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Diagnostic Proficiency Testing

Centre: Czech Republic

Final Report 2019

prepared by
Petr Chrastina

Note: This annual report is intended for participants of the ERNDIM DPT Czech Republic scheme. The contents should not be used for any publication without permission of the Scientific Advisor.

Note: Results of your laboratory are marked with arrows.

The fact that your laboratory participates in ERNDIM schemes is not confidential, however, the raw data and performance scores are confidential and will only be shared within ERNDIM for the purpose of evaluating your laboratories performance, unless ERNDIM is required to disclose performance data by a relevant government agency. For details please see the terms and conditions on page18 and the ERNDIM Privacy Policy on www.erndim.org.

1. Geographical distribution of participants

Twenty-one laboratories from 15 countries have participated in the Diagnostic Proficiency Testing scheme in 2019, for details see the below table:

Country	Number of participants
Austria	1
Croatia	1
Cyprus	1
Czechia	1
Denmark	1
Finland	1
France	1
Germany	6
Latvia	1
Lithuania	1
Malaysia	1
People's Republic of	1

China	
Poland	1
Portugal	1
Slovakia	2

2. Design and logistics of the scheme including sample information

The scheme has been designed and planned by Petr Chrastina as Scientific Advisor and coordinated by Xavier Albe as scheme organiser (sub-contractor on behalf of CSCQ), both appointed by and according to procedures laid down the ERNDIM Board.
CSCQ dispatches DPT EQA samples to the scheme participants and provides a website for on-line submission of results and access to scheme reports. Existing DPT and Urine MPS scheme participants can log on to the CSCQ results submission website at:
https://cscq.hcuge.ch/cscq/ERNDIM/Initial/Initial.php

2 surveys	Round 1: patients A, B and C
	Round 2: patients D, E and F

Origin of patients: All six urines were obtained from patients with known diagnoses. Four urine samples have been provided by the scheme organizers and one sample has been provided by Department of Clinical Biochemistry of University Children's Hospital in Bratislava. The common sample was from DPT center Switzerland (distributed in all five DPT schemes).

In 2019 the samples have been heat-treated and apart from the common sample A were re-analyzed in our department after receiving the samples from CSCQ (samples were shipped via courier after 3 days at ambient temperature to mimic possible changes that might arise during transport). In all six samples prepared and checked by us the typical metabolic profiles were preserved after heat treatment and shipment from CSCQ.
Mailing: samples were sent by DHL; FedEx or the Swiss Post at room temperature.

3. Tests

Analyses of amino acids, organic acids, mucopolysaccharides, oligosaccharides and purines/pyrimidines were required in 2019.

4. Schedule of the scheme

Sample distribution by CSCQ	February 5, Tuesday
Start of analysis of Survey 2019/1	March 4, Monday
Survey 2019/1 – results submission	March 25, Monday
Survey 2019/1 – report	May 17, Friday
Start of analysis of Survey 2019/2	June 3, Monday
Survey 2019/2 – results submission	June 24, Monday
Survey 2019/2 – report	July 15, Monday
Annual meeting of participants	September 3, Tuesday
Annual report 2019	December 2019

5. Results

20 of 21 labs returned results for both surveys, mainly by the deadline.

	Survey 1	**Survey 2**
Receipt of results	20	21
No answer	1	0

6. Web site reporting

The website reporting system is compulsory for all centres. Please read carefully the following advice:

- Selection of tests: **don't select a test if you will not perform it**, otherwise the evaluation program includes it in the report.
- Results
  - Give quantitative data as much as possible.
  - Enter the key metabolites with the evaluation **in the tables** even if you don't give quantitative data.
  - If the profile is normal: enter "Normal profile" in "Key metabolites".
  - **Don't enter results in the "comments" window**, **otherwise your results will not be included in the evaluation program.**
- Recommendations = **advice for further investigation**.
  - Scored together with the interpretative score.
  - Advice for treatment are not scored.
  - **Don't give advice for further investigation in "Comments on diagnosis"**: it will not be included in the evaluation program.

