ERNDIM DPT Center Prague

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Proficiency Testing Centre Czech Republic
Annual Report 2014

1. Introduction

In 2014 proficiency testing in our centre was running as a regular ERNDIM scheme.

2. Geographical distribution of participants

Nineteen laboratories from 14 countries have participated in our Diagnostic Proficiency Testing scheme in 2014, for details see the below table:

Country	Number of participants
Austria	1
Croatia	1
Cyprus	1
Czech Republic	1
Denmark	1
Finland	1
Germany	4
Latvia	1
Malaysia	1
Netherland	1
Philippines	1
Poland	1
Portugal	1
Slovakia	3
in total	**19**

3. Logistics of the scheme

- ✓ Two surveys: 2014/1 – samples A, B and C
  2014/2 – samples D, E and F

  Origin of samples: Five urines obtained from patients with known diagnoses (samples were provided by the DPTC participants and by the organizers) + a common sample from DPTC Switzerland (distributed in all five DPT schemes).
- ✓ The samples with addition of thiomersal have been heat-treated and were re-analyzed in our Institute after receiving the samples from CSCQ that were shipped via courier 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 undergoing this treatment.

- ✓ This year the samples for the 2014 Diagnostic Proficiency Testing scheme were distributed via CSCQ in Geneva. On 31st March 2014 the urinary samples were distributed to the participants at ambient temperature using the courier. Based on the report of the courier all parcels were delivered within 3 days.
- ✓ The following protocol for heat inactivation is being used: Thiomersal 100 mg/l of urine is added and urine is heated at 56 °C for one hour in water bath (this temperature is checked in urinary sample and not only in the water bath). The urinary samples have been frozen until shipment.
- ✓ Tests required in 2014: amino acids, organic acids, mucopolysaccharides, oligosaccharides and purines/pyrimidines

4. Schedule of the scheme in 2014

Sample distribution	March 31, Monday
Start of analysis of Survey 2014/1	April 7, Monday
Survey 2014/1 – results submission	April 25, Friday
Survey 2014/1 – report	July 18, Friday
Start of analysis of Survey 2014/2	June 9, Monday
Survey 2014/2 – results submission	June 27, Friday
Survey 2014/2 – report	August 18, Monday
Annual meeting of participants	September 8, Tuesday
Annual report 2014	April 2015

5. Submission of results

	2014/1	**2014/2**
in time	19	19

6. Samples

Sample A

This sample was obtained from a 16 years old boy with alfa-mannosidosis due to alfa-mannosidase deficiency. The diagnosis was confirmed by enzymatic analysis. The sample was taken from our repository.

Analytical performance: 17 participants performed analysis of OLS. The pattern of OLS characteristic for alfa-mannosidosis was considered a correct analytical finding. Abnormal OLS pattern without specified diagnosis was considered partially correct. The analytical performance was good (84%).

Interpretative proficiency and recommendation: The diagnosis of alfa-mannosidosis (alfa-mannosidase deficiency) was considered correct. Fourteen laboratories reached correct diagnosis. Confirmation of diagnosis by enzyme assay of alfa-mannosidase activity preferably in plasma/fibroblasts/leucocytes and/or mutation analysis of MAN2B1 gene were considered helpful. The proficiency score for this sample was good (87%).

Critical errors: The failure to perform and/or recommend OLS analysis is considered by ERNDIM SAB as a critical error which would prevent establishing the correct diagnosis.

Overall impression: Typical DPT sample with good proficiency score.

Sample B

Patient: This sample was obtained from an 18 years old boy with iminodipeptiduria due to prolidase deficiency. The diagnosis is solely based on demonstrating the urinary excretion of iminodipeptids. This sample was contributed by Dr. Wanda Gradowska from the Children´s Memorial Health Institute in Warsaw.

Analytical performance: The presence of iminodipetides in amino acids analysis of native urine and/or elevated concentration of proline and hydroxyproline after acidic hydrolysis of urine were considered a correct result. The analytical performance was good (84%), only 3 labs failed to detect iminodipetides.

