

Category 1 external quality assessment program for serum creatinine

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Background: The Commission of Analytical Quality and the Committee of External Quality Programs of Spanish Society of Laboratory Medicine (SEQC) in collaboration with the Dutch Foundation for the Quality organized the first national category 1 External Quality Assessment Programs (EQAP) pilot study. The aim is to evaluate the standardization of serum creatinine measurements in the Spanish laboratories through a category 1 external quality assurance program with commutable material and reference method assigned values.

Methods: A total of 87 Spanish laboratories were involved in this program in 2015. Each day a sample control was measured by duplicate during 6 consecutive days. Percentage deviations and coefficients of variation obtained were compared with quality specifications derived from biological variation.

Results: A total of 1044 creatinine results were obtained. Laboratories were coded in 11 different method-traceability combinations. Only enzymatic methods get all results within the acceptability limits.

Discussion: To participate in a category 1 EQAP is a valuable tool to assess the standardization degree in our country; a big effort should be made to promote laboratories to change their procedures and to use enzymatic creatinine methods, in order to achieve a satisfactory standardization degree for this important analyte.

Keywords: Creatinine; external quality assessment programs (EQAP); standardization; traceability; commutability

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Introduction

In recent years, the need to standardize analytical methods has significantly increased, because patients might be treated by physicians receiving results from multiple laboratories within the healthcare system. This fact implies

the need to assure interchangeability of patients' results through improving standardization of laboratory tests. Standardization has a special relevance for serum creatinine, since its measurement is essential in the estimation of the renal function and may have a clear impact on patient care

(classification and treatment of patients with renal chronic disease) (1).

In 1998, the European directive 98/79/CE (2) gave to the external quality assessment programs (EQAP) the responsibility to monitor the performance of *in vitro* diagnosis medical devices within the European market.

In 2011, EQAP were classified into six categories (3), according to their ability to verify the degree of standardization of the participating measurement procedures. A category 1 EQAP uses commutable control materials with target values assigned by certified reference methods, being a valuable tool to evaluate the degree of standardization and to estimate the accuracy of the participating laboratories (4).

The EQAP classification of the Spanish Society of Clinical Biochemistry and Molecular Pathology (SEQC) belongs to fifth category (replicate analyses of non-commutable materials with no values assigned by reference system), which allows us to evaluate the imprecision and to make a comparison with other laboratories with the same analytical method.

In 2015, the Spanish Society of Laboratory Medicine (SEQC) in collaboration with the Dutch Foundation for the *Stichting Kwaliteitsbewaking Medische Laboratorium Diagnostiek* (SKLM) carried out a pilot category 1 EQAP for 17 biochemistry analytes (alanine aminotransferase, aspartate aminotransferase, bilirubin, calcium, chloride, creatinine kinase, creatinine, alkaline phosphatase, gamma glutamyltransferase, glucose, lactate dehydrogenase and glomerular filtration rate (eGFR, obtained from the equation used for each laboratory), magnesium, potassium, total protein, sodium urate). This study focuses only on creatinine results

Aim

To evaluate the standardization degree for serum creatinine testing in Spanish laboratories

Methods

A set of six control materials, at different concentrations, prepared by SKML were distributed in a single express shipment at -80°C and delivered within a 24 hours' time period to 87 laboratories all over Spain. They were fresh-frozen human serum samples (commutable) with values assigned by certified reference methods covering a wide measurable range for the most of the analytes.

The instructions given by SEQC to all participant laboratories were: Samples had to be maintained at -20°C for all over the study period (maximum two weeks). They were measured in duplicate for 6 consecutive days for each material. Every laboratory sends 12 results to SEQC office using its current online system, to be individually and collectively evaluated.

Creatinine target values were measured by isotope dilution mass spectrometry (IDMS) by the *Deutsche Vereinigte Gesellschaft für Klinische Chemie und Laboratoriumsmedizin e.V.* (DGKL) laboratory (Bonn, Germany) which is included in JCTLM database.

For each laboratory and control sample, percentage deviations of the mean of paired values versus the true value (PD) were calculated, as well as coefficients of variation (CV) calculated from duplicated test samples. PD and CV obtained were compared with the quality specifications for total allowable error (TEa) derived from biological variation, at desirable level (5). These are widely used criteria, defined in the Stockholm consensus conference (6) and confirmed in the Milan strategic conference (7).

When results are grouped (i.e., according to method), the percentage deviation of the median of each group versus the reference value is calculated for each control sample. Then, results are compared against the specification derived from biological variation for systematic error (5).

