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A category 1 EQA scheme for comparison of laboratory performance and method performance: An international pilot study in the framework of the Calibration 2000 project

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ABSTRACT

Introduction: In the modern healthcare service, patients receive care in multiple hospitals and healthcare settings. Therefore, harmonization of results from different methods and instruments, both between and within laboratories, is of the utmost importance. The present pilot study aims to test the use of a Category 1 EQA scheme across four European countries by assessing the current level of equivalence of test results.
Method: This work was led by the Dutch External Quality Assurance Scheme SKML and involved 28 laboratories from three regions in the UK, Spain and Portugal, and 120 laboratories from The Netherlands. A set of six commutable samples, targeted with reference methods, were circulated and 18 biochemistry analytes were tested.
Results and conclusions: The Total Error (TE) score, defined as the probability (%) that results are within the Total Error Acceptable (TE_A) limits, for the eighteen analytes was calculated. Our data show that there is a need for further harmonization of laboratory data, in particular for electrolytes (calcium, chloride, magnesium, sodium), enzymes (ALT, amylase, AST, LDH), lipids (HDL-cholesterol), and for substrates (creatinine, total protein). Lack of performance consistency between instruments was seen for most analytes. The lack of harmonization is still present despite manufacturer claims of established traceability.

1. Introduction

Most efforts in the management of analytical quality in clinical chemistry and laboratory medicine have focused on the reduction of within-laboratory variation and the assessment of between-laboratory variation. In recent years the importance of minimizing bias, both between laboratories and within a laboratory, has become paramount. Patients are frequently treated by a team of physicians rather than one, often extending across several healthcare settings and making use of information from several laboratories. In monitoring patients during treatment, the absence of bias from one measurement to the next, together with minimum imprecision is essential. Calibration and harmonization of results from different analyzers, both between and within laboratories, and the continuity of such harmonization in time are, therefore, of the utmost importance. Small assay biases may have a large impact on patient classification and on the number of patients to be treated, particularly for assays for which cut-off values are used. This is true, for example, in lipid and lipoprotein analyses, in which stringent cut-off values are used throughout the world for the prevention and treatment of cardiovascular diseases. It is also true for creatinine in the estimation of renal function and for human growth hormone in hGH deficiency.

The American Association for Clinical Chemistry (AACC) conference in October 2010 focused on the roadmap [1] to reach harmonization for analytes for which no reference system is defined. However, even for analytes for which such systems exist, standardization is often lacking. The process is defined as standardization if the analyte is clearly defined and reference method and standards exist. Harmonization is confined to describe processes where one or more of these elements are missing. External Quality Assessment (EQA) schemes should play a central role in achieving harmonization and in trueness verification. It is widely

Abbreviations: EQA, external quality assessment; TE, total error; IVDD, in vitro diagnostic medical devices directive.

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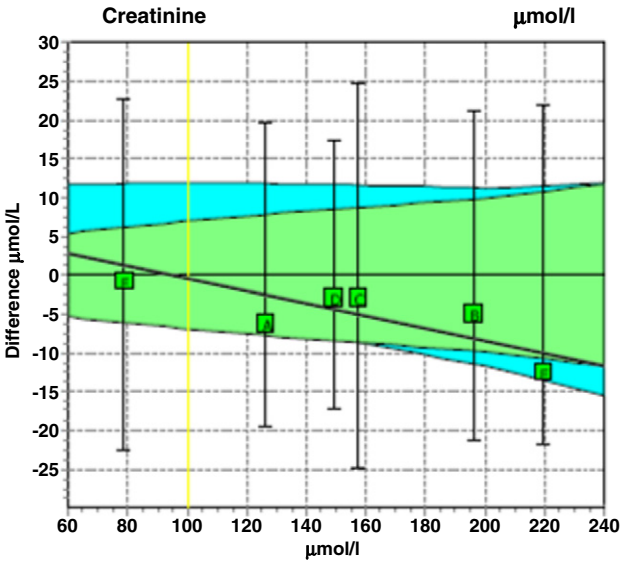

Sample	You	Ref	Cons	CV	Meth	Anal
A	120	126.3	126	5.1%	127	126
B	191	196.0	196	3.6%	196	192
C	154	157.0	159	5.2%	162	139
D	146	149.0	150	3.8%	162	149
E	207	219.4	218	3.3%	218	215
F	78	78.7	84	9.1%	82	80
Total	149	154	156	4.2%	156	151
Precision	1.8%			2.7%		
Count	6		754		261	60
Outliers	0		42		14	2

Regression line Y=7 + 0.920X
Statistics valid for your
Method: Alk. Picrate, kinetic with compensation
-group: Jaffe
Analyser: Olympus AU2700

Fig. 1. Example of a difference plot of the Combi scheme. The green area is TE_A tolerance area around the reference method target. The blue area is state of the art tolerance limit around the consensus mean value. The green squares are your results for samples A–F. The black line is your regression line. Vertical bars indicate ± 3SD between labs. Precision is within-lab CV. Anal. is your analyzer.

accepted that we need commutable materials [2,3], reference method target values and tolerance limits based on the biological variation concept [4–6]. EQA schemes having these characteristics have been denoted as Category 1 schemes [7]. The importance of using this concept in EQA schemes was stressed recently in several sessions during the Bio-Rad Convocation of Experts on Laboratory Quality 2010 in Bardolino, Italy [8] again in 2011 in Salzburg, Austria. In the Calibration 2000 project of the Dutch NEQAS organizer SKML, this was achieved for several analytes [9–15]. The In Vitro Diagnostic Medical Devices Directive (IVDD) requires traceability to reference systems [16]. These systems are defined for a number of analytes. For these analytes trueness verification is possible and harmonization is within reach.