Interpretative proficiency and recommendation: Prolidase deficiency was considered the correct diagnosis. Confirmation of diagnosis by enzyme assay of prolidase activity in fibroblasts or erythrocytes or lymphocytes and/or mutation analysis was considered helpful. Recommendation to carry out analysis of iminodipetides for those participants that did not perform iminodipetides analysis was considered also helpful. The proficiency score for this sample was good (87%).

Overall impression: Moderately difficult DPT sample with good proficiency score.

Sample C

Patient: This sample was obtained from an 8 years old girl with mitochondrial complex V (ATP synthase) deficiency (3-methylglutaconic aciduria type IV) due to mutation in TMEM70 gene. The diagnosis was confirmed by molecular genetic analysis. This sample was contributed by the Dr. Darina Behulova from Department of Clinical Biochemistry of University Children's Hospital in Bratislava.

Analytical performance: Elevated excretion of 3-methylglutaconate was considered correct the key analytical result; in addition presence of 3-methylglutarate and 2-ethylhydracrylate was observed by 12 and 7 participants, respectively. The analytical performance was good (89%), only 2 labs failed to detect 3-methylglutaconate and 3-methylglutarate.

Interpretative proficiency and recommendation: Since the metabolite profile in urine does not permit distinguishing the four types of 3-methylglutaconic acidurias, a non-specified 3-methylglutaconic aciduria or 3-methylglutaconic aciduria type IV was considered correct diagnosis. Suspicion for other types of 3-methylglutaconic aciduria was considered helpful but incomplete. Confirmation of diagnosis by mutation analysis was considered helpful. The proficiency score for this sample was suboptimal (68%).

Critical errors: The failure to recognize abnormal 3-methylglutaconate excretion is considered by ERNDIM SAB as a critical error which would prevent establishing the correct diagnosis.

Overall impression: Typical DPT sample with slightly suboptimal proficiency score.

Sample D

This sample was obtained from a 6 years old boy with 3-hydroxy-3-methylglutaric aciduria due to 3-hydroxy-3-methylglutaryl-CoA-lyase deficiency. The diagnosis was confirmed by molecular genetic analysis. This sample was contributed by the Dr. Darina Behulova from Department of Clinical Biochemistry of University Children's Hospital in Bratislava.

Analytical performance: Elevated excretion of 3-hydroxy-3-methylglutarate was considered correct the key analytical result, in addition presence of 3-hydroxyisovalerate, 3-methylglutarate and 3-methyglutaconate was observed by participants. The analytical performance was excellent (100%).

Interpretative proficiency and recommendation: 3-hydroxy-3-methylglutaric aciduria was considered the correct diagnosis. Confirmation of diagnosis by enzyme assay of 3-hydroxy-3-methylglutaryl-CoA-lyase activity in fibroblasts or lymphocytes and/or mutation analysis was considered helpful. The proficiency score for this sample was excellent (100%).

Overall impression: Easy DPT sample with excellent total proficiency score.

Sample E (common sample)

Patient: The common sample provided by the DPTC Switzerland was obtained from a 8-year old boy with hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome. The diagnosis was confirmed by molecular genetic analysis.

Analytical performance: All participants performed analysis of amino acids. Only 4 participants observed increased excretion of homocitrulline, such analytical finding was considered correct and scored by 1 point. 18 participants detected elevated excretion of orotic acid, such analytical finding was also considered correct and scored by 1 point. The analytical performance was rather poor (55%).

Interpretative proficiency and recommendation: The diagnosis of HHH syndrome was considered correct while suspicion for other urea cycle disorder was considered helpful but incomplete. Confirmation of diagnosis by mutation analysis was considered helpful. The proficiency score for this sample was suboptimal (68%).

Overall impression: The total proficiency score of this difficult DPT sample from a patient with a rare IEM was suboptimal.

Sample F

Patient: This sample was obtained from an 13 years old boy suffering from mucopolysaccharidosis type I due to deficiency of alpha-L-iduronidase. The diagnosis was confirmed by enzymatic analysis. This sample was contributed by the Dr. Darina Behulova from Department of Clinical Biochemistry of University Children's Hospital in Bratislava.