Results

A total of 1,044 creatinine results were obtained in this pilot study. The number of laboratories and instruments participating in the study, classified according to a method-traceability code system, are presented in *Table 1*. From the total, two laboratories did not correctly describe their methodology (one user of Siemens Advia 2400 and one user of Roche Cobas 8000 did not know their method or their traceability, as can be seen in *Table 1*). Two types of reports were performed:

Individual laboratory reports

Results were published in the same website as the remaining SEQC-EQAP (<http://contcal.org>). This site is restricted to participants and guarantees confidentiality of data by using lab-code identification.

For each control sample and individual result, the percentage deviation (PD) versus the true value is reported. Every PD higher than the desired limit for total error

Table 1 Method-traceability based on manufacturer information, number of laboratories and instruments used in the study

Method	# Labs	Instruments
Kinetic alkaline picrate compensated, traceable to IDMS	31	Roche Cobas 8000, 6000 and Cobas Integra 400 plus
Kinetic alkaline picrate not compensated, traceable to SRM 967a	16	Abbott Architect C1600 and Ci 8200. Horiba Pentra 400
Kinetic alkaline picrate compensated, traceable to SRM 967a	15	Beckman Coulter AU 5800, 5430, 400. Siemens Advia 2400, 1800, and Advia XPT
Kinetic alkaline picrate not compensated, traceable to SRM 909b	6	Sentinel ILAB 650, Beckman Coulter AU 5800 and 5400
Kinetic alkaline picrate compensated, traceable to SRM 914a	5	Siemens Vista 1500, Dimension EXL and Siemens Advia 2400
Kinetic alkaline picrate not compensated, traceable to SRM 914a	4	Siemens Vista 1500, Advia 2400 and 1500, and Dimension EXL
Enzymatic, traceable to IDMS	3	Roche Cobas 8000 and 6000
Enzymatic, traceable to SRM 914a	2	Siemens Vista 500 and 1500
Dry chemistry, traceable to SRM 914a	2	Orthos Vitros 250 and 5600
Kinetic alkaline picrate not compensated, traceable to IDMS	1	Spinreact Spin 640
Kinetic alkaline picrate compensated, traceability not declared	1	Siemens Advia 2400
Enzymatic, traceable to SRM 967a	1	Horiba Pentra 200

Data ordered according to the number of participating laboratories. SRM, serum reference material.

derived from biological variation is depicted in red colour, whereas those that fell within this limit are depicted in green.

Intra-laboratory imprecision, expressed in terms of coefficient of variation (CV) is calculated from duplicated samples and averaging the six concentration levels (lots).

The results obtained by the group of laboratories using same method and traceability are also shown in the individual laboratory report. For each control sample, group-CV and group-PD are shown.

Overall report

After removing methods with only one participant as well as the two laboratories without declared traceability, participants are divided into 12 different types of method-traceability combination. The most frequent method used was kinetic alkaline picrate compensated, traceable to IDMS followed by not compensated, traceable to serum reference material (SRM) 967a (Table 1).

Table 2 shows the statistics (mean, CV and PD) obtained for each control sample and by each method-traceability combination.

Figure 1 depicts the mean of percentage deviation for each method-traceability group compared with the reference value, for all samples distributed. This represents a general view of the global systematic error for the entire measured concentration interval. Desirable limit for the systematic error derived from biological variation (4%), is depicted in dotted green lines.

If we analyse method by method separately, we can conclude that only enzymatic methods got all the individual results of each laboratory within the acceptable limits of desirable TAE (Figure 2).

Although estimated PD average of the compensated alkaline picrate method traceable to IDMS fell into the desirable limits, not all individual results fulfil the goal for TAE (Figure 3). Moreover, compensated alkaline picrate methods with different traceability than IDMS, showed more dispersion of data and more results were outside the limits.

Related to alkaline picrate non compensated method, all individual results were outside desirable limits at low concentrations (Figure 4).

It is necessary to highlight, as a general view, that alkaline picrate kinetic method (compensated or non compensated)

Table 2 Mean, CV and PD obtained by each method-traceability group and control sample. Desirable systematic error based on biological variation (4%)