The Calibration 2000 project in The Netherlands produces materials [9–15] for general clinical chemistry, proven to be commutable in conformity with the Clinical and Laboratory Standards Institute (CLSI) C53A [17]. The samples are targeted with reference methods, undertaken in either The Joint Committee for Traceability in Laboratory Medicine (JCTLM) listed Reference laboratories or in International Federation of Clinical Chemistry and Laboratory medicine (IFCC) network laboratories, if available, and results are processed in the Combi EQA scheme [11–14] in which participating laboratories assay several samples covering the clinically relevant concentration range. The scheme uses the biological variation based Total Error allowable (TE_A) at the desirable level as tolerance limit. Harmonization of minimal acceptable performance criteria among EQA organizers is desirable [18].

The present study is a pilot study. It aims to test the use of a Category 1 EQA scheme across the countries, UK, Spain, Portugal and The Netherlands, and to compare in a pilot study the performance of the participating laboratories and the methods used. The results of the pilot study are seen as a preliminary view of the role of category 1 EQA to improve harmonization in Europe.

2. Methods

In the SKML Combi scheme, 24 samples are analyzed for general chemistry parameters in the course of a year, i.e. at a frequency of one sample per 2 weeks. For lipids, a separate dedicated batch of 24 samples is used. The samples are prepared according to exactly the same protocol as previously prepared samples which were proven to be commutable [9–15]. In short, two master samples are prepared, one from pooled normal human left over sera and one from pooled normal human sera, spiked with abnormal pools, minerals, recombinant human enzymes and human albumin. The master pools are mixed in ten proportions thus obtaining 12 concentration levels. After dispensing, vials are frozen at −84 °C. Previously prepared samples according to this procedure were repeatedly proven to be commutable, whether master, spiked or mixed samples. Throughout the years commutability has been monitored by including a native, single donation spy-sample that is prepared according to CLSI C37-A2. Concentrations cover the range of clinical interest. The samples are targeted by JCTLM listed laboratories for electrolytes and substrates, and by IFCC or CDC network laboratories for enzymes and lipids. Information on reference methods and laboratories used is provided as supplementary data. Biological variation based tolerance limits are used (TE_A desirable).

Thirty laboratories from three European countries participated in this study in addition to 120 regularly participating Dutch SKML EQA Combi scheme. Ten laboratories each participated from the UK, Spain (one lab with two procedures for all analytes, except for lipids) and Portugal. The UK laboratories' inclusion in this study was solely based on expression of interest from laboratories that had received an invitation to participate. The authors have had no previous knowledge of the analytical performance for the participating laboratories.

The Spanish and the Portuguese laboratories were selected from those laboratories falling within the 20th percentile of the target deviation of their national EQA schemes. However, the participating laboratories range from small independent health care laboratories to large laboratories serving teaching hospitals, a mix of size and analytical platforms, which reflects the same distribution in each country.

A set of six samples for general chemistry and a set of six samples for lipids frozen at −80 °C, were transported on dry ice to a central laboratory in each of the three countries, and stored at −80 °C. The frozen samples were distributed on dry ice from the central laboratory to the participating laboratories. Samples arrived thawed in two Portuguese laboratories and these were discarded. Since most of the laboratories

