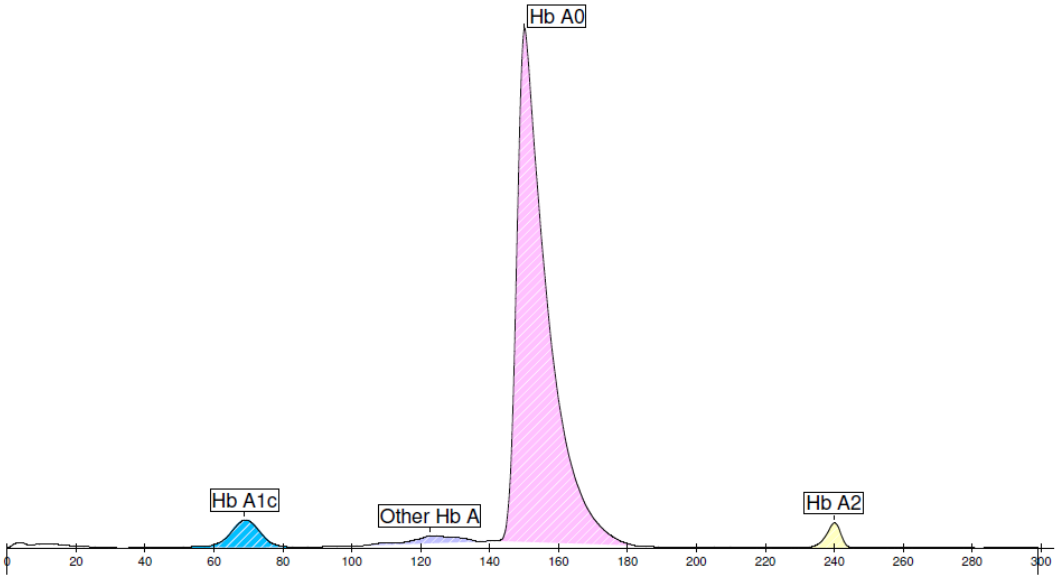
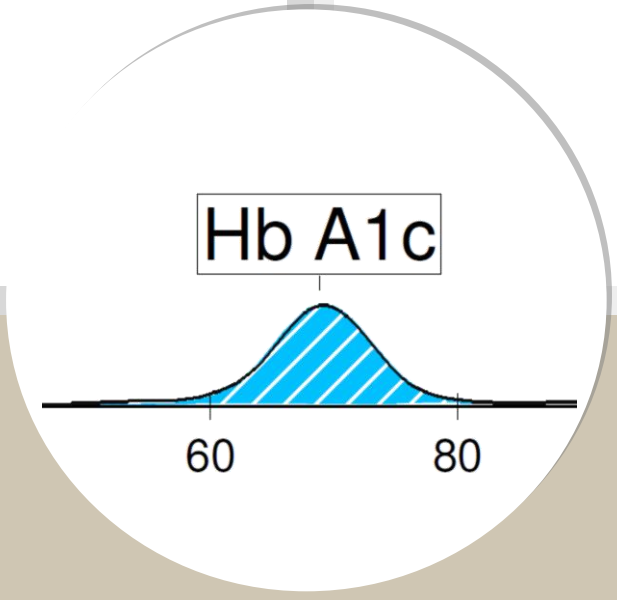
META - ANALYSIS





Hb A1c
by Sebia Capillary Electrophoresis

Analytical performances meta-analysis

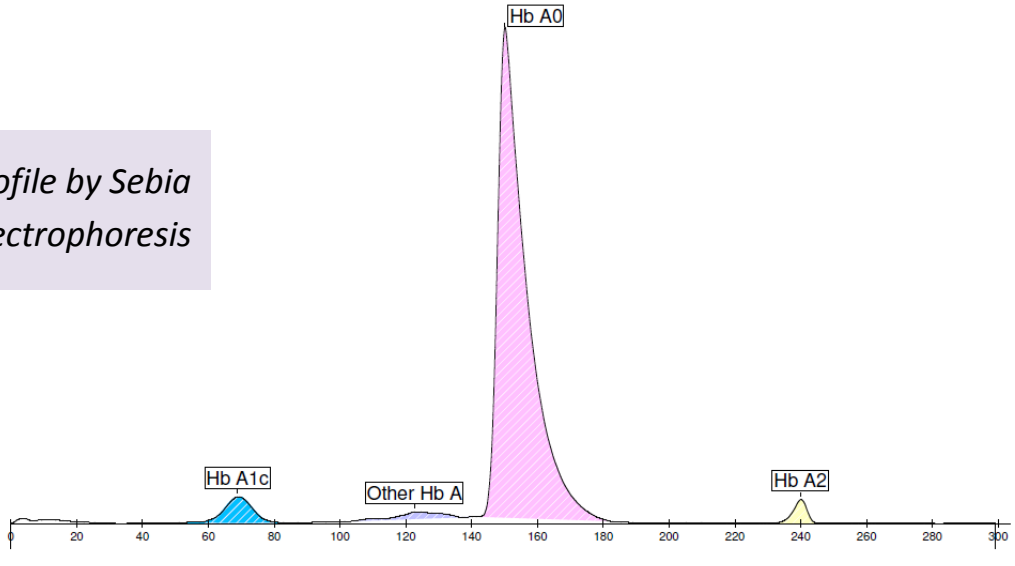
Second Edition

The Hb A1c analysis by Sebia capillary electrophoresis was made first available on CAPILLARYS 2 FLEX-PIERCING in 2011. This technological breakthrough was then deployed on MINICAP FLEX-PIERCING (2013) and more recently on CAPILLARYS 3 TERA (2014).

In less than a decade, many scientific evidences have been generated. This document has been issued from a bibliographical review of analytical performances already published, communicated or currently in press.

The Sebia Hb A1c capillary electrophoresis provides to all laboratories a robust and accurate technique for the quantification of Hb A1c, at a high throughput. Its high resolution allows in parallel the detection of hemoglobinopathies and thalassemias, giving to the laboratories useful information for the correct interpretation of the Hb A1c values.

Hb A1c profile by Sebia capillary electrophoresis



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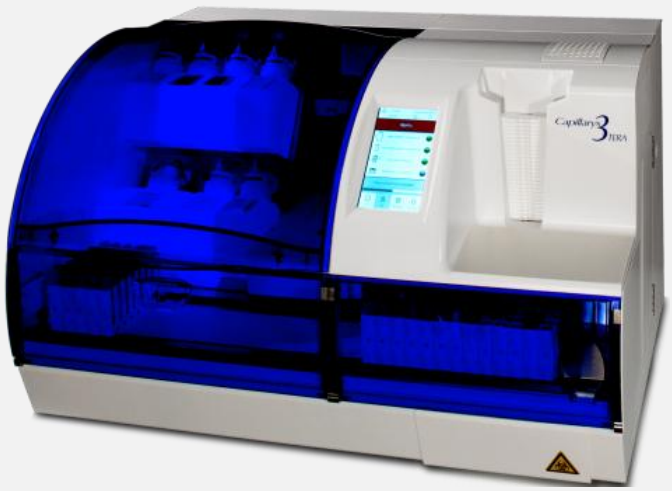
The CAPILLARYS 3 TERA, last generation of capillary electrophoresis instrument, for Hb A1c measurement



Accuracy represents the closeness of agreement between a measurement result and the value of the measurand. Accuracy is a qualitative performance characteristic that includes both Trueness and Precision. Precision can be quantified as the Standard Deviation (SD) or Coefficient of Variation (CV) by repeating measurements on the same sample using the same method (Repeatability or Reproducibility study). Guidance recommends an intra-laboratory CV (derived from IQC) <3% (IFCC units) (<2% NGSP units) and an overall inter-laboratory CV (derived from EQA) <5% (IFCC units) (<3.5% NGSP units) or <4.5% (IFCC units) (<3% NGSP units) within one method.

Adapted from Menditto A. et al, Accred Qual Assur. 2007;12:45-47 and from Weykamp C., Ann Lab Med. 2013 Nov;33(6):393-400.

CAPILLARYS 2 FLEX-PIERCING

"The high- and normal-level controls were both analysed once daily (Modular), twice daily (Tosoh G7) or once daily on each capillary (Capillarys) during the study period. Tosoh G7 and Capillarys showed similar precision, with CV well below the specification of less than 2% CV for diagnostic use, while Modular presented poorer precision." **[Reference 1]**

Table 1. Imprecision as evaluated by analysis of controls at two levels.

Control	Instrument	Mean (HbA1c %)	CV (%)
High	Roche Modular P	9.96	1.62
	Tosoh G7	10.01	1.28
	Sebia Capillarys 2 FP	9.47	0.91
Low	Roche Modular P	6.00	2.10
	Tosoh G7	6.06	0.80
	Sebia Capillarys 2 FP	5.74	1.32

"Currently, an intra-laboratory imprecision (% CV) of 2%[1] is recommended. All assays except the Bio-Rad Variant II Turbo (low QC = 2.97% CV), Roche Integra 800 (low QC = 2.4% CV), and Siemens DCA Vantage-lot 1 (high QC = 2.65% CV) met this goal at the 2 clinically relevant Hb A1c levels (low and high) tested." **[Reference 2]**

Table 1. Assay performance characteristics across platforms/sites: imprecision and bias across 2 QC levels.

	Low QC			High QC				
Assay platform	Mean	% Bias[a]	% CV[b]	Mean	% Bias	% CV	Linear regression[c]	r^2
Variant II	5.09	−4.99	1.43	9.74	2.00	1.33	$1.107x - 0.834$	0.991
Variant II Turbo	5.18	−0.08	2.97	10.07	0.10	1.81	$0.999x + 0.012$	0.999
Tosoh G8	5.75	3.99	1.28	9.60	4.98	0.80	$1.064x - 0.130$	0.999
Capillarys 2	5.24	−0.33	1.66	7.93	−0.01	1.33	$0.998x + 0.016$	0.999
Integra 800	5.61	5.76	2.40	9.90	4.07	1.18	$1.014x + 0.242$	0.997
DCA Vantage-lot 1	5.31	−0.34	1.88	10.31	2.72	2.65	$1.038x - 0.161$	0.989
DCA Vantage-lot 2	5.23	−0.37	1.93	10.49	1.73	1.81	$1.024x - 0.109$	0.991

[a] % Bias = 100 × (observed mean − assigned value)/assigned value.
[b] Precision calculations follow CLSI EP-5A.
[c] Linear regression of assay results compared to NGSP results measured on a Tosoh HPLC.

[1] *in NGSP unit (%).*

"On the commercial version tested, the intra-assay CVs were comprised between 0.85 % and 1.62 % and the between-assays CVs were lower than 1.45 % for patient samples and 1.66 % for internal quality control samples, when calculated from values expressed in NGSP units (%). When values were calculated using results expressed in IFCC units (mmol/mol), CVs were lower than 2.14 % for intra-assay reproducibility and 1.97 % for between-assays reproducibility." **[Reference 3]**

CAPILLARYS 3 TERA

"Four patient samples and two control samples were run simultaneously on all 12 capillaries. The total CV for the 12 capillaries varied between 0.8 and 2.2%" **[Reference 4]**

Table 1. Two control samples and four patient samples were run on all 12 capillaries. The mean value, standard deviation (SD) and coefficient of variation (CV %) for the 12 capillaries were calculated for each sample.

	Mean	SD	CV%
Control sample 1	31.8 mmol/mol	0.58 mmol/mol	1.8
Control sample 2	62.9 mmol/mol	0.51 mmol/mol	0.8
Patient 1	33.0 mmol/mol	0.74 mmol/mol	2.2
Patient 2	71.6 mmol/mol	0.90 mmol/mol	1.3
Patient 3	95.1 mmol/mol	1.08 mmol/mol	1.1
Patient 4	105.6 mmol/mol	1.00 mmol/mol	0.9

"At normal and high HbA1c levels, within-run and total CV% were below 1.4% (NGSP units) and below 2% (IFCC units) for both analyzers, showing excellent precision, based on the analytical goals from the national health care survey of WIV-ISP[2]." **[Reference 5]**

[2] *Scientific Institute of Public Health.*

MINICAP FLEX-PIERCING

"Within-day imprecision, shown in Figure 1, was within acceptable limits (Sp < 0.229) for all but the laboratory using the DCA Vantage and 2 laboratories using the Nycocard." [Reference 6]

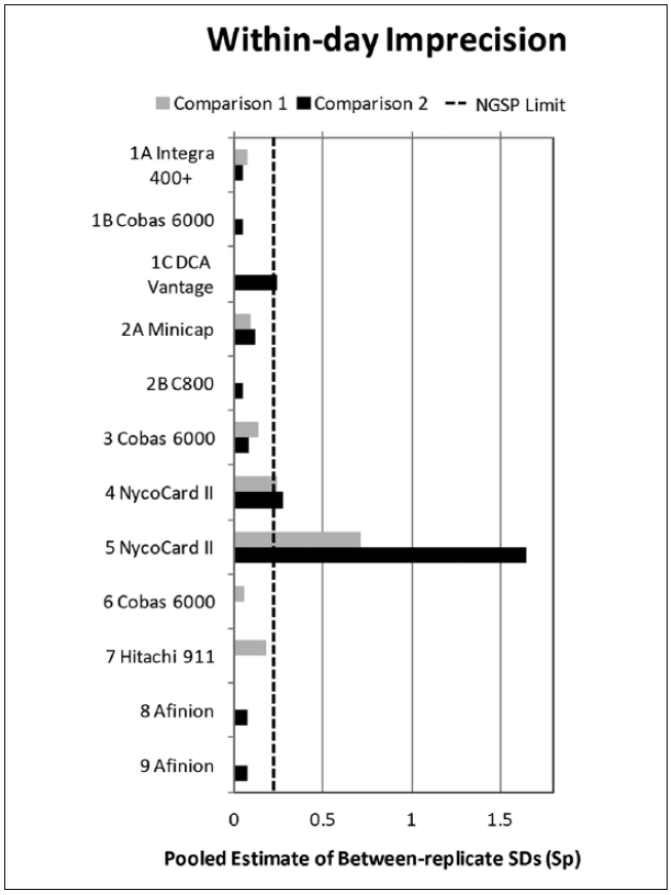


Figure 1. Within-day imprecision shown as the pooled estimate of between-replicate SDs (sp) for each laboratory (referenced by numbers 1-9) using each method (referenced by letter A or B). The dashed line is the NGSP network monitoring limit.

