sciendo

Original professional paper

DOI:10.2478/rrlm-2021-0027

Atellica CH 930 chemistry analyzer versus Cobas 6000 c501 and Architect ci4100 - a multi-analyte method comparison

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Abstract

Large clinical laboratories often rely on multiple chemistry analyzers. However, when a new analyzer is introduced, the laboratory must establish whether the old and new methods are comparable and can be used interchangeably. In this study, we compared the newly introduced Atellica CH930 chemistry analyzer with the already established Architect ci4100 and Cobas 6000 c501 from our laboratory.

Patient samples were randomly selected from daily routine testing and a total of 22 analytes were investigated. Total error (TE_{obs}) between test (Atellica) and comparative (Architect and Cobas) methods was calculated at relevant medical decision levels (MDL). For demonstrative purposes, the assessment of method comparability was based on three different criteria: allowable total error (TE_a) derived from biological variation (BV), CLIA proficiency testing criteria for acceptable analytical performance, and CLIA-calculated Sigma metrics. These sets of analytical performance specifications were also compared, and their strengths and limitations are discussed in this paper.

Performance of Atellica CH930 against Architect ci4100 was acceptable or nearly acceptable at 82%, 95%, and 64% of the 22 investigated MDLs across 9 analytes, according to BV-TE_a, CLIA-TE_a, and CLIA-calculated Sigma metrics, respectively. Similarly, performance of Atellica CH930 against Cobas 6000 c501 was acceptable or nearly acceptable at 61%, 93%, and 63% of the 54 investigated MDLs across 22 analytes, according to BV-TE_a, CLIA-TE_a, and CLIA-calculated Sigma metrics, respectively. However, method comparability should not be evaluated by a "one size fits all" approach as some analytes require different criteria of acceptability, ideally based on medically allowable error and clinical outcome.

Received: 21st July 2021; Accepted: 9th September 2021; Published: 20th September 2021

Introduction

Laboratory medicine has long become essential to medical care, with about 70% of medical decisions being influenced by in vitro diagnostic tests [1]. Due to its pivotal role, laboratory medicine is also one of the fastest growing areas in medicine. With ever-improving techniques and technologies, new methods are introduced in clinical laboratories at an unprecedented rate. As modern automated laboratory analyzers are

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generally faster and more precise, new methods have lower inherent error of measurement and have become increasingly more reliable and cost-effective. However, errors in the clinical laboratory are inevitable. Hence, it is the laboratory's responsibility to identify the manifold sources of error and address them according to national and international rules, regulations and quality standards such as described by the International Organization for Standardization (ISO) or by the Clinical Laboratory Standards Institute (CLSI), to name a few.

Replacing old methods with new ones is a natural and logical process for clinical laboratories aiming at improved performance and better patient care. However, a newly-introduced analyzer or method can itself be a source of error. Often, new analyzers must either run alongside with old ones or replace them altogether. In both cases, the laboratory must establish whether the two methods are comparable, that is, if the methods can be used interchangeably without adversely affecting medical decision-making and clinical outcome in patients. As comparability studies are frequently performed in clinical laboratories, many publications in scientific journals have approached the topic of method-comparison methodology [2]. Usually, statistical analysis of paired results from the two methods is needed, but the applicability of the new method must also be judged by considering the cost of a new analyzer, the cost and availability of reagents and calibration material, the space occupied by a new analyzer, operator education, waste handling, etc [2]. While decisions regarding applicability are based almost exclusively on local and subjective assessments, decisions concerning analytical performance usually depend on statistical analyses and objective criteria of acceptability [2].

The aim of this study was to determine the degree of comparability between the newly-introduced Atellica Solution CH 930 chemistry analyzer (Siemens AG, Germany) and the already established chemistry analyzers from our laboratory: Architect ci4100 (Abbott, US) and Cobas 6000 c501 (Roche, Switzerland).

Material and Methods

Study design

This study was performed between April and June 2020 in the Central Laboratory of Târgu Mureș County Emergency Clinical Hospital (Mureș County, Romania). Prior to this period, the operators of both the test and the comparative methods underwent a process of familiarization with the operation, maintainance procedures, calibration, function monitoring, and sample preparation of the new Atellica Solution CH 930 clinical chemistry analyzer. Daily quality control (QC) was performed for over 30 days before the study and throughout its entirety, using three levels of Bio-Rad controls (Ref 694, 695, 696; Lot 45830). Over the same period, calibration was performed regularly according to the manufacturer's instructions and occasionally if needed, using Atellica CH calibrators from Siemens Healthineers (Siemens AG, Germany). Data were not collected during the familiarization period.

According to EP09-A3 guideline [3], the comparative method can be the laboratory's current method, the method used by the manufacturer in the labeled claims, or a recognized reference method. In this study, the new Atellica Solution analyzer was compared with the laboratory's current method, that is with two chemistry analyzers already established in our laboratory: Cobas 6000 c501 and Architect ci4100, which are both part of a permanent proficiency testing/external quality assessment program (PT/EQA). Therefore, throughout the study, the difference between the test and comparative methods is referred to simply as analytical difference (D_A), and

not bias. At the end of the comparative study, all 3 methods were tested against the same PT/EQA sample of unknown analyte concentrations.

Sample collection and processing

This study was performed on unhemolyzed patient samples which were randomly selected from routine testing at our laboratory and analyzed in singlicate directly from serum-separating tubes on both the test and comparative methods. For comparison of Atellica CH 930 with Architect ci4100, a short chemistry panel of 9 commonly investigated analytes was tested: alanine transaminase, aspartate aminotransferase, creatine kinase, creatinine, glucose, potassium, sodium, total bilirubin, and urea. For comparison of Atellica CH 930 with Cobas 6000 c501, an extended chemistry panel of 22 routine analytes was tested: albumin, alkaline phosphatase, alanine transaminase, amylase, aspartate aminotransferase, calcium, cholesterol, creatine kinase, creatinine, bilirubin (direct), gamma-glutamyl transferase, glucose, iron, lactate dehydrogenase, magnesium, potassium, sodium, bilirubin (total), protein (total), triglycerides, urea, and uric acid. Further information can be found in Table 1.

