HbA1c – challenges for the laboratory (and for the EQA organizer) – internal and external QC

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EFLM course October 26th – 27th 2014

HbA1c

Standardization and quality requirements – the Swedish perspective

External QC: check of trueness and accuracy
Internal QC: check of reproducibility

Impact of EQA on users: action to be taken by the participants
Impact of EQA on producers: action to be taken by the EQA organizer

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HbA1c, a short Swedish background

The *reformation* of calibration

- until 2010: results traceable to the HPLC procedure Mono S (not NGSP/DCCT!), and values reported with %-unit, on the Mono S scale.
- from 2011: results traceable to the IFCC reference method and values given with the “mmol/mol”-unit, on the IFCC scale.
- from 2014 HbA1c results are good enough to be recognized for diagnosis of DM in Sweden, under the condition that quality requirements are met.

The Equalis EQA scheme for HbA1c

- 10 yearly distributions of fresh pooled ’left over’ EDTA blood samples, level often in the level 30 – 70 mmol/mol.
- Samples are collected Mondays, distributed by mail Tuesdays and measured Wednesdays (latest Fridays).

Target values for the EQA material

- until 2010: mean values from selected Mono S laboratories.
- from 2011: mean values from (two) three ”IFCC secondary reference methods” performed by the European Reference Laboratory (ERL) in Holland.
- (from 2015: Mono S values again??)

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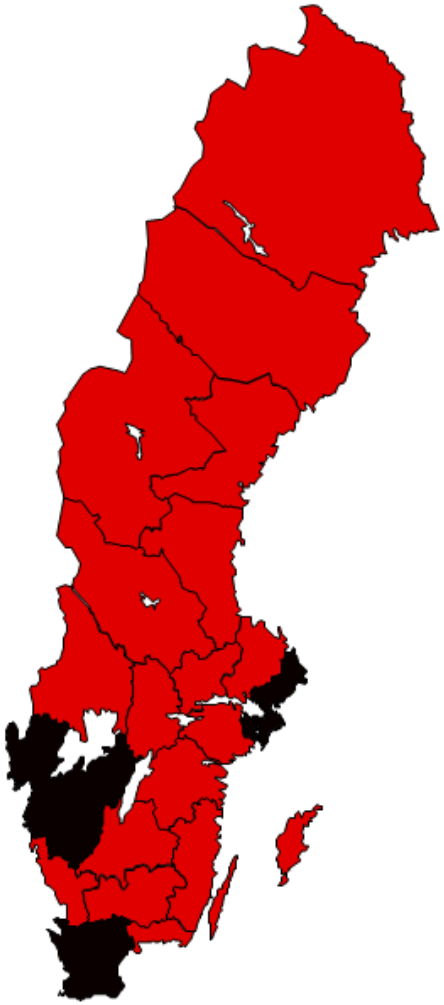
Sweden



449 964 km²
9.6 miljon inhabitants

20 counties and
290 independent municipalities

90 hospitals and
1500 primary health care centers
governed by local authorities

1.2 miljon HbA1c tests per year

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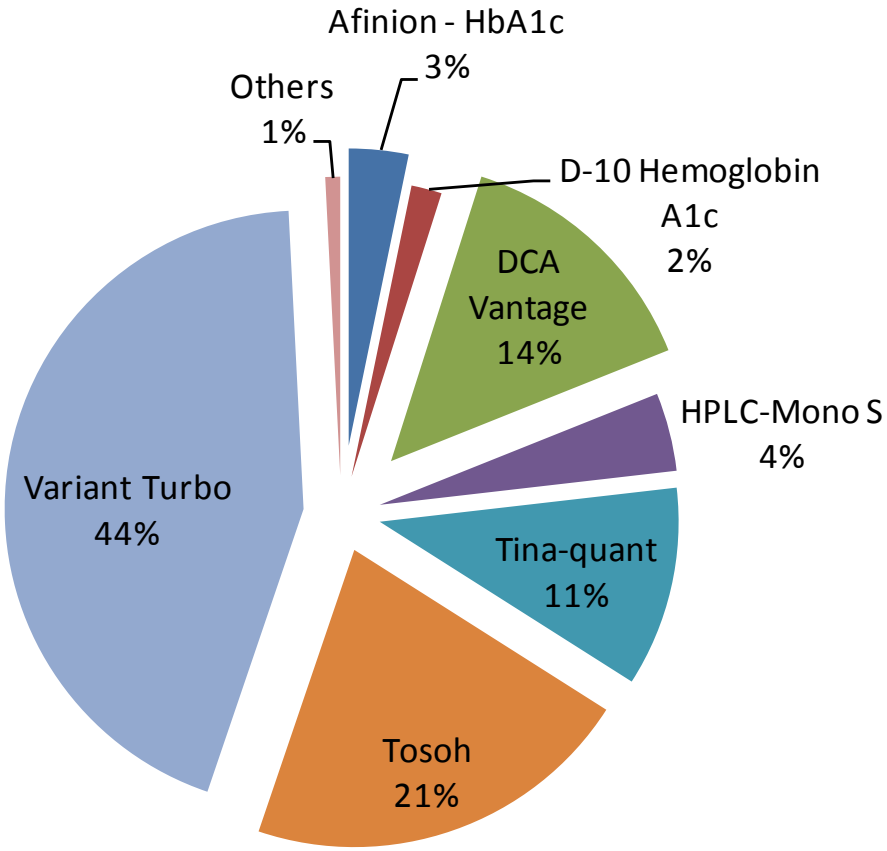
The HbA1c methods in use in Sweden



1,2 miljoner HbA1c - resultat 2013

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The unit . . .

”mmol/mol” or ”%” does not matter!

It is **the scale** that matter.

IFCC scale, NGSP scale (or Mono S scale).

”mmol/mol” is the preferred unit to indicate the use of the IFCC scale for measurement, the ”IFCC unit”.

Both ”%” and ”mmol/mol” are units which can be used within the SI.

The term ”SI-unit” for ”mmol/mol”, might be a signal for ”not for use in US”….

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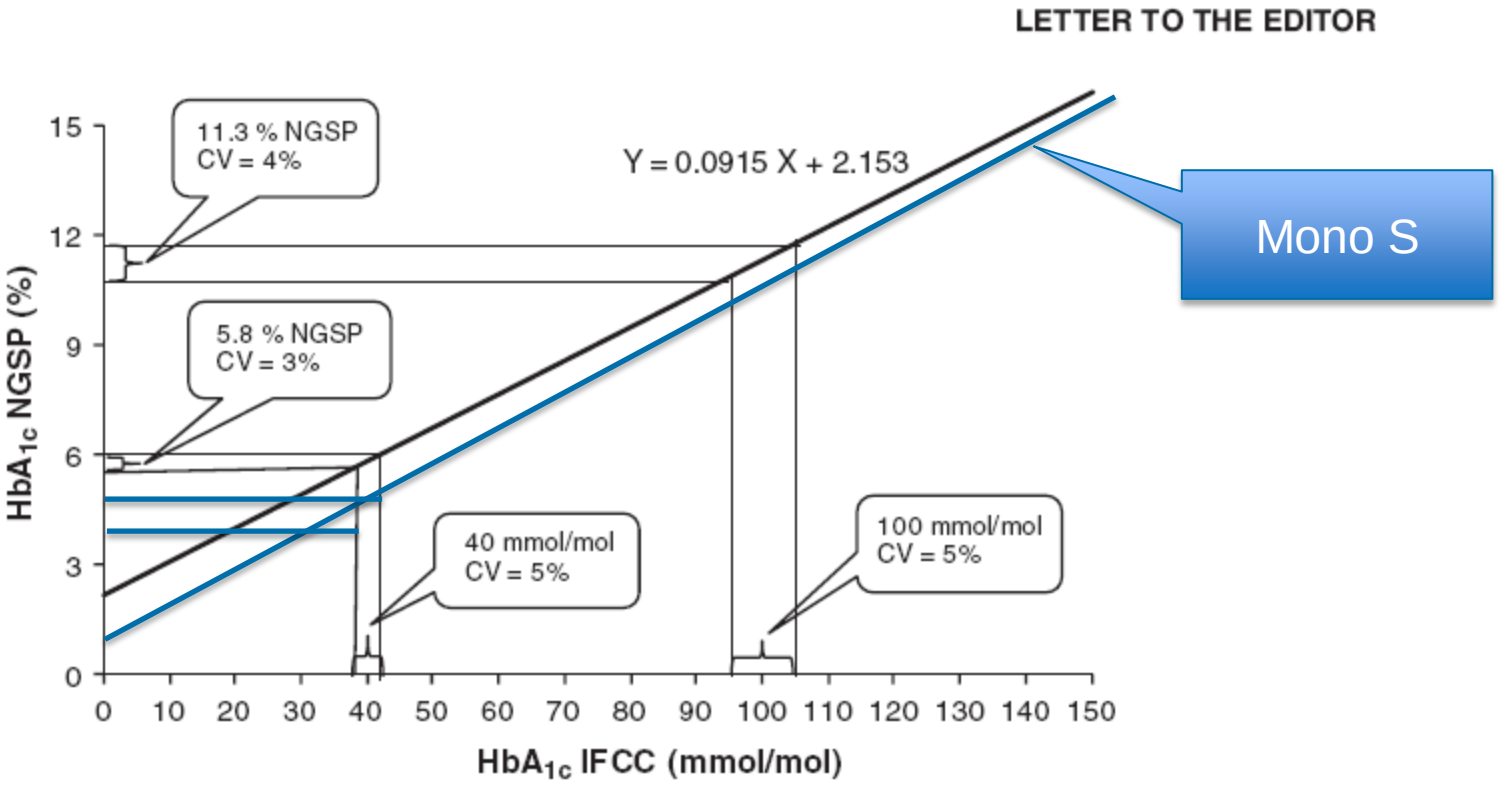
Three separate scales makes the life complicated



DIABETES TECHNOLOGY & THERAPEUTICS, Volume 13, Number 12, 2011

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Three separate scales makes the live complicated

EQUALIS Uppsala 2011-07-25 1 (3)

The variation (CV % NGSP) is 6% CV at the mean HbA1c value of 7,1 HbA1c %. What is the corresponding CV% expressed in IFCC units?

Note that the coefficient of variation varies with the level of HbA1c.

CV% (IFCC) = (mean x CV% x 10,93)/(mean x 10,93 – 23,54)

CV% (IFCC) = 7,1 x 6 x 10,93/(7,1 x 10,93 – 23,54) = 8,6%

What is the corresponding CV% expressed in NGSP units?

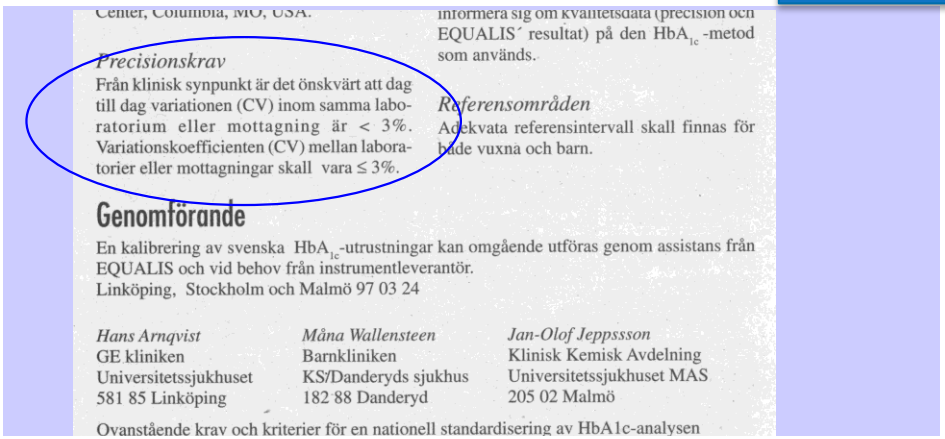
Note that the coefficient of variation varies with the level of HbA1c.

CV% (NGSP) = (mean x CV% x 0,952)/(mean x 0,952 + 1,205)

CV% (NGSP) = 6,5 * 5*0,952/(6,5 * 0,952 + 1,205) = 4,2 % CV

Quality goal in Sweden 1997: 3% CV

n.b. CV for Mono S scale
2.5% on NGSP scale
4% on IFCC scale



Center, Columbia, MO, USA.