Accuracy represents the closeness of agreement between a measurement result and the value of the measurand. Accuracy is a qualitative performance characteristic that includes both Trueness and Precision. Trueness can be quantified as bias, which is the difference between the mean of several measurements and a Certified Reference Material and its true value (obtained with the IFCC Reference Measurement Procedure or NGSP Secondary Reference Laboratory procedure, for example).
Adapted from Menditto A. et al, Accred Qual Assur. 2007;12:45-47.

CAPILLARYS 2 FLEX-PIERCING

"The mean absolute bias (NGSP unit, %) (IFCC unit, mmol/mol) of control samples[3] (n = 20) ranged from − 0.097% (− 1.055 mmol/mol) (Capillarys 2) to 0.134% (1.459 mmol/mol) (G8std), with a mean relative bias of − 1.4% (Capillarys 2) to 1.7% (G8std). All HbA1c results of control samples were considered acceptable". **[Reference 7]**

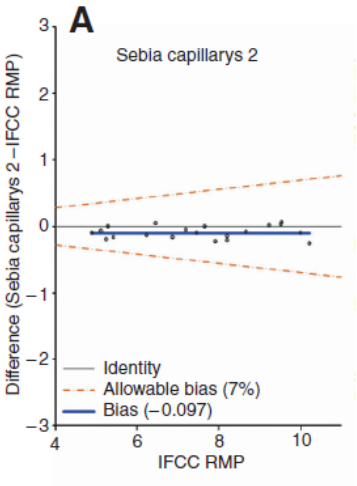
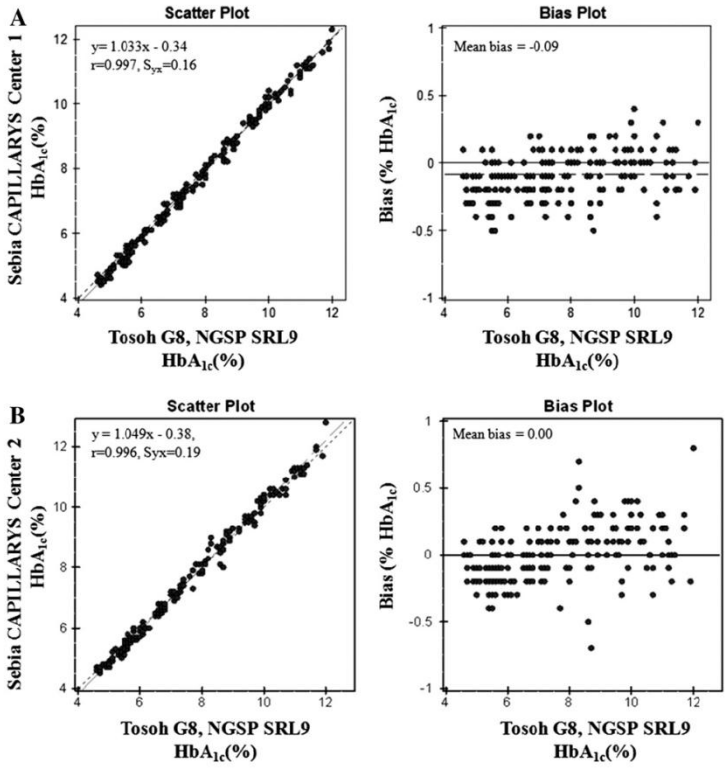


Figure 1: Difference plots of control samples[3] (n = 20, A-E) […] (A, F) Capillarys 2 capillary electrophoresis.

"Immunoassay and CE showed relatively better concordance with IFCC RMP than HPLC assays in this study."

[3] *In this study, Hb A1c of control samples and samples with Hb variants were measured by the IFCC Reference Measurement Procedure (IFCC RMP).*

"The HbA1c values obtained with the Capillarys 2 Flex Piercing at each center also correlated well with the NGSP secondary reference laboratory method (r ≥ 0.995 for both centers) and mean bias was −0.09% (−1.0 mmol/mol) HbA1c (Capillarys 2 center 1 vs. Tosoh G8, NGSP SRL9) and 0.00% (0 mmol/mol) HbA1c (Capillarys 2 center 2 vs. Tosoh G8, NGSP SRL9). Ninety-five % (center 1) and 97% (center 2) of single Capillarys 2 results were within ±6% of the SRL9 mean. NGSP manufacturer certification criteria require that 37/40 or 92.5%, results be within ±6% of the SRL mean" **[Reference 8]**



"Comparing a single result to the NGSP mean result (as would be done for NGSP certification) showed that N 92.5% of Capillarys 2 results were within 6% of the NGSP mean at each center (95% at center 1 and 97% at center 2), indicating that these methods pass the NGSP criteria for manufacturer and both Level I and Level II laboratory certifications." **[Reference 8]**

"Percentage bias was calculated from the linear regression relationships over the range of NGSP target value-assigned Hb A1c levels and found to differ significantly across assay platforms (Fig. 2). The Integra 800 and Bio-Rad Variant II showed the highest variability in percentage bias across the Hb A1c values tested." **[Reference 2]**

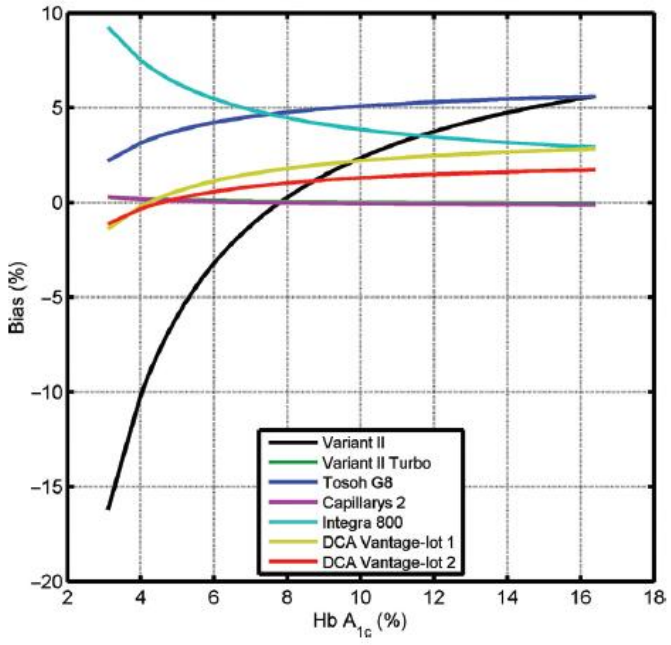


Fig. 2. Percentage bias compared to NGSP results across a range of Hb A1c concentrations.

CAPILLARYS 3 TERA

"According to the analytical goals of the WIV-ISP[4], there is an excellent trueness on all levels for the Sebia Capillarys 3 Tera, while the Bio-Rad D-100 shows a slightly negative bias in the high concentration range but still acceptable according to the WIV-ISP[4] criteria." **[Reference 5]**

MINICAP FLEX-PIERCING

"The first comparison study[5] revealed bias results within 6% of the NGSP target value for all laboratories except for both laboratories using the Nycocard and 1 result for the laboratory using the Hitachi 911. […] Some results from both laboratories using the Nycocard, 1 laboratory using the Cobas 6000, the laboratory using the DCA Vantage, and 1 laboratory using the Afinion were outside of acceptable limits for the second comparison[5]." **[Reference 6]**

[4] *Scientific Institute of Public Health.*

[5] *In these studies, the Diabetes Diagnostic Laboratory assigned values to each sample based on the mean of multiple analyses by 2 different NGSP secondary reference laboratories (SRLs); SRL9 using Tosoh G8 HPLC and SRL3 using Trinity Ultra[2].*

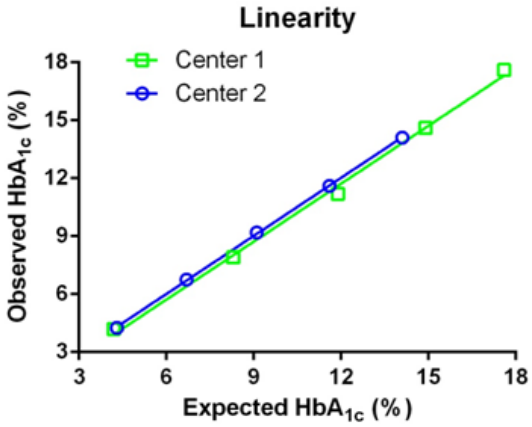
CAPILLARYS 2 FLEX-PIERCING

[Reference 9]

Analyzers	Linearity					
	HbA_{1c}, %		95% CI		R^2	Regression line equation
	low	high	A	B		
Capillarys 2FP	3.5	15.3	0.95–1.09	- 1.06–0.30	0.9978	y = 1.0193 x – 0.3812
Tosoh G8	3.6	14.9	0.88–1.11	- 0.67–1.62	0.9932	y = 0.9938 x + 0.4744
Premier Hb9210	4.2	14.9	0.87–1.11	- 0.75–1.79	0.9920	y = 0.9900 x + 0.5207
Roche c501	4.0	13.3	- 0.62–0.20	0.97–1.06	0.9990	y = 1.0107 x – 0.2094

Table 1. Precision and linearity of HbA1c values analyzed by the four analyzers. […] Linearity was calculated using NGSP units (%). 95% CI - confidence intervals of 95%. R^2 - coefficient of correlation. The regression line equation is presented as y = A x + B. A - regression line slope. B - regression line intercept.

"The method was linear for HbA1c results from 4.2% to 17.6% (22 to 169 mmol/mol, center 1) and 4.3% to 14.1% (23 to 131 mmol/mol, center 2), with correlation coefficients of 0.998 and 1.00, respectively, and the differences between measured and expected values were within ±6%." [Reference 8]



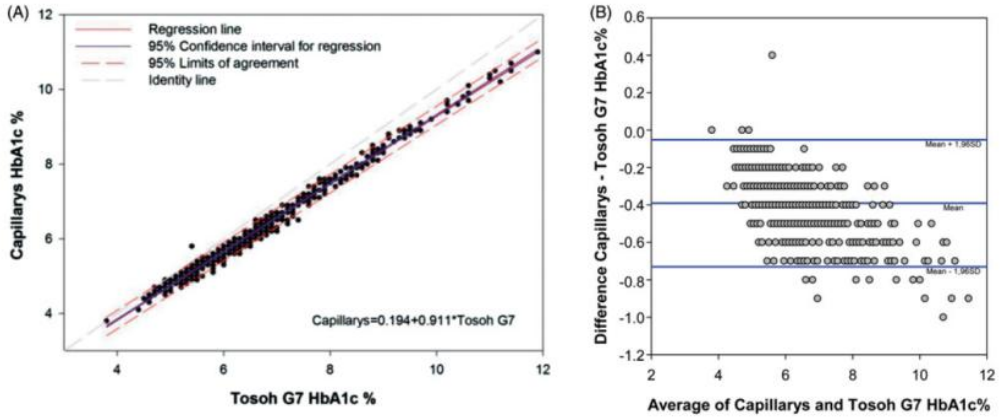
Supplemental Figure 2. Linearity study. Green, center 1 and blue, center 2.