Method comparison

The Coefficient of analytical variation (CV_A) of the test method was calculated for all three control levels from daily QC data. Analytical difference (D_A) between test and comparative methods was calculated at medical decision levels (MDL) [4] based on Passing-Bablok regression equations. For enzymes, cholesterol, creatinine, triglycerides, urea, and uric acid, the lowest MDL [4] was excluded from analysis due to lack of clinical relevance. Total Error (TE) between test and comparative methods was calculated with the formula

$$TE_{obs} = 1.65\ CV_A + D_A$$

where $1.65\ CV_A$ is the random error and D_A is the systematic error. The acceptance limits for method comparison were based on three different criteria: analytical quality specifications derived from biological variation, CLIA proficiency testing criteria for acceptable analytical performance and SixSigma medical decision chart with TE_a according to CLIA [5]. Data on biological variation were obtained from the Biological Variation Database of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM, https://biologicalvariation.eu/) and, when not available, from the Biological Variation Database compiled by Dr. Carmen Ricos and colleagues [6]. Quality specifications derived from biological variation were calculated as shown below, using the internationally recognised analytical goals for imprecision and bias based on biological variation [6, 7]. The tool for single-analyte Six Sigma evaluation was provided by www.westgard.com. Normalized method decision charts for multi-analyte Six Sigma evaluation (Figure 1) were generated using a Microsoft-Excel based tool created by the authors following a model published by Smolcic and Bilic-Zulle [8].

Optimum:	$CV_A \leq 0.25 \times CV_I$	Optimum:	$D_A \leq 0.125(CV_I^2 + CV_G^2)^{1/2}$
Desirable:	$CV_A \leq 0.50 \times CV_I$	Desirable:	$D_A \leq 0.250(CV_I^2 + CV_G^2)^{1/2}$
Minimum:	$CV_A \leq 0.75 \times CV_I$	Minimum:	$D_A \leq 0.375(CV_I^2 + CV_G^2)^{1/2}$

Optimum:	$TE_a \leq 1.65\ (0.25\ CV_I) + 0.125(CV_I^2 + CV_G^2)^{1/2}$
Desirable:	$TE_a \leq 1.65\ (0.50\ CV_I) + 0.250(CV_I^2 + CV_G^2)^{1/2}$
Minimum:	$TE_a \leq 1.65\ (0.75\ CV_I) + 0.375(CV_I^2 + CV_G^2)^{1/2}$

The equations above show the levels of analytical goals for imprecision (CV_A) and analytical difference (D_A, substitute for bias) based on biological variation. If an agreement is desired between the test and comparative methods, both parameters must meet the specified performance criteria and can therefore be conveniently combined as TE_a (Total Error allowable) for which three similar levels of analytical goals can be set.

CV_A – coefficient of analytical variation (imprecision), D_A – difference (systematic error, substitute for bias), CV_I – coefficient of variation (intra-individual) derived from biological variation, CV_G – coefficient of variation (inter-individual) derived from biological variation.

Statistical processing

All data were processed and organized using Microsoft Excel software (Microsoft Corporation, USA). Correlation, linear regression and Passing-Bablok regression statistical tests were performed on all data sets using MedCalc v14 software. The difference (D_A) between methods was calculated at each MDL using Passing-Bablok regression equations, and further combined with the CV_A of the test method in order to calculate the total error observed (TE_{obs}) between methods. SixSigma scores were calculated using a Microsoft Excel-based tool.

Results

All numerical data are presented in Tables 1-5. The following abbreviations will be used for the 22 analytes investigated in this study: Alb – albumin, ALP – alkaline phosphatase, ALT – alanine transaminase, Amy – amylase, AST – aspartate aminotransferase, Ca – calcium, Chol – cholesterol, CK – creatine kinase, Crea – creatinine, DBil – bilirubin (direct), GGT – gamma-glutamyl transferase, Gluc – glucose, LDH – lactate dehydrogenase, Mg – magnesium, K – potassium, Na – sodium, TBil – bilirubin (total), TProt – protein (total), Trig – triglycerides, UA – uric acid; Iron and Urea are not abbreviated.

Discussions

Atellica Solution features

The new Atellica Solution from Siemens Healthineers (Germany) was introduced in our laboratory at the end of the year 2019. This flexible and scalable system integrates high throughput immunoassay (IM 1300) and chemistry (CH 930) analyzers with a rapid bidirectional variable-speed magnetic sample transport line, multi-camera vision system with 360° view, intelligent scheduling software, automated scheduling and delivery of controls and calibrators from an onboard refrigerated compartment, and other features designed for minimal operator intervention and turnaround times.

Total analytical error and method comparison rationale

As described above, the laboratory must determine whether the newly-introduced method is comparable with the current methods in our laboratory. Method comparison studies investigate total analytical error (TE) which is the summation of random error and systematic error. Random error is caused by variability in the operation of the method and does not relate to the true value, but is a matter of precision [2]. The counterpart of precision is imprecision, which is calculated as either standard deviation (SD) from the mean or a coefficient of variation (CV). Close monitoring of imprecision through QC procedures is important as it allows the examiner to determine whether changes in the value of a measurand can be explained by the inherent imprecision of the method alone, or other undesired factors should be considered and investigated. Systematic error, also known as bias or inaccuracy, is a measure of trueness, which is another essential

Table 1. Samples used for method comparison. A variable number of samples was randomly picked each day. The duration of the comparison study is measured in days and can be different between analytes. Total number of samples (n) is provided for each analyte as well as the lowest/highest recorded value and the median value.

Assay	Units	Days	n	Min. value	Max. value	Median value
Atellica CH 930 vs Architect ci4100						
ALT	U/L	11	245	6	3061	24
AST	U/L	11	291	8	3644	30
Crea	mg/dL	11	326	0.25	16.19	0.90
CK	U/L	14	111	15	8658	172
Gluc	mg/dL	11	337	43	510	113
K	mmol/L	12	219	2.15	6.68	4.06
Na	mmol/L	12	226	121	168	141
TBil	mg/dL	12	231	0.12	18.06	0.60
Urea	mg/dL	11	336	6.6	321.4	43.1
Atellica CH 930 vs Cobas 6000 c501						
Alb	g/dL	14	155	1.37	5.20	3.00
ALP	U/L	15	172	37	934	105
ALT	U/L	13	298	5	2145	28
Amy	U/L	13	162	9	1540	60
AST	U/L	13	312	7	866	35
Ca	mmol/L	21	154	1.03	4.10	2.23
Chol	mg/dL	15	178	45	369	173
CK	U/L	16	164	10	9123	79
Crea	mg/dL	13	301	0.09	8.61	0.82
DBil	mg/dL	11	182	0.05	19.90	0.54
GGT	U/L	14	157	7	1426	98
Gluc	mg/dL	13	318	38	428	103
Iron	µmol/L	20	154	0.4	55.1	9.5
LDH	U/L	6	129	38	5889	257
Mg	mmol/L	17	62	0.26	1.37	0.77
K	mmol/L	13	341	1.97	7.81	4.02
Na	mmol/L	13	338	118	182	140
TBil	mg/dL	13	168	0.10	25.60	0.98
TProt	g/dL	13	158	3.02	10.59	5.62
Trig	mg/dL	15	179	27.1	801.3	131.4
Urea	mg/dL	13	303	5.8	373.2	49.5
UA	mg/dL	15	160	1.5	23.9	5.6

aspect of quality assurance. Accuracy is all the more important in clinical laboratories because significantly innacurate values no longer reflect the biological status of the patient and may adversely affect clinical decision. Since perfect methods of measurement do not exist, the best estimate of a true value is a value produced by a reference method [2]. However, according to EP09-A3 guideline [3], the comparative method can be not only a recognized reference method, but also the method used by the manufacturer in the labeled claims, or the laboratory's current

Table 2. The imprecision of Atellica CH 930, calculated as CV (%) derived from daily QC, compared with the analytical goals for imprecision as per the QC material manufacturer and derived from biological variation. Data were presented for all 22 investigated analytes at all control levels.