Method/Traceability	Sample E		Sample D		Sample A		Sample C		Sample F		Sample B	
	\bar{x}	CV (%) PD (%)	\bar{x}	CV (%) PD (%)	\bar{x}	CV (%) PD (%)	\bar{x}	CV (%) PD (%)	\bar{x}	CV (%) PD (%)	\bar{x}	CV (%) PD (%)
Enzymatic, traceable to IDMS	54.2	2.4 4.4	95.9	1.08 3	37.5	1.7 3.1	179.2	1 3.4	200	1.65 3.9	262.5	1.51 2.4
Enzymatic, traceable to SRM 914a	54.6	5.4 0.7	96.2	3.57 0.3	135.7	1.5 -1.3	176.1	2.1 -1.7	198.7	1.28 -0.7	264.3	0.920 0.7
Alkaline picrate kinetic compensated, traceable to IDMS	56.2	6.4 3.7	96.1	5.34 0.2	136	6.2 -1.1	176.7	5.7 -1.4	197.2	6.08 -1.4	257.7	5.05 -1.8
Alkaline picrate kinetic compensated, traceable to SRM 914a	65.4	5.9 20.7	104.6	3.07 9.1	142.8	5.5 3.8	180.6	3.8 0.8	206.9	3.49 3.4	262.4	3.73 0.1
Alkaline picrate kinetic compensated, traceable to 967a	62.2	12.8 14.7	101.1	7.30 5.4	137	5.6 -0.4	182.2	4.5 -1.7	195.2	4.24 -2.3	254.3	3.13 -3.1
Alkaline picrate Kinetic not compensated, traceable to 909b	66.7	4.99 23.0	102.8	3.45 7.2	142.4	3.6 4.6	178.4	5.5 -0.5	196.2	3.67 -1.9	250	4.29 -4.8
Alkaline picrate Kinetic not compensated, traceable to 914a	70.4	6.89 29.8	107.5	1.37 12.1	147.5	3.0 7.3	183.6	1.2 2.5	205.1	0.74 2.6	268.1	2.12 1.5
Alkaline picrate Kinetic not compensated, traceable to 967a	71.4	1.65 31.4	106.3	2.74 10.9	143.7	2.9 4.5	184.6	3.6 3	204.6	5 2.3	266.9	3.22 1.7
Dry Chemistry, traceable to SRM 914a	51.0	4.53 -5.9	91.1	4.53 -5	131.7	0.9 -4.2	178.3	2.8 -0.5	196.0	1.06 -2	270.1	1.69 2.8

Reference values are given as target value ± (expanded uncertainty). \bar{x} , mean; CV, interlaboratory coefficient of variation; PD, percentage deviation; IDMS, isotope dilution mass spectrometry; SRM, serum reference material from the National Institute of Standards and Technology (NIST).

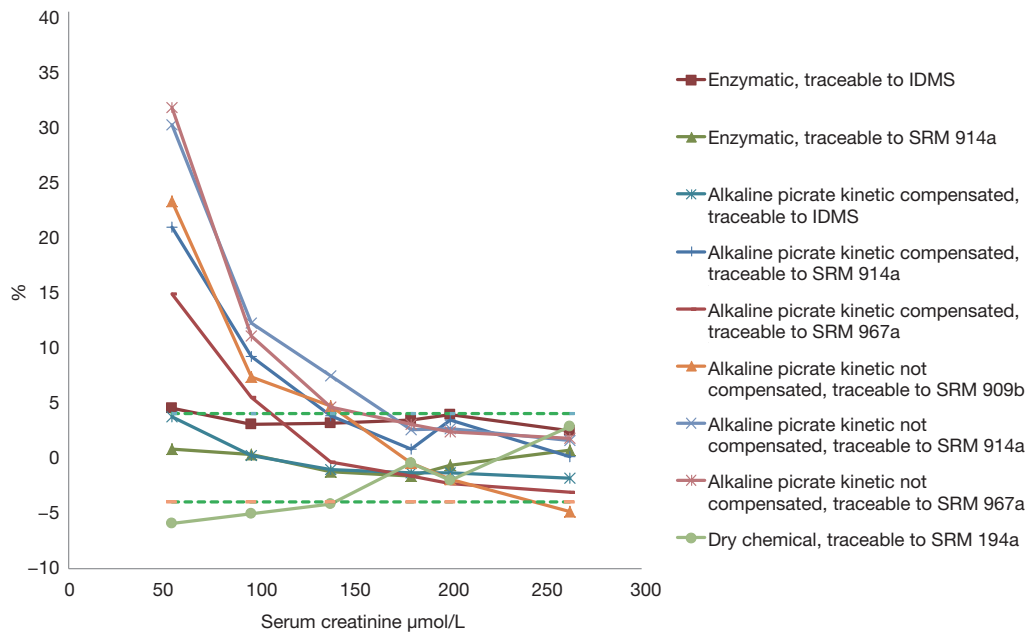


Figure 1 Percentage deviation for each method-traceability mean compared with the reference method value the six samples distributed. Y axis, percentage deviation (PD %) related to the certified value; X axis, serum creatinine concentration (µmol/L).

