06 = 0.366, round to 0.4 %HbA1c
- 5% chance that my value will fall outside of 5.7 – 6.5 (± 0.4)
- Here, concerned with the right side of the distribution so there is a 2.5% chance that my A1c will be > 6.5
- However, to be diagnosed with diabetes this value must be confirmed (ADA)
- Chance of the second value being > 6.5 %HbA1c is also 2.5%
- Therefore, 0.025 x 0.025 = 0.000625 x 100 = 0.0625%
- Or, **6 out of 10,000**

C. What could go wrong?

OK – US study, Norway, Switzerland and Sweden may not be representative of some of USA POC settings!

1. Bad instrument or calibration
2. Bad Cartridge
3. Bad Sample
   - » capillary vs. venous, short sample, too much sample, drop on exterior of capillary tube, clotted sample
4. Damaged cartridge
5. Dirty cartridge
6. Cartridge installed wrong

- The next presenter will go into detail of all the mitigating steps that address each of these concerns

My Conclusions

- Analytic performance of Afinion A1c is indisputable in laboratory settings
- Other studies suggest that this is also true in GP office settings
- Strong mitigating solutions for user error and instrument failure (more to follow)
- We use the DCA in a POC setting and are comfortable for all of the above reasons
- The clinicians greatly appreciate the rapid access to HbA1c results

Alere™ Knowing now matters.™

Mitigations of Potential Sources of Error

Frank Frantzen, Ph.D.

Alere Technologies, Oslo, Norway

Potential Sources of Error

Analyzer Malfunctions

Lot-to-Lot Variations

Assay Processing Errors

User Errors:

- Incorrect Cartridge Storage Conditions
- Compromised Sample
- Incorrect Operating Conditions
- Incorrect User Operation

Mitigation of Analyzer Malfunction

All instruments have a fixed factory calibration

Comprehensive quality control testing performed prior to release

There have been no drifts in analyzer calibration and no Medical Device Reports (MDRs) associated with an erroneous result arising from compromised Afinion instruments in 10 years on market

Mitigation of Analyzer Malfunction

Instrument self-test

- Flash integrity
- Light level check
- Camera check
- Dust check
- Lens check
- Geometry check
- Motors check and calibration of transport system position
- Pumps are calibrated

Mitigation of Lot to Lot Variation

The cartridge barcode contains the test lot calibration

Each test lot is calibrated against an internal reference lot

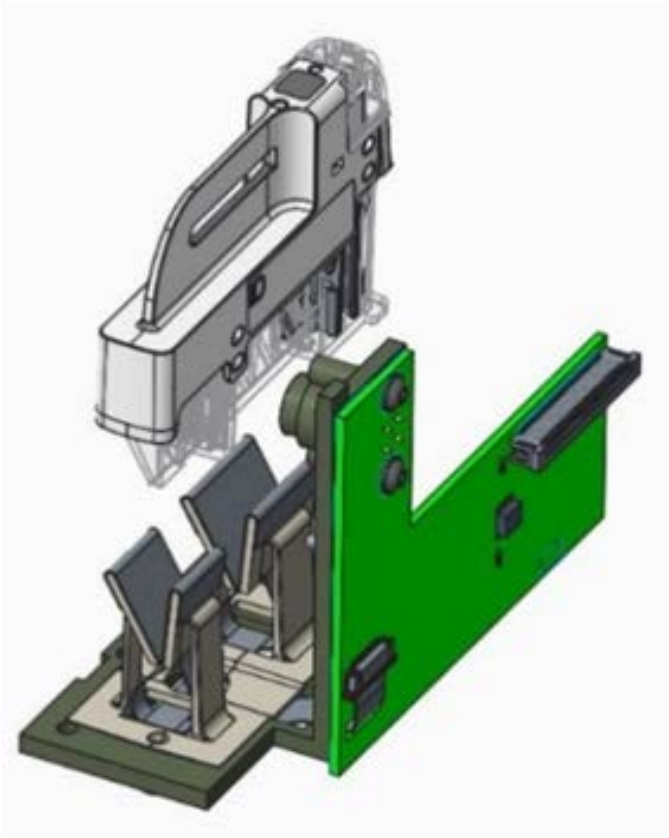
Internal reference lot is assured to be aligned with the NGSP reference:

- Collaboration with International Federation of Clinical Chemistry (IFCC) network lab
- Bimonthly monitoring
- NGSP and IFCC certification
- External Quality Assurance (EQA) surveillance

Mitigation of Assay Processing Errors

The Alere Afinion HbA1c Dx test is continuously monitored within the analyzer during sample processing

- Temperature sensors
- Pressure sensor
- Clock
- Camera inspections
- Motor movements
- Position sensors



IR sensor

Mitigation of Operator Errors

Incorrect Cartridge Storage Conditions

Labeling

- Clearly instructs product storage temperatures and duration on the cartridge boxes and in the package insert

Expired cartridges identified via barcode

Alere has validated storage conditions that exceed those stated in the labeling

Mitigation of Operator Errors

Sample

Afinion HbA1c Dx measures a ratio of glycated Hb to total Hb

- Not senstive to sample volume variations (insufficient or excess)
- Not sensitive to dilution by interstitial fluid

Problems typical with other fingerstick assays (such as glucose) also do not apply

- Differences in oxygen tension between capillary and venous blood
- Differences between non-anticoagulated capillary blood and anticoagulated venous blood

Mitigation of Operator Errors

Compromised Sample

Hemolyzed Sample

- Flow rate differences will be detected by the analyzer – test aborted
- Moderate hemolysis does not interfere
- Gross hemolysis unlikely in fingerstick samples

Clotting

- Microclot detection rejects results from clotted samples that may occur with delayed testing

Mitigation of Operator Errors

Incorrect Operating Conditions - Temperature

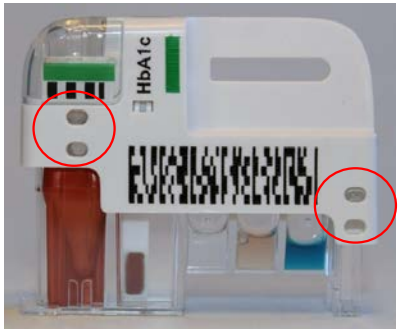
The Analyzer

- If the ambient temperature is outside of the operating temperature range the analyzer renders itself inoperable and reports an appropriate message

The Cartridge

- If the cartridge temperature is outside of limits - test will be aborted

Mitigation of Operator Errors



Test Cartridge Handling

Operator drops the cartridge

- Analyzer camera will detect a damaged cartridge
- Analyzer camera will detect loss of sample during capillary inspection
- Test will be aborted

Operator inserts used cartridge into the analyzer

- Analyzer camera will detect a used cartridge
- Test will be aborted

Mitigation of Operator Errors

Test Cartridge Handling

Operator Contaminates the Exterior of the Cartridge

Examples: lotion, glove powder and blood on the outside of the test cartridge in the optical reading area

- Analyzer camera checks for uniformity of the detection area – test will be aborted

Mitigation of Operator Errors

Operator Skill Level

- The test procedure is extremely simple
- Operator intervention of calibration is not possible
- Analyzer includes the option to set unique codes for given operators
- Training materials including instructional videos are made available to customers

External Quality Control Testing

Labeling instructs the user to perform periodic external quality control testing as regulated by local, state or federal regulations

External control test results are stored in a separate log within the analyzer

Quality Control (QC) lock-out function

Results of “Untrained” Users

10 years on market CLIA waived monitoring

- No MDRs

Data from external QA programs indicate lab quality performance in POC settings outside of the lab

Alere™ Knowing now matters.

Distinction of Moderate Complexity Test from CLIA Waived Test

Frank Frantzen, Ph.D.

Alere Technologies, Oslo, Norway

Alere's Proposal to Ensure that the New Moderate Complexity Test is Not Used in CLIA Waived Settings

Properties of the two Alere Afinion™ HbA1c cartridges

Test Name	Alere Afinion HbA1c Dx	Alere Afinion HbA1c
Assay catalog number	**New**	1115015
Compatible with analyzer Alere Afinion AS100 - Moderate complexity	Yes	Yes
Compatible with analyzer Alere Afinion AS100 - CLIA waived	**No**	Yes
Compatible with installed base	**No**	Yes

Alere's Proposal to Ensure that the New Moderate Complexity Test is Not Used in CLIA Waived Settings