Assay	Units	QC level	Target mean	Mean	Target CV (%)	QC CV (%)	CV_i (%)	Biological variation goals for CV (%)	
Alb	g/dL	1	2.50	2.54	5.89	2.16	1.4	Optimum	0.35
		2	3.60	3.60	5.00	1.52		Desirable	0.70
		3	4.39	4.40	4.67	1.43		Minimum	1.05
ALP	U/L	1	37.8	31.1	17.06	5.58	5.3	Optimum	1.32
		2	159	143.4	8.49	2.25		Desirable	2.65
		3	296	274.6	7.26	1.72		Minimum	3.98
ALT	U/L	1	30.3	25.2	12.27	4.49	10.1	Optimum	2.52
		2	93.4	85.8	7.82	3.05		Desirable	5.05
		3	209.5	197.3	6.56	2.72		Minimum	7.57
Amy	U/L	1	44.8	46.6	6.97	2.08	6.6	Optimum	1.65
		2	137.5	142	4.91	1.62		Desirable	3.30
		3	288	293.5	4.51	1.66		Minimum	4.95
AST	U/L	1	47.5	44.4	8.15	2.98	9.6	Optimum	2.40
		2	125	114.5	6.80	3.00		Desirable	4.80
		3	279	256.5	6.27	4.13		Minimum	7.20
Ca	mmol/L	1	1.575	1.484	5.24	3.57	2.1	Optimum	0.53
		2	2.575	2.470	4.37	3.04		Desirable	1.05
		3	3.515	3.425	3.34	2.25		Minimum	1.58
Chol	mg/dL	1	107.3	110.9	5.45	1.74	6.0	Optimum	1.50
		2	181	185.6	4.70	1.42		Desirable	3.00
		3	276	279.1	4.35	1.34		Minimum	4.50
CK	U/L	1	266	268.8	9.02	2.51	15.0	Optimum	3.75
		2	557	551.4	8.98	1.91		Desirable	7.50
		3	1067.5	1033.6	9.02	2.16		Minimum	11.25
Crea	mg/dL	1	0.783	0.792	10.98	5.17	4.5	Optimum	1.13
		2	1.825	1.842	6.99	4.29		Desirable	2.25
		3	6.350	6.420	4.88	3.55		Minimum	3.38
DBil	mg/dL	1	0.299	0.323	21.24	13.28	36.8	Optimum	9.20
		2	1.500	1.418	11.67	7.75		Desirable	18.40
		3	2.805	2.713	10.43	5.75		Minimum	27.60

GGT	U/L	1	31.6	27.8	12.03	16.74	9.1	Optimum	2.28
		2	86	80	7.97	5.68		Desirable	4.55
		3	135.5	128	7.20	4.11		Minimum	6.82
Gluc	mg/dL	1	58	58.8	5.00	2.15	5	Optimum	1.25
		2	117.5	117.3	4.47	1.92		Desirable	2.50
		3	351.5	348.7	3.91	1.46		Minimum	3.75
Iron	µmol/L	1	12.75	12.37	10.00	9.90	26.5	Optimum	6.63
		2	27.20	27.46	9.93	4.29		Desirable	13.25
		3	40.65	41.70	9.90	3.68		Minimum	19.88
LDH	U/L	1	127	114.9	7.68	3.74	5.2	Optimum	1.30
		2	181.5	164.2	6.20	2.73		Desirable	2.60
		3	414	410.9	4.59	2.20		Minimum	3.90
Mg	mmol/L	1	0.475	0.455	11.05	4.39	2.9	Optimum	0.73
		2	1.095	1.070	7.53	3.08		Desirable	1.45
		3	1.470	1.678	18.37	2.03		Minimum	2.17
K	mmol/L	1	2.59	2.51	3.86	0.92	4.1	Optimum	1.03
		2	4.08	3.95	3.06	0.58		Desirable	2.05
		3	7.47	7.29	2.51	0.70		Minimum	3.08
Na	mmol/L	1	118.5	116.2	2.32	0.71	0.5	Optimum	0.13
		2	144	140.9	2.08	0.57		Desirable	0.25
		3	161.5	158.6	2.01	0.68		Minimum	0.38
TBil	mg/dL	1	0.70	0.70	9.79	0.01	21.8	Optimum	5.45
		2	3.40	3.38	6.09	5.03		Desirable	10.90
		3	7.80	7.56	5.51	4.47		Minimum	16.35
TProt	g/dL	1	3.80	3.76	4.47	0.88	2.6	Optimum	0.65
		2	5.42	5.41	3.87	0.76		Desirable	1.30
		3	6.60	6.54	3.60	0.79		Minimum	1.95
Trig	mg/dL	1	99.6	108.5	7.23	3.90	20	Optimum	5.00
		2	143.5	151.5	6.10	2.49		Desirable	10.00
		3	218.5	226.0	5.38	1.77		Minimum	15.00
Urea	mg/dL	1	30.4	31.7	7.39	3.58	13.9	Optimum	3.48
		2	87.1	89.3	5.41	2.57		Desirable	6.95
		3	151.3	152.8	4.88	3.86		Minimum	10.43
UA	mg/dL	1	3.5	3.6	7.06	3.07	8.6	Optimum	2.15
		2	6.0	6.2	5.58	3.34		Desirable	4.30
		3	9.9	10	4.71	3.26		Minimum	6.45

Table 3. Comparison of Atellica CH 930 (test method) and Architect ci4100 (comparative method) chemistry analyzers for 9 commonly investigated analytes. Six Sigma scores and TE_{obs} were calculated at each medical decision level (MDL). TE_{obs} was compared with TE_a as per CLIA and biological variation data.