CAPILLARYS 3 TERA

"Using the Bio-Rad linearity kit, linearity was demonstrated for HbA1c values ranging from 3.8% (18 mmol/mol) to 18.5% (179 mmol/mol). For both analyzers, linearity was excellent (R>0.997) according to the analytical goals of the WIV-ISP[6]. […] Results were similar when using mixtures of two patient samples with high and low HbA1c, although the range was slightly narrower—namely, 5.0% (31mmol/mol) to 15.3% (143 mmol/mol)." [Reference 5]

[6] *Scientific Institute of Public Health.*

CAPILLARYS 2 FLEX-PIERCING Vs HPLC methods



[Reference 1]

Figure 3. Deming regression and Bland-Altman plots for method comparisons. In the Bland-Altman plots are shown mean bias and 95% limits of agreement. Samples with haemoglobin variants were excluded.

"Figure 1 shows correlation and Bland-Altman plots between G8 HPLC and Sebia Capillarys 2-FP. The graphic (Fig. 1A) highlights a good correlation […] and a minimal dispersion respect to media, the Bland-Altman plot shows good agreement (95% C.I.; Fig. 1B)." [Reference 10]

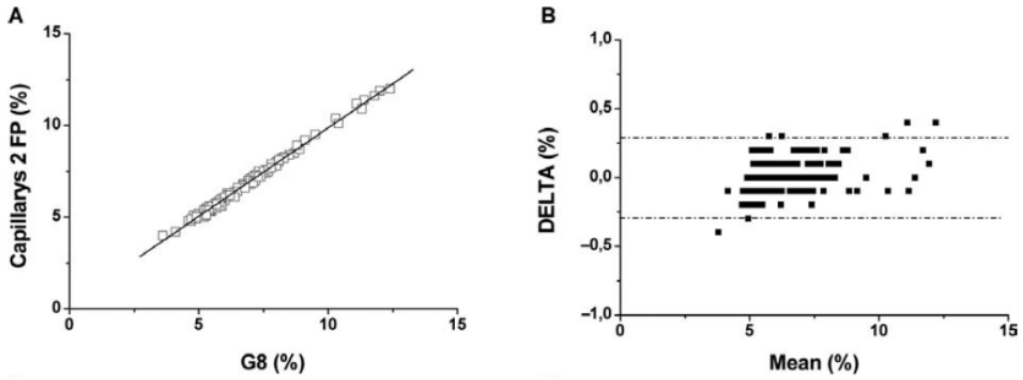
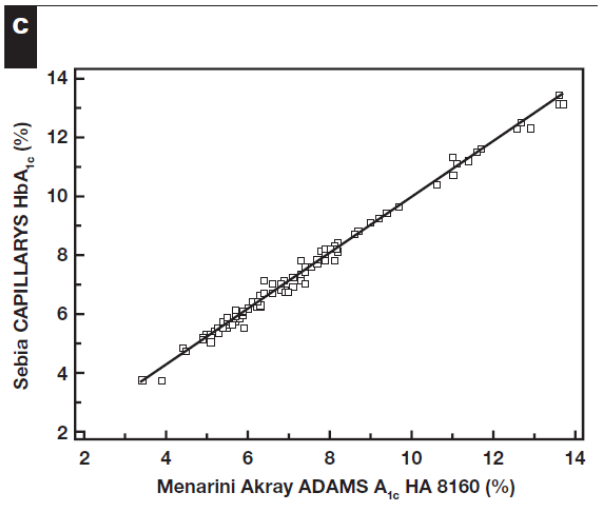


Fig. 1. Comparison between HbA1c values obtained with Capillarys 2-FP, G8, and Variant II analyzers. (A) Correlation plot with linear regression line (y=0.9636x+0.227, R^2 =0.9939 for G8 HPLC; 200 blood samples). (B) Bland-Altman difference plot comparing HbA1c results of Capillarys 2-FP and G8 analyzer.

"HbA1c values obtained with CAPILLARYS 2 Flex Piercing and Menarini/Arkray HA-8160 analyzers were very well correlated […]. The coefficient of correlation obtained was 0.9970 (P < .0001); linear regression, y = 0.2000 + 1.0000x (95% confidence interval intercept, 0.2-0.31; slope, 0.985-1.000)." **[Reference 11]**



"[…] both methods gave closely similar values and no significant deviation from linearity was observed. An excellent correlation between both methods was noted (r=0,99, p<0.0001)." **[Reference 12]**

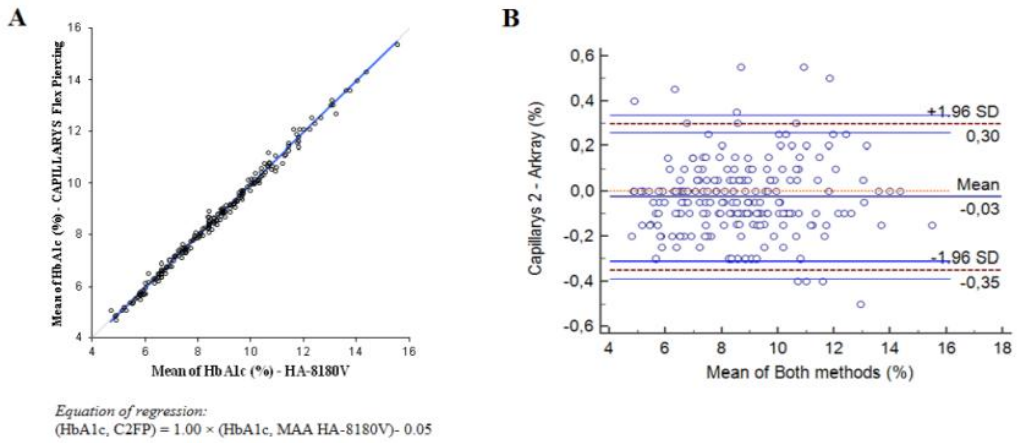
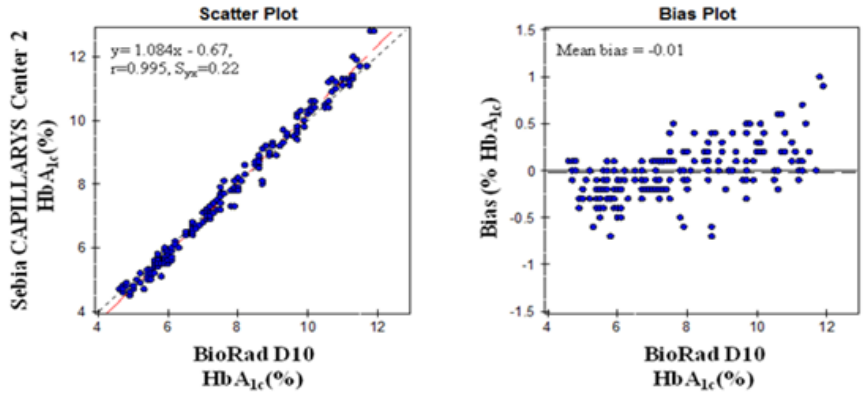


Figure1. (A) Scatter plot for HbA1c (%) with CE and HPLC. (B) Bland and Altman plots of HbA1c (%) measured with CE and HPLC[7].

[7] *In this study, CE refers to Sebia CAPILLARYS 2 FLEX-PIERCING and HPLC to Arkray ADAMS A1c HA-8180V.*

"HbA1c values correlated well between the Capillarys 2 Flex Piercing instruments at the 2 centers and also with those of the comparison methods (Tosoh G8 and Bio-Rad D10), with minimal bias." **[Reference 8]**



Supplemental Figure 1. Graphs (scatter plot and bias plot) showing HbA1c values obtained with Capillarys 2 at center 2 compared to Bio-Rad D10.

"The same statistical analyses were performed between Variant II and Capillarys 2-FP. The correlation value is significant (R^2 =0.99, P<0.0001) and the dispersion shown in the Bland-Altman plot is good." **[Reference 10]**

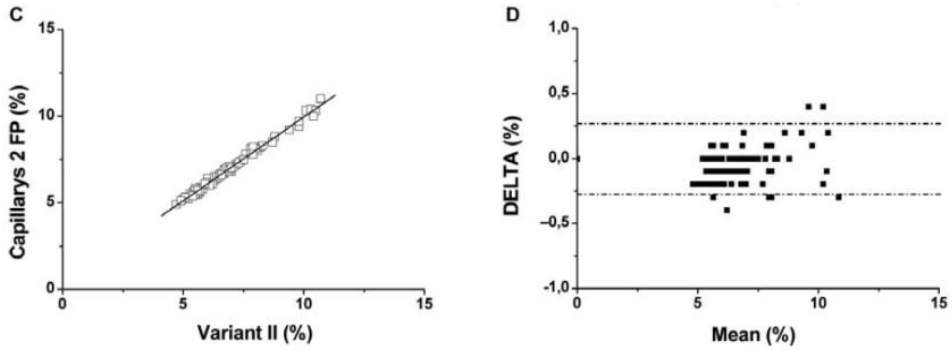
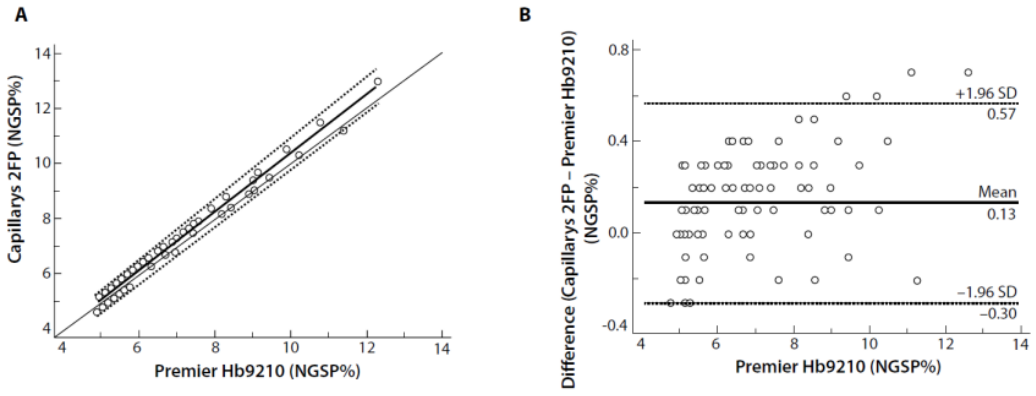


Fig. 1. Comparison between HbA1c values obtained with Capillarys 2-FP, G8, and Variant II analyzers. […] (C) Correlation plot with linear regression line of HbA1c values obtained with Capillarys 2-FP and Variant II analyzer for 107 blood samples (y = 0.9662x + 0.279, R^2 = 0.9958 for Variant II HPLC). (D) Bland-Altman difference plot comparing HbA1c results of Capillarys 2-FP and Variant II analyzer.

CAPILLARYS 2 FLEX-PIERCING Vs Boronate Affinity methods

"The correlation between the Capillarys 2FP and Premier Hb9210 analyzers, expressed in NGSP units, is described with the Passing-Bablok regression fit: Y = 1.07 (95% confidence interval (CI): 1.03 to 1.10) X - 0.31 (95% CI: - 0.51 to - 0.08), without significant deviation from linearity (P = 0.13) (Figure 1A). The Bland-Altman plot showed a mean absolute difference of 0.13% HbA1c (Figure 1B). All samples had less than 7% relative difference." **[Reference 9]**



CAPILLARYS 2 FLEX-PIERCING Vs Immunoassay and Enzymatic methods

"In the Bland Altman Plot, measurements with Capillarys 2 Flex Piercing were –0.021 lower than measurements with Dimension RxL Max. Passing Bablok regression for the 404 patient samples of cohort Y was Y = 6.11 × 10^{-15} + 1.00 x as regression line. […] Spearman's rank correlation coefficient showed good correlation with r = 0.961 and with P < 0.001" **[Reference 13]**

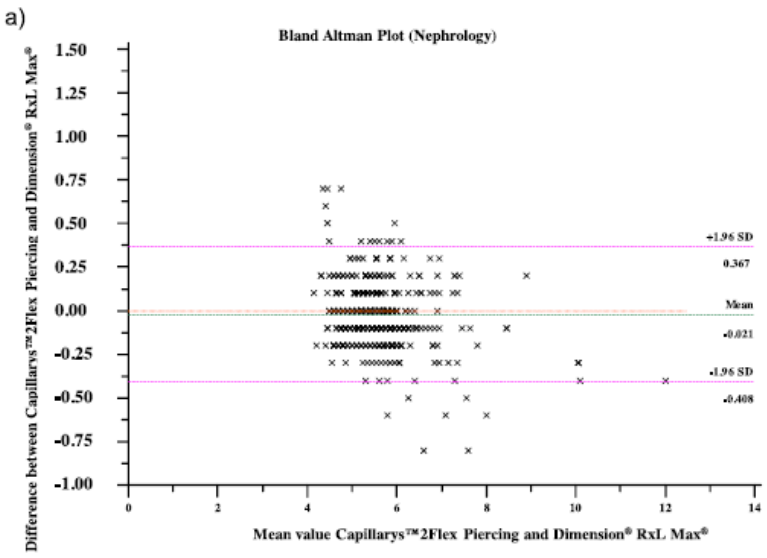


Fig. 1 - Pair wise method comparison according to Bland Altman Plot: (a) Capillarys 2 Flex Piercing vs Dimension RxL Max