Precisionskrav

Från klinisk synpunkt är det önskvärt att dag till dag variationen (CV) inom samma laboratorium eller mottagning är < 3%. Variationskoefficienten (CV) mellan laboratorier eller mottagningar skall vara ≤ 3%.

informera sig om kvalitetsdata (precision och EQUALIS´ resultat) på den HbA_{1c}-metod som används.

Referensområden

Adekvata referensintervall skall finnas för både vuxna och barn.

Genomförande

En kalibrering av svenska HbA_{1c}-utrustningar kan omgående utföras genom assistans från EQUALIS och vid behov från instrumentleverantör.
Linköping, Stockholm och Malmö 97 03 24

Hans Arnqvist	*Måna Wallensteen*	*Jan-Olof Jeppsson*
GE kliniken	Barnkliniken	Klinisk Kemisk Avdelning
Universitetssjukhuset	KS/Danderyds sjukhus	Universitetssjukhuset MAS
581 85 Linköping	182 88 Danderyd	205 02 Malmö

Ovanstående krav och kriterier för en nationell standardisering av HbA1c-analysen

Svensk Förening	Svensk förening för	Svenska Diabetes-
för Allmänmedicin	Sjuksköterskor i Diabetesvård	förbundet
Ordförande	Ordförande	Ordförande

The quality goal for External QC was reformulated in 2004 to an accuracy goal: 5% of resulats within +/- 0.4 % (Mono S scale) appr 4 mmol/mol (IFCC scale) from target

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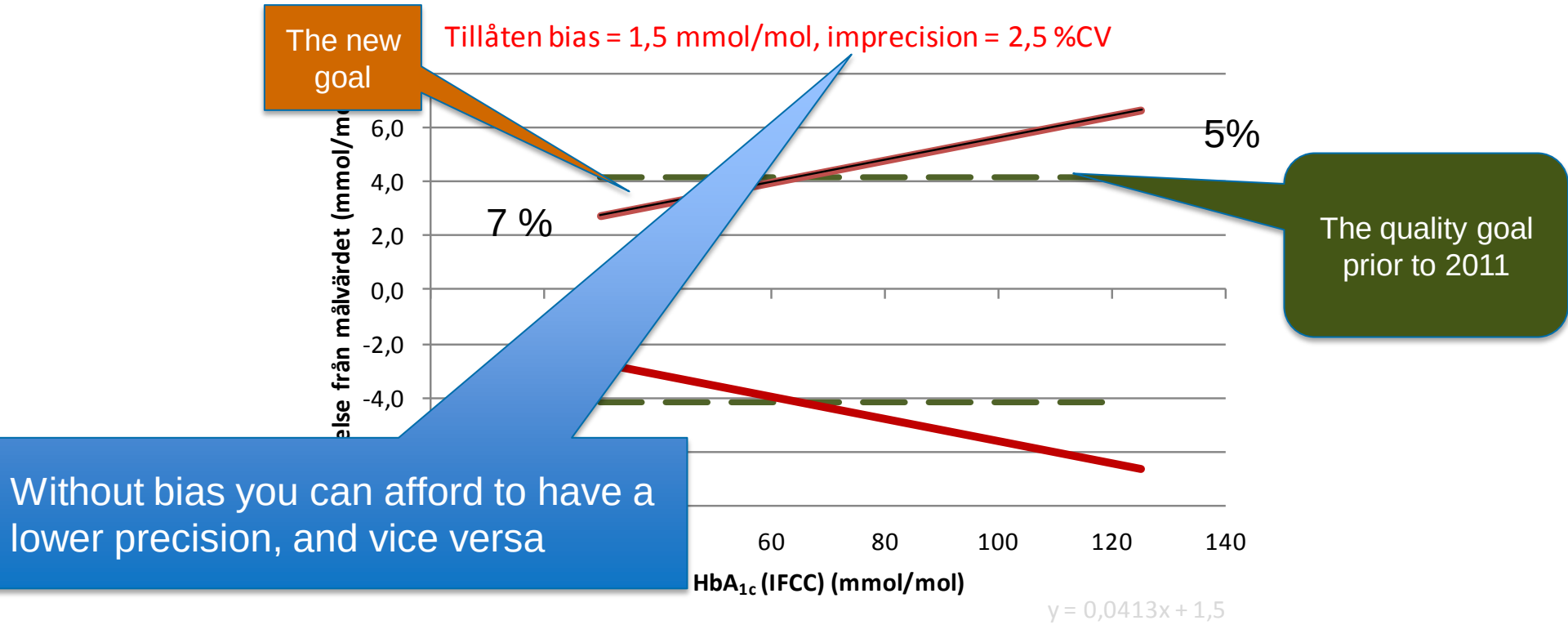
2011: turning traceability to IFCC reference measurment procedure

Quality goal for accuracy +/-4 mmol/mol was modified to:

1,5 mmol/mol ±2,5% CV (IFCC scale)

The revised quality goal for accuracy from 2011



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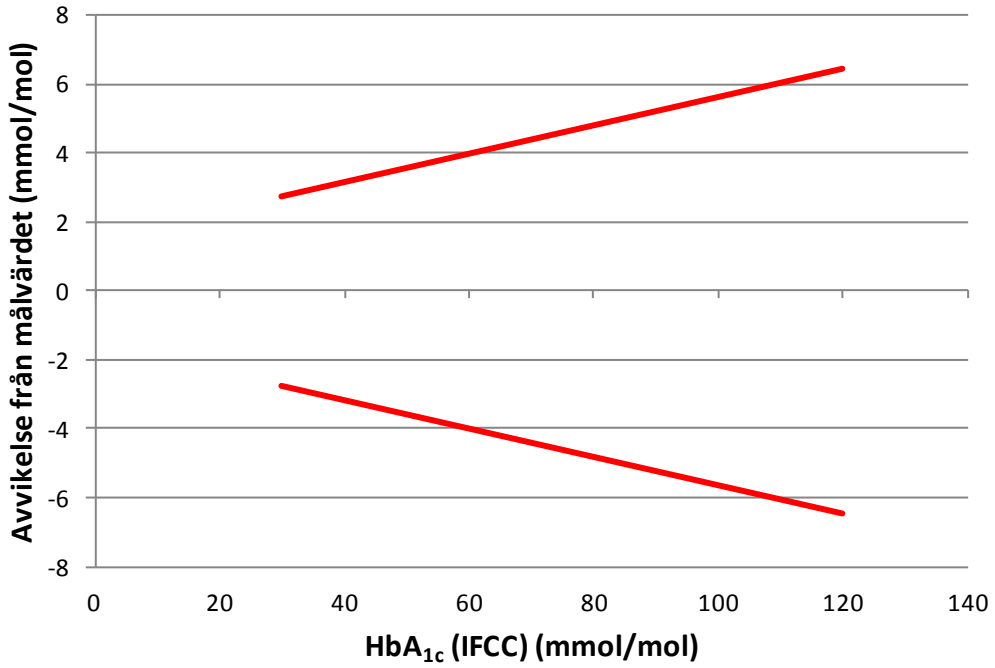
Is the quality qoal realistic?



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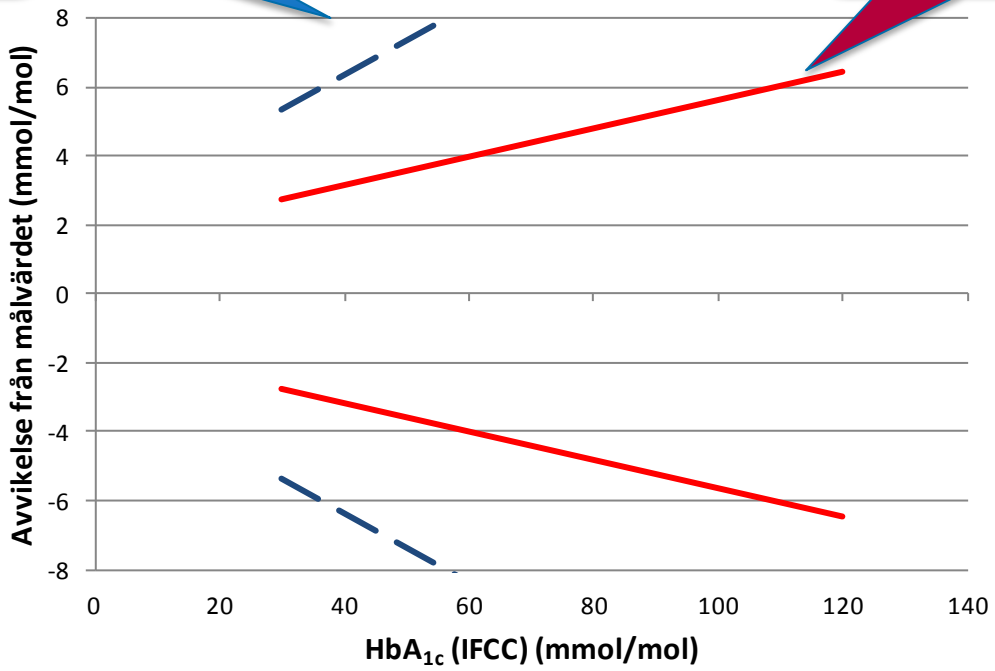
+/- 10% NGSP

NGSP goal in CAP survey 2009!

The Swedish goal!



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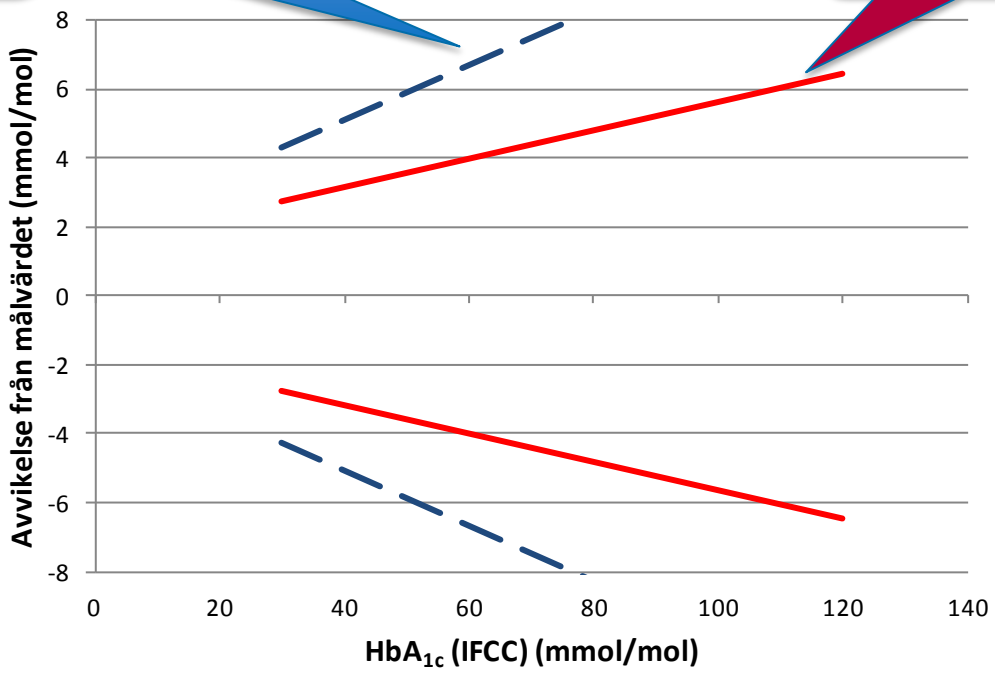
+/- 8% NGSP

NGSP goal in CAP survey 2010!

The Swedish goal!!