Atellica CH 930 vs Architect ci4100									
Method comparison data						Performance criteria			Sigma metric
Assay	Units	MDL	CV_A (%)	D_A (%)	TE_{obs} (%)	Biological variation TE_a (%)		CLIA TE_a (%)	
ALT	U/L					Optimum	8	20	
		60	3.05	4.2	9.2	Desirable	16.1		5.2
		300	2.72	7.2	11.7	Minimum	24.1		4.7
AST	U/L					Optimum	6.8	20	
		60	2.98	8.8	13.7	Desirable	13.6		3.8
		300	4.13	10.6	17.4	Minimum	20.5		2.3
CK	U/L					Optimum	11.3	30	
		240	2.51	3.2	8	Desirable	22.6		> 6
		1800	2.16	0.2	3.8	Minimum	33.8		> 6
Crea	mg/dL					Optimum	3.7	15	
		1.6	4.29	1.4	8.5	Desirable	7.4		3.2
		6	3.55	1.8	7.7	Minimum	11.1		3.7
Gluc	mg/dL	45	2.15	1.2	4.8	Optimum	3.3	10	4.1
		120	1.92	1.4	4.6	Desirable	6.5		4.5
		180	1.92	1.9	5.1	Minimum	9.8		4.2
K	mmol/L	3	0.92	2.9	4.4	Optimum	2.4	6.7	> 6
		5.8	0.58	3.1	4	Desirable	4.8		> 6
		7.5	0.70	3.1	4.3	Minimum	7.3		5.1
Na	mmol/L	115	0.71	1.7	2.9	Optimum	0.3	2.7	2.5
		135	0.57	1.5	2.4	Desirable	0.7		2.6
		150	0.57	1.3	2.3	Minimum	1		2.4
TBil	mg/dL	1.4	0.10	8.6	8.8	Optimum	13.5	20	> 6
		2.5	5.03	9.2	17.5	Desirable	26.9		2.1
		20	4.47	9.9	17.3	Minimum	40.4		2.3
Urea	mg/dL					Optimum	8.9	9	
		56	3.58	7.7	13.6	Desirable	17.8		0.4
		107	2.57	5.5	9.7	Minimum	26.6		1.4

method. For practical reasons, in this study the new Atellica Solution biochemistry analyzer CH 930 was compared with the laboratory's current validated methods: Architect ci4100 and Cobas 6000 c501.

Architect ci4100 is currently the biochemistry analyzer in our emergency department laboratory. Thus, the comparison between Architect ci4100 and Atellica CH 930 was performed on a limited panel of 9 essential and commonly investigated analytes (see Table 1). In contrast, the comparison was performed on an extensive panel of 22 routine analytes for Cobas 6000 c501 (see Table 1), since this analyzer serves all clinical departments of our hospital and therefore accomodates a wider range of analytes.

Observed imprecision of Atellica CH 930

It must be noted that the precision of Atellica CH 930 chemistry analyzer, measured as CV derived from daily QC, was well within the allowed CV stated by the QC material manufacturer for all analytes, at all control levels (see Table 2), except for Iron (Control level 1: QC CV 9.9% vs Target CV 10%) and GGT (Control level 1: QC CV 16.74% vs Target CV 12.03%). This is a welcome yet predictable finding as the imprecision figures for QC material are known to be often very wide [9]. On the other hand, analytical performance requirements based on biological variation (BV) are considerably more demanding and therefore introduce a stricter, but more reliable set of analytical goals for imprecision. As presented in Table 2, Atellica CH 930 fulfilled or narrowly missed the BV analytical goals for *optimum* precision at all 3 control levels for 8 out of 22 investigated analytes: amylase, cholesterol, creatine kinase, potassium, total bilirubin, total protein, triglycerides, and urea. Various combinations of goals for *optimum* and *desirable* precision were achieved among the 3 control levels for each of the following 6 analytes: ALT, AST, direct bilirubin, glucose, iron, and uric acid. ALP, GGT, LDH showed a mixture of inacceptable/ *minimum*/ *desirable* precision, while inacceptable precision (CV > CV for *minimum* precision) was observed at all 3 control levels for albumin, calcium, creatinine, sodium, and at 2 out of 3 control levels for magnesium. Such diversity of results reflects the stark contrast between precision requirements of commercial QC material manufacturers and those derived from BV. Moreover, it shows that the expectation to always achieve in practice the optimum or desirable BV analytical goals, may sometimes be unrealistic [10].

Observed vs allowable total analytical error

Total error observed (TE_{obs}) between the test and comparative methods was calculated at each medical decision level (MDL). The figures are presented in Tables 3 and 4 along with total allowable error (TE_a) limits as per CLIA and BV data. There are 3 levels of analytical goals for BV-TE_a: optimum (O), desirable (D), and minimum (M) [7]. TE_{obs} that fails to meet the minimum specifications is considered inacceptable (F). While minimum specifications for BV- TE_a may be too permissive, optimum BV- TE_a may sometimes be too demanding and difficult to achieve in practice. Therefore, desirable TE_a is the standard analytical goal in most laboratories that use performance specifications derived from BV [6].

As shown in Table 3, TE_{obs} between Atellica CH 930 and Architect ci4100 met or even exceeded the desirable analytical goals at all MDLs for 6 out of 9 analytes: ALT (2D-3D), creatine kinase (2O-3O), glucose (1D-2D-3D), potassium (1D-2D-3D), total bilirubin (1O-2D-3D), and urea (2D-3D). For AST (2D-3M), TE_{obs} met the desirable analytical goal at just one MDL, while less than desirable performance at all 3 MDLs was observed for creatinine (2M-3M) and sodium (1F-2F-3F). Since inacceptable precision can easily determine inacceptable TE, failure to meet the desirable analytical goals for TE was expected for creatinine and sodium, given the inacceptable CV_A recorded for these 2 analytes (see Table 2). Since the BV-derived analytical performance specifications (APS) are not well suited for all analytes [11], such "failures" should not always be judged too harshly. However, creatinine and sodium are among the analytes that have been proposed for the BV-derived APS [11] and we should therefore consider that the TE_{obs} for these 2 analytes between Atellica CH 930 and Architect ci4100 is inacceptable.

Table 4 shows the comparison data for Atellica CH 930 vs Cobas 6000 c501. TE_{obs} met or even exceeded the BV desirable analytical goals at all 3 MDLs for 13 out of 22 analytes: ALP (2O-3O), amylase (2D-3D), cholesterol (2D-3O),

Table 4. Comparison of Atellica CH 930 (test method) and Cobas 6000 c501 (comparative method) chemistry analyzers for 22 routine analytes. Six Sigma scores and TE_{obs} were calculated at each medical decision level (MDL). TE_{obs} was compared with TE_a as per CLIA and biological variation data. *MDL values for Bilirubin (direct) were not available and thus considered identical to Bilirubin (total).

