Recommendations for POCT Quality Control Focusing on HbA1c

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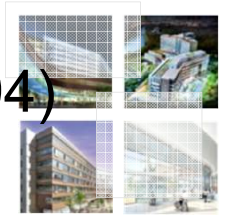
1. HbA1c 표준화 동향
2. HbA1c testing의 Performance Standards
3. HbA1c POC 검사의 Quality Status
4. HbA1c POC 검사의 질 향상 방안

1. HbA1c 표준화 동향

Worldwide HbA1c Standardization

- National Initiatives for the harmonization of HbA1c
  - USA
    - National Glycohemoglobin Standardization Program (NGSP)
    - Bio-Rex 70 resin (DCCT traceable)
  - Japan
    - JDS/JSCC
    - KO500 HPLC
  - Sweden
    - Mono S method
- Large difference were present in HbA1c results between each organization
- An international reference system to harmonize the national programs was needed
  - IFCC : Working group on Standardization of HbA1c (1994)
  - Reference method : HPLC with MS or HPLC with CE



Diabetologia (2007) 50:2042–2043

CONSENSUS STATEMENT

Consensus statement on the worldwide standardisation of the HbA_{1c} measurement

The American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation

- HbA1c test results should be standardised worldwide, including the reference system and results reporting.
- The new IFCC reference system for HbA1c represents the only valid anchor to implement standardisation of the measurement.
- HbA1c results are to be reported worldwide in IFCC units (mmol/mol) and derived NGSP units (%), using the IFCC–NGSP master equation.
- If the ongoing 'average plasma glucose study' fulfils its a priori specified criteria, an HbA1c-derived average glucose (ADAG) value calculated from the HbA1c result will also be reported as an interpretation of the HbA1c results.
- Glycaemic goals appearing in clinical guidelines should be expressed in IFCC units, derived NGSP units and as ADAG.

2010 New criteria for Dx of Diabetes

Table 3—*Criteria for the diagnosis of diabetes*

1. A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

2. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*

OR

3. 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).

*In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

Table 2—*Categories of increased risk for diabetes**

FPG 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l) [IFG]

2-h PG in the 75-g OGTT 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11.0 mmol/l) [IGT]