7. Scoring and evaluation of results

Information regarding procedures for establishment of assigned values, statistical analysis, interpretation of statistical analysis etc. can be found in generic documents on the ERNDIM website.
The scoring system has been established by the International Scientific Advisory Board of ERNDIM. Two criteria are evaluated: 1) analytical performance, 2) interpretative proficiency also considering recommendations for further investigations.

A	Analytical performance	Correct results of the appropriate tests	2
		Partially correct or non-standard methods	1
		Unsatisfactory or misleading	0
I	Interpretative proficiency & Recommendations	Good (diagnosis was established)	2
		Helpful but incomplete	1
		Misleading or wrong diagnosis	0

The total score is calculated as a sum of these two criteria. The maximum to be achieved is 4 points per sample. The scores were calculated only for laboratories submitting results.

Scoring and certificate of participation: scoring is carried by a second assessor who changes every year as well as by the scientific advisor. The results of DPT Czech Republic 2019 have been also scored by Dr. Brian Fowler, from DPT Switzerland. At the SAB meeting in 21st October 2019, the definitive scores have been finalized. The concept of critical error was introduced in 2014. A critical error is defined as an error resulting from seriously misleading analytical findings and/or interpretations with serious clinical consequences for the patient. Thus, labs failing to make a correct diagnosis of a sample considered as eligible for this category will be deemed not to have reached a satisfactory performance even if their total points for the year exceed the limit set at the SAB. For 2019, the SAB decided that sample F has to be considered as a critical error for the labs who failed to recognize abnormal excretion of homocitrulline and orotate. Sample E was classed as 'educational', since the metabolite pattern was particularly challenging.

A certificate of participation will be issued for participation and it will be additionally notified whether the participant has received a performance support letter. This performance support letter is sent out if the performance is evaluated as unsatisfactory. Three performance support letters will be sent by the Scheme Advisor for 2019. Any partial submitters will receive a letter from the ERNDIM Executive Administrator, Sara Gardner.