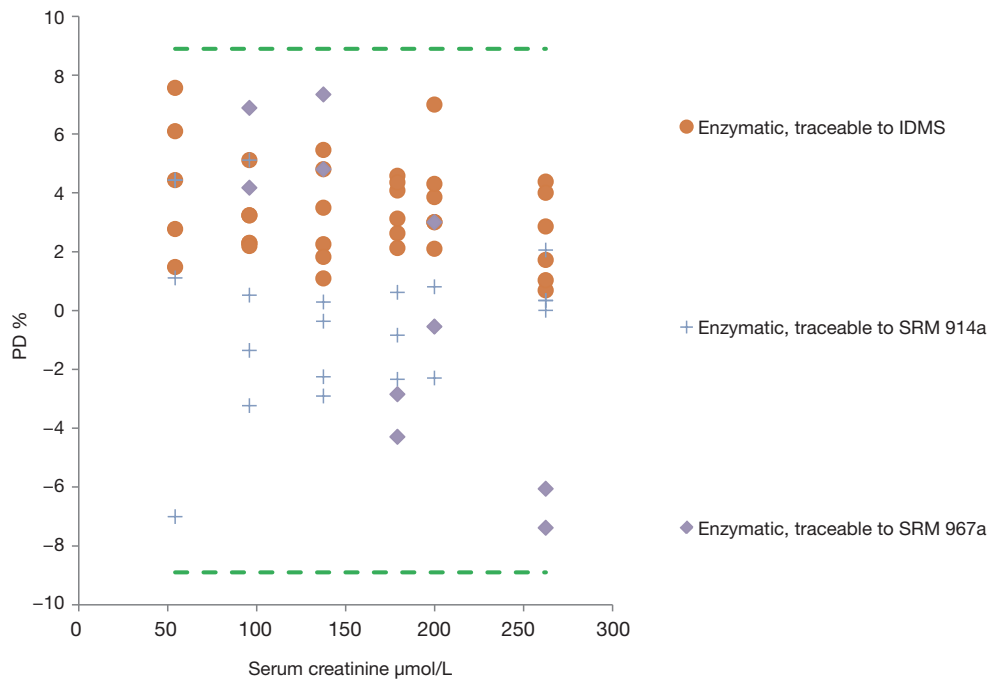


Figure 2 Percentage deviation of individual results for enzymatic methods. Y axis, percentage deviation (PD %) related to the certified value; X axis, serum creatinine concentration (µmol/L).

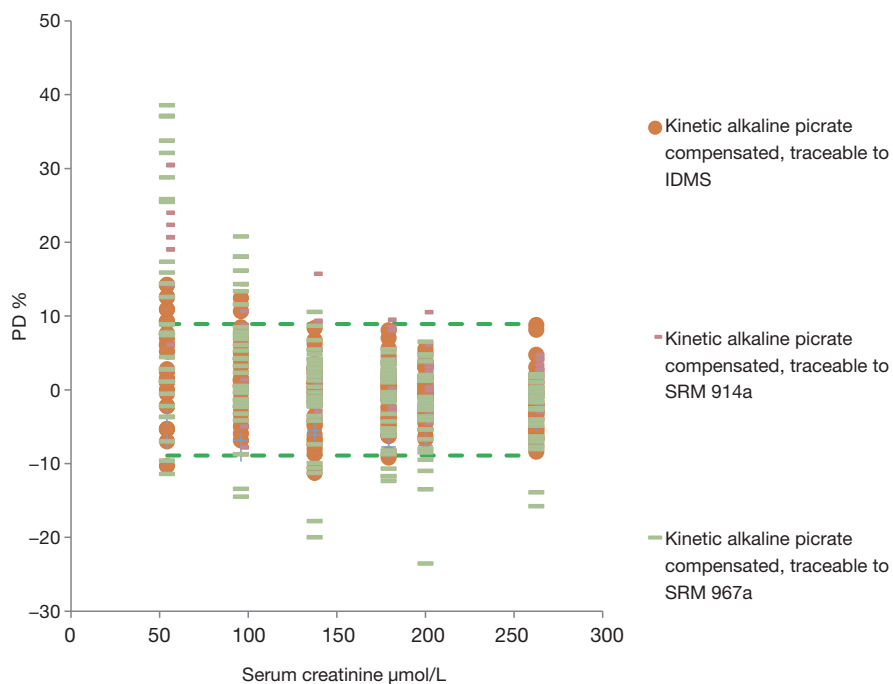


Figure 3 Percentage deviation of individual results for alkaline picrate compensated methods. Y axis, percentage deviation (PD %) related to the certified value; X axis, serum creatinine concentration ($\mu\text{mol/L}$).