A1C 5.7–6.4%

HbA1c accuracy-based survey in Korea

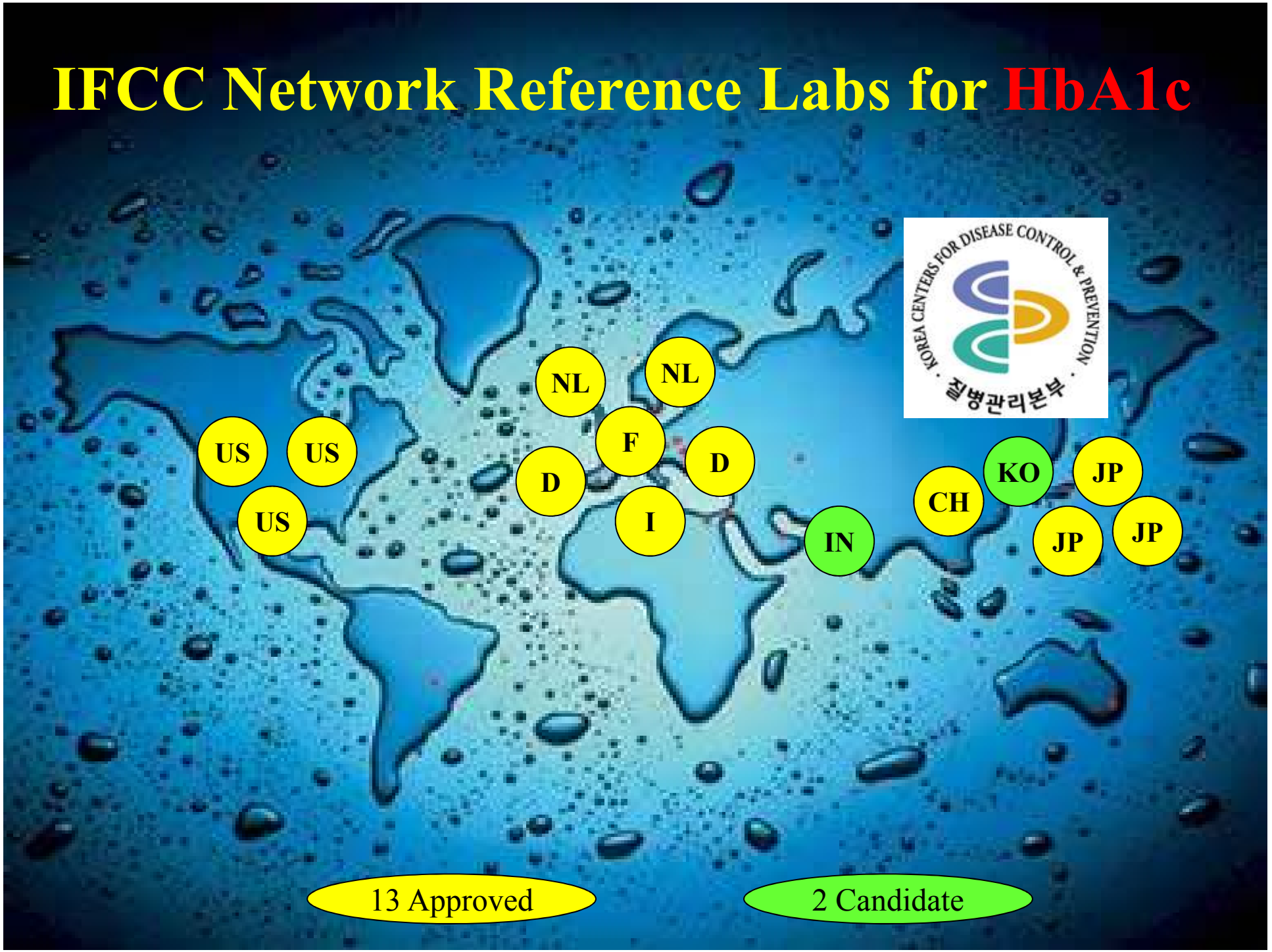
- Clinical Chemistry Subcommittee,
  The Korean Association of Quality Assurance for Clinical Laboratory,
  - In 2007, HbA1c PT was started with the scheme of twice yearly frequency, three samples per trial
  - From 2008 Trial, accuracy-based survey
  - 240 laboratories
- Commutable Survey specimens
  - No matrix effect
  - Fresh EDTA whole blood donated from normal control and diabetes patients
- Reference target value
  - Accuracy-based PT : target value measured by reference method
  - From ReCCS, Japan
- Most methods showed relatively good CVs of less than 5%
- Some methods such as POCT method showed poor CVs.
- **It is important that laboratories review their performance in this accuracy-based survey over time when selecting or evaluating HbA1c assay methods.**

Setting up the National Reference Laboratory in Korea

- 질병관리본부와 대한진단검사의학회 간 MOU 체결
  - 2011
  - 우리나라 검사결과의 표준화를 위한 MOU

- MOU 체결에 따라서 질병관리본부내에 Lipid, Cr, HbA1c에 대한 표준검사방법 (reference measurement procedure)를 확립하기로 함

IFCC Network Reference Labs for HbA1c



IFCC International Federation of Clinical Chemistry and Laboratory Medicine

Network

HbA1c

Candidate laboratories of the IFCC Network laboratories for HbA1c

INDIA Suraksha Diagnostic Pvt. Ltd. Dr. Bhaskar Bhattacharya	(NABL Accredited Laboratory) BB-99, Prafulla Kanan VIP Park, KestopurX CALCUTTA 700101 INDIA Phone: +91 33 8420515430/ +91 33 8091544683 Email: bhaskarbh@gmail.com bhaskar@surakshanet.com
KOREA Korea Centers for Disease Control and Prevention Dr. Serim Kim, Prof. Junghan Song	Osong Health Technology, Administration Compex 187 Osongsaengmyeong2(i)-ro, Gangoe-myeon, Cheongwon-gun Chungcheongbuk-do KOREA Phone: +82 43 719 7393 Fax: +82 43 719 7528 Email: srkim1982@korea.kr songjhcp@snu.ac.kr

Back

2. HbA1c 검사의 Performance Standards

- Precision
- Accuracy

Performance standards - Precision

- Goodall et al. Clin Chem Lab Med 2007;45:1083
  - 6.0%와 6.5%를 감별할 수 있는 CV
    - 3% CV : 6.0% (±2SD 5.64-6.36), 6.5% (6.11-6.89%)
    - 2% CV : 6.0% (±2SD 5.76-6.24), 6.5% (6.24-6.76%)
  - Biological variation
    - CVa < 0.5 CVb (within-subject biological variation) = 2.1%
  - Recommendation by the key clinical associations : EASD, ADA, IDF
    - clinicians acting on differences of 0.35%-0.5% as being significant
    - precision of 2%

- Ideal analytical imprecision : <2%
- This criterion is very strict, however, and difficult to meet, even for certain laboratory-based methods (immunoassays).