Properties of the two Alere Afinion™ AS100 Analyzer versions

Analyzer version	Alere Afinion AS100 Moderate complexity	Alere Afinion AS100 CLIA waived
Analyzer catalog number	**New**	1115175
Operator Manual	Yes	Yes
Quick Guide HbA1c	Yes	Yes
Quick Guide HbA1c Dx	Yes	**No**
QC lockout – configurable	Yes	Yes
Operator lockout – configurable	Yes	Yes
Startup screen	-	**"CLIA waived" displayed during self test**
Tests that can be run	All cleared Alere Afinion tests	Alere Afinion HbA1c

Alere Afinion HbA1c Test Procedure: Current Waived Assay for Diabetes Monitoring

1	2	3	4	5
				
Switch on the Alere Afinion™ AS100 Analyzer. The Analyzer will perform a self test (2-3 min).	Open the Alere Afinion™ HbA1c foil pouch and remove the Test Cartridge.	Collect a sample using the integrated sampling device.	Place the Test Cartridge in Analyzer. The assay processing will start immediately upon closing the lid.	The test results is displayed in 3 minutes.

Alere Afinion HbA1c Dx (Mod. Complex) Test Procedure:
Using an Existing Alere Afinion AS100 Analyzer in a Waived Setting with Current Software

1

Switch on the Alere Afinion™ AS100 Analyzer.

The Analyzer will perform a self test (2-3 min).

2

Open the Alere Afinion™ HbA1c foil pouch and remove the Test Cartridge.

Foil pouch labeled HbA1c Dx

3

Collect a sample using the integrated sampling device.

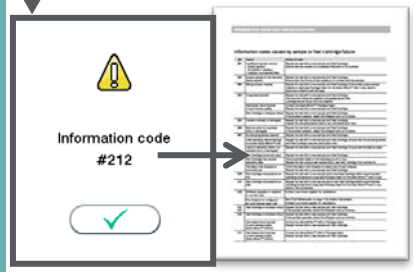
4

Place the Test Cartridge in Analyzer.

The assay processing will start immediately upon closing the lid.

5

The test results is displayed in 3 minutes.



The code is explained in the user manual

Alere Afinion HbA1c Dx (Mod. Complex) Test Procedure: *Using a New Mod. Complex Alere Afinion™ AS100 Analyzer*

1

Switch on the Alere Afinion™ AS100 Analyzer.

The Analyzer will perform a self test (2-3 min).

2

Open the Alere Afinion™ HbA1c foil pouch and remove the Test Cartridge.

Foil pouch labeled HbA1c Dx

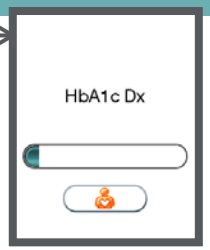
3

Collect a sample using the integrated sampling device.

4

Place the Test Cartridge in Analyzer.

The assay processing will start immediately upon closing the lid.



HbA1c Dx displayed during processing

5

The test results is displayed in 3 minutes.

Two decimal place test result

Could the Afinion HbA1c Dx Be Run in a CLIA Waived Lab?

No

Distinct product ordering codes, descriptions and CLIA statements in the labeling would prevent a CLIA waived lab from ordering the moderate complexity Afinion HbA1c Dx

If an existing customer did somehow order the wrong test by mistake:

- The assay would not run on the current installed base with the current software version
- Their product labeling would describe a different indication for use and CLIA statement alerting them to the error

Alere™ Knowing now matters.™

Summary

Rick San George, Ph.D.

Vice President, Clinical Affairs, Alere

Closing Summary

- There are tangible benefits with POC testing for diagnosis of diabetes, especially in underprivileged and underserved communities
- Alere Afinion HbA1c Dx is accurate, precise and exhibits total error <6%
- Likelihood of false negative/false positive is low
- Risks to patient in the event of a false negative/false positive are minimal
- Sources of error have been effectively mitigated
- Alere's proposed approach ensures that CLIA waived laboratories cannot use the new moderate complexity test

Closing Summary

- Alere Afinion HbA1c Dx clearance with moderate complexity requires that sites perform QC, participate in PT, and have laboratory trained operators - this is no different than cleared central laboratory tests
- CLIA waiver of the Alere Afinion HbA1c Dx would require that Alere demonstrate equal performance to the central laboratory in CLIA waived settings with intended use operators without increased chance of erroneous results

Closing Summary

- All POC HbA1c tests do not have the same performance
- All laboratory systems do not have the same performance
- Each system, whether POC or central laboratory, should be judged on it's own merits and not those of the collective 'category'

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Thank you