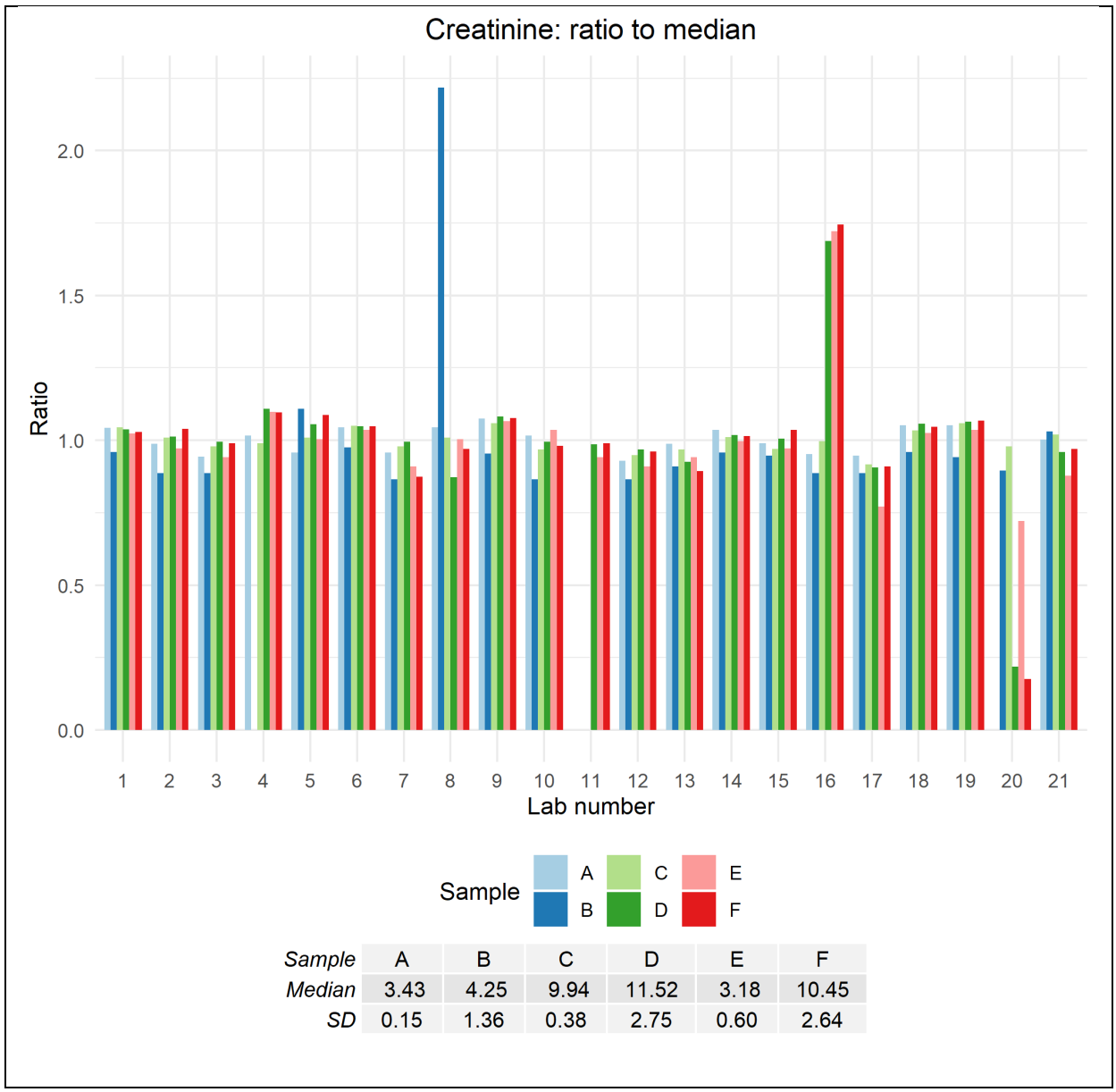
7.1. Score for satisfactory performance

Performance of the participant that obtained at least 12 points from the maximum of 20 (60%) and more within the calendar year and that did not receive "critical error" mark is considered satisfactory.

8. Results of samples and evaluation of reporting

8.1. Creatinine measurement for all samples

Creatinine determination was mostly satisfying. There were 3 outlier values. Creatinine values are expressed in the figure as the ratio of each measurement over the median of all labs.



Sample	A	B	C	D	E	F
Median	3.43	4.25	9.94	11.52	3.18	10.45
SD	0.15	1.36	0.38	2.75	0.60	2.64

8.2. Patient A

Adenine phosphoribosyltransferase deficiency

Patient details provided to participants
The female was admitted to hospital due to a history of pain on passing urine. Had been treated but urine collected off treatment.

Patient details
The sample was obtained from a woman with adenine phosphoribosyltransferase deficiency, diagnosis was confirmed by molecular genetic analysis.

Analytical performance
Seventeen labs performed analysis of purines and pyrimidines and 11 of them reported elevated excretion of 2,8-dihydroxyadenine, such analytical finding was considered correct and scored by 2 points. Elevated excretion of adenine was considered partially correct and scored with 1 point. The analytical performance was poor (55%).

Interpretative proficiency and recommendations
The diagnosis of adenine phosphoribosyltransferase (APRT) deficiency was considered correct. Confirmation of diagnosis by enzyme assay of adenine phosphoribosyltransferase activity in fibroblasts/erythrocytes and/or mutation analysis of the *APRT* gene were considered helpful. The diagnosis of APRT deficiency based on clinical information was scored with 1 point. Suspicion of other disorders of purine and pyrimidine metabolism was considered helpful but incomplete and scored with 1 point. Recommendation to carry out purines and pyrimidines analysis for those participants that did not perform this analysis was considered also helpful. The proficiency score for this sample was rather poor (63%).

Critical errors
No critical error for this sample.

Overall impression
Typical DPT sample with poor proficiency score (59%).