Atellica CH 930 vs Cobas 6000 c501									
		Method comparison data				Performance criteria			Sigma metric
Assay	Units	MDL	CV_A (%)	D_A (%)	TE_{obs} (%)	Biological variation TE_a (%)		CLIA TE_a (%)	
Alb	g/dL	2	2.16	12.4	16	Optimum	1.3	10	0
		3.5	1.52	6.6	9.1	Desirable	2.6		2.2
		5.2	1.43	4.1	6.5	Minimum	3.9		4.1
ALP	U/L					Optimum	5.3	30	
		150	2.25	1.4	5.1	Desirable	10.5		> 6
		400	1.72	1.8	4.7	Minimum	15.8		> 6
ALT	U/L					Optimum	8	20	
		60	3.05	10.4	17.8	Desirable	16.1		3.1
		300	2.72	12.4	16.9	Minimum	24.1		2.8
Amy	U/L					Optimum	6.6	30	
		120	1.62	7.0	9.6	Desirable	13.2		> 6
		200	1.66	6.5	9.2	Minimum	19.8		> 6
AST	U/L					Optimum	6.8	20	
		60	2.98	11.2	16.2	Desirable	13.6		3
		300	4.13	12.2	19.1	Minimum	20.5		1.9
Ca	mmol/L	1.75	3.57	5.4	11.3	Optimum	1.3	7.7	0.6
		2.75	3.04	2.5	7.5	Desirable	2.5		1.7
		3.37	2.25	1.6	5.3	Minimum	3.8		2.7
Chol	mg/dL					Optimum	4.5	10	
		200	1.42	2.7	5	Desirable	9.1		5.1
		240	1.34	2.2	4.4	Minimum	13.6		5.8
CK	U/L					Optimum	11.3	30	
		240	2.51	1.7	5.9	Desirable	22.6		> 6
		1800	2.16	1.4	5	Minimum	33.8		> 6
Crea	mg/dL					Optimum	3.7	15	
		1.6	4.29	0.3	7.3	Desirable	7.4		3.4
		6	3.55	0.7	6.5	Minimum	11.1		4
DBil*	mg/dL	1.4	7.75	2.6	15.4	Optimum	22.3	20	2.2
		2.5	5.75	2.9	15.7	Desirable	44.5		3
		20	5.75	3.2	12.7	Minimum	66.8		2.9

						Optimum	9.4		
GGT	U/L	50	5.68	8.5	17.9	Desirable	18.9	20	2
		150	4.11	7	13.8	Minimum	28.3		3.2
		45	2.15	1	4.6	Optimum	3.3		4.2
Gluc	mg/dL	120	1.92	0.4	3.6	Desirable	6.5	10	5
		180	1.92	0.7	3.9	Minimum	9.8		4.8
		9	9.90	2.5	18.8	Optimum	15.3		1.8
Iron	µmol/L	39	3.68	3	9	Desirable	30.7	20	4.6
		70	3.68	3.7	9.8	Minimum	46		4.4
						Optimum	3.8		
LDH	U/L	300	2.73	5	9.5	Desirable	7.7	20	5.5
		500	2.20	4	7.6	Minimum	11.5		> 6
		0.6	4.39	3.9	11.1	Optimum	2		4.8
Mg	mmol/L	1	3.08	3.2	8.3	Desirable	4	25	> 6
		2.5	2.03	2.6	5.9	Minimum	6		> 6
		3	0.92	3	4.6	Optimum	2.4		4
K	mmol/L	5.8	0.58	2.9	3.8	Desirable	4.8	6.7	> 6
		7.5	0.70	2.8	4.0	Minimum	7.3		5.6
		115	0.71	1.7	2.9	Optimum	0.3		1.4
Na	mmol/L	135	0.57	1.5	2.7	Desirable	0.7	2.7	2.1
		150	0.57	1.3	2.3	Minimum	1.0		2.5
		1.4	0.10	12.1	12.3	Optimum	13.5		> 6
TBil	mg/dL	2.5	5.03	12.1	20.4	Desirable	26.9	20	1.6
		20	4.47	12.1	19.5	Minimum	40.4		1.8
		4.5	0.88	3.0	4.5	Optimum	1.7		> 6
TProt	g/dL	6	0.76	4.0	5.3	Desirable	3.5	10	> 6
		8	0.79	4.7	6.0	Minimum	5.2		> 6
						Optimum	13.5		
Trig	mg/dL	150	2.49	2.3	6.4	Desirable	27.0	25	> 6
		400	1.77	1.6	4.5	Minimum	40.6		> 6
						Optimum	8.9		
Urea	mg/dL	56	2.57	11.4	15.7	Desirable	17.8	9	0
		107	2.57	9.7	13.9	Minimum	26.6		0
						Optimum	6.0		
UA	mg/dL	8	3.34	8.5	14.0	Desirable	12.0	17	2.5
		10.7	3.26	8.6	14.0	Minimum	18.0		2.6

Table 5. PT/EQA results for the test method (Atellica CH 930) and both comparative methods (Architect ci4100 and Cobas 6000 c501). The test was not performed for amylase, but 4 additional analytes were investigated: chloride, high-density lipoprotein cholesterol (HDL-C), inorganic phosphate (IP), and low-density lipoprotein cholesterol (LDL-C).

Assay	Units	EQA global results		Architect ci4100		Atellica CH 930		Cobas 6000 c501	
		Target	SD	Result	Z score	Result	Z score	Result	Z score
Alb	g/dL	5.20	0.30			5.5	1.00	5.30	0.33
ALP	U/L	311.5	51.2			293	-0.36	276	-0.69
ALT	U/L	184	14.5	180	-0.28	188	0.28	169.3	-1.01
AST	U/L	173	11.9	167	-0.51	183	0.84	165.9	-0.60
Ca	mmol/L	3.38	0.17			3.54	0.94	3.49	0.60
Chloride	mmol/L	128	6.4	133	0.78	130	0.31		
Chol	mg/dL	217	10.8			216	-0.09	213.3	-0.34
CK	U/L	288.1	30.3	288	0	279	-0.30	295	0.23
Crea	mg/dL	3.57	0.33	4.07	1.52	4.12	1.66	3.59	0.06
DBil	mg/dL	1.32	0.21	1.41	0.43	1.50	0.86	1.29	-0.14
GGT	U/L	88	4.5			78	-2.22	87	-0.22
Gluc	mg/dL	202	10.1	203	0.1	198.1	-0.39	202	0
HDL-C	mg/dL	64	6.8			60.1	-0.57	54.4	-1.41
IP	mmol/L	1.97	0.11			2.12	1.36	1.98	0.09
Iron	µmol/L	51.76	2.59			53.07	0.50	50.52	-0.48
LDH	U/L	343.5	17.2			341	-0.14	348	0.26
LDL-C	mg/dL	136.3	9.9			142.1	0.58	129.7	-0.67
Mg	mmol/L	1.40	0.08			1.45	0.63	1.42	0.26
K	mmol/L	5.87	0.34	5.80	-0.21	5.68	-0.56	5.82	-0.15
Na	mmol/L	157.7	10.8	152	-0.53	155	-0.25	153	-0.43
TBil	mg/dL	3.72	0.33	3.85	0.39	3.70	-0.06	3.22	-1.52
TProt	g/dL	8.30	0.42			7.92	-0.90	8.04	-0.62
Trig	mg/dL	182	9.1			194.2	1.34	187.5	0.60
Urea	mg/dL	87	4.6	85.4	-0.35	92	1.08	86.3	-0.15
UA	mg/dL	8.30	0.42			8.8	1.19	8.0	-0.71