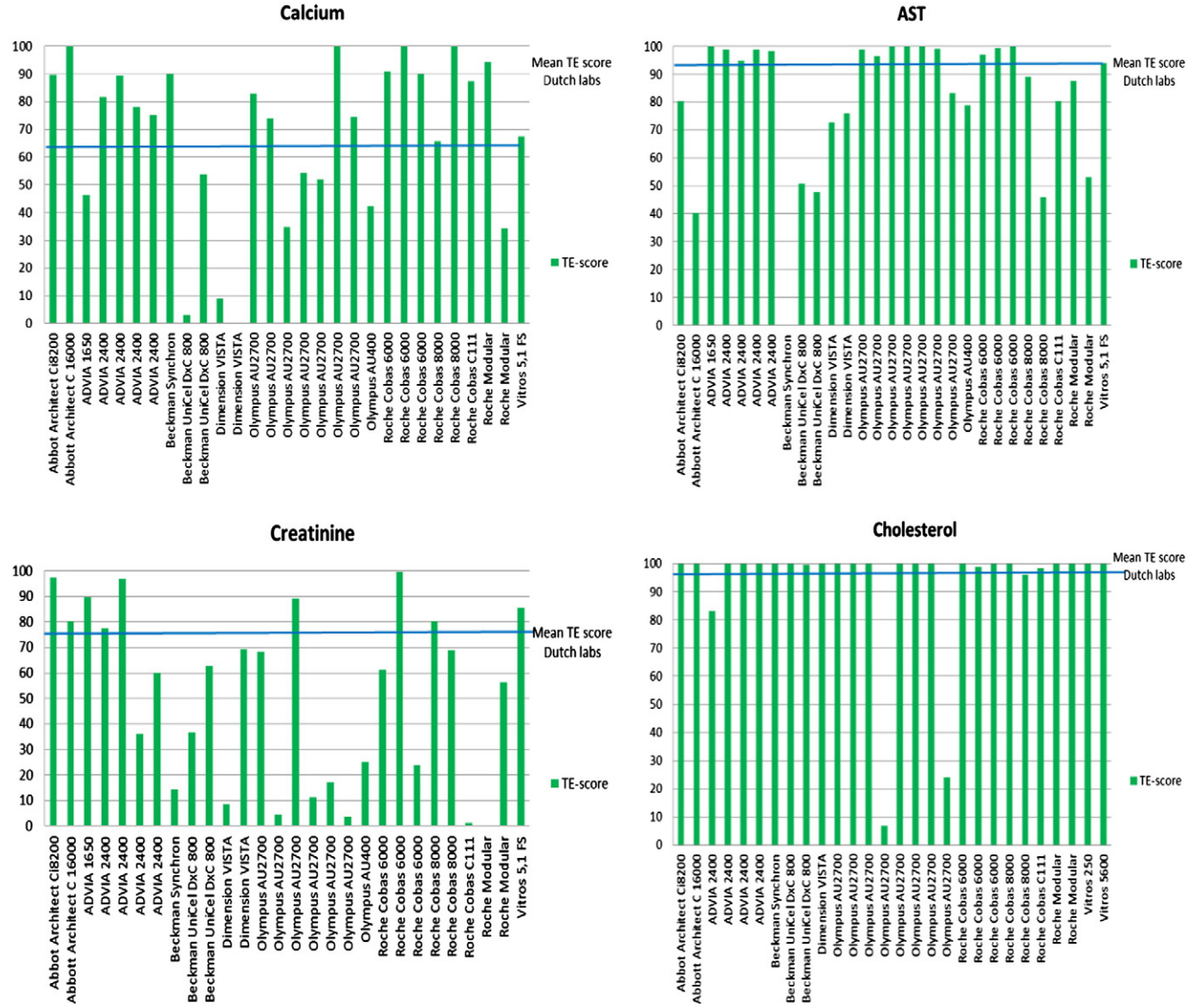

Fig. 2. TE scores per analytical platform for 28 laboratories. TE scores vary considerably within users of instruments from the same manufacturer. The blue line represents the average TE score for The Netherlands laboratories.

did not have a −80 °C freezer available, the laboratories were asked to analyze the samples as soon as possible after receipt or to store the samples at −20 °C and analyze them within 1 week (the period of stability, as determined by the sample provider). The Dutch participants received their sets of samples at the start of the year and kept them at −80 °C until analysis.

Laboratories were asked to analyze 18 analytes for which target values were obtained from reference laboratories using internationally recognized reference methods and reference materials. They comprised:

5 electrolytes: calcium, chloride, magnesium, potassium, sodium;
6 enzymes: ALT, amylase, AST, CK, Gamma-GT, LDH;
2 lipids: cholesterol, HDL-cholesterol; and
4 substrates and a formula: creatinine, eGFR (F, 55y, Caucasian), glucose, total protein, uric acid.

The laboratories were asked to use their routine methods with no adaptations compared to routine practice. The laboratories reported their results, methods, and the instruments used. The laboratories in the UK and Spain mostly reported SI units, while the laboratories in Portugal mostly reported conventional units. Conventional units were converted to SI units by the organizer of the pilot study. In a few cases the reported results were not in agreement with the reported units and corrections were made. One Spanish laboratory reported creatinine in SI units after converting from conventional units (mg/dL), but using a wrong converting factor. This mistake did not affect the eGFR results, because a formula for creatinine values in mg/dL was used. Results for creatinine of this laboratory were discarded. Four Spanish laboratories used a pancreatic amylase assay instead of total amylase and their results were discarded.

2.1. Statistical methods

In the Combi scheme report, each round and for each analyte the individual laboratory data is displayed as a difference plot of the six results compared with the reference method values (Fig. 1). A tolerance area is constructed around the reference values based on the TE_A (desirable) limit [4,5]. In the Combi scheme the desirable TE_A limit ($TE_A = 1.65 \times 0.5 \times CVw + 0.25\ \sqrt{(CVw^2 + CVb^2)}$) is used rather than the minimal or optimal limits as alternative approaches suggested by Fraser [6]. Linear regression is calculated from the laboratory results against the consensus method group mean value. As the samples are

Table 1
TE_A, average TE scores, and %TE scores ≥95%.