8.3. Patient B

No IEM

Patient details provided to participants
This boy was referred at the age of 3 years with short stature and skeletal malformations. The sample was collected at the age of 3 years; patient did not receive any therapy.

Patient details
The sample was obtained from a boy without any evidence for an inherited metabolic disorder after extensive metabolic screening. Mildly elevated excretion of cystine and dibasic amino acids was reported in this sample, but the finding was not confirmed in the repeated samples.

Analytical performance
All labs performed analysis of amino acids and 19 of them reported elevated excretion of cystine and/or dibasic amino acids, such analytical finding was considered correct and scored by 2 points. Abnormal excretion of lysine only was considered partially correct and scored with 1 point. The analytical performance was very good (93%).

Interpretative proficiency and recommendations
We considered the report of “no IEM”, non-specific finding, cystinuria or lysinuric protein intolerance a good diagnosis, which was scored with 2 points. The proficiency score for this sample was good (90%).

Critical errors
No critical error for this sample.

Overall impression
Easy DPT sample with very good proficiency score (91%).

8.1. Patient C

Sialidosis type I due to neuraminidase deficiency

Patient details provided to participants
A 19 years old man presented with hypotonia, macrocephaly, hepatomegaly and psychomotor retardation. The sample was obtained at the age of 19 years; patient did not receive any therapy.

Patient details
This sample was obtained from a 19 years old man with sialidosis type I due to neuraminidase deficiency, diagnosis was confirmed by molecular genetic analysis.

Analytical performance
19 labs performed OLS analysis and 15 of them reported a correct analytical finding "OLS profile characteristic for sialidosis", which was scored with 2 points. Abnormal OLS pattern suspected for other oligosaccharidoses or elevated sialic acid were considered partially correct and scored with 1 point. The analytical performance was good (85%).

Interpretative proficiency and recommendations
The diagnosis of sialidosis type I due to neuraminidase deficiency was considered correct. Suspicion of other oligosaccharidoses was considered helpful but incomplete and scored with 1 point. Confirmation of diagnosis by enzyme assay of neuraminidase in leukocytes or cultured fibroblasts and/or mutation analysis of the *NEU1* gene was considered helpful. Recommendation to carry out oligosaccharide analysis for those participants who did not perform this analysis was considered also helpful and scored with 1 point. The interpretative proficiency score for this sample was good (90%).

Critical errors
No critical error for this sample.

Overall impression
Typical DPT sample with good proficiency score (88%).

8.1. Patient D

Mucopolysaccharidosis type II

Patient details provided to participants

A 2 years old boy was referred for short stature, macrocephaly, inguinal hernia and hepatosplenomegaly. The sample was collected at the age of 10 years; patient received specific therapy.

Patient details

This sample was obtained from a 10 years old boy with mucopolysaccharidosis type II due to iduronate 2-sulfatase deficiency, diagnosis was confirmed by molecular genetic analysis.

Analytical performance

Elevated excretion of glycosaminoglycans (1 point) was considered a correct analytical result. Increased proportion of dermatan sulfate only was scored as correct analytical result (2 points). Analytical performance was good (88%).

Interpretative proficiency and recommendations

The diagnosis of mucopolysaccharidosis type II was considered correct, while suspicion for MPS (other types of MPS or non-specified MPS) was considered helpful but incomplete. Confirmation of diagnosis by enzyme assay of iduronate 2-sulfatase activity in fibroblasts/leucocytes and/or mutation analysis of *IDS* gene were considered helpful. Recommendation to carry out analysis of GAG fractionation for those participants that did not perform this analysis was considered also helpful. The proficiency score for this sample was very good (88%).

Critical errors

No critical error for this sample.

Overall impression

Typical DPT sample with good total proficiency score (88%).

8.1. Patient E

Formiminoglutamic aciduria

Patient details provided to participants

A 19 years old man was referred for hepatomegaly, abdominal pain and dyskinesia. The sample was obtained at the age of 19 years; patient did not receive any therapy.

