ERNDIM
Quantitative Schemes
Special Assays in Urine

ANNUAL REPORT 2018

Scheme Organiser	Scientific Advisor	Website for reporting results	Administration office
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Madrid-Winterswijk, 21 December 2018

1. Purpose

The purpose of the ERNDIM External Quality Assurance Scheme for Special Assays in Urine is the monitoring of the analytical quality of the quantitative assay of a range of analytes in urine in laboratories involved in the diagnosis of patients with inherited metabolic disorders. For details see www.erndimqa.nl

2. Participants

A total of 197 datasets (172 labs) have been submitted, for 2 of them an annual report could not be generated due to insufficient data submission. 3 laboratories did not submit results at all.

3. Design

The Scheme has been designed, planned and coordinated by the scientific advisor (Dra. Begoña Merinero) and Dr. Cas Weykamp as scheme organizer (subcontractor on behalf of SKML), both appointed by and according to the procedures of the ERNDIM Board. The design includes samples and reports which are connected to provide information with a balance between short-term and long-term reports and between detailed and aggregated information.

Samples

The scheme consisted of 8 lyophilised samples, all prepared from the same basic urine but with various amounts of added analyte. The samples were identical two by two: the pairs, analytes and their source as well as the added amounts are in the table below. Samples have been tested for stability and homogeneity according to ISO 13528.

Table 1.

Analyte	Source:	Units	Added Amounts			
			Sample Pair 2018. 01 - 06	Sample Pair 2018. 02 - 07	Sample Pair 2018. 03 – 05	Sample Pair 2018. 04 – 08
4-OH-Glutamic acid*	Sigma 76157	µmol/L	25,1	0,0	12,4	49,9
5-Aminolevulinic acid*	Sigma A3785	µmol/L	14,9	0,0	5,1	30,3
5-OH indolacetic acid	Sigma H8876	µmol/L	58,1	97,9	28,0	13,0
Carnitine free	Sigma C0283	µmol/L	1,0	136	336,0	486
Creatine	Sigma C3630	µmol/L	2000	1500	0,0	500
Creatinine	Sigma C6257	mmol/L	1,5	0,0	5,0	3,0
D,L-Glyceric acid*	TCLG0332	µmol/L	930	140	280	0,0
Galactitol	Sigma D0256	µmol/L	46,0	121	196	296
Glycolic acid	Sigma G8284	µmol/L	0,0	50,1	125	201
Guanidinoacetate	Aldrich G11608	µmol/L	964	466	0,8	166
Homocitrulline*	BioConnect SC-269298	µmol/L	2,0	9,9	0,0	5,0
Homovanillic acid	Sigma H1252	µmol/L	27,4	11,9	97,3	57,3
Lactic acid	Sigma L7022	mmol/L	5,9	8,9	2,9	0,0
L-Cystine	Sigma C8755	µmol/L	2000	300	1000	0,0
MPS (Chondroitin sulfate)	Sigma C6737	mg/L	17,0	47,0	97,0	147
Orotic acid	Sigma O2750	µmol/L	99,0	59,2	2,1	29,1
Oxalic acid	Sigma O0136	µmol/L	77,9	0,0	478	278
Pipecolic acid	Sigma P2519	µmol/L	29,9	40,4	20,4	1,8
Sialic acid	Sigma A2388	µmol/L	0,0	125	200	275
Succinylacetone	Sigma D1415	µmol/L	40,4	30,0	5,4	19,9
Sulfocysteine	Sigma C2196	µmol/L	10,3	3,3	33,0	20,1

***** *New Spiked*

Reports

All data-transfer, the submission of data as well as the request of reports proceeded via the interactive website www.erndimqa.nl which can also be reached through the ERNDIm website (www.erndim.org). The results of your laboratory are confidential and only accessible to you (with your name and password). The anonymised mean results of all labs are accessible to all participants. Statistics of the respective reports are explained in the general information section of the website.