Analyte	TE_A	NL	NL	PT	PT	ES	ES	UK	UK
	%	Av TE score (%)	% TE sc >95%	Av TE score (%)	% TE sc >95%	Av TE score (%)	% TE sc >95%	Av TE score (%)	% TE sc >95%
Calcium	2.4	64	18	65	0	64	27	73	10
Chloride	1.5	64	16	39	0	81	30	72	30
Magnesium	4.8	61	28	57	13	67	22	79	30
Potassium	5.8	94	77	89	63	97	82	97	70
Sodium	0.9	47	5	26	0	42	9	47	20
ALT	14.6	93	84	80	63	83	45	87	40
Amylase	26.3	85	77	53	43	59	40	90	90
AST	15.2	94	82	76	38	88	64	79	30
CK	30.3	99	96	83	63	98	91	100	100
Gamma-GT	22.2	97	93	83	75	90	91	89	80
LDH	11.4	84	76	24	13	63	55	9	0
Cholesterol	8.5	97	87	91	88	90	90	98	90
HDL-cholesterol	11.1	83	55	100	100	74	60	82	60
Creatinine	8.9	76	41	52	13	33	0	65	20
eGFR (F, 55y, Caucasian)	8.9	66	47	62	33	64	27	57	25
Glucose	7.2	93	67	88	63	92	73	96	90
Total protein	3.4	58	28	53	13	77	36	64	30
Uric acid	12.4	98	96	93	63	99	91	99	100
Overall		**81**		**67**		**75**		**77**	

measured on different days, the residual SD of the regression line represents the within-laboratory SD_{WL}. The difference between the mean of the six laboratory results and the average of the six reference values is the bias. Using SD_{WL} at the average concentration of the six samples the probability is estimated that the laboratory results will be within the TE_A tolerance area. This probability is the percentage of the density function (the broadness of which is defined by SD_{WL}) around the laboratory bias that is within the TE_A area. The TE score equals this percentage. By definition TE includes bias and imprecision. Causes of lower TE scores could be significant positive or negative bias, or a large within-laboratory SD. Increasingly, minimal acceptable performance criteria based on the biological TE_A concept are being utilized within laboratories. The level of acceptance is defined by Fraser [6] as minimal, desirable or optimal. In the SKML scheme, performance is considered to be acceptable if the results of a laboratory are within the desirable TE_A area with a probability of 95%.

For each analyte the TE scores of the individual laboratories of the UK, Spain and Portugal were plotted against and compared with the average TE score of the Dutch laboratories. For each analyte, the individual laboratory results sorted by instrument were also plotted. Average TE-scores and the percentage TE scores >95% were calculated for the four countries.

3. Results

Fig. 1 shows an example of a difference plot of the six results of a single laboratory for creatinine. The green area represents the TE_A area around the reference values. The blue area is the state of the art tolerance area for the method group consensus values. The blue area in this case shows a positive deviation from the reference values in the lower concentration range as is expected for the Jaffe method group. The plot shows your regression versus the TE_A tolerance area, versus your method group state of the art tolerance area, and the method group state of the art (blue area) versus the TE_A green area. The within-lab CV is calculated as the residual CV of the regression line. The TE score for this laboratory equals 97%. In the SKML Combi concept a TE score of 95% is considered acceptable. Next to the difference plot a table is reported to the participants summarizing the results.

The reference values of the six general chemistry and the six lipid samples for the selected 18 analytes, arranged by analyte group (electrolytes, enzymes, lipids, substrates), the standard uncertainties, the reference methods and the reference laboratories, are provided as supplementary data.

Fig. 2 shows an example of TE scores of individual laboratories for four analytes sorted by instrument. With the exception of cholesterol, the other three analytes (AST, calcium and creatinine) show inconsistency of TE scores even within a single analytical platform. This lack of performance consistency between instruments and within instrument was seen for all electrolytes, and enzymes (data not shown), and is in agreement with previously reported results [19].

Table 1 presents the TE_A values [5], average TE scores of the four countries and the percentage of laboratories that had a TE score ≥95%. The Netherlands' TE score was the highest at 81%, followed by the UK's at 77%, Spain's at 75% and Portugal's at 67%.

TE scores for all electrolytes, except potassium, in all of the four countries are low (Table 1, Fig. 3). Urgent improvement in harmonization is needed particularly for calcium, chloride, magnesium and sodium where less than 30% of the true TE scores were above the 95% criterion. The same observation was maintained for the enzymes. The highest TE score was seen for CK and GGT. However, a wide variation in TE score within and between countries has been recorded for ALT, AST and amylase. For amylase, laboratories show two types of TE scores, either TE above 95% or a very low score often zero. Calibration to a method different from the reference method is the main cause of low TE scores. Four Spanish laboratories analyzed pancreatic amylase instead of total amylase. The results of these laboratories were removed as they were testing a different analyte.

With the exception of The Netherlands, Portugal, Spain and the UK showed poor TE scores for LDH with many scores of zero obtained and 19 out of 28 laboratories having scores below 10% (Fig. 4). This is due to the fact that a number of laboratories are using a pyruvate to lactate method rather than the IFCC reference method utilizing lactate as a substrate. These methods vary by a factor of 2 and will therefore have a profound effect on bias, which explains the poor TE score for these laboratories.

In general the TE scores for enzymes in The Netherlands are higher, and a larger percentage of the laboratories score above the 95% limit, as compared to the other countries.