Patient details

The sample was obtained from a 19 years old man with formiminoglutamic aciduria due to deficiency of glutamate formiminotransferase, diagnosis was confirmed by molecular genetic analysis.

Overall impression

All participants analyzed organic acids, only 6 of them reported elevated excretion of hydantoin-5-propionic acid. The Scientific Advisory Board classed this sample as 'educational', since the metabolite pattern in this sample was particularly challenging.

Figure 1: Organic acids profile (GC/MS) in urine

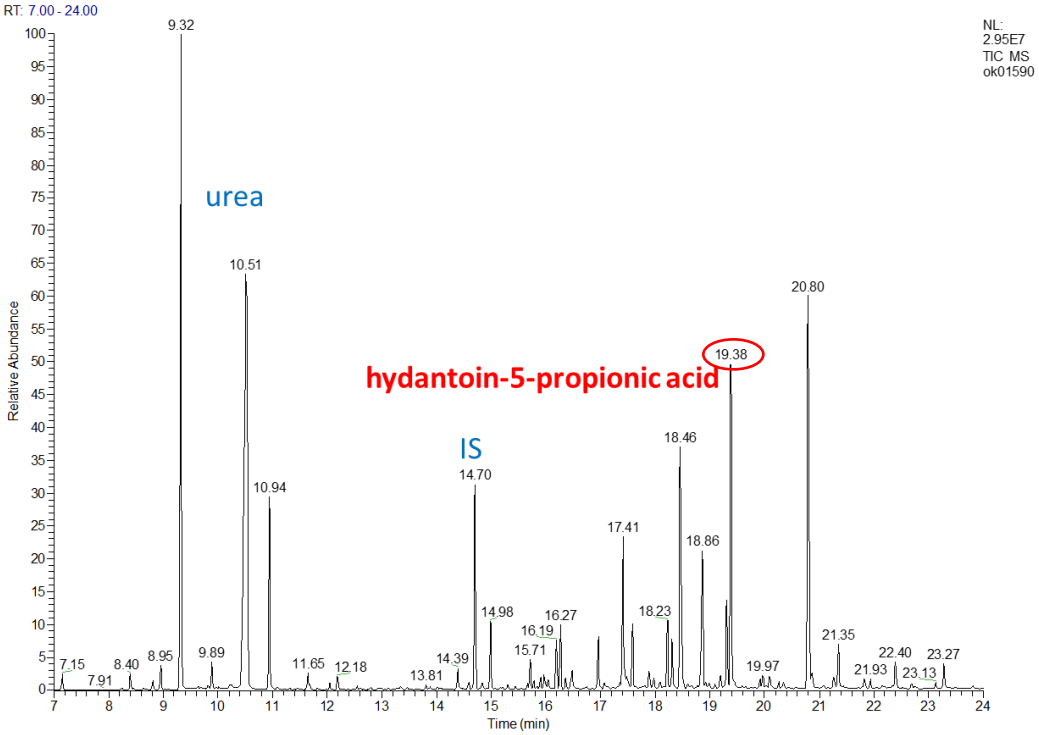
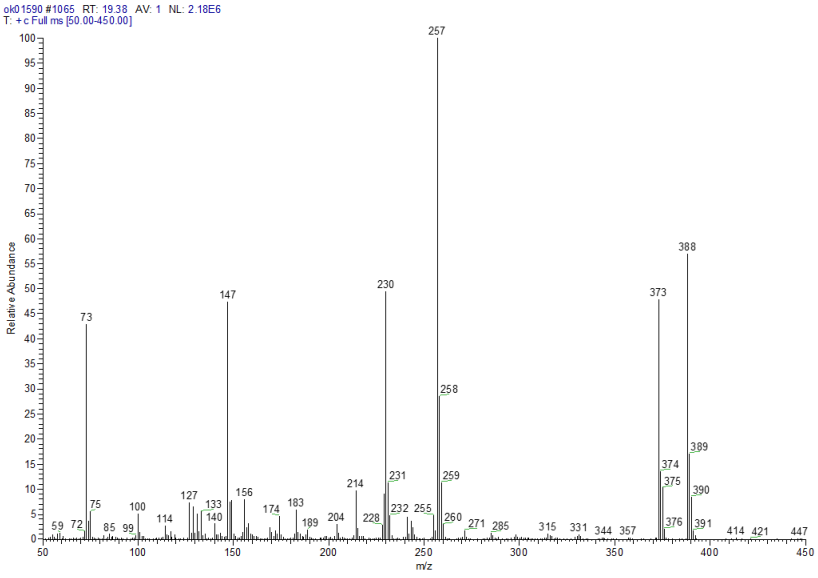