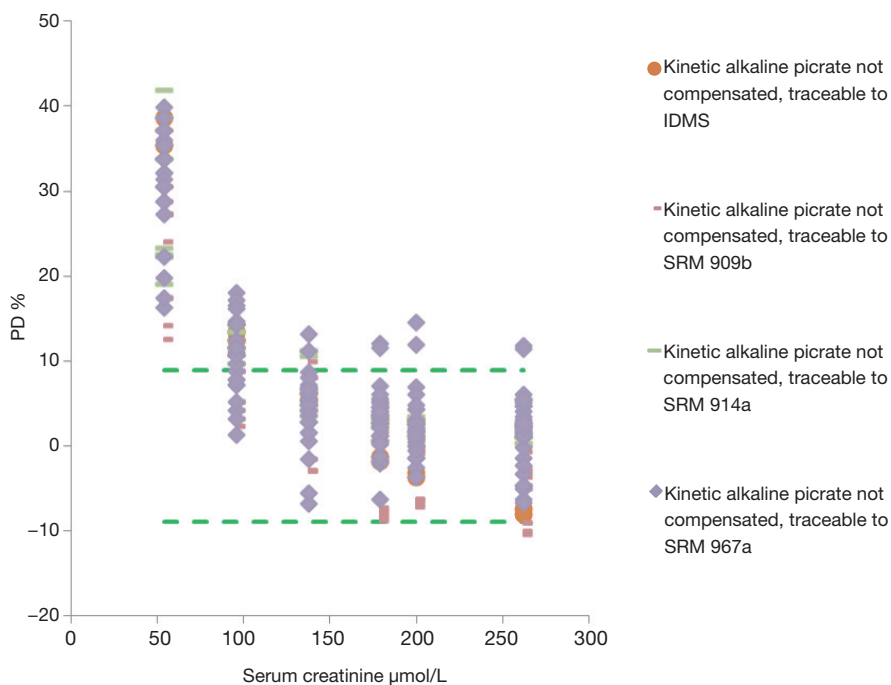


Figure 4 Percentage deviation of individual results for alkaline picrate non compensated methods. Y axis, percentage deviation (PD %) related to the certified value; X axis, serum creatinine concentration ($\mu\text{mol/L}$).

showed a remarkable overestimation of creatinine from 10% to 35% at creatinine concentration below 100 $\mu\text{mol/L}$, where clinical decision making are frequently made especially in women and pediatric population. These results are independent of the analytical platform used for creatinine testing.

Discussion

The main conclusion arisen from this study is that only enzymatic methods seem to obtain suitable results, regardless of their traceability and of the instrument applied related to the intended clinical use of creatinine in clinical practice. This had already been noticed by Weykamp *et al.* (8), who observed a strong positive bias for creatinine determined by the alkaline picrate (Jaffé) method, probably caused by endogenous interfering components; so they recommended not using the Jaffé method. Also, Jassam *et al.* (9), running another EQAP in 87 European laboratories, confirmed that only the enzymatic method reached the specifications recommended by the National Kidney Disease Program Education (KDIGO) (10).

The wide variability in the traceability chain used by *in vitro* diagnostic devices seems not to have a great influence in standardization of creatinine testing. What is important is to provide clear information regarding traceability and not only to show the analytical principle. Laboratories have found important troubles when codifying their methods traceability. In order to avoid misinterpretations, we have recoded them upon information provided by manufacturers. However, a big effort should be made to clarify this information in order to facilitate laboratory knowledge of their methods.

Furthermore, the healthcare impact of false positive creatinine results is of utmost importance because of the consequent false low glomerular filtration rate, which could generate wrong clinical decisions. Subsequently, unnecessary complementary diagnostic tools would be requested to the patients with an added needless economical expense as well as potential damage to the patient. This situation is even more important in women and pediatric population healthcare.

Further outcomes studies should be done to assess the impact of inaccurate creatinine results over patient misclassification and then directly over the clinical decision making. In our country a big effort should be made to promote laboratories to change their procedures and to use enzymatic creatinine methods, in order to achieve a

satisfactory standardization degree for this relevant analyte.

In conclusion, to participate in a category 1 EQAP is a valuable tool to assess the standardization of laboratory tests. The lack of standardization for creatinine, evidenced in our country, could potentially lead to errors in interpreting laboratory reports; this situation should be radically changed.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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