Analytical performance: Elevated excretion of glycosaminoglycans and increased proportion of dermatan sulphate were considered a correct analytical result. Increased excretion of GAGs without report on dermatan sulphate elevation was scored as partially correct. Analytical performance was good (82) %.

Interpretative proficiency and recommendation: The diagnosis of mucopolysaccharidosis type I was considered correct while suspicion for MPS (other types of MPS or non-specified MPS) was considered helpful but incomplete. Confirmation of diagnosis by measurement of α-L-iduronidase in leukocytes or cultured fibroblasts was considered helpful. The interpretative proficiency score for this sample was good (82%).

Critical errors: The failure to perform and/or recommend mucopolysaccharides analysis is considered by ERNDIM SAB as a critical error which would prevent establishing the correct diagnosis.

Overall impression: Typical DPT sample with good proficiency score.

7. Scoring of results

ERNDIM are being encouraged by the European Society of Human Genetics to harmonise scheme performance assessments with the other European genetic laboratory EQA providers. ERNDIM has defined criteria for critical error (i.e. an error that would be unacceptable to the majority of labs and would have a serious adverse effect on patient management), which has been implemented for DPT 2014 evaluation.
The summary of scoring criteria is given below:

A	Analytical performance	Correct results of the appropriate tests	2
		Partially correct or non-standard methods	1
		Unsatisfactory or misleading (in some instances will be evaluated also as a critical error)	0
I	Interpretative proficiency	Good (diagnosis was established and appropriate further tests were recommended)	2
		Helpful but incomplete	1
		Misleading/wrong diagnosis (will be most likely evaluated also as a critical error)	0

The **total score** is calculated as a sum of these two criteria. The maximum that can be achieved is 4 points per sample, i.e. 12 points per survey and 24 points in 2014. Scores assigned by organizer and agreed at the Annual Meeting have been reviewed by an independent advisor from another DPT Centre and scoring was finalized after any possible discrepancies had been resolved at the March 2015 ERNDIM Scientific Advisory Board meeting.

8. Score of participants for individual samples

Lab no	Sample A			Sample B			Sample C		
	A	**I**	**T**	**A**	**I**	**T**	**A**	**I**	**T**
1	2	2	**4**	2	2	**4**	2	2	**4**
2	2	2	**4**	2	2	**4**	2	2	**4**
3	2	2	**4**	2	2	**4**	2	2	**4**
4	2	2	**4**	0	1	**1**	2	1	**3**
5	2	2	**4**	2	2	**4**	2	0	**2**
6	2	2	**4**	2	2	**4**	2	2	**4**
7	2	2	**4**	2	2	**4**	2	2	**4**
8	2	2	**4**	2	2	**4**	1	1	**2**
9	2	2	**4**	2	2	**4**	2	2	**4**
10	2	2	**4**	2	2	**4**	2	1	**3**
11	2	2	**4**	2	2	**4**	2	2	**4**
12	2	2	**4**	0	0	**0**	0	0	**0**
13	1	2	**3**	2	2	**4**	2	2	**4**
14	0	0	**0**	2	2	**4**	2	2	**4**
15	2	2	**4**	2	2	**4**	2	2	**4**
16	2	2	**4**	2	2	**4**	2	2	**4**
17	0	0	**0**	2	2	**4**	0	0	**0**
18	2	2	**4**	2	2	**4**	1	2	**3**
19	1	1	**2**	0	0	**0**	1	1	**2**