- POC testing (Shephard DS. Point Care 2006;5:177)
  - It would seem inappropriate to impose this goal on POC testing devices measuring Hb A1c.

CV%		
Top 20% of Laboratories	**50% of Laboratories (Median)**	**90% of Laboratories**
2.0	2.7	5.1

  - Currently, an imprecision of 3% CV is a more realistic, though not optimal goal
  - Imprecision goal : optimal 2%, desirable 3%, minimum 4%

Performance standards - Accuracy

- NGSP certification
  - Manufacturer : 95% CI of differences within ±0.75% HbA1c
  - Level I Lab : 95% CI of differences within ±0.70% HbA1c
  - Level II Lab : 95% CI of differences within ±0.75% HbA1c

- Accuracy-based proficiency testing
  - CAP (Pass limit)
    - 2006 (±15%), 2008(±12%), 2009(±10%), 2010(±8%), 2011 (±7%)
  - 대한임상검사정도관리협회
    - 2008(±12%), 2010(±10%), 2012(±8%),

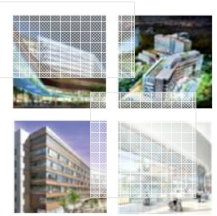
Laboratory Medicine Practice Guidelines

Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus

Edited by David B. Sacks

NATIONAL ACADEMY of CLINICAL BIOCHEMISTRY
THE ACADEMY OF AACC

- Laboratories should use only Hb A1c assay methods that are certified by the NGSP as traceable to the DCCT reference. The manufacturers of Hb A1c assays should also show traceability to the IFCC reference method. (GPP)
- Laboratories that measure Hb A1c should participate in a proficiency-testing program, such as the College of American Pathologists Hb A1c survey, that uses fresh blood samples with targets set by the NGSP Laboratory Network. (GPP)
- Desirable specifications for Hb A1c measurement are an intralaboratory CV<2% and an interlaboratory CV <3.5%. At least 2 control materials with different mean values should be analyzed as an independent measure of assay performance. (B, low)
- Hb A1c may be used for the diagnosis of diabetes, with values ≥6.5% being diagnostic. An NGSP certified method should be performed in an accredited laboratory. Analogous to its use in the management of diabetes, factors that interfere with or adversely affect the Hb A1c assay will preclude its use in diagnosis. (A moderate)
- Point-of-care Hb A1c assays are not sufficiently accurate to use for the diagnosis of diabetes. (B moderate)



3. HbA1c POC 검사의 Quality Status

POCT 장비 종류

- DCA 2000 or DCA Vantage (Siemens, USA)
  - Latex agglutination inhibition immunoassay / 6 min
- In2it (Bio-Rad, USA)
  - affinity separation / 10min
- Afinion (Axis-Shield, Norway)
  - affinity separation / 5 min
- Nycocard (Axis-Shield, Norway)
  - affinity separation / 3 min.
- Clover (Infopia, Korea)
  - affinity separation / 5 min.
- InnovaStar (DiaSys, Germany),
  - agglutination immunoassay / 11 min
- A1CNow (Bayer, USA)
  - immunoassay / 5 min
- Quo-Test (Quotient Diagnostics, UK)
  - affinity separation / 3 min.

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

Clinical Chemistry 56:1
44–52 (2010)

- Precision
- Accuracy
- Lot to lot difference

Precision

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.