Figure 2: Mass spectrum of hydantoin-5-propionic acid (3tms)



8.1. Patient F

Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome

Patient details provided to participants

This boy was referred at the age of 14 months with developmental delay, liver dysfunction and increased ammonia. The sample was collected at the age of 9 years; patient received specific therapy.

Patient details

The sample was obtained from a 9-year old boy with hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome. The diagnosis was confirmed by molecular genetic analysis.

Analytical performance

All participants performed analyses of amino acids. Only 3 participants observed increased excretion of homocitrulline, such analytical finding was considered correct and scored by 1 point. 20 participants detected elevated excretion of orotic acid, such analytical finding was also considered correct and scored by 1 point. Elevated excretion of uracil was considered partially correct and scored with 1 point. The analytical performance was poor (55%).

	Urinary AA (patient on treatment)							Orotic acid
IEM	**Orn**	**Cit**	**Hcit**	**ASA**	**Arg**	**Cys**	**Lys**	
NAGS/CPS1 deficiency		N-↑			N-↑			**N**
OTC deficiency		N-↑			N-↑			↑
Citrullinemia I	↑	↑↑↑	↑		↑	N-↑	↑	↑
Citrin deficiency	↑	↑↑			↑	N-↑	↑	↑
Argininosuccinic aciduria		↑	↑	↑↑↑	N-↑			↑
Arginase deficiency	↑	↑	↑	↑	↑↑↑	↑	↑	N-↑
LPI	↑	↑	↑		↑	↑	↑↑↑	↑
HHH syndrome	↑	↑	↑↑		↑	N-↑	N-↑	↑
Gyrate atrophy	↑↑↑				↑	↑	↑	N
Cystinuria	↑				↑	↑↑↑	↑	N

Interpretative proficiency and recommendations

The diagnosis of HHH syndrome was considered correct while suspicion for other urea cycle disorder with exception of argininosuccinic aciduria was considered helpful but incomplete. Confirmation of diagnosis by mutation analysis was considered helpful. The proficiency score for this sample was poor (55%).

Critical errors

The failure to recognize abnormal excretion of orotate and homocitrulline is considered by the ERNDIM SAB as a critical error, which would prevent establishing the correct diagnosis; critical error was assigned to one participant in our scheme.

Overall impression

Typical DPT sample with poor proficiency score (55%).

9. Scores of participants

All data transfer, the submission of data as well as the request and viewing of reports proceed via the DPT-CSCQ results website. The results of your laboratory are confidential and only accessible to you (with your username and password).The anonymous scores of all laboratories are accessible to all participants and only in your version is your laboratory highlighted in the leftmost column.

Detailed scores – **Round 1**

Lab n°	Patient A Adenine phosphoribosyltransferase deficiency			Patient B No IEM			Patient C Sialidosis type I due to neuraminidase deficiency			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	2	4	2	2	4	2	2	4	12
2	2	2	4	2	2	4	2	2	4	12
3	2	2	4	2	2	4	2	2	4	12
4	2	2	4	2	2	4	1	2	3	11
5	2	2	4	2	2	4	1	1	2	10
6	2	2	4	2	2	4	2	2	4	12
7	2	2	4	2	2	4	2	2	4	12
8	2	2	4	2	2	4	2	2	4	12
9	2	2	4	2	2	4	2	2	4	12
10	2	2	4	2	2	4	2	2	4	12
11	--	--	--	--	--	--	--	--	--	0
12	0	1	1	2	2	4	0	1	1	6
13	0	0	0	2	2	4	2	2	4	8
14	0	1	1	2	2	4	2	2	4	9
15	0	0	0	2	2	4	2	2	4	8
16	0	1	1	2	2	4	2	2	4	9
17	0	0	0	2	2	4	2	2	4	8
18	2	2	4	2	2	4	2	2	4	12
19	0	0	0	2	2	4	2	2	4	8
20	0	0	0	0	0	0	0	0	0	0
21	0	0	0	1	0	1	2	2	4	5