For cholesterol the average TE scores were above 90% and over 85% of the laboratories satisfied the criterion of TE score ≥95% (Table 1 and Fig. 5). However, the HDL methods have not matched the consistently high performance seen with cholesterol. While the Portuguese achieved a TE score of 100% for all the participating laboratories, other countries demonstrated a wider variation in performance (Fig. 5).

For creatinine (Table 1 and Fig. 6) low average scores were obtained as well as low percentages of TE scores ≥95%, indicating that many

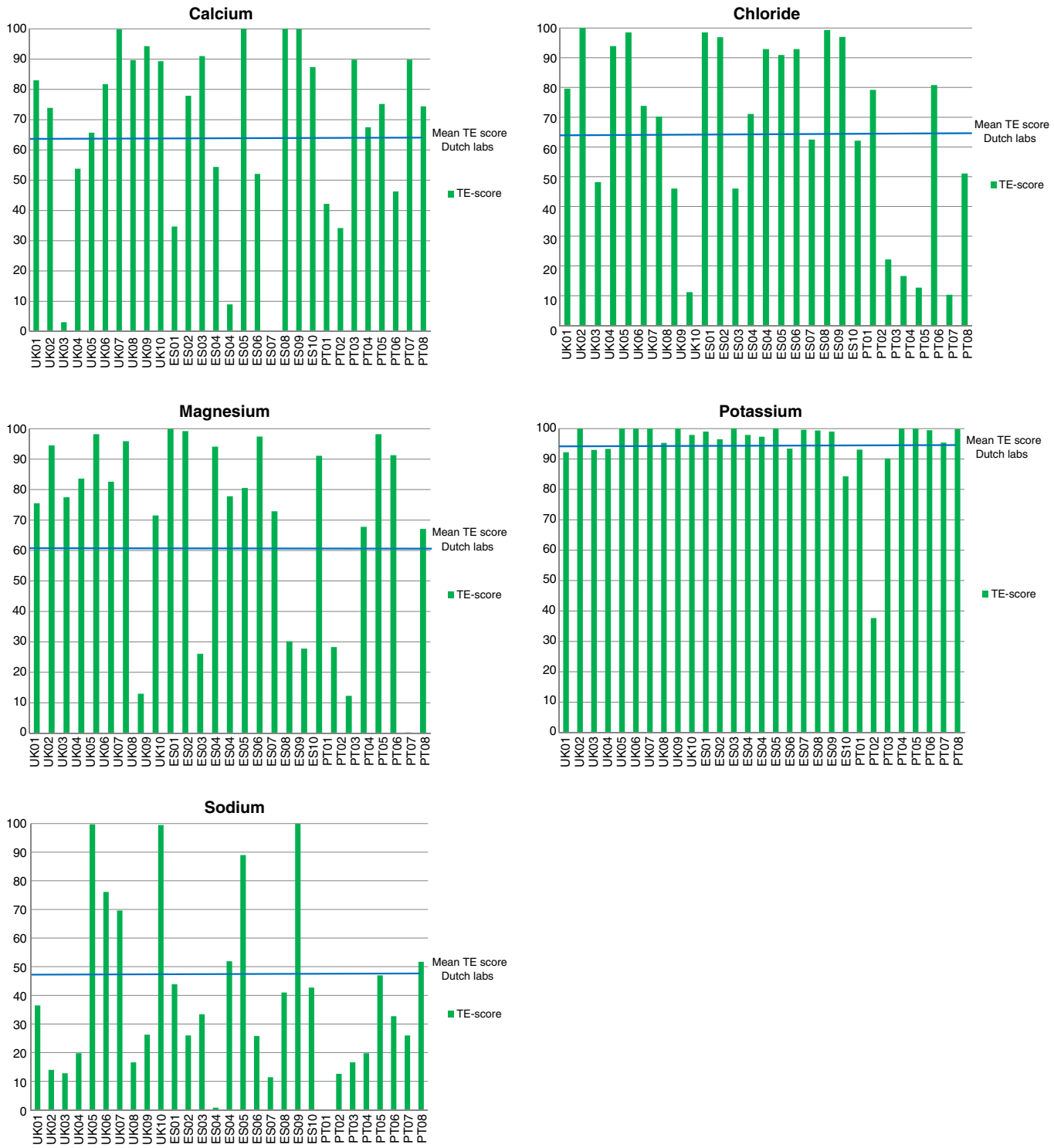

Fig. 3. Electrolytes, TE scores of individual laboratories per country (region). The blue line represents the average TE score for The Netherlands laboratories.

laboratories failed to achieve minimal acceptable performance. Instruments showed widely varying results. The Jaffé methods had the lowest score (data not shown), which is in agreement with previously reported results [20].

This has a consequence for eGFR, which was calculated using different formulae the 23 participating laboratories. Average TE scores were below 70% and less than half of the laboratories attained a TE score of 95%.

Glucose and uric acid met the acceptable performance criterion of a TE score >95% for the majority of participating laboratories in the four countries.

The data for Total Protein indicated unsatisfactory performance, with average TE scores well below 95% and more than 70% of the laboratories failing the 95% criterion. Fig. 6 illustrates the widely varying individual scores.