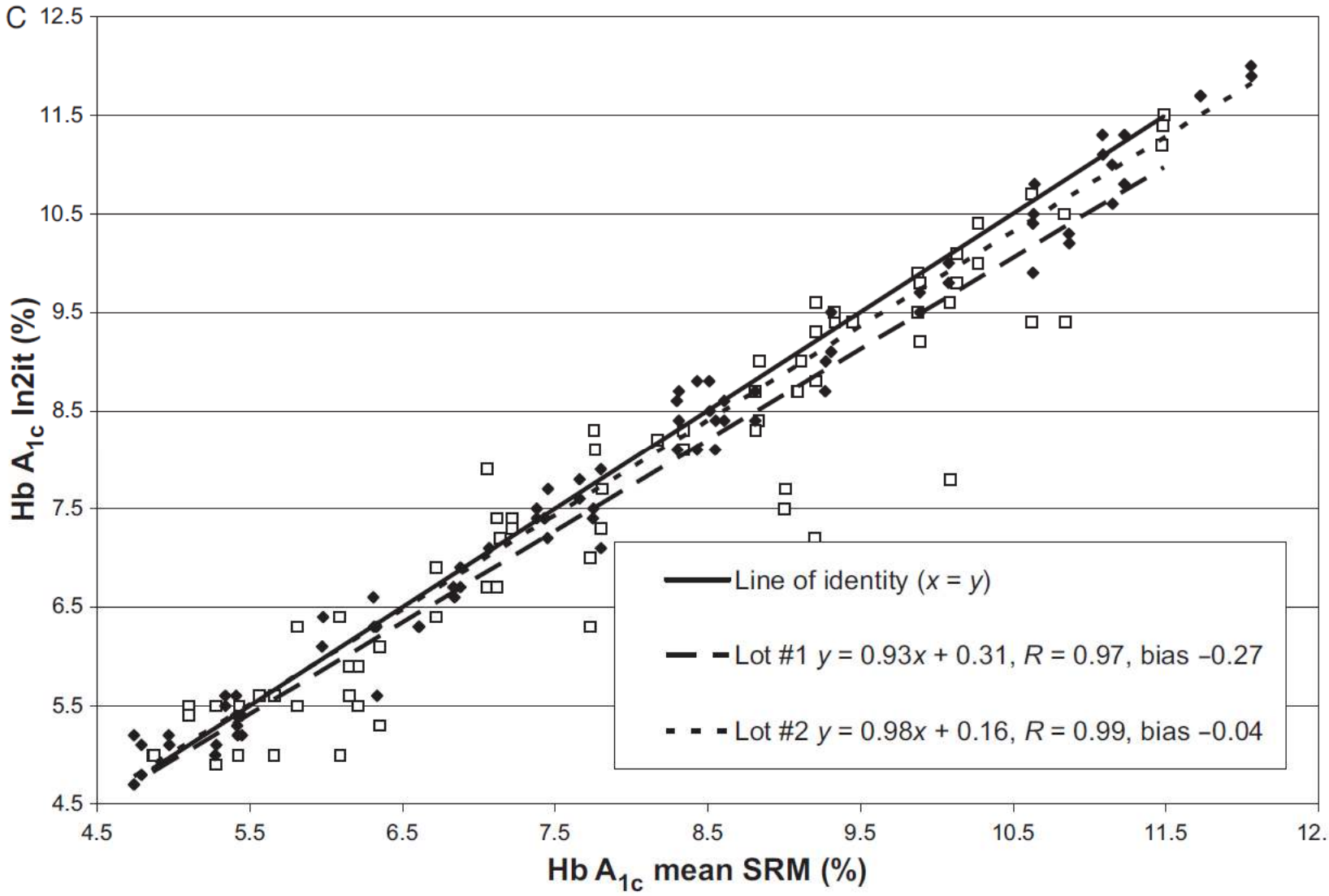
Accuracy

Table 2. EP-9 results, calculations of NGSP certification criteria and *P* values calculated with Chow statistics to test for the overall differences in slope and intercept per method for reagent lot number 1 and 2.[a]