creatine kinase (2O-3O), creatinine (2D-3D), direct bilirubin (1O-2O-3O), GGT (2D-3D), glucose (1D-2D-3D), iron (1D-2O-3O), potassium (1D-2D-3D), total bilirubin (1O-2D-3D), triglycerides (2O-3O), and urea (2D-3D). Good performance was observed also for ALT where TE_{obs} narrowly missed (*) the BV analytical goals for desirable TE at both MDLs (2M*-3M*). Lesser and/or mixed performance among MDLs was observed for the following 3 analytes: AST (2M-3M), LDH (2M-3D), and uric acid (2M-3M). Since AST and uric acid both have satisfactory CV_A (random error), their performance was affected by a high D_A (systematic error) caused by high slope values: AST (y = -0.76 + 1.125x) and uric acid (y = -0.04 + 1.09x). Finally, inacceptable performance was observed for albumin (1F-2F-3F), calcium (1F-2F-3F), magnesium (1F-2F-3M), sodium (1F-2F-3F), and total protein (1M-2F*-3F), mainly due to the highly demanding analytical goals caused by low BV. However, given that calcium, magnesium, sodium, and total protein have been proposed for the BV-derived APS [11], we should

consider that the TE_{obs} for these 4 analytes between Atellica CH 930 and Cobas 6000 c501 is inacceptable.

In clear contrast with desirable analytical goals derived from BV data, CLIA's requirements for analytical performance are generally less demanding (see Table 4, BV-TE_a vs CLIA-TE_a). Thus, the performance of Atellica CH 930 compared to Architect ci4100 achieved or narrowly missed CLIA's requirements for all analytes at all MDLs (see Table 3), except for urea (all MDLs). However, being an analyte with high biological variation, urea is one of those notable exceptions where CLIA-TE_a is uncharacteristically more stringent than BV-TE_a, along with direct bilirubin, GGT, iron, total bilirubin, and triglycerides. In a similar fashion, TE_{obs} between Atellica CH 930 and Cobas 6000 c501 achieved or narrowly missed CLIA-TE_a requirements for all analytes at all MDLs (see Table 4) except for albumin (MDL 1), calcium (MDL 1), and urea (all MDLs). CLIA's less stringent requirements are all the more evident when looking at analytes with low BV where TE_{obs} was inacceptable as per BV-TE_a, but acceptable according to CLIA-TE_a (albumin, calcium, creatinine, magnesium, sodium, total protein). The popularity of both CLIA and BV-derived sets of APS, along with the evident contrast between the two, raise questions about the differences in method performance assessment and limits of acceptability across laboratories [12].

Sigma metrics for assessment of laboratory analytical performance

For the laboratory, it is important to avoid outliers and false positive/negative results. These erroneous results are the manifestation of the laboratory's total analytical error and can be viewed as "defects" generated by the measurement process. Sigma metrics is a technique to quantify (and then minimize) defects, that originated in the manufacturing industry and was first used in medical laboratories in the year 2000 [10]. The "Sigma" in Six Sigma refers to the benchmarking scale upon which all process defects are judged (σ), while the "Six" refers to the ideal performance where the defined acceptable limits of a process can fit six standard deviations [10]. The sigma metric (SM) is calculated using the equation SM = (TE_a% - bias%) / CV% and it can be used to calculate the number of defects per million opportunities (DPMO). For instance, 6σ corresponds to 3.4 DPMO (99.99966% yield), 3σ to 66,807 DPMO (93.3% yield), and 1σ to 691,462 DPMO (30.9% yield) [10]. Thus, most clinical laboratories using sigma metrics require that a minimum of 3σ be achieved. Six Sigma has proved to be a comprehensible, useful and easy-to-use tool for visualization and tracking of analytical performance in the laboratory [10] and for method comparison studies [13]. Moreoever, the simplicity of assessing overall analytical performance with a single, adimensional metric, makes Six Sigma a great benchmarking tool and therefore a good candidate for the worldwide harmonization of clinical laboratories APS. Nevertheless, standing in the way of harmonization is the TE_a component of the SM equation, which greatly varies between laboratories and especially across different countries [10]. As already mentioned, laboratories employ various analytical goals for TE_a [10, 12], the most popular being those derived from BV data or issued by relevant organizations such as CLIA, the College of American Pathologists (CAP), the German medical association for the quality assurance of laboratory medical examinations (RiliBÄK), and the Royal College of Pathologists of Australasia (RCPA). In this study, bias was replaced with the D_A between the test and comparative methods and sigma metrics were computed at all MDLs using CLIA-TE_a.

The SMs computed for Atellica CH 930 vs Architect ci4100 at all 3 MDLs were presented in Table 3. SM values above 3 were observed for

the following analytes: ALT, creatine kinase, creatinine, glucose, and potassium. For AST, SM values below 3 were observed at only one MDL. Sodium and total bilirubin showed lesser performance, with SM values between 2 and 3. Low SM values, between 0 and 2, were observed for urea. For comparison of Atellica CH 930 with Cobas 6000 c501, SMs are shown in Table 4. SM values above 3 were observed at all MDLs for 11 analytes: ALP, amylase, cholesterol, creatine kinase, creatinine, glucose, LDH, magnesium, potassium, total protein, and triglycerides. SM values below 3 were observed at just one MDL for ALT, AST, direct bilirubin, GGT, and iron. SM values lower than 3 at multiple MDLs were observed for the other analytes, with Urea again showing the lowest performance (0σ at all MDLs). However, Six Sigma performance depends on the chosen TE_a value [10, 13], and the results would be quite different for some analytes if BV-TE_a were to be used instead of CLIA-TE_a. Figure 1 was generated in order to better visualize the differences in Six Sigma analytical performance between choosing either BV-TE_a or CLIA-TE_a as the acceptable limits of the measurement process. With only a demonstrative purpose, Figure 1 exclusively shows the charts of Atellica CH 930 vs Cobas 6000 c501 as this comparison covers a wider range of analytes. The type of chart shown in Figure 1 (normalized MEDx chart – normalized method decision chart) enables the simultaneous presentation of multiple methods on the same chart. Performance parameters (imprecision/oX and inaccuracy/oY) are expressed relatively (normalized), as a percentage of TE_a.