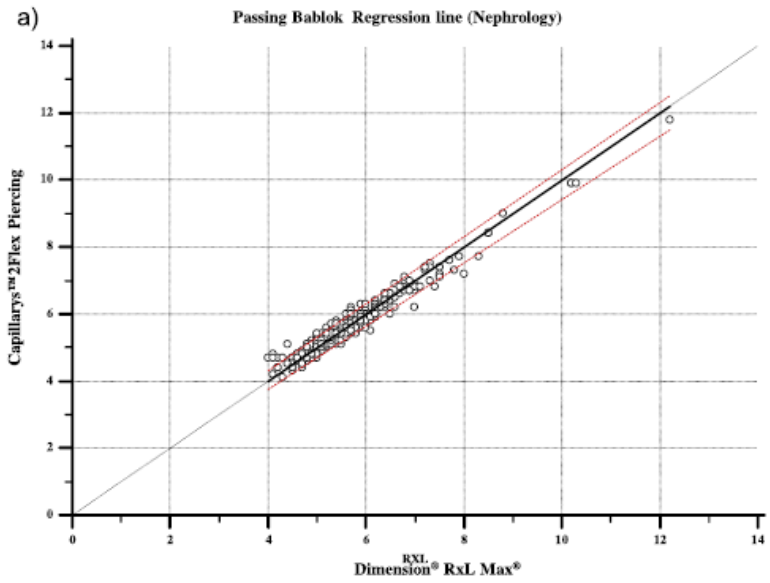


Fig. 2 - Regression line of pair wise method comparison according to Passing Bablok: (a) Capillarys 2 Flex Piercing vs Dimension RxL Max

"In this present study, TINIA and CE results were consistent with each other according to the Bland-Altman plot and linear regression graph." **[Reference 14]**

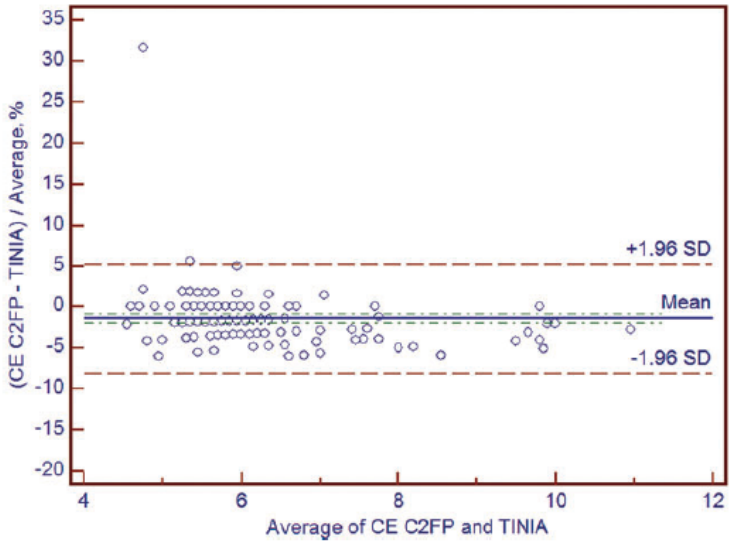


Figure 1 - Bland-Altman plot. […] CE C2FP, capillary electrophoresis (Capillarys 2 Flex-Piercing, Sebia); TINIA, turbidimetric inhibition immunoassay (Roche, Integra 400, Tina-quant Hemoglobin A1c Gen.2). Data analyzed in NGSP units (percentage of hemoglobin).

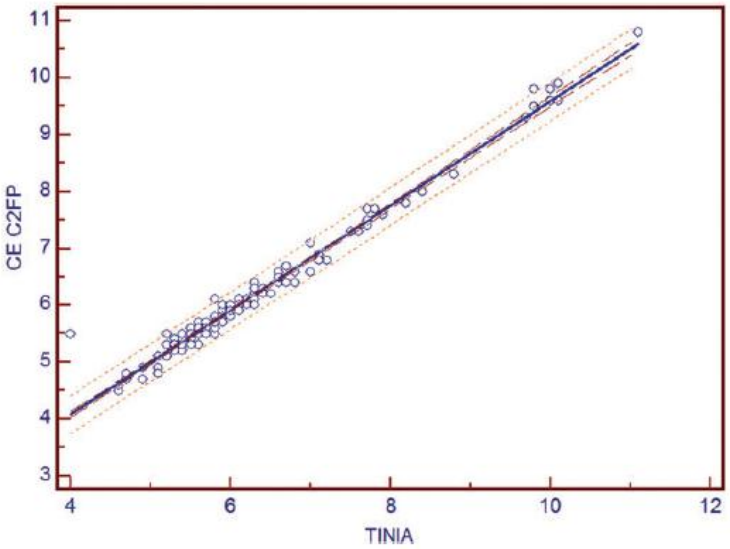


Figure 2 Linear-regression graph of the two methods for all the data. Regression equation is $y = 0.94x + 0.50$, n = 159, r = 0.98 ($p < 0.0001$ and 95% confidence interval for r = 0.9732 - 0.9856), $r^2 = 0.96$. CE C2FP, capillary electrophoresis (Capillarys 2 Flex-Piercing, Sebia); TINIA, turbidimetric inhibition immunoassay (Roche, Integra 400, Tina-quant Hemoglobin A1c Gen.2). Data analyzed in NGSP units (percentage of hemoglobin).

CAPILLARYS 3 TERA Vs HPLC methods

[Reference 5]

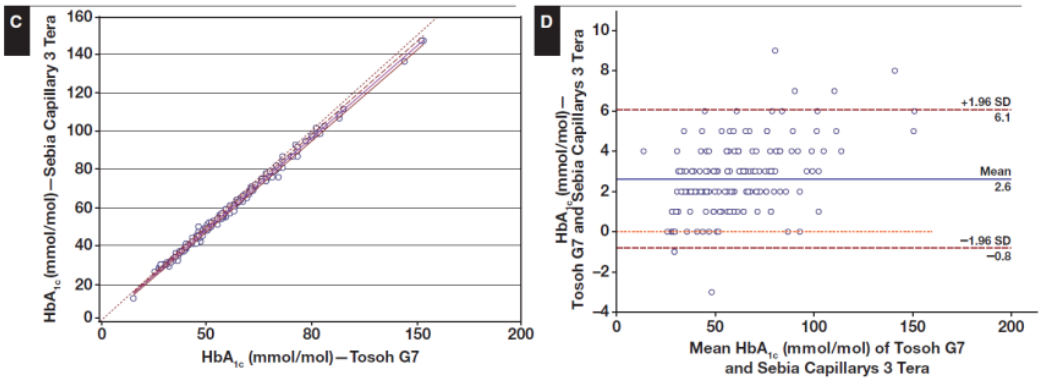


Figure 1 Passing-Bablok regression analysis and Bland-Altman plot of hemoglobin A1c (HbA1c) results (International Federation of Clinical Chemistry units) using whole-blood patient samples, obtained with […] the Sebia Capillarys 3 Tera (C, D) in comparison with the Tosoh HLC-723G7.

[Reference 5]

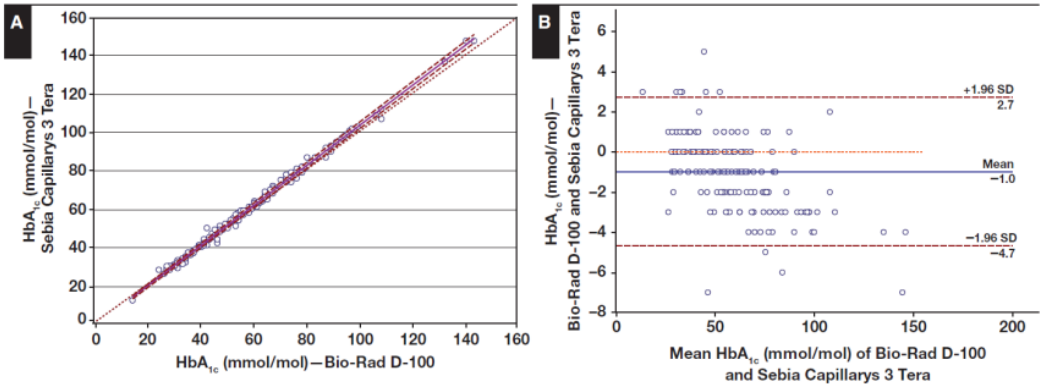


Figure 2 Passing-Bablok regression analysis (A) and Bland-Altman plot (B) of hemoglobin A1c (HbA1c) results (International Federation of Clinical Chemistry units) using whole-blood samples obtained with the Bio-Rad D-100 in comparison with the Sebia Capillarys 3 Tera.

CAPILLARYS 3 TERA Vs Immunoassay and Enzymatic methods

"A total of 142 samples were analyzed on both Cobas 6000 and Capillarys 3 Tera. The equation for the correlation between the two methods was Cobas 6000 (y) = 0.982 x Capillarys 3 Tera (x) + 0.975; R^2 = .994. After exclusion of the sample with the highest HbA1c value the correlation was y = 1.003x - 0.3246; R^2 = .996." **[Reference 4]**

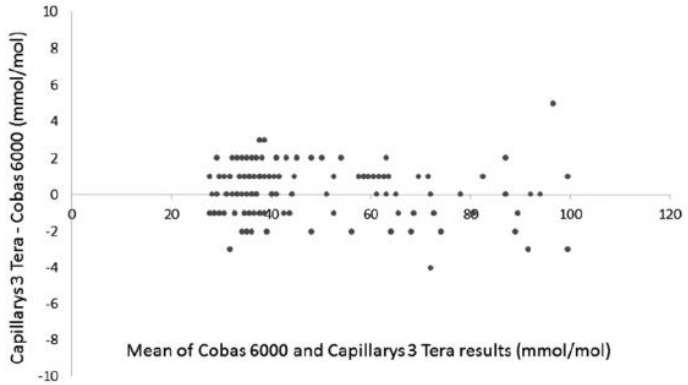


Figure 2. Comparison between HbA1c analyzed with Cobas 6000 and Capillarys 3 Tera ($n = 142$ samples). Bland-Altman plot presenting mean of the two measurements (x-axis) versus the difference between the two measurements (y-axis).

CAPILLARYS 2 FLEX-PIERCING

Labile Hb A1c

"A glucose concentration less than 277.78 mmol/L (LA1c < 10.9%) did not interfere with HbA1c quantification on any of the four analyzers[8]." **[Reference 9]**

"There was no interference from labile HbA1c (up to 11%, 97 mmol/mol) […]. No additional peaks (i.e. for labile HbA1c or carbamylated hemoglobin) were observed on the Capillarys 2 electropherograms." **[Reference 8]**

"The quantification of HbA1c by Capillarys 2 Flex Piercing analyzer was not influenced by the presence of LA1c[9] until 10 %. No additional peak was detected on the separation profile, and no modification of HbA0 and HbA1c peak areas was noticed." **[Reference 3]**

Carbamylated hemoglobin

"For cHb[10] effect, data are listed in Table2 […]. Paired sample t-test revealed no statistically significant difference […] overall HbA1c levels (low pool, p=0.37; normal pool, p=0.77; high pool, p=0.86)." **[Reference 12]**

[KCNO] mmol /l	HbA_{1c} on CAPILLARYS Flex Piercing, %(mmol/mol)		
	Low pool	Median pool	High pool
0	4.95 (30.6)	5.90 (41.0)	9.15 (76.5)
0.15	5.00 (31.2)	6.15 (43.7)	9.15 (76.5)
0.5	5.00 (31.2)	6.00 (42.1)	9.30 (78.1)
1.0	4.90 (30.1)	5.95 (41.5)	9.30 (78.1)
Blank tube	4.95 (30.6)	5.85 (40.5)	9.35 (78.7)

Table 2 The effect of cHb[10] on HbA1c determination

"There was no interference from […] carbamylated hemoglobin, BUN[11] (97 mg/dl, 34.6 mmol/l) […]. No additional peaks (i.e. for labile HbA1c or carbamylated hemoglobin) were observed on the Capillarys 2 electropherograms" **[Reference 8]**

[8] *In this study, the four analyzers used were: Sebia CAPILLARYS 2 FLEX-PIERCING, Tosoh G8, Trinity Premier Hb9210 and Roche Cobas c501 Tina-quant Gen. 2.*
[9] *LA1c means "labile Hb A1c".*
[10] *cHb means "carbamylated hemoglobin".*
[11] *BUN means "blood urea nitrogen".*

"Similarly, the presence of cHb[12] (until 8 %) did not interfere with the quantification of HbA1c, and generated no modification of the separation profile." **[Reference 3]**

Hemoglobin F

"This evaluation showed that none of the CE methods tested is subject to interference with HbF up to 23% on the measurement of HbA1c. MINICAP Flex Piercing, CAPILLARYS 2 Flex Piercing and CAPILLARYS 3 TERA can reliably report accurate HbA1c results in case of elevated HbF." **[Reference 15]**