Lab no	Sample D			Sample E			Sample F		
	A	I	T	A	I	T	A	I	T
1	2	2	**4**	1	2	**3**	2	2	**4**
2	2	2	**4**	2	2	**4**	2	2	**4**
3	2	2	**4**	2	2	**4**	2	2	**4**
4	2	2	**4**	0	1	**1**	1	2	**3**
5	2	2	**4**	1	1	**2**	2	2	**4**
6	2	2	**4**	1	2	**3**	2	2	**4**
7	2	2	**4**	1	1	**2**	2	2	**4**
8	2	2	**4**	2	2	**4**	2	2	**4**
9	2	2	**4**	1	1	**2**	2	2	**4**
10	2	2	**4**	1	1	**2**	2	2	**4**
11	2	2	**4**	2	2	**4**	2	2	**4**
12	2	2	**4**	1	1	**2**	2	2	**4**
13	2	2	**4**	1	1	**2**	1	1	**2**
14	2	2	**4**	1	1	**2**	0	0	**0**
15	2	2	**4**	1	2	**3**	2	2	**4**
16	2	2	**4**	1	1	**2**	2	2	**4**
17	2	2	**4**	0	1	**1**	0	0	**0**
18	2	2	**4**	1	1	**2**	2	1	**3**
19	2	2	**4**	1	1	**2**	1	1	**2**

A – Analytical score, I – Interpretative score, T – Total score

9. Total score of participants for individual surveys and their performance in 2014

Lab no	Survey 2014/1 [points]	Survey 2014/2 [points]	Total point 2014
1	12	11	**23**
2	12	12	**24**
3	12	12	**24**
4	8	8	**16**
5	10	10	**20**
6	12	11	**23**
7	12	10	**22**
8	10	12	**22**
9	12	10	**22**
10	11	10	**21**
11	12	12	**24**
12	4	10	**14**
13	11	8	**19**
14	8	6	**14**
15	12	11	**23**
16	12	10	**22**
17	4	5	**9**
18	11	9	**20**
19	4	8	**12**

10. Score summary in 2014

Sample	Diagnosis	Analytical [%]	Interpretatative and recommendations [%]	Total [%]	Number of critical errors
A	***α-mannosidosis***	84	87	86	2
B	***iminodipeptiduria***	84	87	86	0
C	***3-methylglutaconic aciduria type IV***	82	74	78	2
D	***3-hydroxy-3-methylglutaric aciduria***	100	100	100	0
E	***HHH syndrome***	55	68	62	0
F	***MPS type I***	82	82	82	2

"Easy" and "difficult" samples were included in the surveys. The analytical performance was good to very good for most diagnoses. The interpretative performance was good for most diagnoses.

11. Satisfactory performance

The participants who obtained more than 14 points within the calendar year are considered to be performing satisfactory. Fifteen laboratories returning the results achieved a satisfactory performance of more than 14 points while four laboratories did not reach this threshold. In 6 instances a serious mistake considered as a critical error has been observed in a total of three participating laboratories.

12. Annual meeting of the participants

The annual meeting of participants of the Proficiency Testing Centre Czech Republic took place during the ERNDIM Meeting 2014 in Innsbruck on 2nd September 2014, six laboratories were represented. The following items were discussed during the annual meeting of our DPT centre:

1. Information
   - ERNDIM is aiming at accrediting its activities
   - changes in DPT (sample recruitment and distribution, web based system at CSCQ)
2. Tests required for to 2014
   - amino acids, organic acids, mucopolysaccharides, oligosaccharides and purines/pyrimidines
3. Discussion of results of samples A-F
   - scoring of 2014 results proposed by DPTC Czech Republic organizers has been subsequently evaluated by a second reviewer from an independent DPT center

13. Tentative schedule of DPT scheme and fee in 2015

Sample distribution	March 31, Tuesday
Start of analysis of Survey 2015/1	April 7, Monday
Survey 2015/1 – results submission	April 30, Thursday
Survey 2015/1 – report	May 29, Friday
Start of analysis of Survey 2015/2	June 01, Monday
Survey 2015/2 – results submission	June 22, Monday
Survey 2015/2 – report	July 31, Friday
Annual meeting of participants	September 1, Tuesday
Annual report 2015	March 2016

The annual meeting of participants will take place on September 1st during the SSIEM Annual Symposium in Lyon, France.

The Executive Board and Board of Trustees of ERNDIM determined the DPT fee for 2015 in the amount of 364 €.

14. Certificate of participation and performance in Proficiency Testing for 2014

Results of DPT Scheme are included in the Certificate of participation and performance, which are issued by ERNDIM.

Prague, April 10, 2015

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