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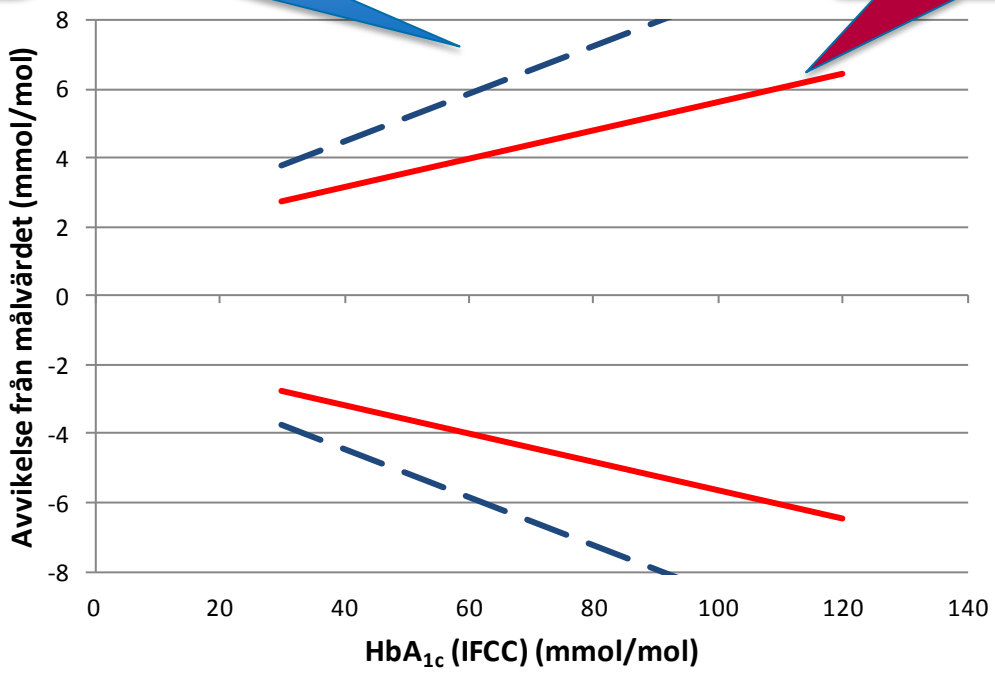
+/- 7% NGSP

NGSP goal in CAP survey 2011--2012!

The Swedish goal!



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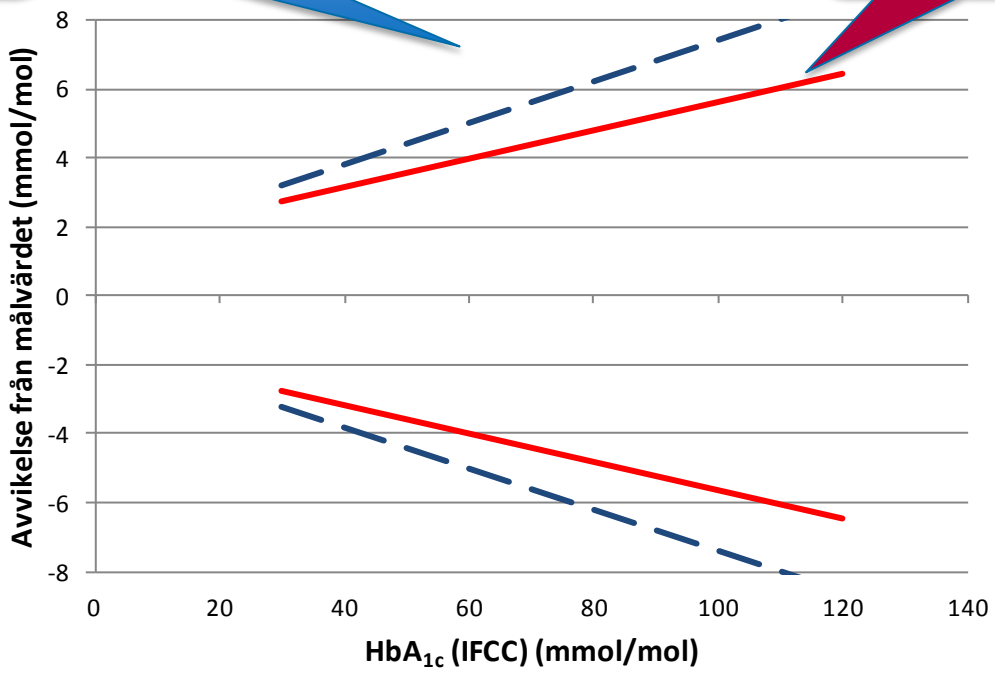
+/- 6% NGSP

NGSP goal in CAP survey 2013!

The Swedish goal!



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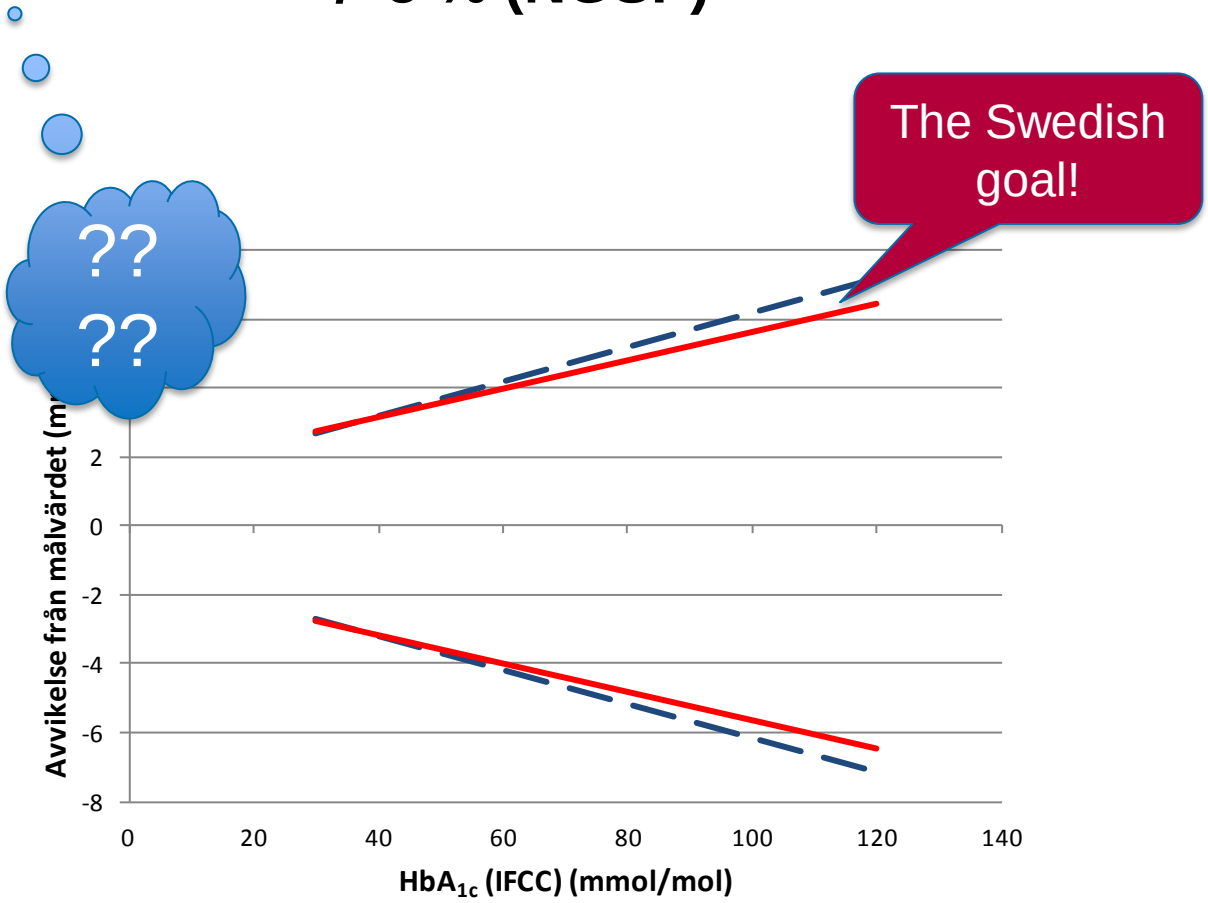
+/- 5 % (NGSP)



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How do the HbA1c results fulfil the quality goal?

In 2011, when IFCC scale was adopted, it was discoverd that several methods had an unexpected bias.

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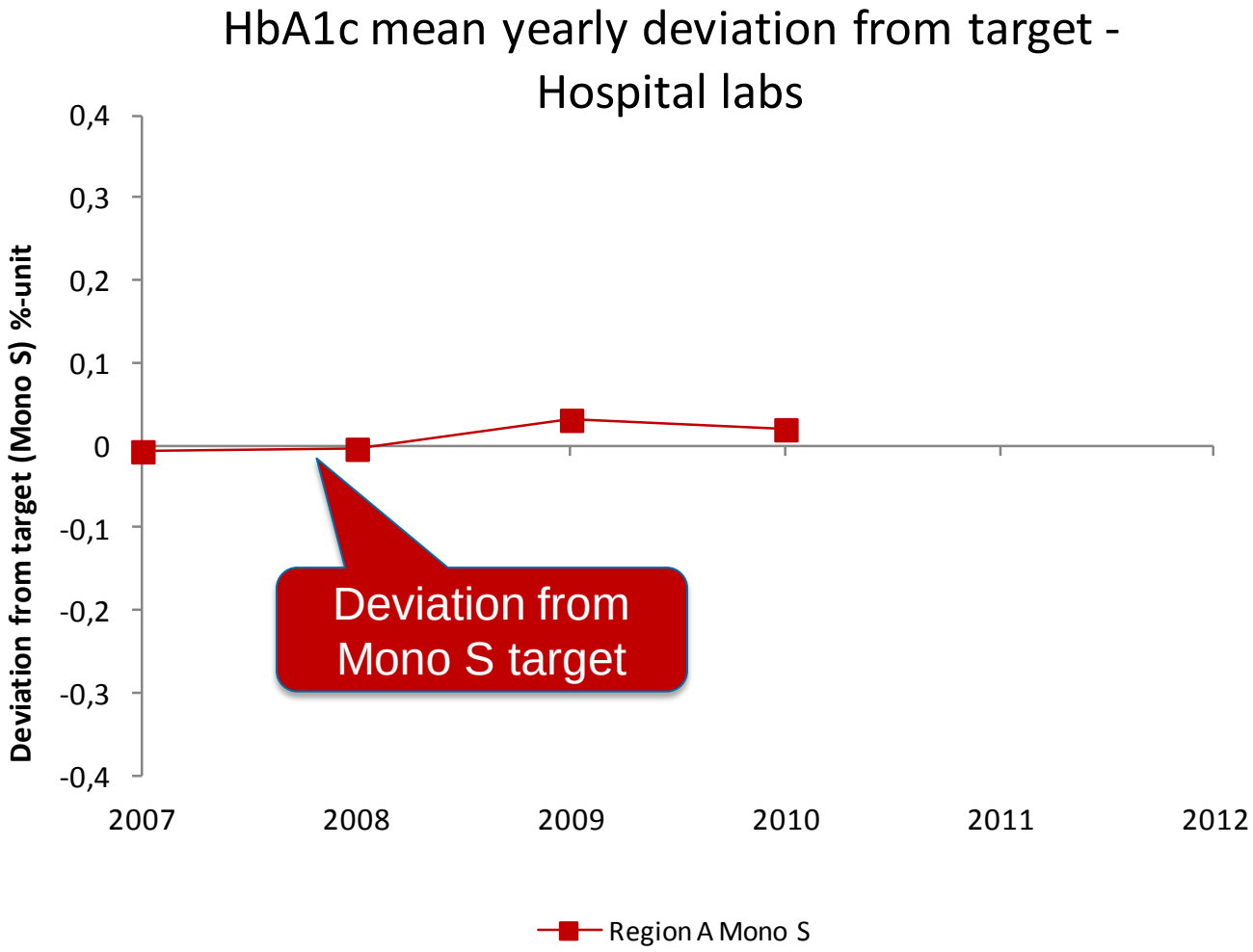
Mean yearly deviation of EQA results for Region A – mostly Mono S