An important characteristic of the website is that it supplies short-term and long-term reports. Short-term reports are associated with the four individual specimens, for each of which there has been a specific deadline in the year 2018. Two weeks after the respective deadlines participants could request their reports and as such had four times up-to-date information on their analytical performance. Although technically not required (the website can work with a delay time zero) a delay time of 14 days has been chosen to enable the scientific advisor to inspect the results and add his comment to the report. Contrary to the fast short-term report is the annual long-term report. The annual report is based on the design-anchored connection between samples which enables to report a range of analytical parameters (accuracy, precision, linearity, recovery and interlab dispersion) once an annual cycle has been completed. The annual report is discussed below.

A second important characteristic of the website is the wide range in aggregation of results which permits labs to make an individual choice for detailed and/or aggregated reports. The most detailed report which can be requested from the website is the "Analyte in Detail" which shows results of a specific analyte in a specific sample (168 such Analyte-in-Detail-reports can be requested in the 2018 cycle). A more condensed report in the "Cycle Review" which summarizes the performance of all analytes in a specific sample (8 such Cycle-Review-Reports can be requested in 2018). The highest degree of aggregation has the Annual Report which summarizes the performance of all analytes of all 8 samples (1 such Annual-Report can be requested in 2018).

4. Discussion of Results in the Annual Report 2018

In this part the results as seen in the annual report 2018 will be discussed. Subsequently we will regard accuracy, recovery, precision, linearity, interlab CV and cross sectional relations. Please print your annual report from the Interactive Website when you read the "guided tour" below and keep in mind that we only discuss the results of "all labs": it is up to you to inspect and interpret the specific results of your laboratory.

4.1 Accuracy

A first approach to describe accuracy is to compare the mean outcome of the eight samples in your lab with the mean of all labs. This is done in the first columns of the annual report. For example, it can be seen that for 5-OH-Indolacetic acid the mean outcome of all labs is 43.8 micromol/liter.

4.2 Recovery

A second approach to describe accuracy is the percentage recovery of added analyte. In this approach it is assumed that the recovery of the weighed quantities is the target value. The correlation between weighed quantities as added to the samples (on the x-axis) and your measured quantities (on the y-axis) has been calculated. The slope of the correlation multiplied with 100% is your recovery of added amounts. Outcome for your lab in comparison to median outcome of all labs is shown in the column "Recovery" in the Annual Report. For all labs the recovery ranges from 14% for L-Cystine to 112% for orotic acid. The overall recovery is 86%.

4.3 Precision

Reproducibility is an important parameter for quality in the laboratory and is encountered in the schemes' design. Samples come in pairs which can be regarded as duplicates from which CV's can be calculated (Intra Laboratory CV as indicator for reproducibility). Outcome for your lab in comparison to the median of all labs is shown in column "Precision" of the Annual Report. Precision ranges from 3.4% for Creatinine to 27.9% for Homocitrulline. The overall precision is a satisfying 12.1%.

4.4 Linearity

Linearity over the whole relevant analytical range is another important parameter for analytical quality. Again this is encountered in the schemes' design. With weighed quantities on the x-axis and your measured quantities on the y-axis the coefficient of regression (r) has been calculated. Outcome for your lab in comparison to the median of all labs is in the column "Linearity" of the Annual Report. It can be seen that the coefficient of regression ranges from 0.799 for L-Cystine to 0.997 for Carnitine Free, Guanidino acetate and Orotic acid.

4.5 Interlab CV

For comparison of outcome for one patient in different hospitals and for use of shared reference values it is relevant to have a high degree of harmonization between results of various laboratories. Part of the schemes' design is to monitor this by calculating the Interlaboratory CV. This, along with the number of laboratories who submitted results, is shown in the column "Data all Labs" in the Annual Report. It can be seen that most laboratories submitted results for Creatinine (135) whereas only 6 submitted results for 4-OH-Glutamic acid. The Interlab CV ranges from 6.12% for Creatinine to 53.2% for 4-OH-Glutamic acid.