A recent performance evaluation of Atellica CH 930 chemistry analyzer was performed at 4 different laboratories across Europe for 13 chemistry analytes [14]. In this study, Atellica CH 930 was compared with the ADVIA XPT systems (one site) and with the ADVIA 1800 systems (three sites) [14]. This robust multicentric study reported that, at the individual-site level, 90% of chemistry assays performed at 4 Sigma or higher (CLIA-TE_a was used) and 100% performed at 3 Sigma or higher, thus concluding in favor of the new Atellica CH 930 analyzer and its use in the clinical laboratory [14]. In our study, when compared with Architect ci4100, Atellica CH 930 reached a 4 Sigma performance or higher at 50% of the investigated MDLs and a 3 Sigma performance or higher at 64% of MDLs (see Table 3). Similarly, when compared with Cobas 6000 c501, Atellica CH 930 reached a 4 Sigma performance or higher at 54% of the investigated MDLs and a 3 Sigma performance or higher at 63% of MDLs (see Table 4).

Analytical total allowable error vs medically allowable error

The practice of establishing APS based on pure analytical rationale and laboratory-centered views is flawed and has its limitations. In contrast, medically allowable error is patient-centered and focuses on clinical outcome. This concept arised in the second half of the 20th century and saw notable contributions from Skendzel, Barnett, and Platt [15]. However, the isolated efforts of several working groups failed to establish a reliable set of medically allowable errors and the little data available were obtained by various methodologies and are rather based on experts' opinion.

While defining the three models for APS derivation, the 2014 Milan consensus placed the model based on the effect of analytical performance on the clinical outcome, at the top of the hierarchy, thus reaffirming the superiority of this patient-centered view of analytical performance in the clinical laboratory [16]. Nevertheless, the lack of an extensive evidence-based database of medically allowable errors, remains a challenge to this day. Such an undertaking would require titanic interdisciplinary efforts starting with clinicians agreeing on medically allowable errors

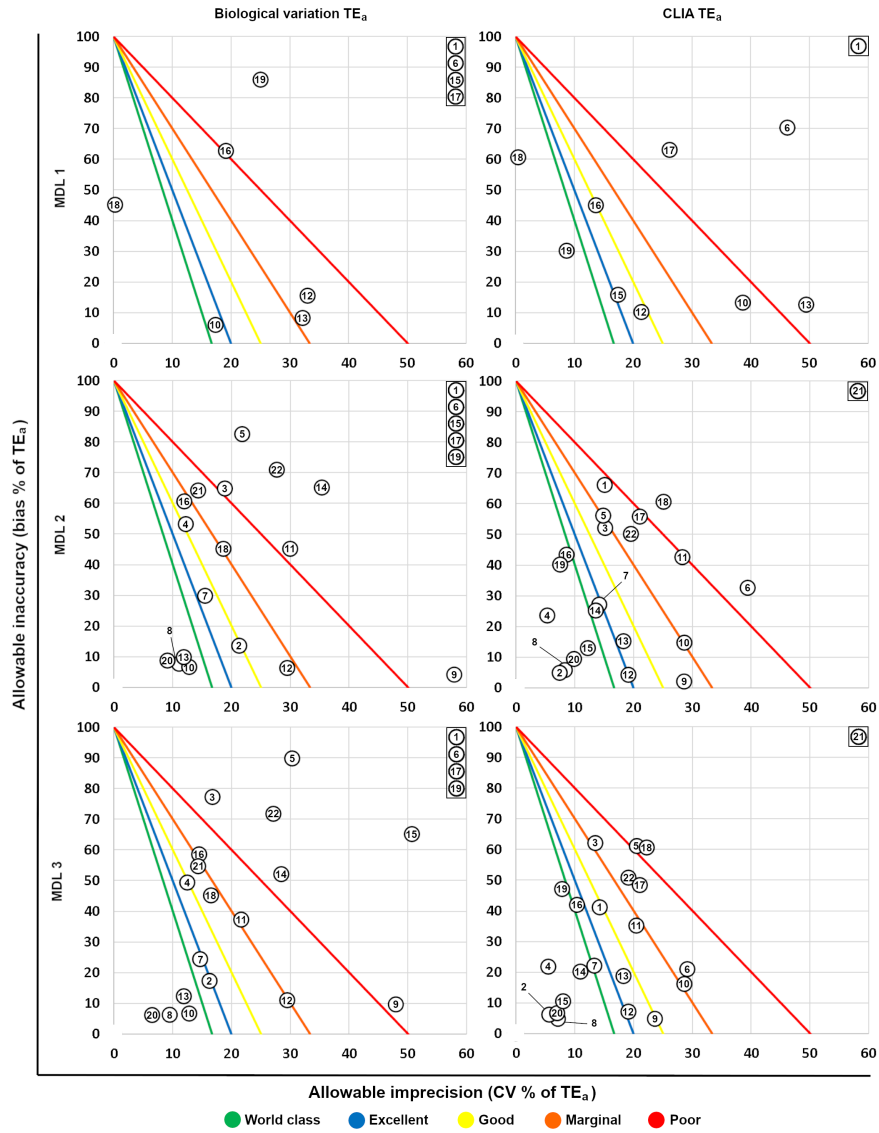

Figure 1. Normalized method decision charts showing Six Sigma performance of the test method (Atellica CH 930) compared with the comparative method (Cobas 6000 c501). In order to visualize the effect of different TE_a values on sigma metrics, charts were generated for each medical decision level (MDL) with either biological variation TE_a or CLIA TE_a as analytical performance limits. Each investigated analyte is represented by a number in a circle. The cassette in the upper-right corner of each graph holds analytes that could not be plotted due to highly inacceptable Six Sigma performances. For enzymes, cholesterol, creatinine, triglycerides, urea, and uric acid, MDL1 was excluded from analysis due to lack of clinical relevance. 1 – Albumin, 2 – Alkaline phosphatase, 3 – Alanine transaminase, 4 – Amylase, 5 – Aspartate aminotransferase, 6 – Calcium, 7 – Cholesterol (total), 8 – Creatine kinase, 9 – Creatinine, 10 – Bilirubin (direct), 11 – gamma-glutamyl transferase, 12 – Glucose, 13 – Iron, 14 – Lactate dehydrogenase, 15 – Magnesium, 16 – Potassium, 17 – Sodium, 18 – Bilirubin (total), 19 – Protein (total), 20 – Triglycerides, 21 – Urea, 22 – Uric acid.

at multiple MDLs, with respect to the inherent particularities of each pathology, medical speciality, and clinical status of the patient. The first steps toward this goal were made for several analytes such as Total/ HDL/ LDL cholesterol, glucose, glycated hemoglobin, albumin, C-reactive protein, cardiac troponins, and hemoglobin [11]. Due to their central and well-defined roles in the decision making of a specific disease or clinical situation, these analytes have been the subject of extensive studies in order to establish cut-off values and multiple decision thresholds for the diagnosis, risk assessment and management of disease [11]. For the same reason, these analytes have already been proposed as candidates for the APS model based on clincal outcome [11]. Hopefully, with the implementation of more evidence-based and universally-accepted cut-off and threshold values, additional steps will also be made toward establishing the medically allowable error at each one of them.