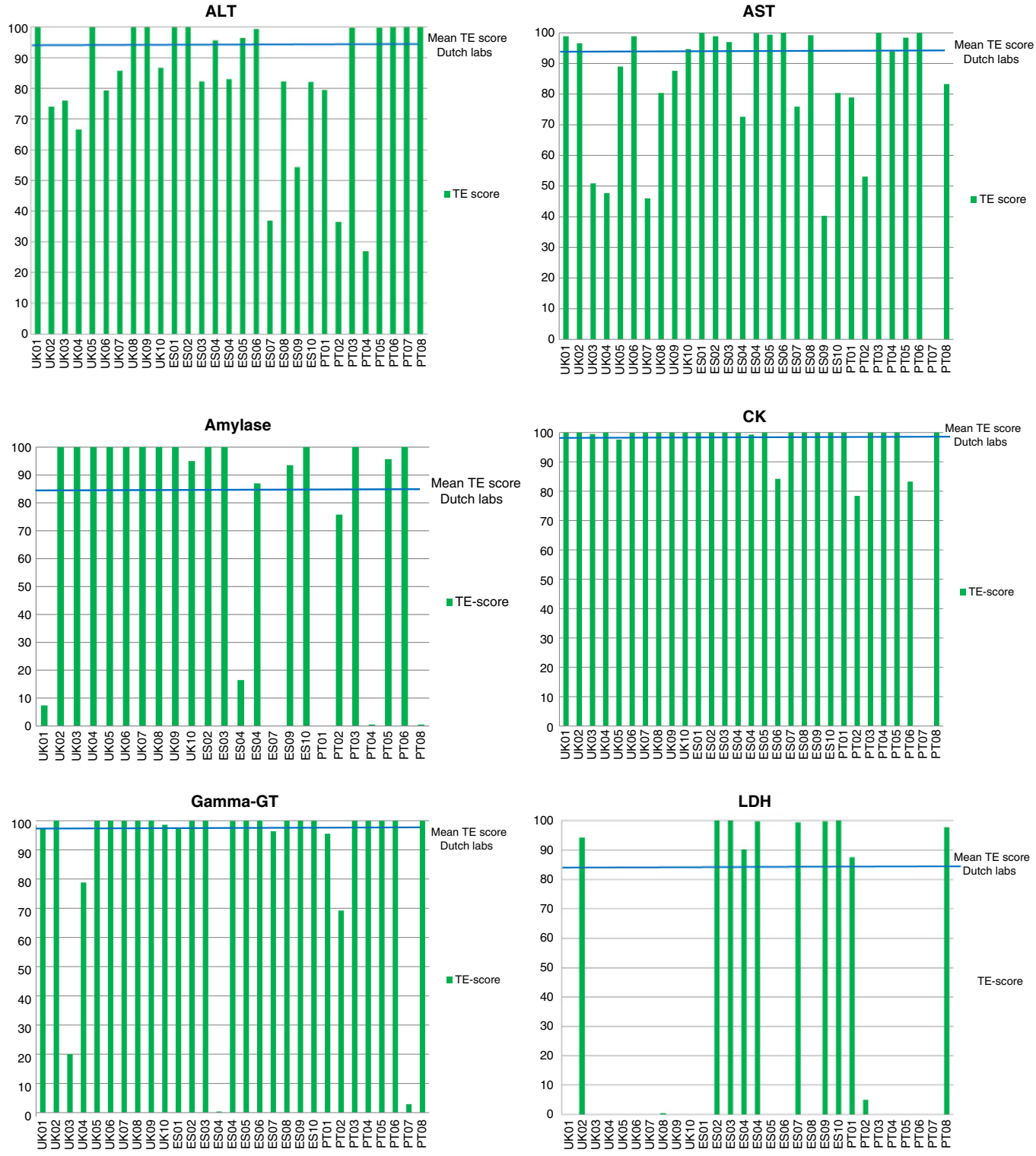

Fig. 4. Enzyme TE scores of individual laboratories per country (region). The blue line represents the average TE score for The Netherlands laboratories.

4. Discussion

In the European Union, the IVDD 98/79/EC [21] demands traceability of test results to a higher order reference material. This means that the results for each instrument type should be comparable with reference method results. However, this pilot study shows considerable within instrument and between laboratory variations in TE scores. Although the number of participating laboratories from outside The Netherlands is small, they may be considered as representative of countries because they are positioned within the 20th percentile of the target deviation distribution in their national EQA schemes (Spain, Portugal) or are representative for a whole region (Yorkshire, UK).