Total hemoglobin

"Varying hemoglobin concentrations from 6.9 to 18.3 g/dl had no effect on HbA1c measurement." **[Reference 8]**

"HbA1c measurement was not affected by the variation of total Hb concentration in the range 34 - 178 g/L" **[Reference 3]**

"HbA1c measurement was not affected by the variation of total hemoglobin concentration in the range of 2.1 g/dL (21 g/L) to 19.5 g/dL (195 g/L)" **[Reference 11]**

Triglycerides and bilirubin

"No interference was observed with Capillarys 2FP […] at the following interfering substance concentrations tested: 445.50 µmol/L bilirubin, 10.21 mmol/L triglyceride, 10.29 mmol/L cholesterol, or 19.10 / 11.90 mmol/L triglycerides/cholesterol." **[Reference 9]**

"No analytical interference of bilirubin and triglycerides was noticed for concentrations reaching 304 µmol/L and 12.8 mmol/L, respectively." **[Reference 3]**

"No analytic interference of bilirubin and triglycerides was noticed for concentrations reaching 16.5 mg/dL (282 µmol/L) and 1,592 mg/dL (18 mmol/L), respectively" **[Reference 11]**

[12] *cHb means "carbamylated hemoglobin".*

Acetylated hemoglobin

"The quantification of HbA1c with the CAPILLARYS 2 Flex Piercing analyzer was not influenced by the presence of AcHb[13] in the range tested (≤6.5% of AcHb[13], as quantified with HPLC using the Menarini/Arkray ADAMS A1c HA-8160)" **[Reference 11]**

Other interferences

"In addition, no significant bias was observed with the results analyzed by the Capillarys 2FP analyzer in the presence of vitamin C up to 250 mg/mL." **[Reference 9]**

CAPILLARYS 3 TERA

Labile Hb A1c

"[…] On the Sebia Capillarys 3 Tera instrument, there was no visual effect on the electropherogram or the quantification of HbA1c. Up to the maximal tested glucose concentration (50 g/L), the absolute bias ranged between -0.3% and 0.1% or -3.0 and 1.5 mmol/mol, which meets the criterion of 0.3% or 3 mmol/mol." **[Reference 5]**

Carbamylated hemoglobin

"[…] On the Sebia Capillarys 3 Tera, the KCNO had a visual effect on the "other HbA" peak, but did not affect the quantification of HbA1c. A maximal absolute bias of -0.3% (-2.0 mmol/mol) was found. For both analyzers, the trueness criteria of the WIV-ISP[14] (0.3% or 3 mmol/mol) were met, except for the samples containing the highest KCNO concentration (1 mmol/L) and analyzed with the D-100 analyzer." **[Reference 5]**

Hemoglobin F

See above (§ CAPILLARYS 2 FLEX-PIERCING) **[Reference 15]**

[13] *AcHb means "acetylated hemoglobin".*
[14] *Scientific Institute of Public Health.*

Total hemoglobin

"Serial dilutions of a patient sample with a hemoglobin concentration of 16.9 g/dL and a normal HbA1c level resulted in a hemoglobin range between 1.7 and 16.9 g/dL. […] The same evaluation was done on the Sebia Capillarys 3 Tera, where optic densities were noted from 0.033 to 0.258, resulting in a maximum bias of -0.2% (-2.0 mmol/mol) at the lowest hemoglobin level. For both analyzers, there was no significant bias detected, even for a hemoglobin concentration of 1.7 g/dL. Both automates gave warnings for the lowest hemoglobin concentrations, although HbA1c results were not affected." **[Reference 5]**

Triglycerides and bilirubin

"Up to a concentration of 15 mg/dL bilirubin and a concentration of 3,360 mg/dL triglycerides, the measured HbA1c values for both analyzers were within 0.2% (2.5 mmol/mol) of the baseline HbA1c values. There was no observed interference on the quantification of HbA1c or in terms of additional/changing peaks in the chromatogram/electropherogram." **[Reference 5]**

CAPILLARYS 2 FLEX-PIERCING

"A carry over was evaluated from a sample with a high HbA1c value (15.7%) that was assayed just before a sample with low HbA1c level (4.8%). Measured bias, mean difference (SD) for C2FP was 0.11% (0.3%) and 0.2% (0.0%) for MAA HA-8180V. A T-test revealed the absence of significant difference between low sample HbA1c value before and after every running on both instruments. Besides, no variant contamination has been illustrated during the experience." **[Reference 12]**

"The difference between the means of the high-low and the low-low sequence samples was 0.06% (0.3 mmol/mol), which is < 3 SD of the low-low values (1 SD of the low-low values = 0.07% (0.7 mmol/mol)), indicating no significant carryover." **[Reference 8]**

CAPILLARYS 3 TERA

"A carryover of 0.12% and -0.02% was calculated for respectively the Bio-Rad D-100 and Sebia Capillarys 3 Tera when analyzed in NGSP units. Both results are lower than the respective error limits (1.16 for the Bio-Rad D-100 and 0.00 for the Sebia Capillarys 3 Tera).Therefore, there was no significant carryover detected between high and low HbA1c samples." **[Reference 5]**

CAPILLARYS 2 FLEX-PIERCING

"The main advantages of the Capillarys 2 Flex Piercing system for HbA1c measurement include the ability to detect hemoglobin variants, high throughput, full automation, small sample volume, and ability to use primary tubes." **[Reference 8]**

"The main advantages of the new capillary electrophoresis system are that it allows full automation testing and the possibility of working from capped whole blood primary tubes (minimum sample volume of 1 mL). Moreover, it enables perfect sample homogenization to be achieved by flipping (7 times) tube racks thus precluding sedimentation. […] As eight samples are analyzed simultaneously, the system provides an enhanced workflow (40 samples/h) […]. The system has a primary capacity of 104 tubes (i.e. 13 sample racks), with uninterrupted throughput and continuous sample track loading." **[Reference 16]**

"A typical electrophoretogram exhibits 3 peaks that correspond to HbA0, HbA1c, and HbA2, and an additional fraction identified as "other HbA" All peaks are well separated, with a good return to baseline between them. Any modification of this profile, usually because of the presence of a hemoglobin variant, is indicated by the software as "atypical profile" with a special color code, thus allowing the rapid and easy identification of samples with hemoglobin variants." **[Reference 11]**

CAPILLARYS 3 TERA

"The Capillarys 3 offers full RFID-based traceability, cap-piercing technology for working directly with capped primary tubes and considerable flexibility for effective workflow organization. With duplicate reagent packs for HbA1c onboard, the instrument has a reagent capacity of approximately 1400 tests without reloading." **[Reference 4]**

External Quality Assessment (EQA) is an external assessment of a laboratory performance in comparison to its peer (between-laboratory concordance) and/or to accuracy based reference method. Applied to Hb A1c, role of EQA is to provide reliable information (inter-laboratory precision, bias) and allowing laboratories to evaluate, among other parameters, the suitability of the method used.
Adapted from Miller WG. et al, Clin Chem. 2011 Dec;57(12):1670-80.

CAPILLARYS 2 FLEX-PIERCING

"Two samples from the Norwegian Clinical Chemistry EQA Programme with assigned values from European Reference Laboratory (ERL) were also analysed (samples 2012-02 and 2012-03). All three studied methods gave higher results than the ERL assigned values (Figure 1(B)), but Capillarys was closer to the assigned values than were the other two instruments." **[Reference 1]**

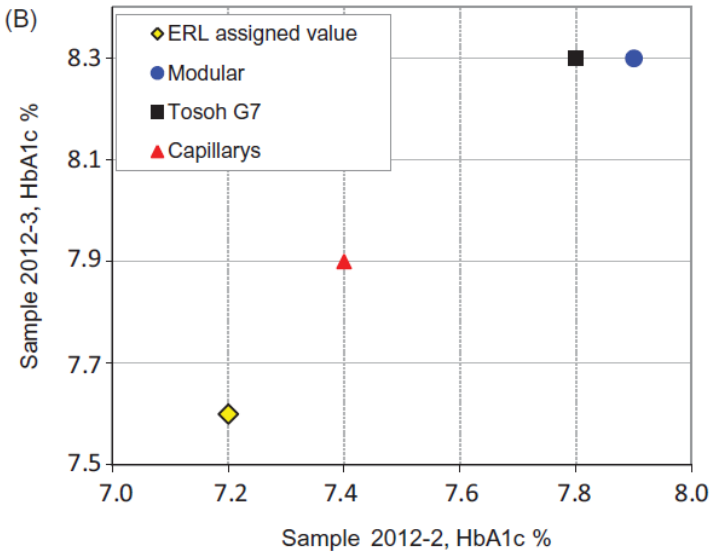


Figure 1. Instrument comparisons using controls. […] B; Results from analysis of two controls from the Norwegian Clinical Chemistry EQA Programme with assigned European Reference Laboratory values.

[Reference 17]

"Most of the mean values were within the limits of the uncertainties around the target values[15], except for Tosoh G7 and G8, whose mean values were always higher in respect to the target values. […]Indeed, either the immunochemical method or the capillary electrophoresis seems to offer, although used by a different number of participants, the same performance as those of two HPLC systems (Bio-Rad and Menarini). On the contrary, only part of the user of a third HPLC method (Tosoh) is able to provide measurements within the TAE[16] limits."

Table 1
Results of the study grouped by method and instruments.

Methods and instruments	Sample 1			Sample 2		
	N° labs (outliers)	CV %	N° labs within TAE 6.0%	N°labs (outliers)	CV %	N° labs within TAE 6.0%
Abbott Architect c4000	1 (0)	–	1 (100)	1 (0)	–	1 (100)
B-Analyst	1 (0)	–	1 (100)	1 (0)	–	1 (100)
Bio-Rad D-10	11 (2)	4.9	9 (82)	11 (2)	3.7	10 (91)
Bio-RadVariant II	25 (1)	5.5	19 (76)	25 (1)	3.7	22 (88)
Bio-Rad Variant IITurbo	14(0)	3.8	12 (86)	14 (0)	3.0	13 (93)
Menarini - HA8160 VP	12 (0)	3.6	9 (75)	12 (0)	3.5	8 (67)
Menarini - HA8160 TP	20 (0)	4.9	17(85)	20 (0)	3.9	16 (80)
Menarini - HA8180 V	5 (0)	1.2	5 (100)	5 (0)	0.9	5 (100)
Roche - Cobas C501	11(0)	2.3	10 (91)	11 (0)	2.2	11 (100)
Roche - Integra 400	3 (0)	4.2	3 (100)	3 (0)	4.0	3 (100)
Roche - Modular	2 (0)	–	0 (0)	2 (0)	–	0 (0)
Sebia - Capillarys HbA1c	22 (0)	3.5	18 (82)	22 (0)	1.6	22 (100)
Sebia - Minicap HbA1c	3 (0)	4.1	3 (100)	3 (0)	2.9	3 (100)
Tosoh - G7	8 (0)	4.0	3 (38)	8 (0)	3.1	3 (38)
Tosoh - G8	49 (0)	3.1	25 (51)	49 (0)	2.5	25 (51)
Tosoh - GX	2 (0)	–	0 (0)	2 (0)	–	2 (100)
Other	1 (0)	–	0 (0)	0 (1)		

[15] *In this study, the Hb A1c target value of the EQA samples was assigned using the IFCC reference measurement procedure, in the version HPLC-capillary electrophoresis. The analyses were performed in a laboratory member of the IFCC network of reference laboratories for Hb A1c and present in the database of the "Joint Committee on Traceability in Laboratory Medicine".*

[16] *TAE means "Total Allowable Error".*

"Three manufacturers meet the 2 sigma criterion of the Sigma-metrix model in both countries and one manufacturer touches even the minimum performance level of the biological variation model." **[Reference 17]**

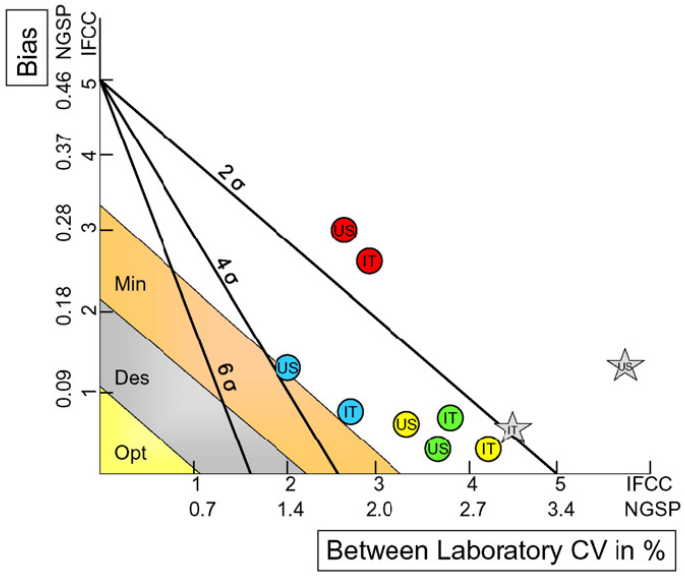


Fig. 3. Quality target models applied to 4 manufacturer/instruments means in the present study and in the CAP 2014 GH2-A survey. Mean within-manufacturer interlaboratory CV on the *x* axis; mean manufacturer absolute bias on the *y* axis. The gray stars represent the overall mean of all laboratories in Italy (star inscribed IT) and United States (US). The dots represent the means of analytical devices of manufacturers in both countries: Tosoh (red), Roche (green), Sebia (blue), and Bio-Rad (yellow).