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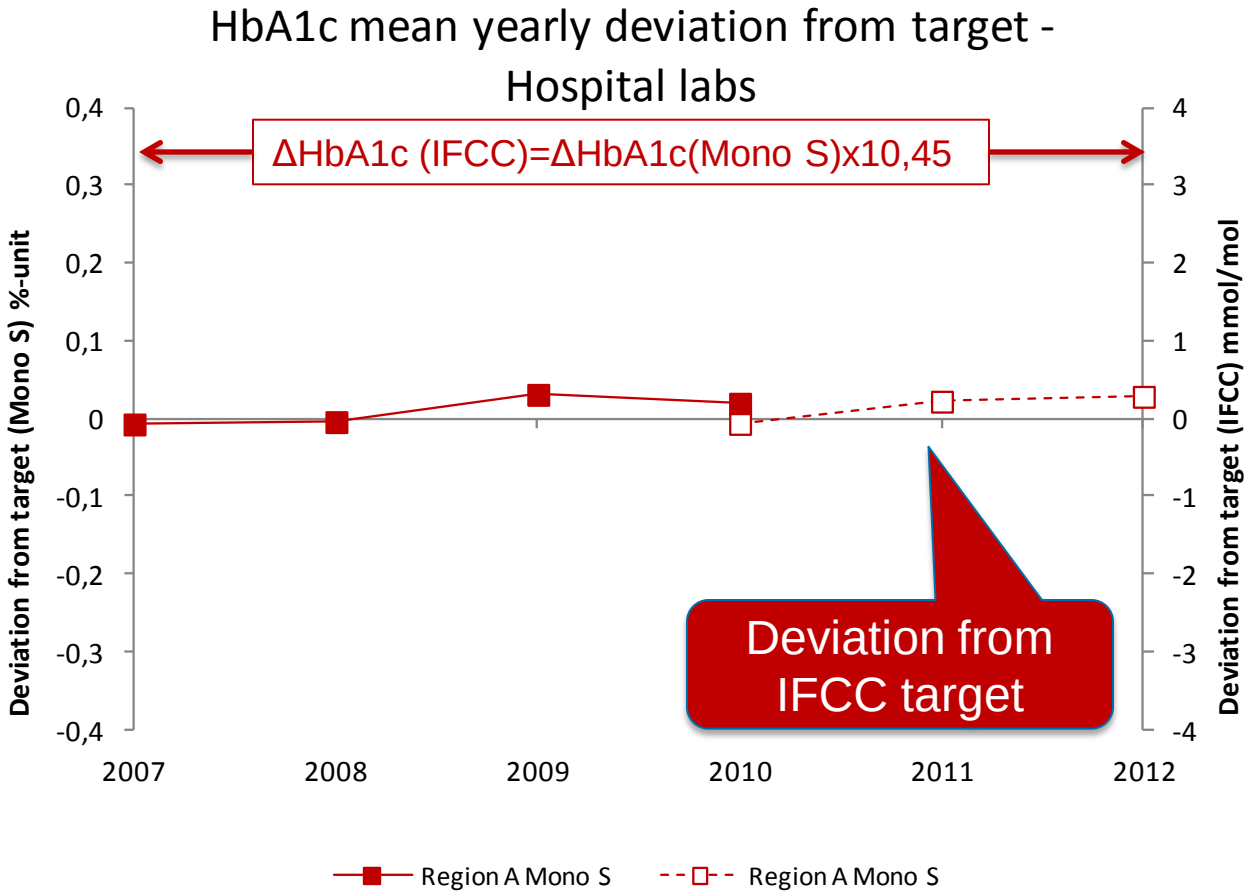
Mean yearly deviation of EQA results for Region A – mostly Mono S



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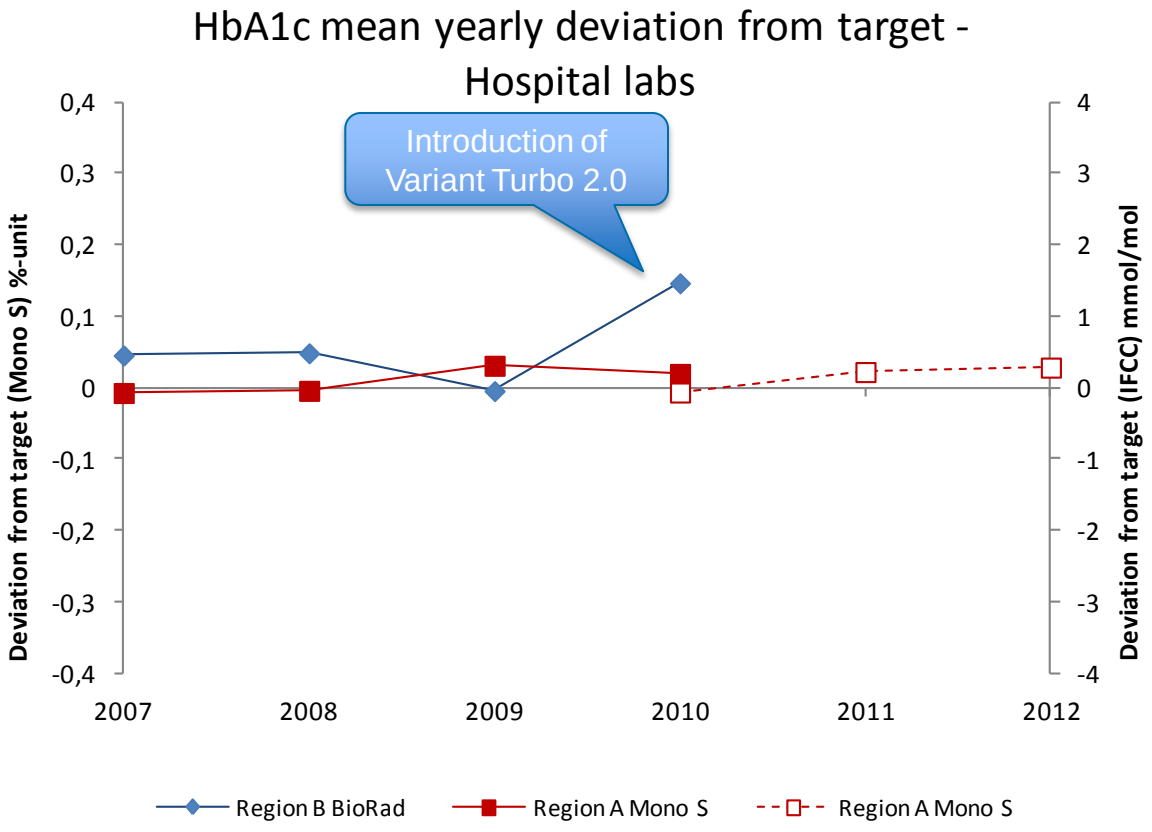
Mean yearly deviation of EQA results for Region B – mostly Bio Rad



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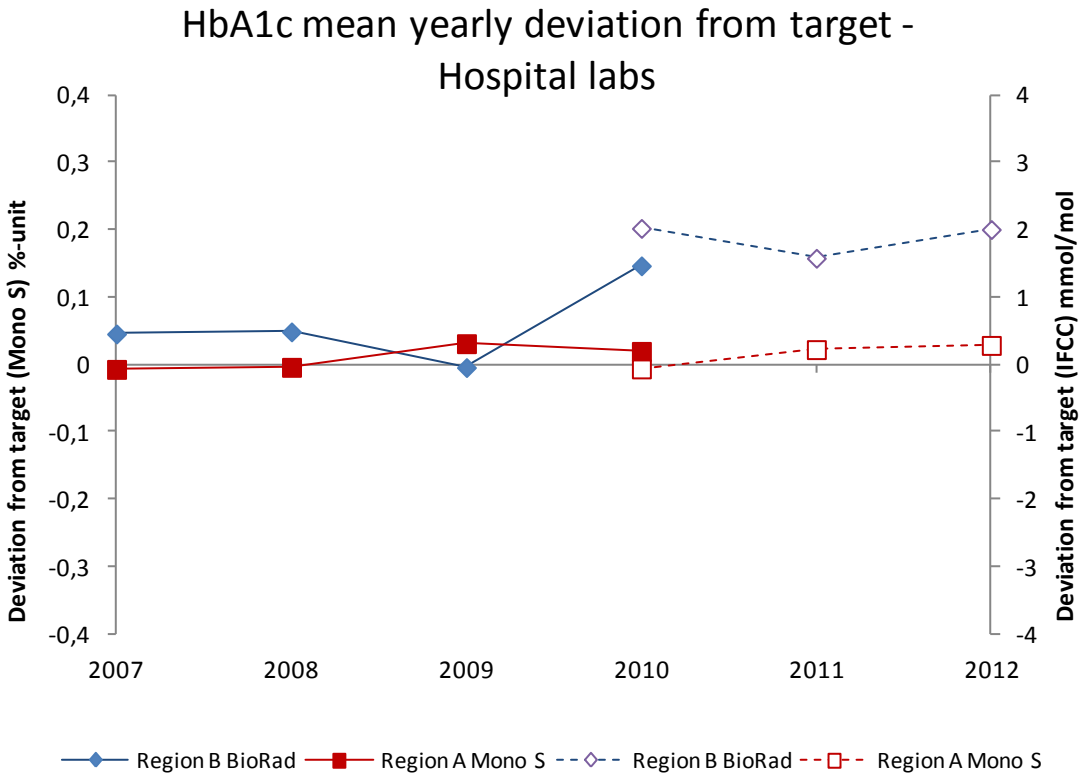
Mean yearly deviation of EQA results for Region B – mostly Bio Rad



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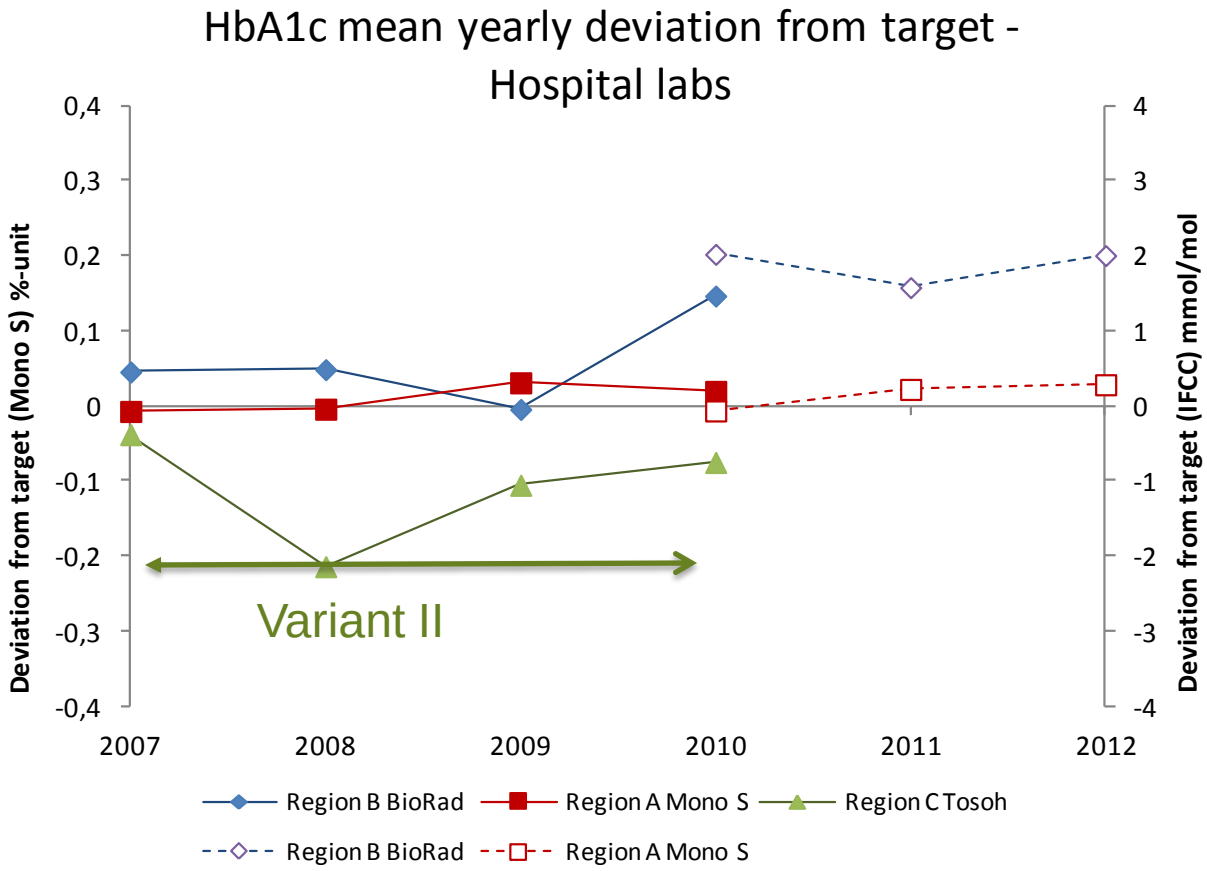
Mean yearly deviation of EQA results for Region C – Variant II and Tosoh G7/G8