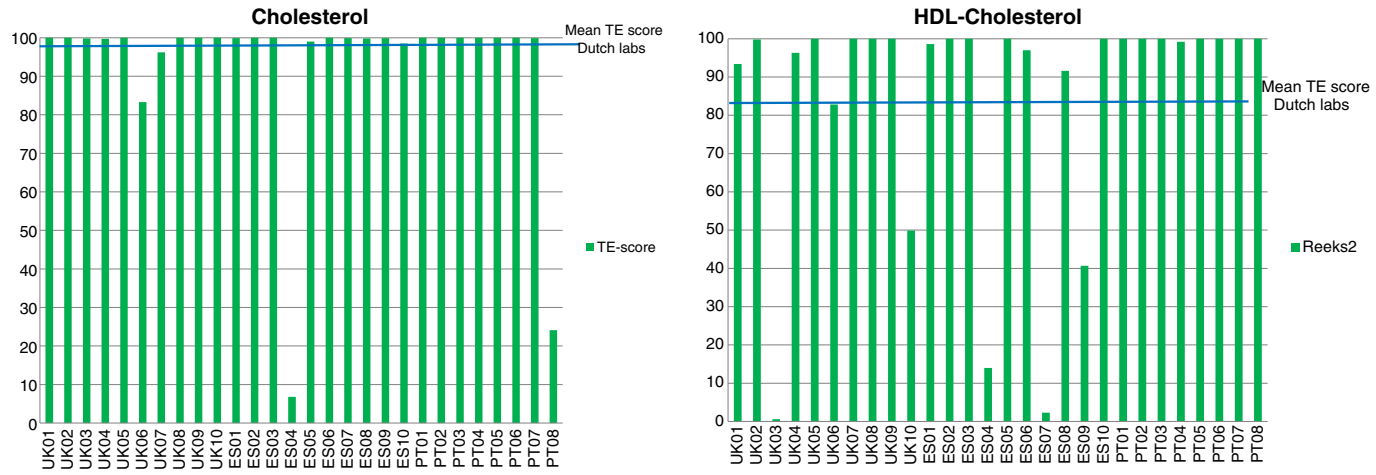

Fig. 5. Lipid TE scores of individual laboratories per country (region). The blue line represents the average TE score for The Netherlands laboratories.

Jansen et al. showed in 2006 [19] that large variation between methods and analytical platforms exist for the enzymes and that in many cases there is a lack of traceability and harmonization despite the IVD requirements. This study shows little improvement with enzyme assays, especially for amylase [22] and LDH [22,23]. Laboratories are still using methods that do not comply with the IFCC recommended methods (e.g. trioside substrate for amylase or pyruvate substrate for LDH) and this should be discouraged. Furthermore, in some enzyme methods e.g. ALT/AST, variation in TE score has been seen within the users of the same instrument. In our view, this finding may be attributed to the use of ALT/AST methods lacking the addition of the co-enzyme pyridoxal phosphate in the reagent pack. The co-enzyme has a variable and marked effect on transaminase activity, especially with AST, which cannot be corrected by calibration. Despite the IFCC recommendations [24,25], manufacturers still market method versions lacking pyridoxal phosphate. Methods that do not contain the co-enzyme cannot be considered traceable. Another source of discrepant (biased) results has been observed for a Spanish laboratory (data not shown) for AST and gamma-GT when a routine calibrator was traceable to a non-commutable reference material, whereas results were correct when correctly calibrated and traceable to a reference method. In these examples, the manufacturers can play a pivotal role in paving the road to harmonization, simply by removing undesirable methods from the market.

The variation in the TE scores in UK, Spain and Portugal cannot be explained by the different analytical platforms. Fig. 2 shows examples of TE ranges for the instruments used. Within the same instrument TE scores vary greatly, in some cases from 0% to 100%. One explanation for this is the production by manufacturers of more than one assay on the same platform for some analytes, e.g. LDH lactate to pyruvate and pyruvate to lactate, and AST/ALT with and without pyridoxal phosphate P5P, whilst traceability demands the IFCC recommendations. Other reasons could be bias due to the use of different factors, different calibrators, and varying within-laboratory SD. The bias could be proportional, constant or mixed i.e. varying across the concentration span. Inspection of the data shows that in many cases all of these errors are present. E.g. for creatinine many laboratories use the non-compensated Jaffé kinetic method, giving a positive bias at low concentration level. Laboratories need to show acceptable precision as well as bias to attain a TE score of 95%. Lack of commutability of the reference material used for routine calibrator traceability has been seen as a major reason for biased results in the Spanish group. The same happens for magnesium and sodium. Our data shows that urgent improvement in harmonization is needed particularly for calcium, chloride, magnesium and sodium where less than 30% of the TE scores were above the 95% criterion. Harmonization of analytes that have a narrow biological variability can be improved by sharing a common but clinically relevant analytical goal [26]. Examples of different kinds of errors made are provided as supplementary data.

All the analytes in this study have a well-defined reference measurement procedure and traceability chain, yet considerable analytical variation has been seen. This suggests that standardization alone is not sufficient to guarantee production of comparable results. Traceability of a method to higher order reference measurement methods does not necessarily mean that the field method results are identical to the reference method results. It requires a functional relationship between the method and the reference method and reference material. From a patient's perspective, results from different laboratories should not only be traceable to the reference method, i.e. show a defined functional relationship to the reference method, but should in addition be standardized, i.e. give equivalent results to the reference method. The Calibration 2000 project [9–11,15] and the present results show that harmonization is achievable for some analytes as shown in the Category 1 EQA scheme. The Combi scheme in its present form, using commutable samples, value assigned with reference methods, and having biological variation-based tolerance limits, has been operational in The Netherlands for over 7 years. In an attempt to replicate The Netherlands experience with larger numbers of laboratories, the Portuguese, the Spanish and the UK EQA scheme organizers are considering collaboration in at least one round per year in the SKML Combi scheme.