Detailed scores – Round 2

Lab n°	Patient D Mucopolysaccharidosis type II			Patient E Formiminoglutamic aciduria			Patient F Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome			
	A	**I**	**Total**	**A**	**I**	**Total**	**A**	**I**	**Total**	**Total**
1	2	2	4	--	--	--	1	2	3	7
2	2	2	4	--	--	--	1	1	2	6
3	2	2	4	--	--	--	1	2	3	7
4	2	2	4	--	--	--	1	1	2	6
5	2	2	4	--	--	--	1	1	2	6
6	2	2	4	--	--	--	1	1	2	6
7	2	2	4	--	--	--	1	1	2	6
8	2	2	4	--	--	--	1	1	2	6
9	2	2	4	--	--	--	1	0	1	5
10	2	2	4	--	--	--	2	2	4	8
11	1	1	2	--	--	--	1	1	2	4
12	0	1	1	--	--	--	1	1	2	3
13	2	2	4	--	--	--	2	1	3	7
14	2	2	4	--	--	--	1	1	2	6
15	2	2	4	--	--	--	2	2	4	8
16	2	1	3	--	--	--	1	0	1	4
17	2	2	4	--	--	--	1	2	3	7
18	2	2	4	--	--	--	1	1	2	6
19	2	2	4	--	--	--	1	1	2	6
20	0	1	1	--	--	--	0	0	0	1
21	2	1	3	--	--	--	1	1	2	5

Total scores

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Critical error
1	4	4	4	4	--	3	19	95	
2	4	4	4	4	--	2	18	90	
3	4	4	4	4	--	3	19	95	
4	4	4	3	4	--	2	17	85	
5	4	4	2	4	--	2	16	80	
6	4	4	4	4	--	2	18	90	
7	4	4	4	4	--	2	18	90	
8	4	4	4	4	--	2	18	90	
9	4	4	4	4	--	1	17	85	
10	4	4	4	4	--	4	20	100	
11	--	--	--	2	--	2	4	20	
12	1	4	1	1	--	2	9	45	
13	0	4	4	4	--	3	15	75	
14	1	4	4	4	--	2	15	75	
15	0	4	4	4	--	4	16	80	
16	1	4	4	3	--	1	13	65	
17	0	4	4	4	--	3	15	75	
18	4	4	4	4	--	2	18	90	
19	0	4	4	4	--	2	14	70	
20	0	0	0	1	--	0	1	5	CE
21	0	1	4	3	--	2	10	50	

Performance

	Number of labs	% total labs
Satisfactory performers (≥ 60 % of adequate responses)	17	81
Unsatisfactory performers (< 60 % adequate responses and/or critical error)	4	19
Partial and non-submitters	1	5

Overall Proficiency

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Total (%)
DPT-CP-2019-A	Adenine phosphoribosyltransferase deficiency	55	63	59
DPT-CP-2019-B	No IEM	93	90	91
DPT-CP-2019-C	Sialidosis type I due to neuraminidase deficiency	85	90	88
DPT-CP-2019-D	Mucopolysaccharidosis type II	88	88	88
DPT-CP-2019-E	Formiminoglutamic aciduria	--	--	--
DPT-CP-2019-F	Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome	55	55	55

10. Annual meeting of participants

The annual meeting of participants of the Proficiency Testing Centre Czech Republic took place during the SSIEM Annual Symposium in Rotterdam on 3rd September 2019, 13 participants from 8 laboratories were represented.