4.6 Cross Sectional Relations

The various parameters as described above often have an interrelation: more than one parameter directs towards good or bad analytical control.
A typical example of good analytical control is Creatinine: many (135) laboratories submitted results, the reproducibility within the labs is good (precision of 3.4%), the Interlab CV is good with 6.12%, linearity is excellent (0.996) and recovery is 101%. Creatinine will be measured in many institutes by the general clinical chemistry lab using commercial analyzers. It is, therefore, not logical to compare it's results with those of chromatographic analyzers.

4.7 Your performance: Flags

In order to easily judge performance of individual laboratories the annual report of an individual laboratory may include flags with different colours in case of poor performance for accuracy, precision, linearity and recovery. Analytes with satisfactory performance for at least three of the four parameters (thus no or only one flag) receive a green flag. Thus a green flag indicates satisfactory performance for analysis of that particular analyte. Criteria for flags can be found in the general information on the website (on this website under general information; interactive website, explanation annual report).

4.8 Poor Performance Policy

A wide dispersion in the overall performance of individual laboratories is evident. Table 2 shows the percentage of flags observed. 48% of the laboratories have no flag at all and thus have attained excellent overall performance. In contrast, at the other extreme there are also 5% of laboratories with more than 25% red flags. Following intensive discussion within the ERNDIM board and Scientific Advisory Board (SAB) and taking into account feedback from participants we have been able to agree on a harmonised scoring system for the various branches of the Diagnostic Proficiency schemes and qualitative schemes. We have also tested a scoring system for the quantitative schemes as described in our Newsletter of Spring 2009. In parallel to this the SAB has agreed levels of adequate performance for all the schemes and these will be re-evaluated annually. The scoring systems have been carefully evaluated by members of the SAB and have been applied to assess performance in our schemes from 2007 onwards. The ERNDIM Board has decided that the Scientific Advisor will judge the performance of the individual laboratories based on these levels of satisfactory performance and issue a letter of advice of failure to achieve satisfactory performance to those laboratories which do not achieve satisfactory performance. The letter is intended to instigate dialogue between the EQA scheme organiser and the participating laboratory in order to solve any particular analytical problems in order to improve quality of performance of labs in the pursuit of our overall aim to improve quality of diagnostic services in this field.

Table 2. Percentage Flags

% Red Flags seen in Annual Report	Percentage Labs In this Category	Cumulative Percentage Of Labs
>25%	5%	5%
25%	5%	10%
20 – 25%	1%	11%
15 – 20%	7%	18%
10 – 15%	9%	27%
5 – 10%	17%	44%
0 – 5%	8%	52%
0%	48%	100%

4.9 Certificates

As for other schemes the performance as it is indicated by the red/green flags in the individual laboratories annual report is summarised in the annual participation certificate. The certificate lists the total number of special assays in the scheme, the number for which results have been submitted and the number for which satisfactory performance has been achieved. It is important to bear in mind that the certificate has to be backed up by the individual annual report in the case of internal or external auditing.

4.10 Additional Specific Remarks of the Scientific Advisor

No remarks.

5. Summary

The Annual Report, dealing with analytical performance in terms of accuracy, precision, linearity, recovery and interlab CV, shows a pattern similar to previous years. For some analytes the overall performance is good, for others (like oxalic acid) results are less satisfying, especially the interlaboratory dispersion. The heterogeneity of the analytes makes it difficult to give a general advice.

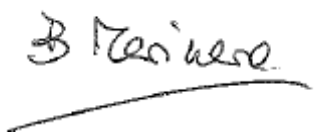
6. Preview Scheme 2019

The design of the 2019 schemes is essentially the same as in 2018.

7. Questions, Comments and Suggestions

If you have any questions, comments or suggestions please address to the scientific advisor of the scheme Dra. Begoña Merinero (begonna.merinero@inv.uam.es) and/or to the scheme organiser Dr. Cas Weykamp (c.w.weykamp@skbwinterswijk.nl).

Madrid, 21 December 2018



Dra. Begoña Merinero
Scientific Advisor

Please note:
This annual report is intended for participants of the ERNDIM Special Assays in Urine scheme. The contents should not be used for any publication without permission of the scheme advisor.