Since 2005, the Spanish Society of Clinical Chemistry (SEQC) have undertaken an educational task in recommending the use of biological variation based as tolerance limits and these criteria are included in the participants' reports. Despite this, the group's results are not as satisfactory as they should be. This is mainly due to the lack of method harmonization and traceability and not to a different culture in quality monitoring practices.

5. Conclusion

The IVDD 98/79/EC demands traceability of test results to a reference system, if available. Our data show that there is a need for further harmonization of laboratory data, in particular for electrolytes (calcium, chloride magnesium, sodium), enzymes (ALT, amylase, AST, LD), lipids (HDL-cholesterol), and for substrates (creatinine, total protein). Lack of performance consistency between instruments was seen for most analytes. The variation in the TE scores cannot be explained by the

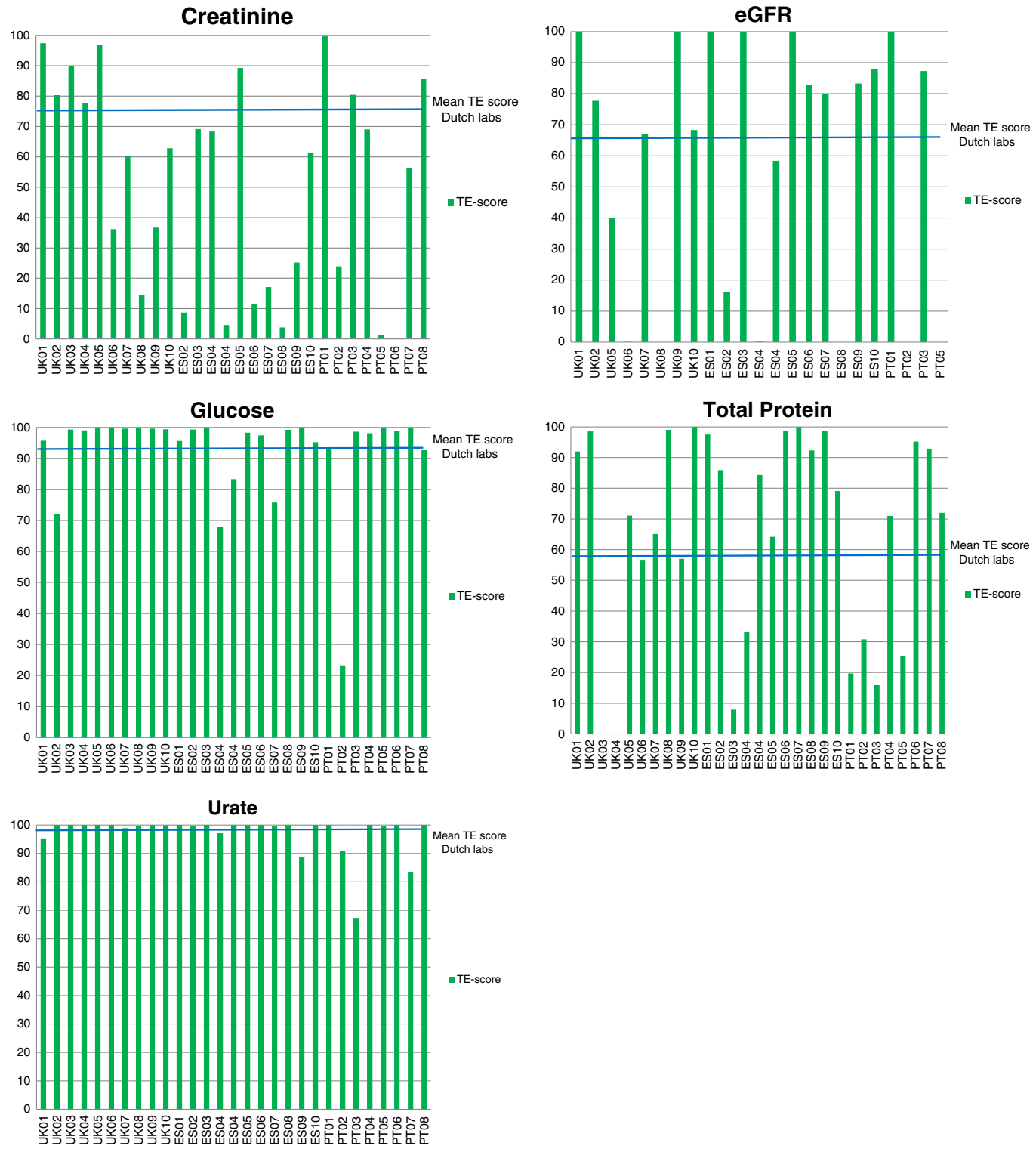

Fig. 6. Substrate TE scores of individual laboratories per country (region). The blue line represents the average TE score for The Netherlands laboratories.

different analytical platforms. Within the same instrument TE scores vary greatly, in some cases from 0% to 100%. Lack of harmonization is still present, despite manufacturers' claims of established traceability. Current data shows that the standardization of methods is insufficient to result in complete consistency in reporting of laboratory results and needs to be followed by harmonization of the methods and practices.

Declarations

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Ethical approval: not required
Guarantor: Dr Rob Jansen

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.cca.2013.11.003.

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