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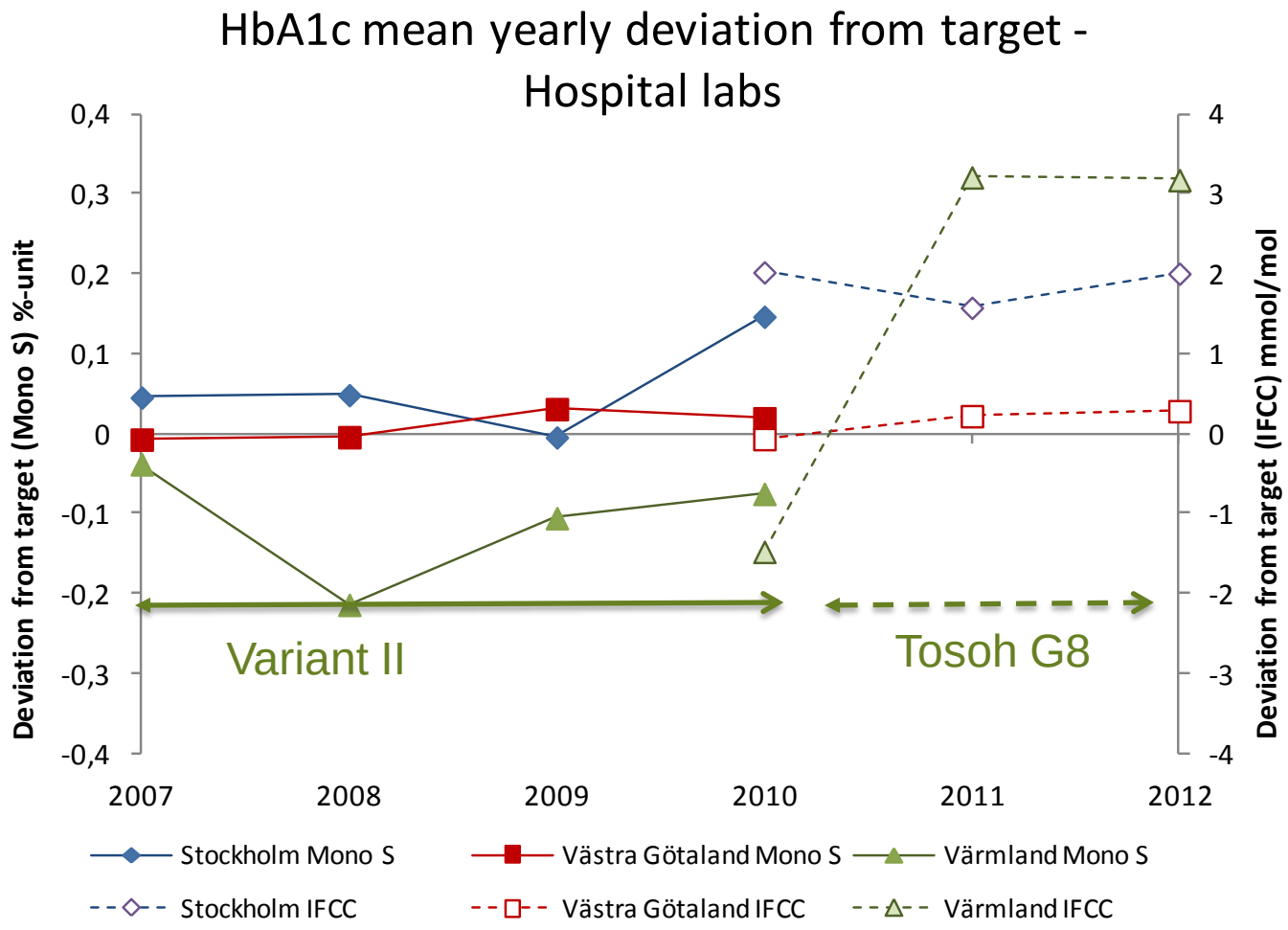
Mean yearly deviation of EQA results for Region C – Variant II and Tosoh G7/G8



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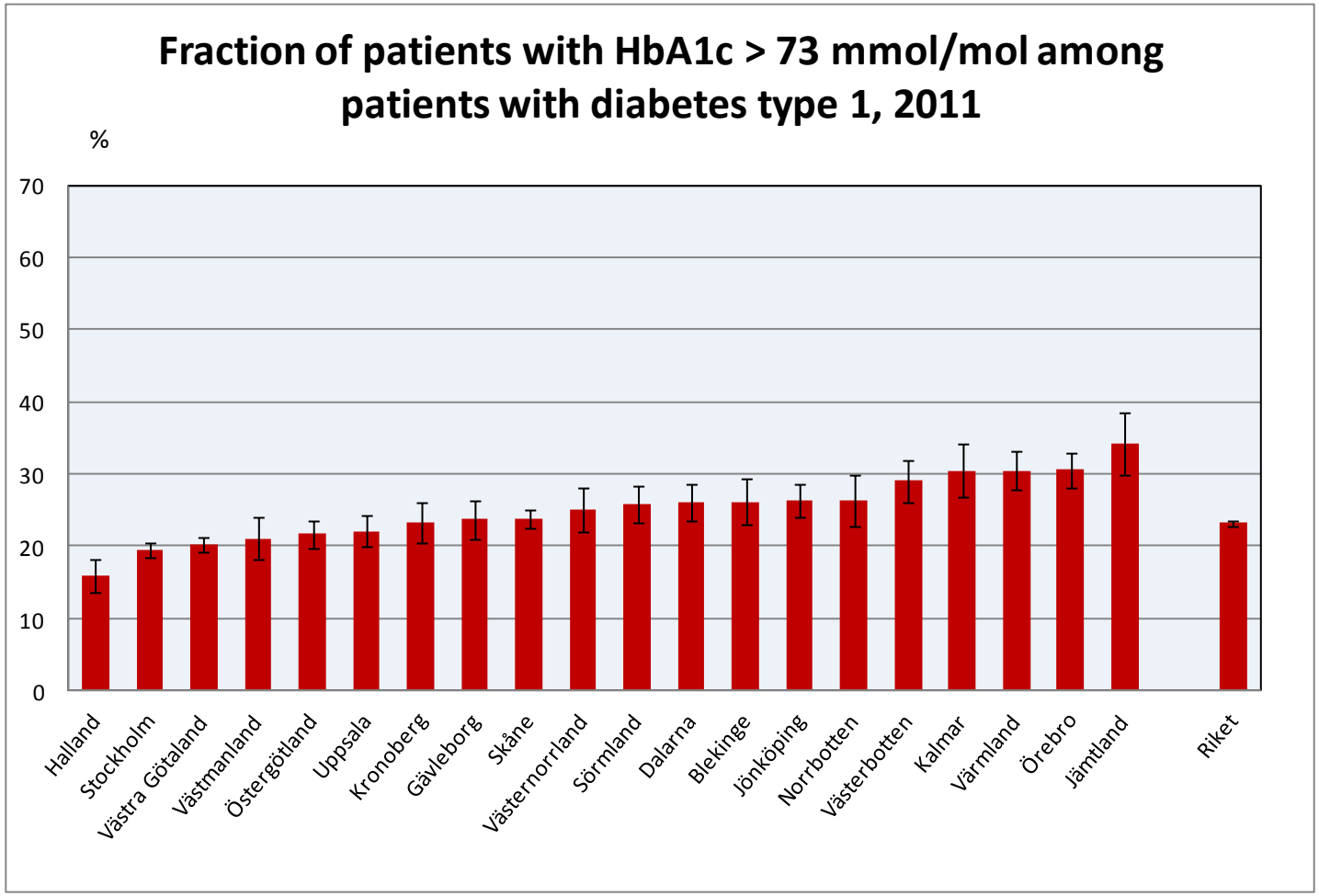
From Nationella Diabetesregistret (NDR) , Göteborg



Impact of calibreration error for HbA1c

1 mmol/mol systematisc error for HbA1c change the fraction of patients above 73 mmol/mol with appr 2,5%

Region x:

systematic error for HbA1c in external QC:

- 2010 = -0,8 mmol/mol
- 2011 = 3,2 mmol/mol

Fraction of type 1 diabetes patients with HbA1c > 73 mmol/mol in NDR

- 2010 = 24%
- 2011 = 30%

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Positive bias after conversion to IFCC calibration in 2011

With a bias of 2 – 3 mmol/mol, nothing is left for imprecision, and these methods did not fulfill the quality goal for performance in EQA.

How to convince the manufacturers?

How to convince the neighbor countries?

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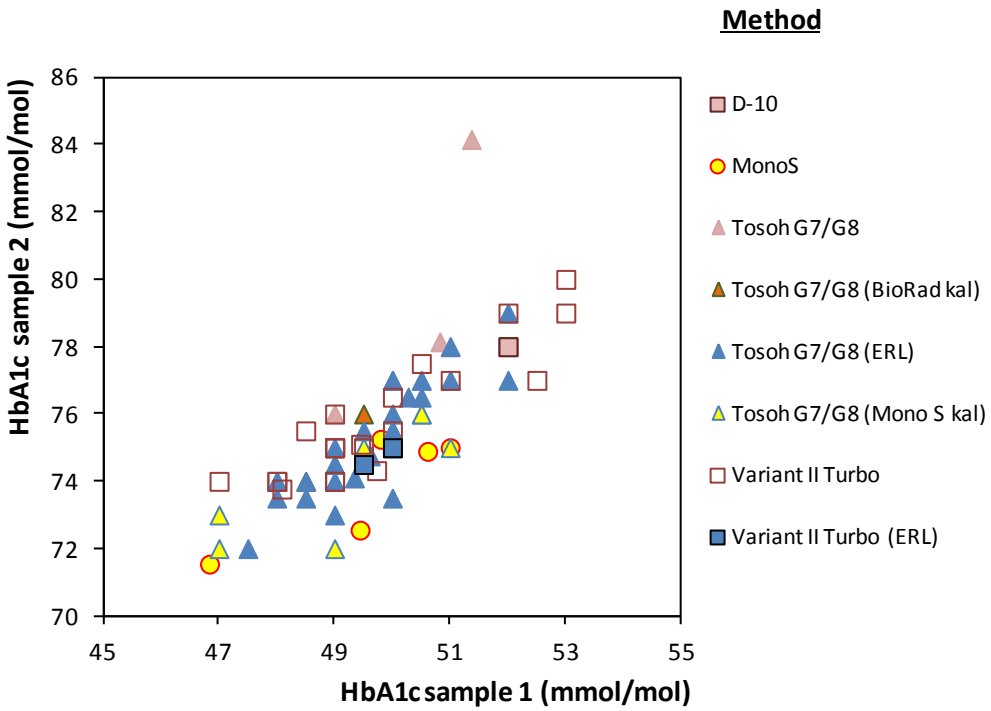
The Swedish – Danish survey 2012



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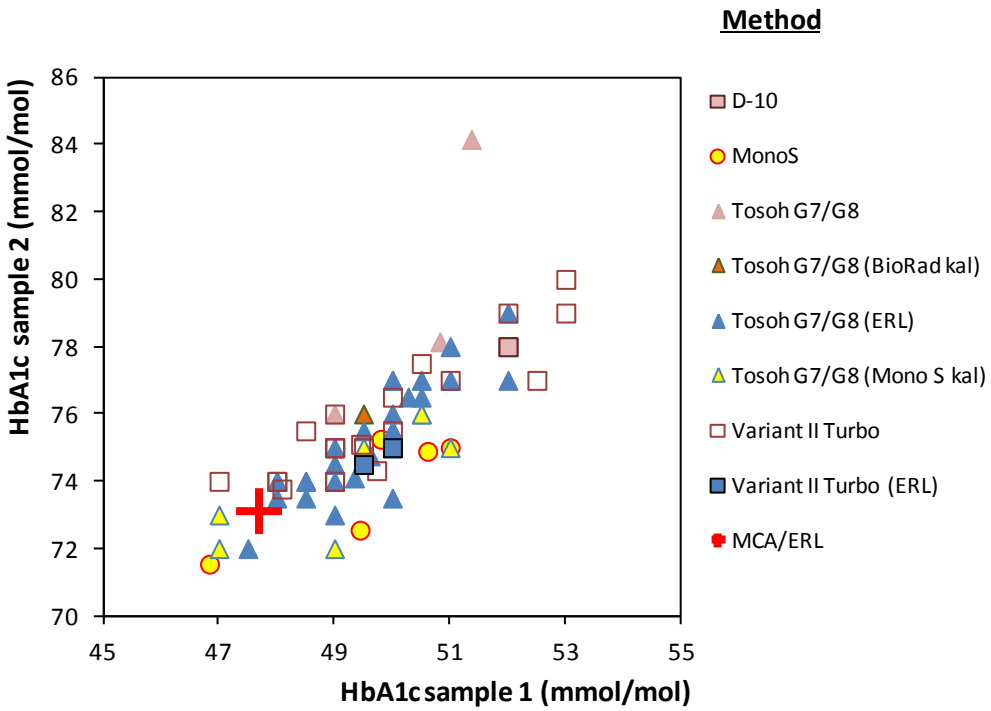