"Bias values[17] are shown in Table 1. Linear regression analysis showed a slope of 1.06 and an intercept of -1.80 for the Tosoh G8 and a slope of 1.02 and an intercept of -0.18 for the Sebia Cap 2FP. […] The bias increases at higher levels for the Tosoh G8 but still remains acceptable, while Sebia Cap 2FP shows overall excellent trueness according to the analytical goals from the national health care survey of the WIV-ISP[18]." **[Reference 18]**

Table 1
Overall Performance Characteristics for the Measurement of HbA_{1c} on the Tosoh G8 and Sebia Cap 2FP

Parameter	Tosoh G8	Sebia Cap 2FP
Trueness (EP9), mmol/mol		
Bias at 30 mmol/mol	0	0
Bias at 60 mmol/mol	2	1
Bias at 90 mmol/mol	4	1

[17] *In this study, bias have been evaluated by using EQC samples of the national health care survey supplied by the WIV-ISP (2011; n = 12) with Hb A1c values set by an IFCC reference method.*
[18] *Scientific Institute of Public Health.*

"In addition, we investigated how the C2FP performed in EQA programs using processed samples. The IFCC monitoring program (targets set with IFCC reference measurement procedure) consists of 12 pairs of frozen whole blood samples. […] An excellent correlation (r = 0.9993) was observed. The bias ranged from 1 mmol/mol at lower HbA 1c levels to 0 mmol/mol at higher HbA 1c levels. The CV derived from the 12 pairs was 1.1%. The ERL[19] EQA program consists of 12 pairs of lyophilized hemolysates (targets set with the IFCC reference measurement procedure). An excellent correlation (r = 0.9981) was seen. The bias was 1 mmol/mol over the whole range, and the CV was 1.4%." **[Reference 19]**

"The accuracy of the method was evaluated by analyzing 10 IFCC value-assigned samples used for the external quality control assessment[20] in our laboratory. No difference of HbA 1c value higher than 3 mmol/mol compared with IFCC targets was noticed, which evidenced a good accuracy of the method." **[Reference 3]**

Table 2 Accuracy of Capillarys 2 Flex Piercing® HbA_{1c} method.

Control samples	HbA_{1c}, mmol/mol		
	Measured values	IFCC target value	Deviation from target value
Sample 1	45	45	0
Sample 2	63	63	0
Sample 3	41	41	0
Sample 4	74	72	2
Sample 5	54	54	0
Sample 6	63	63	0
Sample 7	46	45	1
Sample 8	79	76	3
Sample 9	33	32	1
Sample 10	54	54	0

[19] *ERL means "European Reference Laboratory".*

[20] *In this study, EQA samples were from the Educational Programme 2010 (European Reference Laboratory for Glycohemoglobin, Winterswijk, The Netherlands), and titrated according to the IFCC reference method.*

"The majority of the HPLC instruments meet the 2σ criterion of the SM[21] model, whereas the majority of immunochemical and POCT instruments do not. Only 1 method (labeled N)[22] achieves the minimum performance level of the BV[23] model." **[Reference 20]**

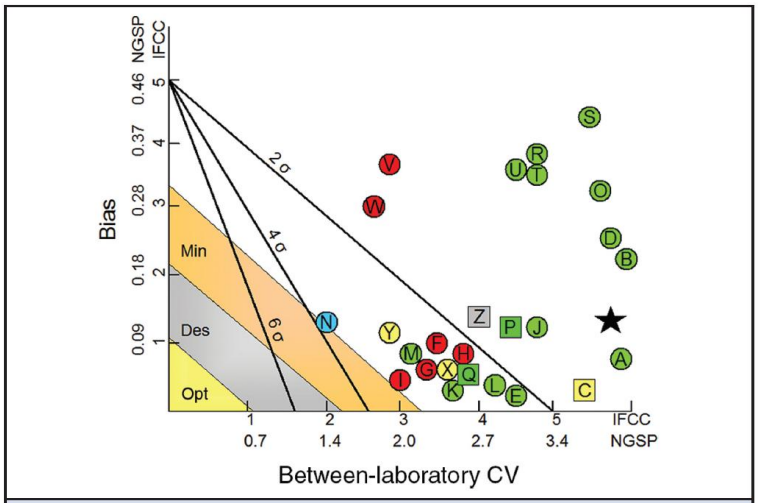


Fig. 2. Models applied to 26 manufacturer/instrument means in CAP 2014 GH2-A survey.
Mean within-manufacturer interlaboratory CV on the *x* axis; mean manufacturer absolute bias on the *y* axis. The black star represents the overall mean of all laboratories. The dots (laboratory instruments) and squares (POCT instruments) represent specific manufacturers with colors for analytical principles: green, immunoassays; red, ion-exchange HPLC; yellow, affinity HPLC; blue, capillary electrophoresis; gray, dry chemistry. Abbott Architect c System (A), Abbott Architect I System (B), Axis-Shield Afinion (C), Beckman AU systems (D), Beckman UniCel DxC Synchron (E), Bio-Rad D10 (F), Bio-Rad Variant II (G), Bio-Rad Variant II Turbo (H), Bio-Rad Variant Turbo 2.0 (I), Roche Cobas c311 (J), Roche Cobas c500 series (K), Roche Cobas Integra 400 (L), Roche Cobas Integra 800 (M), Sebia Capillarys 2 Flex Piercing (N), Siemens Advia Chemistry Systems (O), Siemens DCA 2000/2000+ (P), Siemens DCA Vantage (Q), Siemens Dimension ExL (R), Siemens Dimension RxL (S), Siemens Dimension Vista (T), Siemens Dimension Xpand (U), Tosoh G7 Auto HPLC (V), Tosoh G8 Auto HPLC (W), Trinity Biotech HPLC (X), Trinity Biotech Premier Hb9210 (Y), Ortho Clin Diag Vitros 5,1 FS, 4600, 5600 Chem System (Z). For more details, see online Supplemental Table 1. opt, Optimum; des, desirable; min, minimum.

CAPILLARYS 3 TERA

"The accuracy goal for HbA1c in Sweden, as agreed by Swedish Society for Clinical Chemistry (SFKK) and Swedish external quality assurance organization (Equalis) is that 95% of HbA1c results should be within ±1.5 + 0.041xHbA1c (mmol/mol) from the assigned value of EQA samples. […] five external quality assurance samples from […] Equalis were analyzed in duplicate on the Capillarys 3 Tera. […] The quality goal in relation to the results from reference methods was fulfilled for duplicate measurements for all five samples in relation to the IFCC reference method and to the Mono S procedure (data not shown)." **[Reference 4]**

MINICAP FLEX-PIERCING

See above (§ CAPILLARYS 2 FLEX-PIERCING) **[Reference 17]**

[21] *SM means "Sigma Metrics".*
[22] *The method labeled N refers to CAPILLARYS 2 FLEX-PIERCING*
[23] *BV means "Biological Variation".*

Hb A1c is the measure of hemoglobin glycation. As normal red blood cells (RBC) have a lifespan of 120 days, Hb A1c value reflects the patient's mean glycemia over the last 3 months. Any condition that can alter the RBC lifespan may lead to misinterpretation of the Hb A1c result. Hemoglobin variants and thalassemias are part of these conditions and therefore could affect the clinical significance of Hb A1c. Thus, laboratories must be aware about the presence of hemoglobin variants and thalassemias during Hb A1c measurement.
Adapted from Radin MS. J Gen Intern Med. 2014 Feb; 29(2): 388-394.

CAPILLARYS 2 FLEX-PIERCING

Hemoglobin variants detection

"In the HbA1c-mode of the Capillarys, all measured variants were detected as an aberrant peak." **[Reference 21]**

TABLE 5 Detection of Hb variants in known samples

		Capillarys	
		HbA1c mode	
Genotype group	#	Detection	ID
HbA/S	9	7/7	NA
HbS/S	4	3/3	NA
HbA/E	9	8/8	NA
HbA/C	5	3/3	NA
HbA/D-Punjab	2	2/2	NA
HbA/Lepore	1		
HbA/J-Baltimore	1	1/1	NA
HbA/Muravera	1	1/1	NA

ID, "identification"; NA, "not applicable"; NI, "not identified".

Table 3: Comparisons of five routine HbA_{1c} assays in terms of result reporting and flag signs.[a] **[Reference 7]**

Hb variant	n	Number (%) of samples giving results without flags			
		Capillarys 2	VIIT2.0	G8std	HA-8180
G-Coushatta	47	–	–	24 (51)	–
G-His-Tsou	2	–	–	1 (50)	2 (100)
G-Taipei	1	–	–	1 (100)	–
Queens	41	–	–	41 (100)	41 (100)
Ube-4	11	–	–	11 (100)	11 (100)
Chad	4	–	–	3 (75)	4 (100)
Yamagata	4	–	4 (100)	–	–
Fort de France	1	–	–	1 (100)	1 (100)
Hoshida	1	–	–	1 (100)	–
HBA 52 Gly>Cys	1	–	1 (100)	1 (100)	1 (100)
HBB 146 His>Asn	1	–	1 (100)	1 (100)	–

[a]In VIIT2.0, the presence of peak area value in the variant window at the HbA1c report was regarded as a warning flag, and Tina-quant immunoassay did not report any flag signs. G8 were operated in standard mode.

"In this study we have shown that the capillary electrophoresis Sebia C2FP system allows the detection of HbNY[24] during haemoglobin electrophoresis and HbA1c assay, while this variant is not detected by ion-exchange HPLC Bio-Rad VII-T, boronate affinity HPLC Biotech Ultra2, or immunoassay Roche cobas c501 Tina-quant Generation 3 during HbA1c assay." **[Reference 22]**

"The C2FP (Sebia) analyzer, was able […] to detect the most common Hb variants in our population [Hb S (HBB: c.20A>T), Hb C (HBB: c.19G>A), Hb D-Los Angeles (HBB: c.364G>C), Hb E (HBB: c.79G>A) and Hb J-Baltimore HBB: c.380T>A)] [6]." **[Reference 23]**

"In accordance with the established criteria, we found a positive predictive value (PPV) for detecting […] Hb variants of 100.0%, as no false positives were detected and all of them were true positives, which was confirmed by biology molecular techniques." **[Reference 23]**

"The two forms of this hemoglobin variant[25] appear to co-elute with HbA1c and HbF on the Bio-Rad VARIANT-II Turbo 2.0 HbA1c program, resulting in falsely elevated HbA1c and HbF values." **[Reference 24]**

"On capillary electrophoresis (Sebia CAPILLARYS 2 Flex-Piercing) Hb Wayne resolved from HbA1c, HbA0, and HbF, migrating as two distinct peaks"

"C2FP HbA1c profiles allowed for easy detection of additional peaks corresponding to G-Coushatta, G-Taipei, and Kaohsiung hemoglobin variants." **[Reference 25]**

"In conclusion, Hb A-Ga[26] is an asymptomatic variant of haemoglobin, and is probably underestimated since it is difficult to detect by the traditional HPLC method. CE is a better method to detect Hb A-Ga[15] variant and seems to be suitable for evaluation of HbA1C value in patients with this variant." **[Reference 26]**

"Finally, the analysis of the sample by high resolution capillary electrophoresis (Capillarys 2 Flex-Piercing and Capillarys HbA1c kit from Sebia) showed an additional peak between HbA1c and HbA0 fractions on the electropherogram due to the presence of the variant[27]. The variant[16] peak as well as its glycated formwere completely separated from the HbA0 and HbA1c peaks respectively. The software tagged the result as an atypical pattern, which indicates the presence of additional peaks, and the HbA1c result was 6.8% (51 mmol/mol)." **[Reference 27]**

[24] *HbNY means "Hemoglobin New York".*
[25] *Hemoglobin Wayne.*
[26] *Hb A-Ga means "Hemoglobin Athens-Georgia".*
[27] *Hemoglobin Jerez.*

Thalassemias detection

"The diagnosis of a β-thalassemia is usually based on the accurate measurement of HbA2 by using long separation programs on IE-HPLC or CE instruments. Recently, the HbA1c assay on the C2FP system has been shown to have the ability to separate and quantify the HbA2 fraction, thus allowing for the incidental detection of β-thalassemia." **[Reference 25]**

"Our objective was to compare the HbA2 quantification according to both programs (HbA1c and Hemoglobin programs) used for HbA1c and hemoglobin fractions analysis respectively." **[Reference 12]**

"Linear regression between HbA2 measured with both programs showed an excellent regression equation (HbA2, Hemoglobin program) = 0.27099 + 1.07019 (HbA2, HbA1c program). No significant deviation from linearity between the two programs was noted."