- Analytical difficulties in 2019 surveys
  - sample E: elevated excretion of hydantoin-5-propionic acid in organic acids profile is typical founding for formiminoglutamic aciduria.
  - sample F: Homocitrulline coelutes with methionine in ion exchange chromatography.
- Critical error in HHH syndrome: Participants agreed that the failure to recognize abnormal excretion of homocitrulline and orotic acid should be considered a critical error.

We remind you that attending the annual meeting is an important part of the proficiency testing. The goal of the program is to **improve** the competence of the participating laboratories, which includes the critical review of all results with a discussion about improvements.

11. Information from the Executive Board and the Scientific Advisory Board

- New **reference materials** are now provided by SKML: they are not related to EQA samples anymore. There are two concentration levels for each group of analytes. The most suitable low and high concentration levels are defined by the respective scientific advisors. Analytes and their concentrations will be approximately the same in consecutive batches of control material. These reference materials can be ordered through the ERNDIM website. Participants are encouraged to use them as internal control, but they cannot be used as calibrants. On the website a new section for data management completes the ERNDIM internal Quality Control System. Laboratories have the option to submit results and request reports showing their result in the last run in comparison to defined acceptance limits, their own historical data and the mean of all laboratories using the same batch control material.
- A set of **organic acid mixtures** has been developed by Dr Herman ten Brink in Amsterdam, following request and advice from ERNDIM. The product is currently available at: HJ.tenBrink@VUmc.nl
- **Training**: SSIEM Academy training courses.
  - A 2 days course will be been organized on Monday and Tuesday 20 and 21 April 2020 near Amsterdam. The program for biochemists includes:
    - Aminoacidopathies
    - Hyperammonaemia
    - Urea Cycle Defects.
  - The lectures will be available on the SSIEM website
- **Urine samples**: we remind you that every year, each participant must provide to the scheme organizer at least 300 ml of urine from a patient affected with an established inborn error of metabolism or “normal” urine, together with a short clinical report. If possible, please collect 1500 ml of urine: this sample can be sent to all labs participating to one of the DPT schemes. Each urine sample must be collected from a single patient (don’t send urine spiked with pathological compounds). Please don’t send a pool of urines, except if urine has been collected on a short period of time from the same patient. For “normal” urine, the sample must be collected from a symptomatic patient (don’t send urine from your kids!).

  As soon as possible after collection, the urine sample must be heated at 50 °C for 20 minutes. Make sure that this temperature is achieved in the entire urine sample, not only in the water bath. Send the sample on dry ice by rapid mail or express transport to:

  Petr Chrastina
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  Please send us an e-mail on the day you send the samples.

12. Reminders

We remind you that to participate to the DPT-scheme, you must perform at least:
- Amino acids
- Organic acids
- Oligosaccharides
- Mucopolysaccharides
- Purines/pyrimidines

If you are not performing one of these assays, you can send the samples to another lab (cluster lab) but you are responsible for the results.
Please send quantitative data for amino acids and, as much as possible, for organic acids.

13. Tentative schedule and fee in 2020

Sample distribution	February 11, Tuesday
Start of analysis of Survey 2020/1 Website open	March 9, Monday
Survey 2020/1 - Results submission	March 30, Monday
Survey 2020/1 - Reports	May 29, Friday
Start of analysis of Survey 2020/2	June 8, Monday
Survey 2020/2 – Results submission	June 29, Monday
Survey 2020/2 - Reports	August 28, Friday
Annual meeting of participants	September 1, Tuesday
Annual Report 2020	December 2020

The annual meeting of participants will take place on September 1st, 2020 (in the morning session) during the SSIEM Annual Symposium in Freiburg, Germany.

14. ERNDIM certificate of participation

A combined certificate of participation covering all EQA schemes will be provided to all participants who take part in any ERNDIM scheme. For the DPT scheme this certificate will indicate if results were submitted and whether satisfactory performance was achieved in the scheme.

Date of report, 2019-12-23
Name and signature of Scientific Advisor

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