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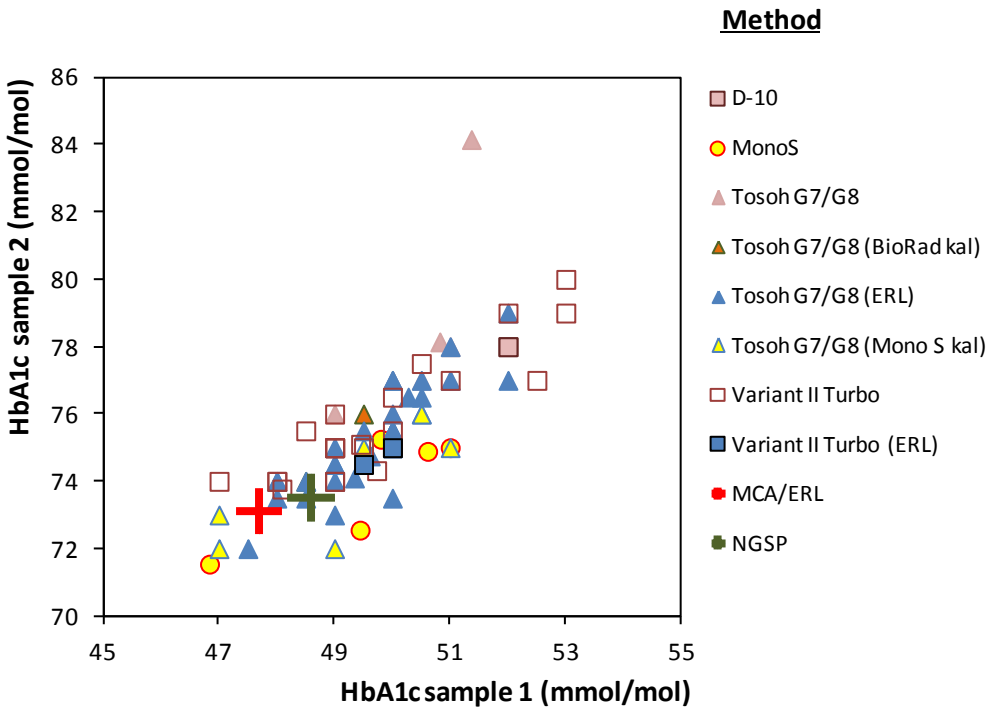

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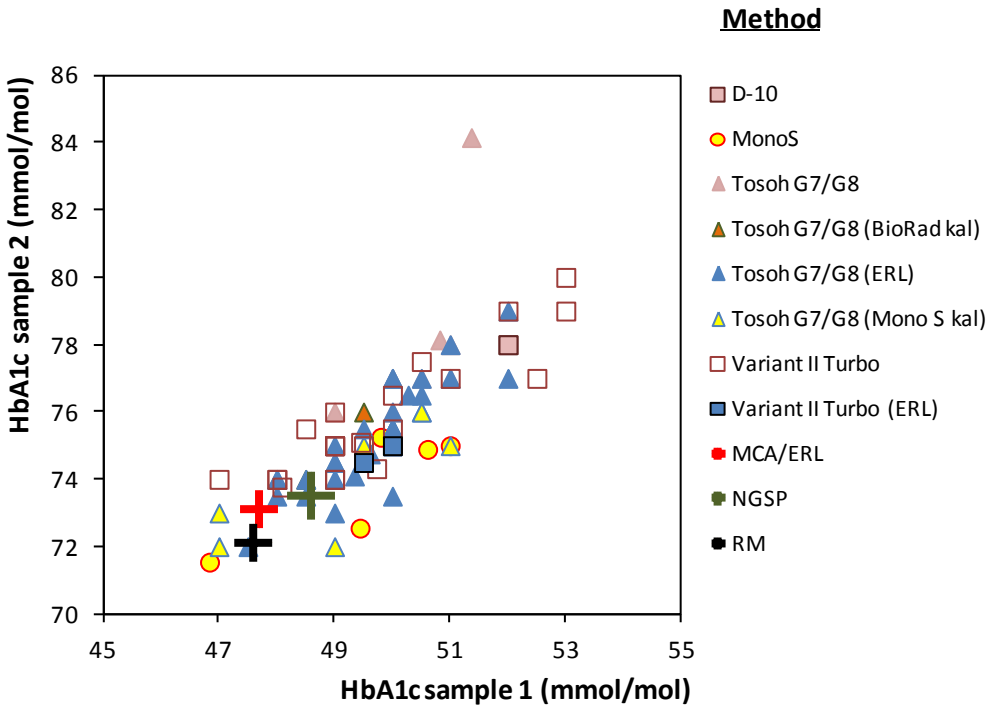

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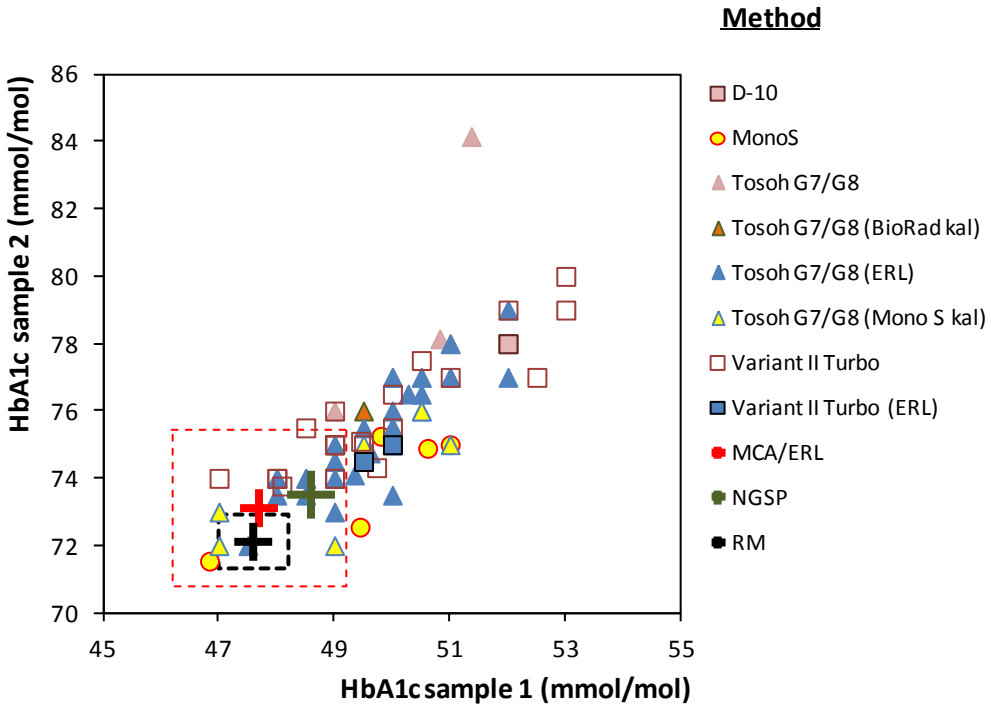
The Swedish – Danish survey 2012



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The neighbours convinced, but not the manufacturers

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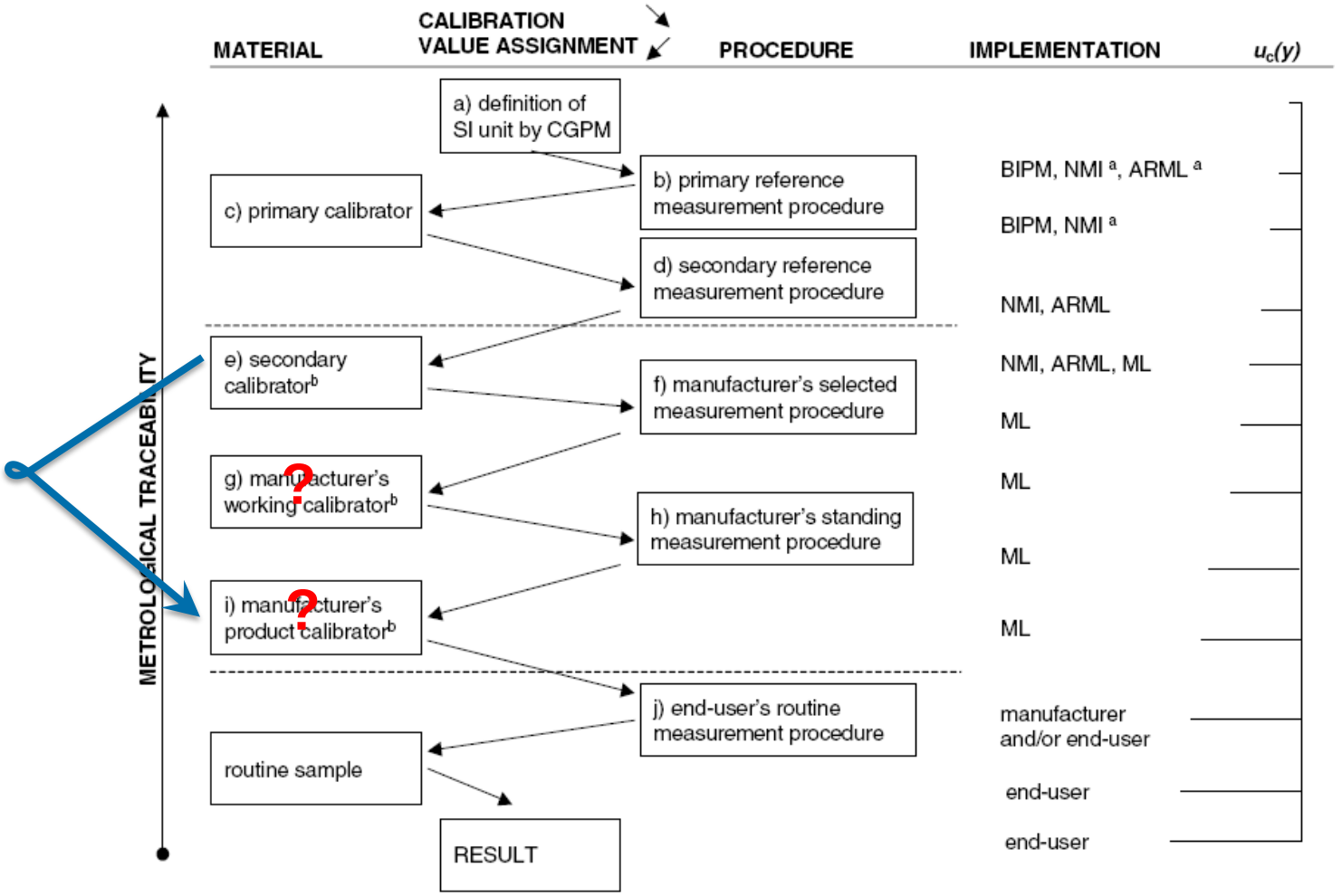
Something was wrong in the traceability chain