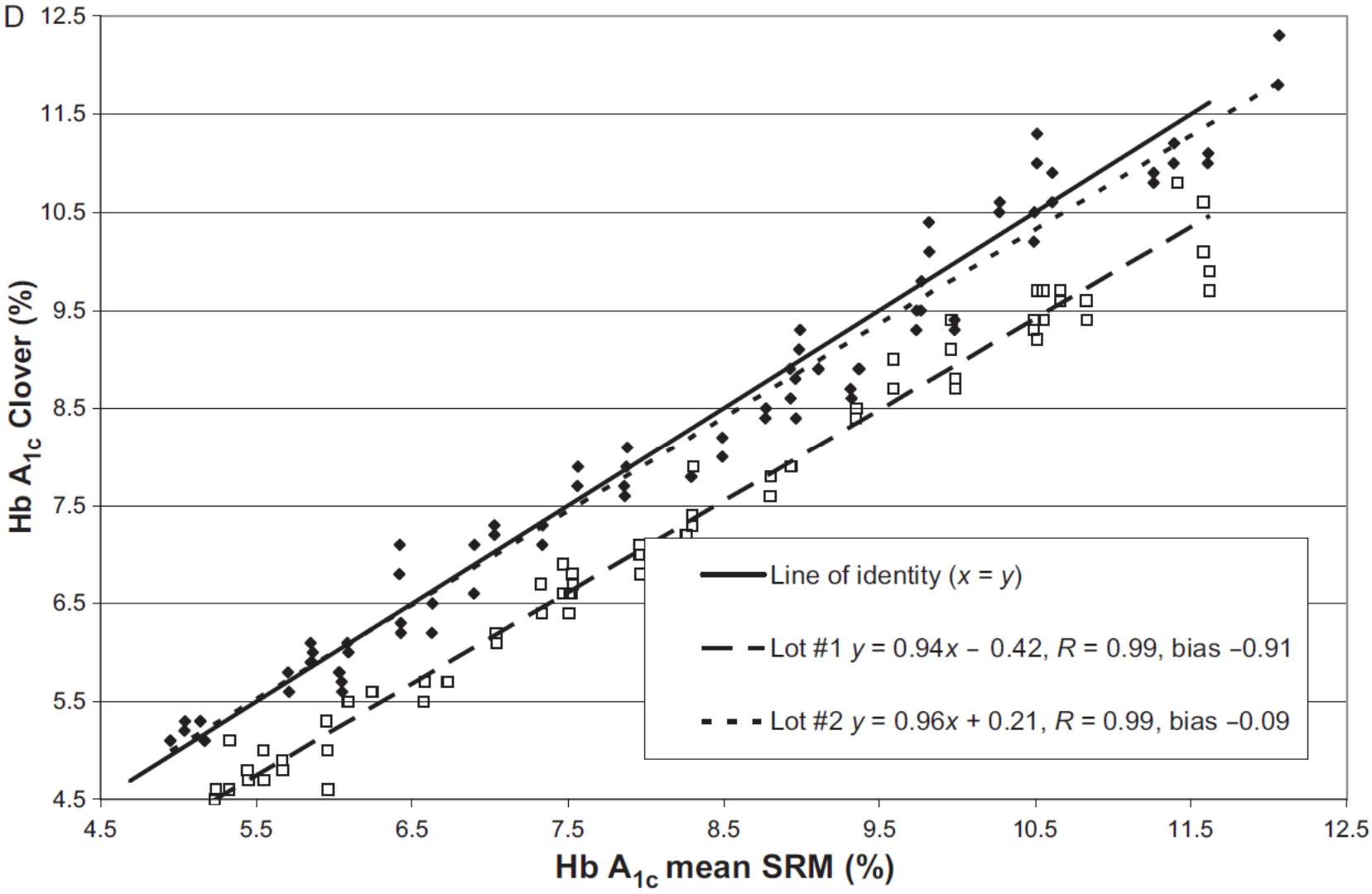
Linear regression lines	Lot number 1	Bias	SD of difference	Total error	NGSP criteria	Lot number 2	Bias	SD of difference	Total error	NGSP criteria	*P* value
In2it (*y*)											
vs Ultra^2 (*x*)[a]	$y = 0.95x + 0.26$	−0.071	0.414	−0.88	Fail	$y = 0.96x + 0.24$	−0.040	0.265	−0.60	Pass	<0.001
vs Tina-quant (*x*)	$y = 0.93x + 0.36$	−0.160	0.454	−1.05	Fail	$y = 0.93x + 0.48$	−0.112	0.338	−0.77	Pass	0.061
vs Tosoh G7 (*x*)	$y = 0.93x + 0.22$	−0.300	0.460	−1.20	Fail	$y = 0.98x + 0.06$	0.113	0.310	−0.72	Pass	<0.001
DCA V. (*y*)											
vs Ultra^2 (*x*)	$y = 0.92x + 0.59$	−0.056	0.343	−0.73	Pass	$y = 1.04x + 0.03$	0.316	0.286	0.88	Fail	<0.001
vs Tina-quant (*x*)[a]	$y = 0.92x + 0.50$	−0.141	0.298	−0.73	Pass	$y = 1.00x + 0.24$	0.244	0.248	0.73	Pass	<0.001
vs Tosoh G7 (*x*)	$y = 0.97x - 0.01$	−0.310	0.290	−0.88	Fail	$y = 1.06x - 0.21$	0.244	0.282	0.80	Pass	<0.001
Afinion (*y*)											
vs Ultra^2 (*x*)[a]	$y = 0.88x + 0.66$	−0.230	0.318	−0.85	Pass	$y = 1.00x - 0.14$	−0.122	0.213	−0.54	Pass	<0.001
vs Tina-quant (*x*)	$y = 0.83x + 0.94$	−0.427	0.473	−1.35	Fail	$y = 0.96x + 0.11$	−0.176	0.258	−0.68	Pass	<0.001