Test and comparative methods vs PT/EQA

All numerical data presented in this study resulted from the comparison of the test method (Atellica CH 930) with the comparative methods (Architect ci4100 and Cobas 6000 c501). The level of agreement between the 3 methods should be acceptable in order for the laboratory to use them interchangeably. Although both comparative methods have already been validated in our laboratory and are part of a permanent PT/EQA program, the method comparison methodology chosen here has one notable limitation, that is, the inaccuracy of the test method remains unknown. Therefore, Atellica CH 930 was enrolled for a one-time participation in the PT/EQA program, along with the two comparative methods (see Table 5). All 3 chemistry analyzers performed well, with Z scores between -2 and 2 for all investigated analytes, except for Atellica's GGT which we have already reported as being problematic throughout the study. Moreover, apart from GGT, there was no investigated analyte where the difference between Atellica's Z score and the Z score of any of the two comparative methods, was greater than 2. While for the uneducated eye these results may seem apparent proof of agreement between methods, one should not jump to conclusions, as these satisfactory PT/EQA results do not necessarily imply that the test and comparative methods are comparable and could be used interchangeably. This is because in a PT/EQA, the analytical performance acceptance limits are defined by a single metric, that is the Z score, whose calculus formula is so that an important inaccuracy can be obscured by a high SD/CV. This heavy reliance of Z score on SD/CV is the more relevant since high SDs/CVs generally occur in such PT/EQA global results, due to the heterogeneity of the participants. For instance, the CV_I for sodium is 0.5%, which means the desirable CV_A of the method should be less than 0.25%. In stark contrast, the global results of the above-mentioned PT/EQA show a target value of 157.7 mmol/L and a SD of 10.8 mmol/L (see Table 5), that is a CV of 6.87%. Therefore, while the limits of acceptance for the measurement process based on biological variation data are computed using a CV of 0.25%, the analytical performance in a PT/EQA is computed using a CV of 6.87%. This is why Atellica's sodium method was proven not comparable with either comparative method (see Tables 2 and 3), while all 3 analyzers performed well in the PT/EQA, with similar Z scores (see Table 5, sodium). In short, heterogeneity among methods is expected in PTs/EQAs, but should not be tolerated within a laboratory with multiple analyzers, at least not when the laboratory's methods are used interchangeably/ alternatively for patient evaluation.

Conclusions

Performance of the newly introduced Atellica

CH 930, as compared with the already established Architect ci4100 was acceptable or nearly acceptable at 82%, 95%, and 64% of the 22 investigated MDLs across 9 analytes, according to BV-TE_a, CLIA-TE_a and CLIA-calculated Sigma metrics, respectively. Similarly, performance of the newly introduced Atellica CH 930, as compared with the already established Cobas 6000 c501 was acceptable or nearly acceptable at 61%, 93%, and 63% of the 54 investigated MDLs across 22 analytes, according to BV-TE_a, CLIA-TE_a and CLIA-calculated Sigma metrics, respectively. However, method comparability should not be evaluated by a "one size fits all" approach as some analytes require different criteria of acceptability, ideally based on medically allowable error and clinical outcome.

There are several models for method comparison studies, all having their strengths and weaknesses. Also, despite recent steps toward standardization of analytical performance goals in the clinical laboratory, various schools of thought remain highly influential among laboratory professionals. These, along with the great variability of quality specifications required by different countries, regulatory agencies or PT/EQA providers, represent an important barrier in the way of harmonization, and significantly contribute to the perpetual lack of regard for evidence-based and patient-centered practices in the clinical laboratory.

Abbreviations

Alb – albumin
ALP – alkaline phosphatase
ALT – alanine transaminase
Amy – amylase
APS – analytical performance specifications
AST – aspartate aminotransferase
BV – biological variation
Ca – calcium
CAP – the College of American Pathologists
Chol – cholesterol
CK – creatine kinase
CLIA – Clinical Laboratory Standards Institute
Crea – creatinine
CV – coefficient of variation
CV_A – coefficient of analytical variation
CV_G – coefficient of inter-individual biological variation
CV_I – coefficient of intra-individual biological variation
D – desirable
D_A – analytical difference between methods (substitute for bias)
DBil – bilirubin (direct)
DPMO – defects per million opportunities
EFLM – European Federation of Clinical Chemistry and Laboratory Medicine
EQA – external quality assessment program
F – inacceptable
GGT – gamma-glutamyl transferase
Gluc – glucose
HDL-C – high-density lipoprotein cholesterol
IP – inorganic phosphate
ISO – International Organization for Standardization
K – potassium
LDH – lactate dehydrogenase
LDL-C – low-density lipoprotein cholesterol
M – minimum
MDL – medical decision level
MEDx chart – method decision chart
Mg – magnesium
Na – sodium
O – optimum
PT – proficiency testing
QC – quality control
RCPA – the Royal College of Pathologists of Australasia
RiliBÄK – the German medical association for the quality assurance of laboratory medical examinations
SD – standard deviation
SM – sigma metric
TBil – bilirubin (total)
TE – total error

TE_a – total error allowable
TE_{obs} – total error observed between methods
TProt – protein (total)
Trig – triglycerides
UA – uric acid

Acknowledgements

We would like to thank our colleagues Andreea Truță and Floredana Șular for their technical assistance with the Atellica CH 930 chemistry analyzer. This study was supported by Sante International SA, the official distributor in Romania for Siemens IVD products.

Authors' contributions

IG, KP, IBM: conceptualization, investigation, methodology, validation, visualization, writing (original draft preparation).
ORO: conceptualization, methodology, validation, supervision, writing (original draft preparation).
MD: conceptualization, methodology, resources, supervision, writing (review and editing).

Conflict of interest

The authors declare that there is no conflict of interest.

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