The temporary solution



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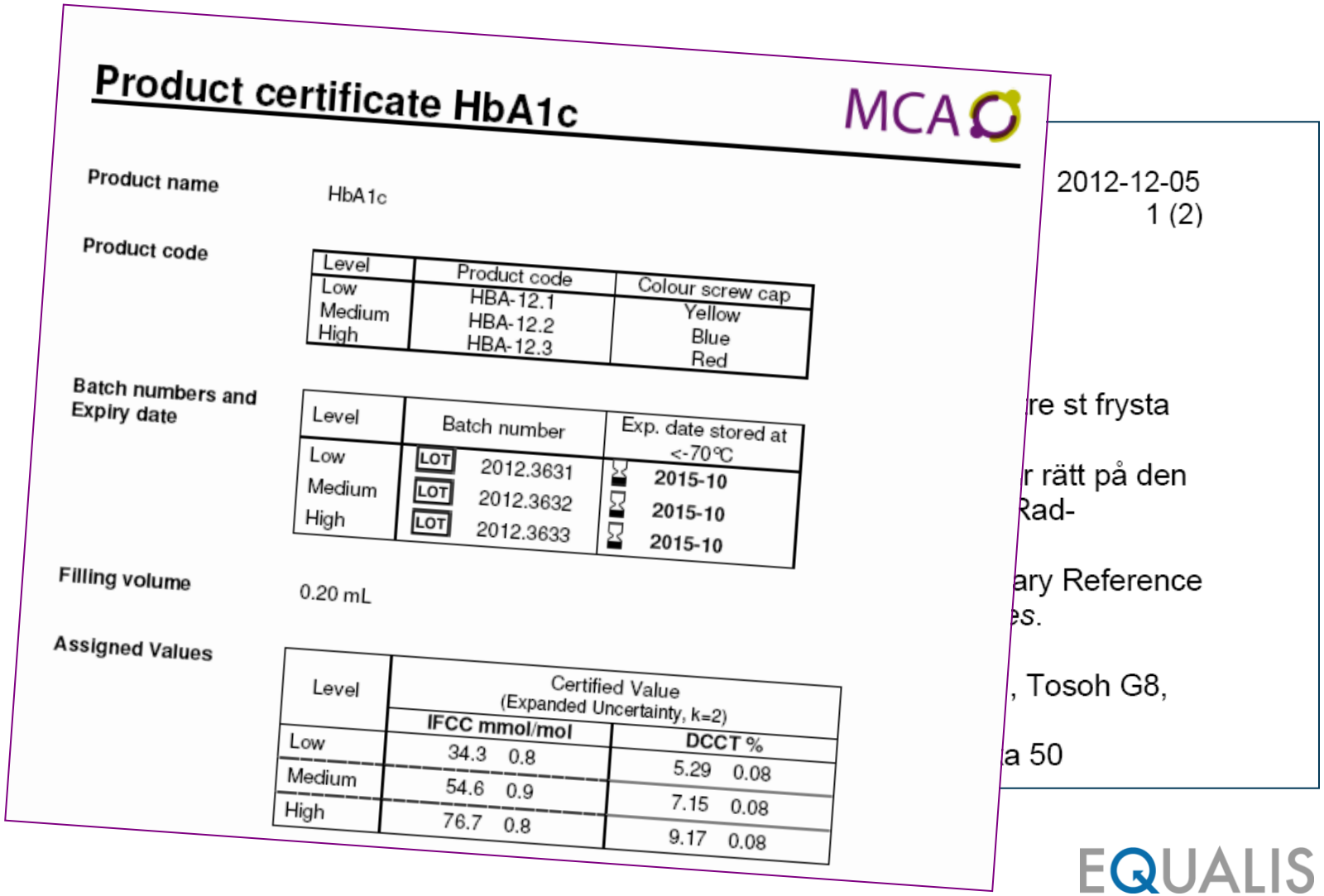
A temporary solution – a fresh frozen whole blood with target values from IFCC (”primary”) reference method



Product certificate HbA1c

MCA

Product name HbA1c

Product code

Level	Product code	Colour screw cap
Low	HBA-12.1	Yellow
Medium	HBA-12.2	Blue
High	HBA-12.3	Red

Batch numbers and Expiry date

Level	Batch number	Exp. date stored at <-70°C
Low	LOT 2012.3631	2015-10
Medium	LOT 2012.3632	2015-10
High	LOT 2012.3633	2015-10

Filling volume 0.20 mL

Assigned Values

Level	Certified Value (Expanded Uncertainty, k=2)	
	IFCC mmol/mol	DCCT %
Low	34.3 0.8	5.29 0.08
Medium	54.6 0.9	7.15 0.08
High	76.7 0.8	9.17 0.08

2012-12-05
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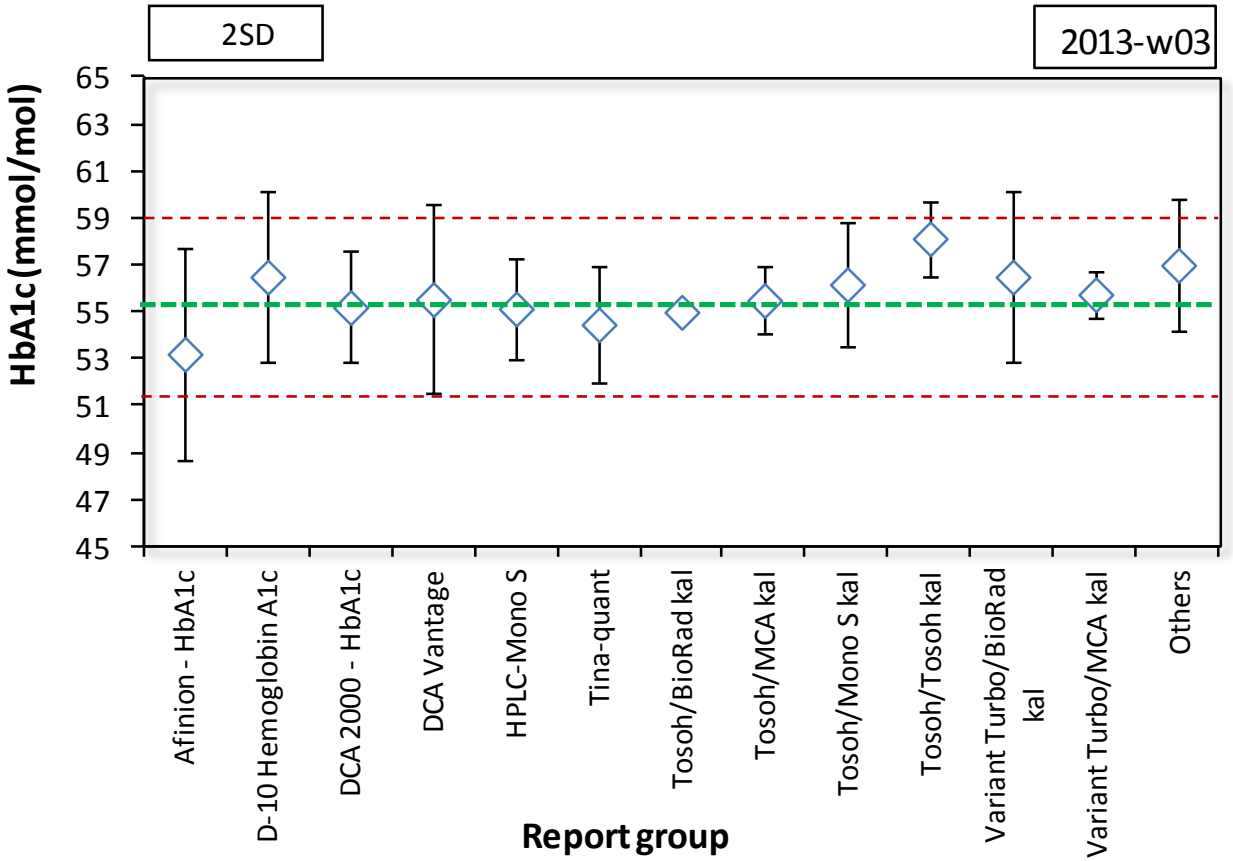
HbA1c EQA January 2013, results per method group



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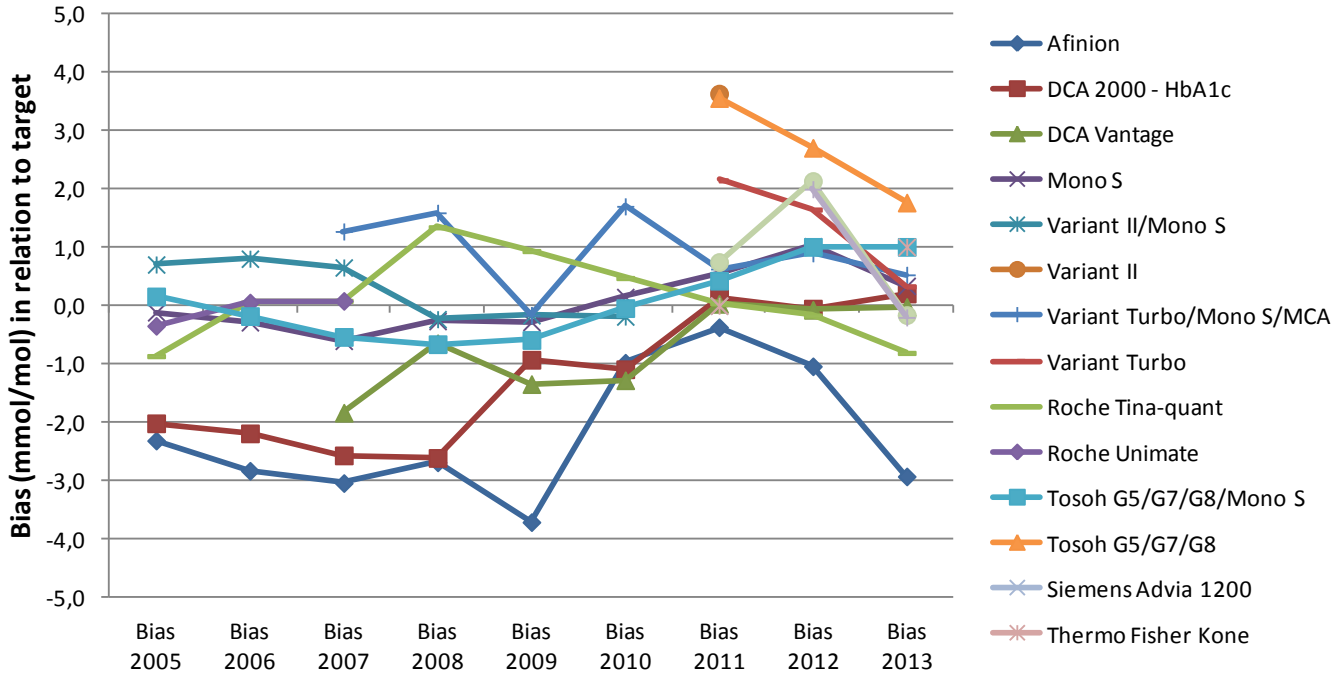
Yearly mean bias per method group in External QC



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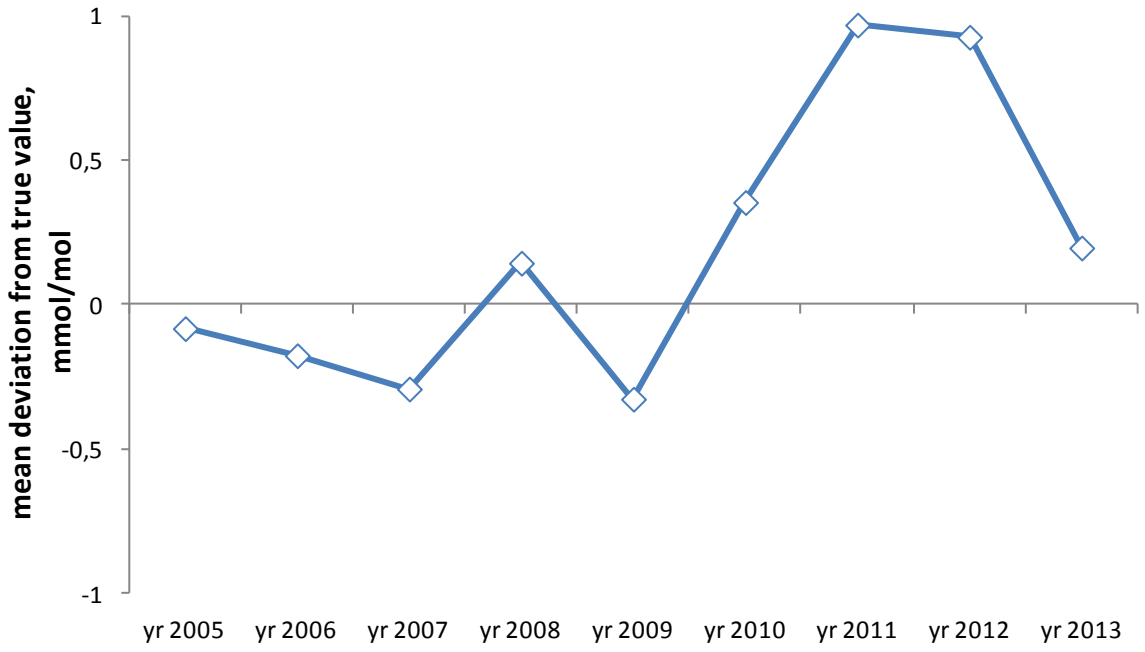
Estimated national yearly HbA1c bias in Sweden