vs Tosoh G7 (*x*)	$y = 0.87x + 0.63$	−0.390	0.410	−1.19	Fail	$y = 0.98x - 0.08$	−0.224	0.284	−0.78	Pass	<0.001
Nycocard (*y*)											
vs Ultra^2 (*x*)[a]	$y = 0.94x + 0.89$	0.405	0.406	1.20	Fail	$y = 0.94x + 0.56$	0.057	0.335	0.71	Pass	<0.001
vs Tina-quant (*x*)	$y = 0.88x + 1.18$	0.212	0.505	1.20	Fail	$y = 0.90x + 0.81$	0.003	0.403	0.79	Pass	<0.001
vs Tosoh G7 (*x*)	$y = 0.93x + 0.83$	0.240	0.440	1.10	Fail	$y = 0.92x + 0.62$	−0.050	0.380	−0.79	Pass	<0.001
Clover (*y*)											
vs Ultra^2 (*x*)[a]	$y = 0.96x - 0.45$	−0.792	0.251	−1.28	Fail	$y = 0.98x + 0.12$	−0.037	0.299	−0.62	Pass	<0.001
vs Tina-quant (*x*)	$y = 0.90x - 0.18$	−0.985	0.345	−1.66	Fail	$y = 0.94x + 0.38$	−0.090	0.371	−0.82	Pass	<0.001
vs Tosoh G7 (*x*)	$y = 0.94x - 0.51$	−0.950	0.310	−1.56	Fail	$y = 0.96x + 0.20$	−0.140	0.370	−0.86	Fail	<0.001
InnovaStar (*y*)											
vs Ultra^2 (*x*)	$y = 0.89x + 0.57$	−0.277	0.399	−1.06	Fail	$y = 0.99x - 0.09$	−0.158	0.374	−0.89	Fail	<0.001
vs Tina-quant (*x*)[a]	$y = 0.84x + 0.82$	−0.470	0.490	−1.43	Fail	$y = 0.96x + 0.13$	−0.231	0.356	−0.93	Fail	<0.001
vs Tosoh G7 (*x*)	$y = 0.89x + 0.46$	−0.437	0.372	−1.17	Fail	$y = 0.98x - 0.06$	−0.261	0.358	−0.96	Fail	<0.001