"Only the Hb-pathy mode on Capillarys 2 was able to detect all 6 β-thalassemia samples. […] HbA1c mode on Capillarys detected all samples but one. However, the sample with discrepant results demonstrated a value close to the cut-off on all devices." **[Reference 21]**

TABLE 4 Measurement of HbA2 in known heterozygote β-thalassemia samples

	Capillarys	
	HbA1c mode	Hb-pathy mode
Samples		
1	4.2	4.5
2	***3.2***	3.6
3	5.4	5.8
4	4.4	4.7
5	5.5	5.7
6	4.8	5.2
Total	**5/6**	**6/6**

NA, not applicable.
italic+bold: lower than 3.5%.

"HbA2 values from the C2FP HbA1c system and Capillarys2 hemoglobin system were well correlated, but were lower in the C2FP HbA1c system (regression equation: y = 0.888x + 0.038; R = 0.967). Therefore, we concluded that HbA2 values determined using the C2FP HbA1c system were reliable." **[Reference 28]**

"The C2FP (Sebia) analyzer, was able to provide accurate values for Hb A2 and Hb F […]. The C2FP (Sebia) is the only Hb A1c commercialized analyzer that allows, on a routine basis, both Hb A2 and Hb F quantification in addition to Hb A1c measurement." **[Reference 23]**

"In accordance with the established criteria[28], we found a positive predictive value (PPV) for detecting β-thal […] of 100.0%, as no false positives were detected and all of them were true positives, which was confirmed by biology molecular techniques." **[Reference 23]**

"It has been demonstrated that an Hb F/Hb A2 index of >0.71 is useful, with a 100.0% sensibility, for detecting σβ-thal trait, avoiding the confirmatory test when having lower results."

"The box-and-whisker plot […] show a complete separation of the HbA2 quantification with the HbA1c program between noncarriers and carriers of the β-thalassemia trait. The results in β-thalassemia carriers (3.1%-6.3%) were statistically different from the noncarriers (1.4%-2.8%) (P < .001)." **[Reference 11]**

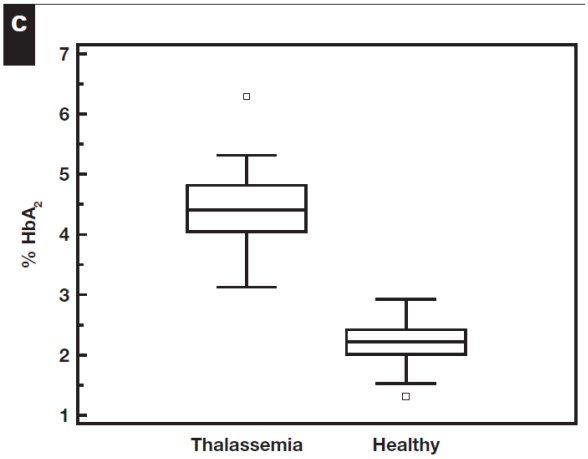


Figure 3 - The percentage of the HbA2 was analyzed with the HbA1c program on CAPILLARYS 2 Flex Piercing for a non-β-thalassemic population (279 samples).[…] C, The box-and-whisker plot shows the frequency of HbA2 in patients with thalassemia and healthy subjects.

[28] *In this study, β-Thalassemia and/or σβ-thalassemia criteria for carrier detection was established as having a Hb A2 value of ≥ 3.2 %, since Hb A2 results from the Hb A1c program revealed a systematic bias of 0.29% (absolute value) being lower than Hb A2 obtained from the Hb program, and/or Hb F value of ≥ 1.9% (corresponding to 2.0% by the Hb program, note the following point) and persistent MCV of <80.0 fL or MCH of <27 pg.*

"The results clearly showed a very good correlation between both techniques, with a coefficient of correlation of 0.9766 (P < .001). These data suggest that, in addition to an accurate interference-free measurement of HbA1c, compared with the hemoglobin program, the HbA1c program on CAPILLARYS 2 Flex Piercing is suitable for detecting β-thalassemia with a reliable measurement of the HbA2." **[Reference 11]**

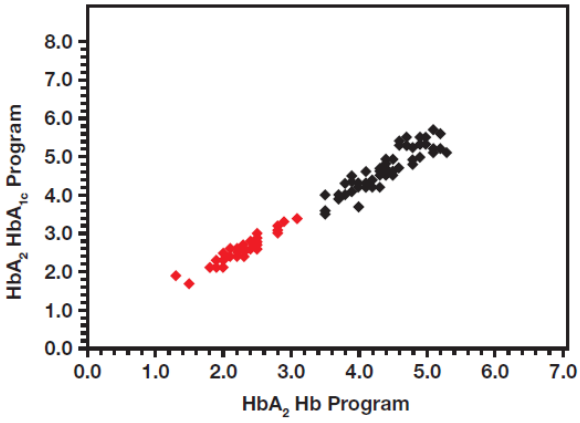


Figure 4 - The HbA2 concentration was tested with capillary electrophoresis (CAPILLARYS 2 Flex Piercing, Sebia, Lisses, France) using the HbA1c program in parallel with the hemoglobin program for 60 normal individuals (red) and 64 β-thalassemia carriers (black). (Correlation, y = 0.9845 x + 0.35, R^2 = 0.9766.)

CAPILLARYS 3 TERA

Hemoglobin variants detection

"HbS and HbC were visually well separated from the HbA0 peak, both for the Bio-Rad and Sebia Capillarys 3 Tera. […] On the Sebia Capillarys 3 Tera analyzer, HbD and HbE were nicely separated from the HbA0 peak." **[Reference 5]**

"Less frequent variants or variant combinations in our population, such as HbO-Arabe, HbSC, HbSS, HbCD, HbG Philadelphia, HbS/HbG Philadelphia, HbJ-Toronto, and HbEE, were detected in the chromatograms/electropherograms and identified by the software on both test instruments. The Sebia Capillarys 3 Tera was also able to detect HbA2' and other not yet identified variants, due to a clear separation of the peaks." **[Reference 5]**

Beside the fact that hemoglobin variants and thalassemias can lead to misinterpretation of the clinical value of Hb A1c, presence of additional hemoglobin fractions can directly interfere with Hb A1c measurement (co-migration or co-elution with Hb A1c or Hb A0 fraction for example). Laboratories must be aware about such analytical interferences.
Adapted from Radin MS. J Gen Intern Med. 2014 Feb; 29(2): 388-394.

CAPILLARYS 2 FLEX-PIERCING

Absence of Hb A

"As expected, for several samples lacking the normal HbA (homozygous Hb S, HbD/β-thalassemia, Hb E/β-thalassemia), no result for HbA1c was reported from Capillarys." **[Reference 1]**

"Analysis of HbSS, HbEE, HbCC, HbDD, and HbSC samples with Capillarys 2 gave no results (data not shown). This was expected as these samples have no HbA and therefore no HbA1c." **[Reference 8]**

"Next, we tested four samples from homozygous (E/E) patients on all systems in order to assess the specificity of the methods for the measurement of HbA1c and therefore determine the risk of obtaining an HbA1c value in homozygous (E/E) samples that do not contain an HbA1c analyte. Only the C2FP system did not detect HbA1c for all four homozygous (E/E) patients (Table 2)." **[Reference 25]**

Table 2 HbA_{1c} values for homozygous E/E carriers (n=4) on Arkray HA-8160, Sebia Capillarys 2 Flex Piercing, Bio-Rad Variant II Turbo, and Trinity Biotech Ultra² systems.

Variant type	Sebia C2FP	Bio-Rad VII-T	Arkray HA-8160	Trinity Biotech Ultra²
E/E	Nr	Nr	Nr	Nr
E/E	Nr	Nr	2.8% 7 mmol/mol	5.5% 37 mmol/mol
E/E	Nr	Nr	Nr	Nr
E/E	Nr	3.4% 14 mmol/mol	Nr	4.8% 29 mmol/mol

Nr, no HbA_{1c} value was reported for this sample by the system.

Thalassemias interferences

"The Bland-Altman plot and t-test for the agreement between the HbA1c measured on the C2FP and HA-8160 or Ultra2 systems revealed that there was no significant bias in […] patients with β-thalassemia (p = 0.075 for C2FP vs. HA-8160, p = 0.589 for C2FP vs. Ultra2). […] However, a significant positive bias above 0.5% was noticed on the VII-T system in 16 of 31 patients with β-thalassemia." **[Reference 25]**

Hemoglobin variants interferences

"Both immunoassay and IFCC RMP could not distinguish HbX from HbA and HbX1c from HbA1c, giving the sum of HbA1c and HbX1c as the result (= [HbA1c + HbX1c]/[HbA0 + HbA1c + HbX + HbX1c]) […].Boronate affinity method actually measure all glycated Hb species including glycated variants which may also result in a potential source of bias […].In contrast, capillary EP could distinguish HbX from HbA and HbX1c from HbA1c in most samples […], and it reflects only HbA1c results (= HbA1c/[HbA0 + HbA1c]). Therefore, if the glycation rate of a variant Hb is different from that of HbA, the HbA1c measured by IFCC RMP, immunoassay and boronate affinity method would not reflect the integrated plasma glucose value of the patient." **[Reference 7]**

"Haemoglobin variants present as important potential interferences in HbA1c analysis. The four common variants Hb S, Hb C, Hb D-Punjab and Hb E in the heterozygous states do not interfere with Capillarys HbA1c measurements." **[Reference 1]**

"A rather good agreement was noticed between the Capillarys 2FP/Roche c501 and Premier Hb9210 analyzers (relative bias < ± 7%); meanwhile, a significant negative bias of HbA1c values was observed systematically on the Tosoh G8 system in comparison with the Premier Hb9210 analyzer (relative bias > ± 7%)." **[Reference 9]**

TABLE 4. HbA_{1c} values for HbE on the Capillarys 2FP, Tosoh G8, Premier Hb9210, and Roche c501 systems

Sample	HbA_{1c}, %				Relative bias from Premier Hb9210, %		
	Premier Hb9210	Capillarys 2FP	Tosoh G8	Roche c501	Capillarys 2FP	Tosoh G8	Roche c501
1	5.5	5.6	4.2	5.4	1.8	**-23.6**	-1.8
2	5.0	4.8	4.2	5.0	-4.0	**-16.0**	0.0
3	5.3	5.3	4.7	5.6	0.0	**-11.3**	5.6
4	5.1	5.2	4.1	5.2	2.0	**-19.6**	2.0
5	5.6	5.9	4.6	5.7	5.4	**-18.0**	1.8
6	5.6	5.3	4.6	5.4	-5.4	**-18.0**	-3.6

The boronate affinity HPLC method with the Premier Hb9210 instrument was used as the comparative method. The bold results show the relative bias > ± 7% (calculated by NGSP units). Relative bias > ± 7% was considered clinically significant (NGSP criterion).

"In our present study, HbA1c analysis using the C2FP revealed a complete separation of HbNY[29] from HbA0 or HbA1c (Case 2), and for this heterozygous HbA/NY sample, it could generate an accurate HbA1c result." **[Reference 22]**

"We can conclude that HbA1c measurement on the C2FP system is not affected by the HbG-Taipei variant." **[Reference 25]**

"In this case, HbG Coushatta led to a persistent error in the reporting of incorrect raw results from CE-HPLC[30]. The chromatography data showed that there was an unknown peak eluting at 1.75 min, which prompted us to reanalyze it with capillary electrophoresis. The capillary electrophoresis gave an HbA1c result of 7.7% (60.6 mmol/mol), which was above the reference interval. This result matched other test results of this patient, including glycated albumin and fasting blood glucose, all indicating elevated blood glucose concentration." **[Reference 29]**

"During this study, we found an Hb variant[31] that produced an extra peak on the Variant II chromatogram.The same sample analyzed with G8 showed an underestimated HbA1c level. Only Capillarys 2-FP did not show any interference with the variant[30] trait. Our data show an uncorrected value of HbA1c in presence of HbD Iran variant using the two HPLC analyzers (G8 and Variant II)." **[Reference 10]**

"The analysis of Hb Jerez behavior by capillary electrophoresis confirms the conclusions of recent studies, where the results indicate that this technique is reliable when measuring HbA1c in presence of common hemoglobin variants. The variant separation from HbA1c and HbA0 and the calculation formula used by this system following IFCC recommendations could explain that the value obtained with this method was in agreement with the patient's glycation level." **[Reference 27]**

"Capillary Electrophoresis was the technique providing the most accurate HbA1c quantification for this patient in comparison with the fructosamine quantification."