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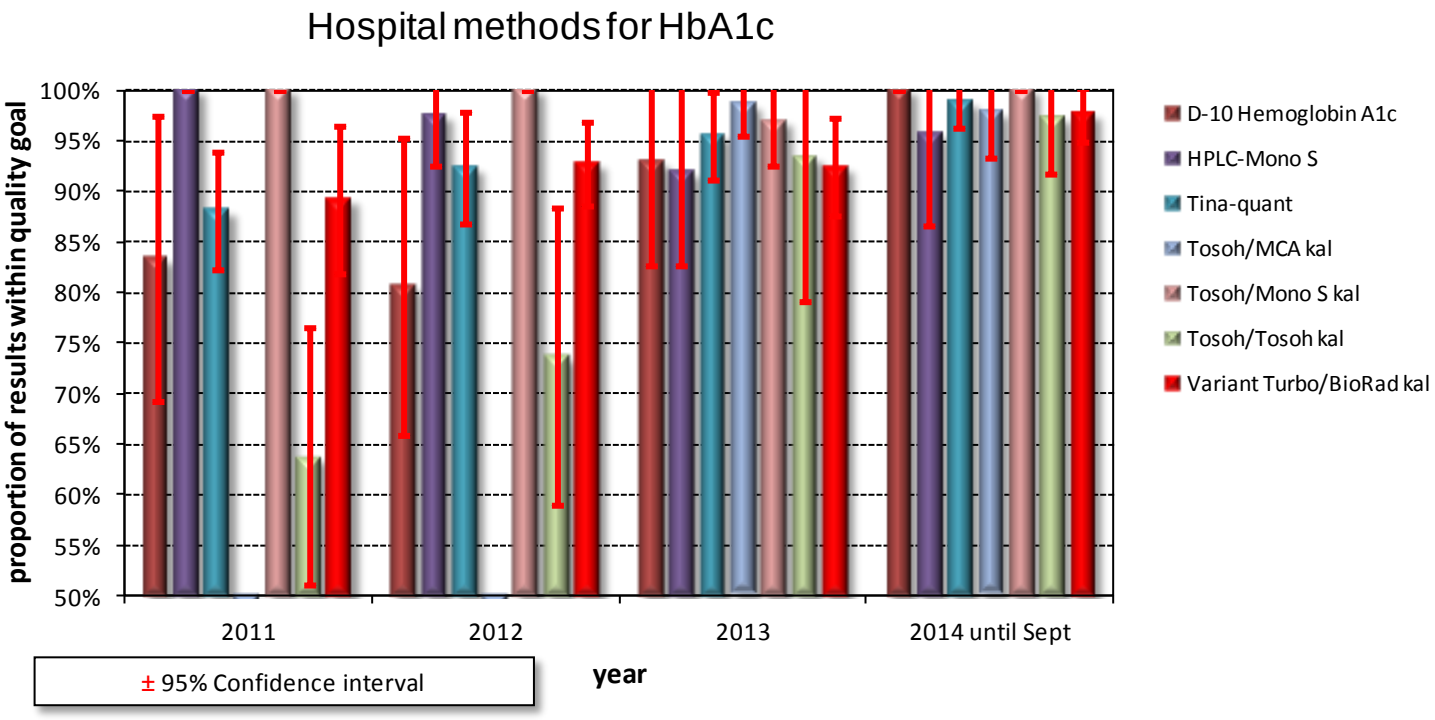
The accuracy has now improved. From 2014 all hospital methods fulfil the goal



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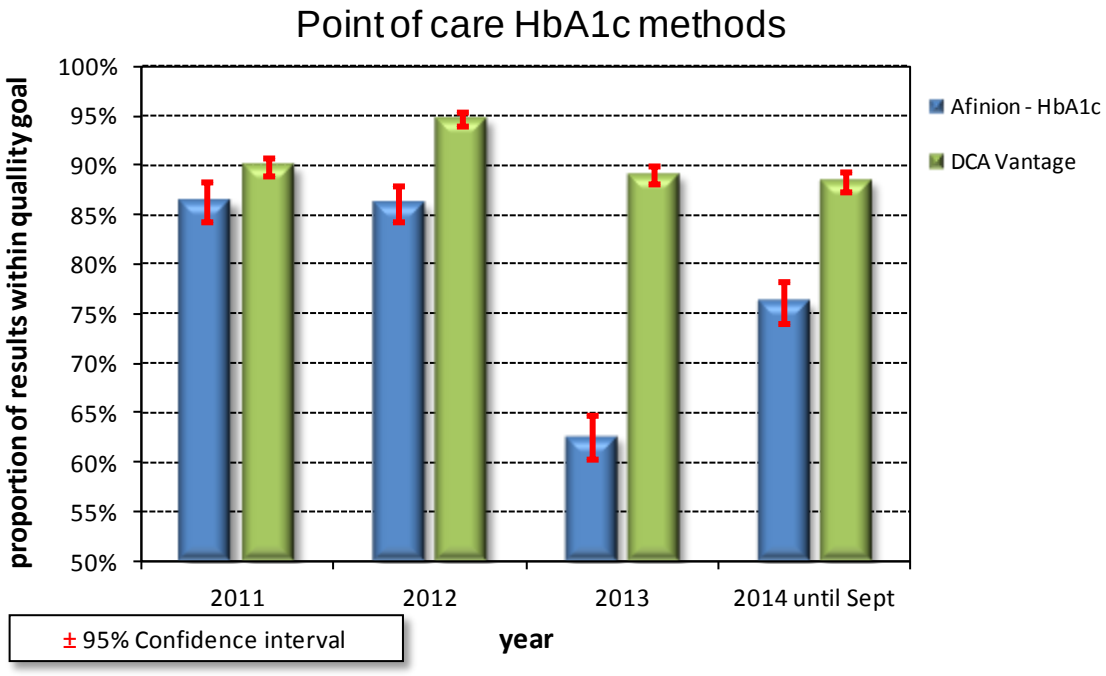
The accuracy of two POCT methds



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HbA1c for diagnostic purposes

After to the improved accuracy, HbA1c (48 mmol/mol) has been implemented for the diagnosis of DM in Sweden from 2014

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How much controls do you need?

The frequency of external and internal QC should reflect the performance and robustness of the method in relation to the quality goal.

Both hospital methods and POCT methods can fulfill the quality requirements.

In US are POCT methods not recommended for diagnostics, because of lack of control of the pre-analytic process!

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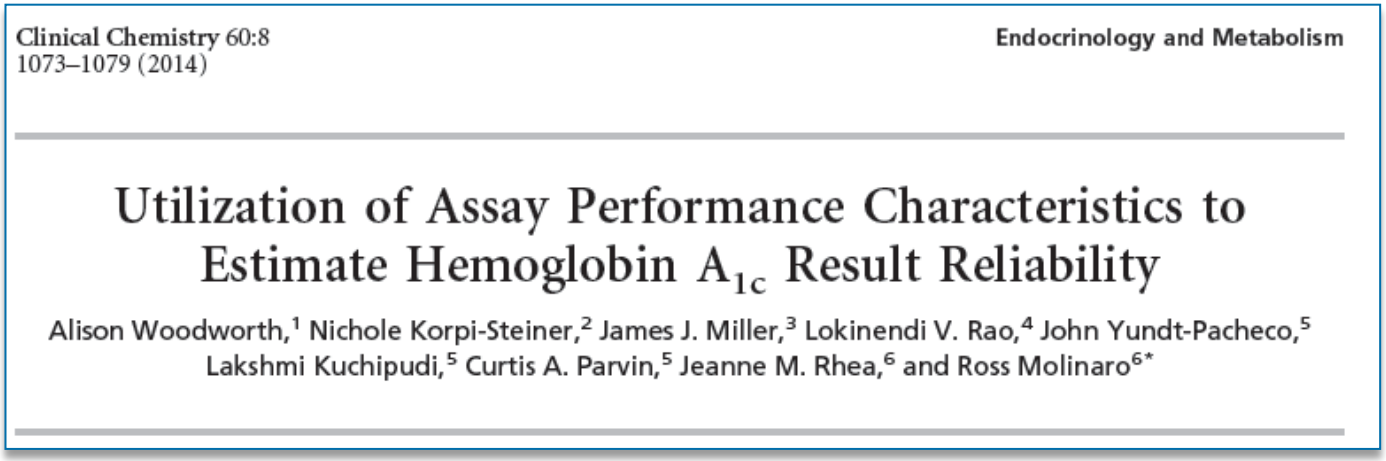
How much controls do you need?



Clinical Chemistry 60:8
1073–1079 (2014)

Endocrinology and Metabolism

Utilization of Assay Performance Characteristics to Estimate Hemoglobin A_{1c} Result Reliability

Alison Woodworth,[1] Nichole Korpi-Steiner,[2] James J. Miller,[3] Lokinendi V. Rao,[4] John Yundt-Pacheco,[5] Lakshmi Kuchipudi,[5] Curtis A. Parvin,[5] Jeanne M. Rhea,[6] and Ross Molinaro[6*]

Biorad Variant Turbo, Tosoh Bioscience G8, Roche Integra 800, Siemens DCA Vantage and Sebia Capillaris 2

To garanti accuracy within +/-6% (NGSP scale) all methods, with one exception, need to be run with internal QC at three levels three times a day!

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Internal QC material often perform less good than patient samples

DCA Vantage	Low				High				
Siemens ktrl	mean	SD	CV	n	mean	SD	CV	n	period
1	33,17	1,59	4,78	12	93,75	3,57	3,81	12	1 mån
2	31,05	3,19	10,27	17	95,60	4,75	4,97	15	5 mån
3	35,94	1,49	4,15	49	98,39	1,55	1,58	49	5 mån
4	35,2	1,2	3,41	9	91,4	2,1	2,33	9	1 mån
5	34,3	1,0	3,02	8	93,8	5,6	5,95	8	1 mån
Bio-Rad ktrl									
1	33,81	0,98	2,89	126	86,3	2,78	3,22	131	12 mån
2	33,69	1,04	3,08	87	85,93	2,31	2,69	82	12 mån

	low				high		
Afinion	mean	SD	CV	n	mean	SD	CV
1	43,5	1,3	3,0		63,3	0,5	0,8
2	44,9	1,4	3,0		65,3	2,3	3,5
3	46,5	2,2	4,8				

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Internal QC

Check of reproducibility –

QC material have often poorer performance than patient samples. Better materials needed!

How often should you measure on a sample material which is not optimal?

- ”Individualized QC Plan”: 3 levels x 3 times each day ?
- Normal ”POCT frequency”: 1- 2 times a week?

The current national recommendation: Internal QC, preferable on two levels, at least each day the device is used for diagnostic purpose.

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Target for materials used for External QC

An accredited EQA scheme must have an accredited target value!

ERL in Holland is not an accredited organization!

The accreditation body has asked Equalis to find other ways to target the materials, if the scheme should continue to be accredited.

Possible solutions to consider:

- de-accreditate the scheme
- find another laboratory than ERL to target the material

(The old Mono S procedure participate in the IFCC monitoring program, and is accredited)

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External QC

For trueness and accuracy control!

The sample material must be commutable.

The target value ought to be accredited.

HbA1c methods change over time. An evaluation at one year might not reflect the performance next year.

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Internal QC

To monitor daily function and reproducibility. If the reproducibility CV is 4 – 6 %, it is very difficult to fulfil the quality goals.

Properties of QC material sometimes differs from patient samples, and reproducibility figures might therefore not reflect the true reproducibility

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Uppsala, Sweden, October 2014

EQUALIS