[a] This row has the same measurement principle as investigated POC method.

Lot to lot difference (1)



Lot to lot difference (2)



- The reproducibility of the production of the different reagent lots of the POC instruments investigated appears inadequate at this moment for optimal clinical use of the test results.
- A manufacturer NGSP certification does not guarantee accuracy of a result produced in the field. We often observed significant differences between lots of reagents in this study.
- In addition users of POC instruments should be required to run daily controls with tight ranges and, as with anyHbA1c method, users should participate in external proficiency-testing schemes.
- It is important that the limitations of current POC instruments and laboratory methods be understood by healthcare professionals, because these limitations may have important clinical implications.

Point-of-Care Assays for Hemoglobin A_{1c}: Is Performance Adequate?

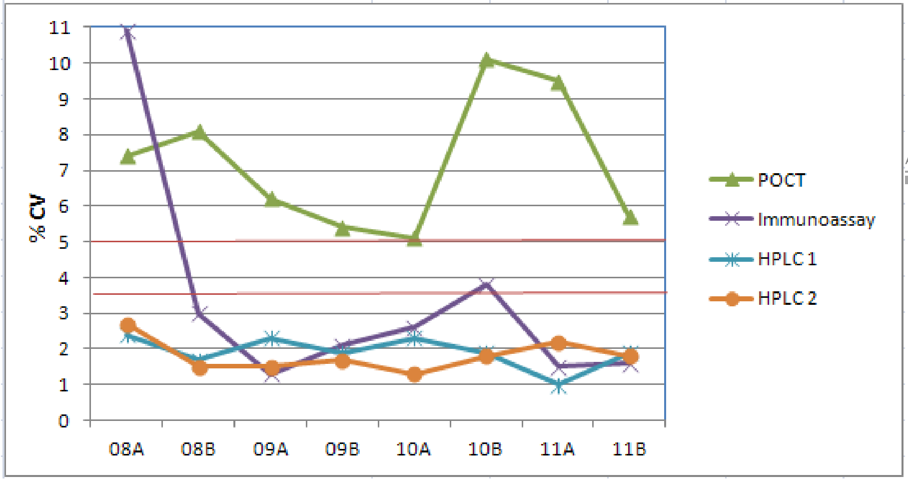
Clinical Chemistry 57:9
1333–1340 (2011)

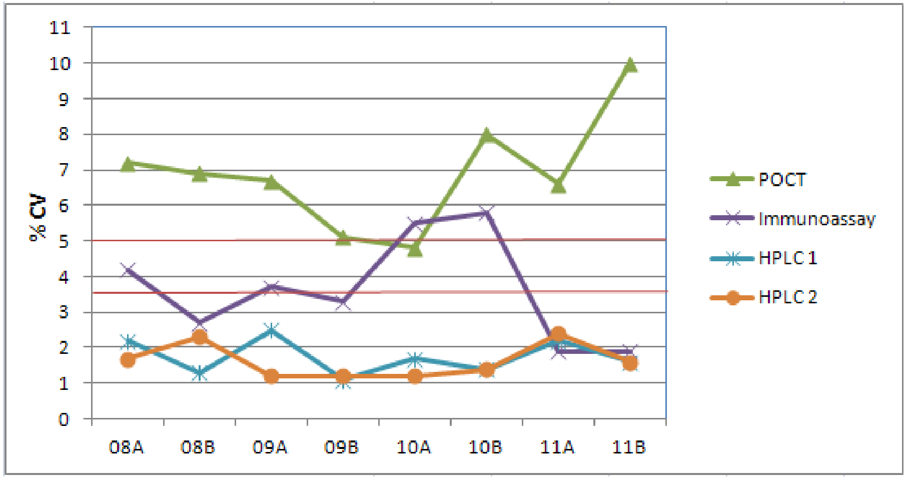
Table 1. Assessment of agreement and imprecision for 3 Hb A_{1c} POC methods.

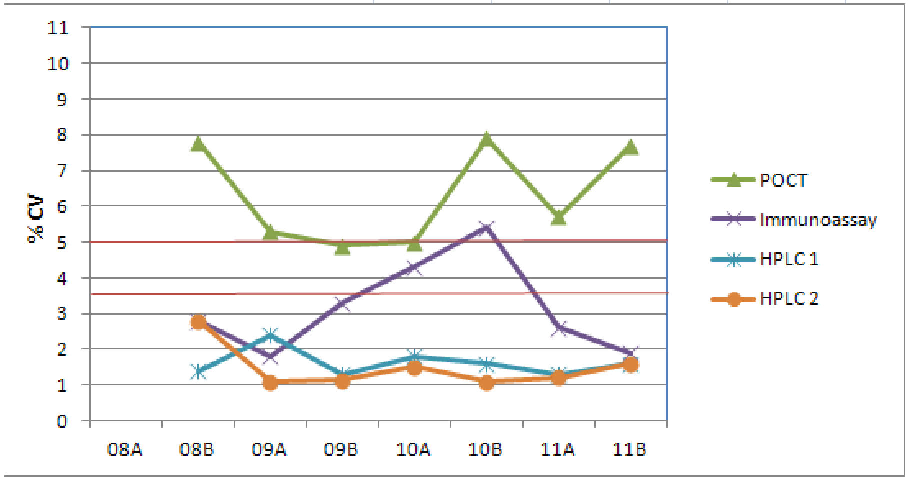
Hb A_{1c} assay/laboratory	Sample[b]	Total Imprecision (CV), %		Bland–Altman 95% confidence limits (lower, upper) of differences, %[a]	
		Lot 1	Lot 2	Lot 1	Lot 2
A1cNow					
Laboratory A (SRL7)	WB1	3.72	3.80	−0.67, 0.63	−0.63, 0.35
	WB2	3.43	3.92		
		Lot 3	**Lot 4**	**Lot 3**	**Lot 4**
Laboratory B (ESRL9)	WB1	—	4.1	**−0.97**, 0.23	**−1.07**, 0.36
	WB2	—	5.1		
		Lot 1	**Lot 2**	**Lot 1**	**Lot 2**
Afinion					
Laboratory A (SRL7)	WB1	2.70[c]	2.06[c]	−0.04, **0.87**	−0.08, 0.65
	WB2	1.94[c]	2.37[c]		
	QC1	1.44	1.39		
	QC2	1.15	1.34		
Laboratory B (ESRL8)				−0.24, 0.68	−0.30, 0.51
		Lot 1	**Lot 2**	**Lot 1**	**Lot 2**
In2it					
Laboratory B (ESRL9)	WB1	—	2.40	−0.59, 0.37	−0.63, 0.16
	WB2	—	3.00		