"The chromatograms of the Tosoh G8 […] illustrate that the investigated variant hemoglobins were separated from other fractions, except for hemoglobin D, which elutes just after HbA, and hemoglobin E, which elutes together with the HbA fraction and thus generates a falsely decreased HbA1c value. On the Sebia Cap 2FP, all the variants investigated were clearly separated and HbA1c was quantified reliably" **[Reference 18]**

[29] *HbNY means "Hb New York"*
[30] *CE-HPLC means "Cation Exchange-HPLC"*
[31] *Hb D-Iran.*

"In the presence of HbC and HbS traits, as well as in the samples with high HbA2 and HbF levels, a satisfactory agreement was found in all centers between the comparison methods and the evaluated technique, the bias being lower than 5 mmol/mol (0.5%). In five samples with HbD and HbE traits, a satisfactory agreement was observed between the Adams Arkray HA-8160 HbA1c and the Capillarys 2 Flex Piercing analyzers (bias <5 mmol/mol or <0.5%), while the Variant II Hemoglobin Testing System showed a clinically significant interference from both traits when the A1C dual program was used." **[Reference 16]**

"In addition, our study has demonstrated that, for each type of Hb variant[32], HbA1c values obtained by CAPILLARYS 2 Flex Piercing were not significantly different from those obtained with the LC-MS method[33]. For the other techniques, a significant absolute difference was observed only in the presence of HbS using Variant II and HbE using Ultra2." **[Reference 30]**

"With the C2FP, all variants were completely separated from A 0 to A 1c. The quantitative effect ranged from 0 mmol/mol (AS and AE) to 2 mmol/mol (AC and AD) and was well within the criterion of < 7% bias recently reset by the NGSP[34]." **[Reference 19]**

Topic	Results SI (IFCC) units, mmol/mol	Results NGSP units, %
Interferences		
AS: quality separation	S completely separated from A	S completely separated from A
(n=5) Trueness HbA_{1c}	Bias 0 mmol/mol	Bias 0.0%
AC: quality separation	C completely separated from A	C completely separated from A
(n=5) Trueness HbA_{1c}	Bias 2 mmol/mol	Bias 0.2%
AE: quality separation	E completely separated from A	E completely separated from A
(n=5) Trueness HbA_{1c}	Bias 0 mmol/mol	Bias 0.0%
AD: quality separation	D completely separated from A	D completely separated from A
(n=5) Trueness HbA_{1c}	Bias 2 mmol/mol	Bias 0.2%
A2: quality separation	A2 completely separated from A	A2 completely separated from A
(n=5) Trueness HbA_{1c}	Bias 1 mmol/mol	Bias 0.1%
F: quality separation	F completely separated from A	F completely separated from A
(n=5) Trueness HbA_{1c}	Bias 1 mmol/mol	Bias 0.1%

Table 1 Performance characteristics of the Sebia C2FP HbA_{1c} analyzer.
[a]48–193 g/L. [b]158 mg/L.

[32] *Hb S, C, D and E.*
[33] *In this study, the LC-MS method corresponds to the IFCC LC-MS reference method.*
[34] *In this study, trueness was assessed using the IFCC reference measurement procedure or using routine procedures that were calibrated off-line using calibrators whose values were assigned with the IFCC reference measurement procedure.*

"Capillarys 2 and Capillarys 3 methods showed no clinically significant interference from any of the variants tested." **[Reference 31]**

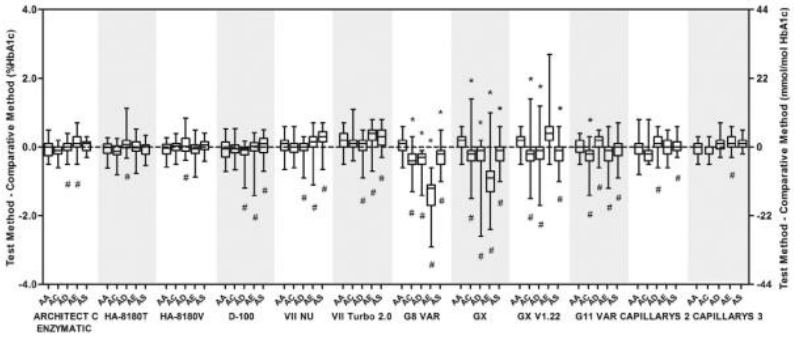


Fig. 1. Box-plots summarizing the absolute differences (%HbA_{1c} and mmol/mol HbA_{1c}) between each test method and the comparison method for HbAA, HbAC, HbAD, HbAE and HbAS. The horizontal line in each box is the median difference between the test and comparison methods. The upper and lower limits of each box correspond to the 25th and 75th percentile of the differences, respectively. The highest and lowest horizontal bars represent the minimum and maximum differences between the test and comparison methods. Differences from HbAA that are statistically significant are indicated (#) below each bar where appropriate; clinically significant differences are indicated (*) above each bar where appropriate.

CAPILLARYS 3 TERA

See above (§ CAPILLARYS 2 FLEX-PIERCING) **[Reference 31]**

CAPILLARYS 2 FLEX-PIERCING

Harmonizing Hemoglobin A_{1c} Testing
NGSP
A better A1C Test means better diabetes care

Certificate of Traceability

Manufacturer Certification

This certifies that ***Sebia***, using ***Capillarys HbA1c on Capillarys 2 Flex-Piercing*** has participated in and successfully completed the NGSP certification for manufacturers and is traceable to the **Diabetes Control and Complications Trial** Reference method. The comparison was performed with: **European Reference Laboratory ESRL#10**

The system evaluated was:

Instrument:	Calibrator Lot:	Application:
Capillarys 2 Flex-Piercing	**05047/01, 06047/01**	**%NGSP=0.09148xIFCC+2.152**
Reagent Lot:	Calibrator Assigned Values:	
05127/80, 09095/01, 22116/01	**36.8 mmol/mol, 88.3 mmol/mol**	

Date of Certification: April 1, 2018 Certification Expires: April 1, 2019

NGSP Steering Committee Chair | NGSP Network Coordinator | SRL director/ supervisor

CAPILLARYS 3 TERA

Harmonizing Hemoglobin A_{1c} Testing
NGSP
A better A1C Test means better diabetes care

Certificate of Traceability

Manufacturer Certification

This certifies that ***Sebia***, using ***CAPI 3 HbA1c on Capillarys 3*** has participated in and successfully completed the NGSP certification for manufacturers and is traceable to the **Diabetes Control and Complications Trial** Reference method. The comparison was performed with: **European Reference Laboratory ESRL#10**

The system evaluated was:

Instrument:	Calibrator Lot:	Application:
Capillarys 3	**22087/01, 23087/01**	**%NGSP=0.09148xIFCC+2.152**
Reagent Lot:	Calibrator Assigned Values:	
05028/01, 26107/01, 11107/01	**37.2 mmol/mol, 86.2 mmol/mol**	

Date of Certification: April 1, 2018 Certification Expires: April 1, 2019

NGSP Steering Committee Chair | NGSP Network Coordinator | SRL director/ supervisor

MINICAP FLEX-PIERCING

Harmonizing Hemoglobin A_{1c} Testing

NGSP

A better A1C Test means better diabetes care

Certificate of Traceability

Manufacturer Certification

This certifies that ***Sebia***, using ***Minicap HbA1c on Minicap Flex-Piercing*** has participated in and successfully completed the NGSP certification for manufacturers and is traceable to the **Diabetes Control and Complications Trial** Reference method. The comparison was performed with: **European Reference Laboratory ESRL#10**

The system evaluated was:

Instrument:	Calibrator Lot:	Application:
Minicap Flex-Piercing	**05047/01, 06047/01**	**%NGSP=0.09148xIFCC+2.152**
Reagent Lot:	Calibrator Assigned Values:	
02056/01, 08045/01, 26067/01	**36.8 mmol/mol, 88.3 mmol/mol**	

Date of Certification: April 1, 2018 Certification Expires: April 1, 2019

NGSP Steering Committee Chair | NGSP Network Coordinator | SRL director/ supervisor

CAPILLARYS 2 FLEX-PIERCING

IFCC International Federation of Clinical Chemistry and Laboratory Medicine
Network on Standardization of HbA1c

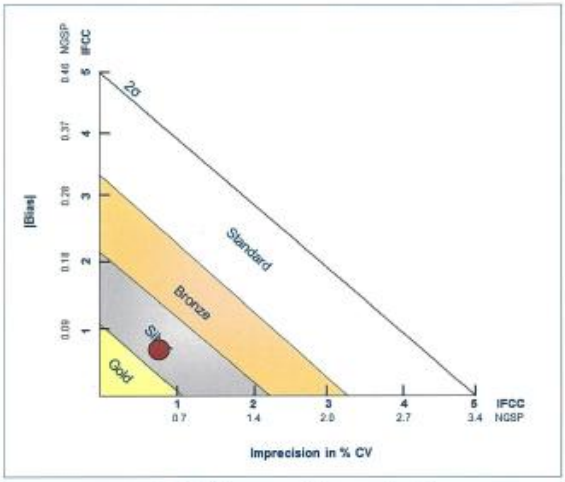
Certificate

Sebia

using

CAPILLARYS HbA1c

participated in the IFCC HbA1c Certification Programme to demonstrate traceability to the IFCC Reference Measurement Procedure and performed as shown below.



Total Error =	1.4	mmol/mol
Bias =	-0.6	mmol/mol
Imprecision =	0.8	%
Grade =	Silver	

Criteria derived from the IFCC model for Quality Targets HbA1c (Clin Chem 2015;61:752-59)

Date of Certification: 01 January 2018

Date of Expiry: 01 January 2019

IFCC Network Coordinator
Dr. C.W. Weykamp

CAPILLARYS 3 TERA

ifcc
International Federation of Clinical Chemistry and Laboratory Medicine
Network on Standardization of HbA1c

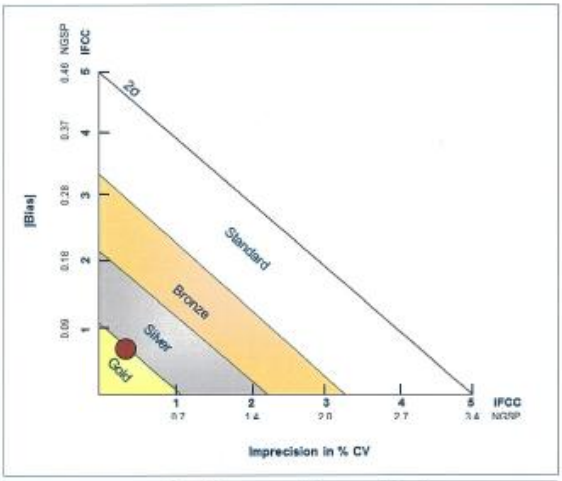
Certificate

Sebia

using

CAPI 3 Hb A1c

participated in the IFCC HbA1c Certification Programme to demonstrate traceability to the IFCC Reference Measurement Procedure and performed as shown below.



Total Error =	1.1	mmol/mol
Bias =	-0.7	mmol/mol
Imprecision =	0.4	%
Grade =	Gold	

Criteria derived from the IFCC model for Quality Targets HbA1c (Clin Chem 2015;61:752-59)

Date of Certification: 01 January 2018

Date of Expiry: 01 January 2019

IFCC Network Coordinator
Dr. C.W. Weykamp

MINICAP FLEX-PIERCING

International Federation of Clinical Chemistry and Laboratory Medicine
Network on Standardization of HbA1c

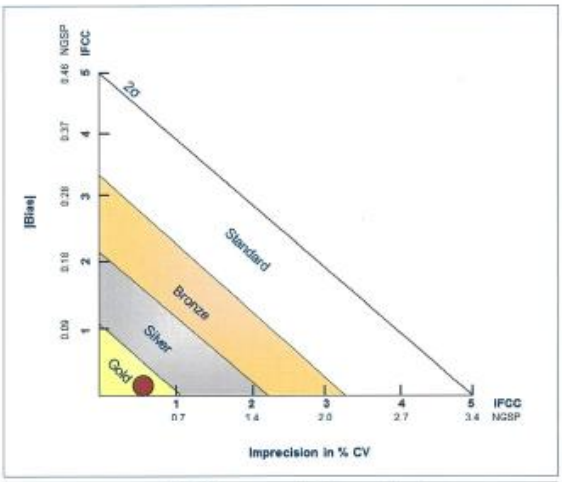
Certificate

Sebia

using

MINICAP Hb A1c

participated in the IFCC HbA1c Certification Programme to demonstrate traceability to the IFCC Reference Measurement Procedure and performed as shown below.



Total Error =	0.7	mmol/mol
Bias =	-0.1	mmol/mol
Imprecision =	0.6	%
Grade =	Gold	

Criteria derived from the IFCC model for Quality Targets HbA1c (Clin Chem 2015;61:752-59)

Date of Certification: 01 January 2018

Date of Expiry: 01 January 2019

IFCC Network Coordinator
Dr. C.W. Weykamp

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