[a] Data are presented as the Hb A_{1c} percentage; a boldface number indicates a failed result.
[b] WB1, whole blood sample 1; QC1, QC material 1.
[c] Data collected over a period of <20 days.

- Imprecision
  - A1CNow : Imprecision >3%
- NGSP certification criteria
  - Two of 4 A1cNow lots and 1 Afinion lot did not pass NGSP certification.
- Lot-to-lot variation is concern
- Clinicians must recognize that although POCT Hb A1c measurement offers convenience in some clinical settings, the performance of some POC methods may not be sufficient to meet clinical needs.







국내 검사방법별 CV trends

대한임상검사정도관리협회

2008-2011년 검사방법별 Interlab. CV

- Optimal : <3.5%
- Desirable goal : <5%

- HPLC : 1.7%, 1.8%
- Immunoassay : 3.4%
- POCT : 6.8%

Perfomance standards - Accuracy

- Accuracy-based PT
  - **대한임상검사정도관리협회**
    - 2008(±12%), 2010(±10%), 2012(±8%),
    - Pass rate (2011_2)
      - Overall pass rate : 96.7%
      - Pass rate of POCT method : 80%

4. HbA1c POC 검사의 질 향상 방안

- 제조회사
- 임상검사실

제조회사 또는 시약 수입회사

- HbA1c POCT 시약 : Lot to lot variation이 큼
- NGSP certification
  - 1년 1회 : 40검체
  - Lot to lot variation를 확인할 수 없음

- 국내 제조 또는 수입되어 검사실에서 사용되는 POCT 시약의 lot 에 대해 검증 필요
  - NGSP 통과한 lot와 실제 국내에서 사용되는 lot가 다를 수 있음
  - 이 경우 국내 사용되는 lot의 성능을 확인 할 수 없음.
  - 국내에서 사용되는 lot에 대한 성능 검증 필요

- 방안
  - 질병관리본부내의 표준검사실
  - 올해 내에 IFCC Network Lab으로 인정받을 예정.
  - 표준검사실과 관련 학회가 중심이 되어 국내에서 제조 또는 수입되고 있는 현장검사용 장비 및 시약에 대한 미국 NSGP와 비슷한 수행능 인증 평가

임상검사실

- 내부정도관리 실시
  - 2개의 서로 다른 농도를 가진 정도관리물질 이용
  - 검사의 정밀도 확인

- 외부정도관리 참여
  - 대한임상검사정도관리협회
  - 검사의 정확도 확인

- HbA1c 검사의 성능 기준은 정밀도는 2% 이내 (POCT의 경우 3% 이내)에 들어야 하고, 정확도는 NGSP 인증과 외부정도관리 기준을 통과하여야 함.

- 그러나 현재 사용되고 있는 POCT 시약 중 일부는 정밀도 및 정확도에서 그 성능기준을 맞추지 못하는 경우가 있음. 또한 로트간 성능의 차이를 보이는 경우가 있음.

- HbA1c 현장검사의 질을 향상시키기 위해서
- 제조(또는 수입)회사에서는 로트간 성능을 일괄되게 유지하고 성능을 검증할 수 있는 방안을 모색하여야 하고,
- 임상검사실에서는 내부정도관리를 통해 검사의 정밀도를 확인하고 외부정도관리의 참여를 통해 정확도를 검증함으로써 검사의 질을 높이는 노력을 하여야 함.

대한민국 의료의 미래

Quantum Lead 21

2012년 5월 1300병상 규모의 글로벌병원으로
새롭게 태어납니다.

THANK YOU FOR YOUR ATTENTION!