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Diagnostic Proficiency Testing

Centre: Switzerland

Final Report 2018

prepared by
Brian Fowler

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

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1. Geographical distribution of participants

In 2018, 22 laboratories from 12 countries subscribed to the scheme. All laboratories submitted results for both sample batches.

Country	Number of participants
Australia	2
Austria	2
Canada	3
Czechia	1
Estonia	1
Germany	3
Hong Kong	1
Israel	1
Norway	1
Sweden	2
Switzerland	1
United States of America	4

Version Number (& Date)	Amendments
[1] version 2 (19th July 2019)	• Page 15: Scientific Advisor signature added to authorization.

2. Design and logistics of the scheme including sample information

Receipt of samples

The urine samples were distributed to participants on **February 5th** at ambient temperature by CSCQ using the courier DHL. Delivery times of samples reported by the courier were all within a maximum of four days and 15 labs reported receipt on the same dates. 5 labs reported receipt 1-7 days later than the courier and one lab 39 days, obviously an error. Specific details regarding your own samples are available on request.

The samples have been heat-treated. They were pre-analysed in our institute after 3 days incubation at ambient temperature (to mimic possible changes that might arise during transport). In all six samples the typical metabolic profiles were preserved after this process. . Three were from our institute, the common sample came from Prague and two had been provided by scheme participants, *K. Ounap, Tartu, Estonia and S. Scholl-Bürgi, Austria,* to whom we express our gratitude.

3. Tests

Ability to analyse amino acids, organic acids, mucopolysaccharides, oligosaccharides and purines/pyrimidines was required in 2018.

4. Schedule of the scheme

Sample distribution	Feb 5th, 2018
Start of analysis of Survey 2018/1	Feb 26th, 2018
Survey 2018/1 - Results submission	March 12th, 2018
Survey 2018/1 - Reports on website	May 4th, 2018
Start of analysis of Survey 2018/2	May 28th, 2018
Survey 2018/2 – Results submission	June 11th, 2018
Survey 2018/2 - Reports on website	July 31st, 2018
Annual meeting of participants	SSIEM, Athens, September 4, 2018
Annual Report 2018	December 2018

We continued to use the evaluation programme to generate individual lab reports and these were made available on the CSCQ website in good time close to the foreseen dates. Feedback on the content and style of these reports is invited.

5. Results

All labs returned results for both the first and second surveys and by the deadline.

	Survey 1	**Survey 2**
Receipt of results	22	22
No answer	0	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

Two criteria are evaluated: analytical performance, interpretative proficiency including recommendations for further investigations. Due to the large variability in reporting results in various countries, recommendations pertaining to treatment are not evaluated in proficiency testing, however they may be considered by the scheme organisers in evaluating interpretation.

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

7.1. Score for satisfactory performance

At least 15 points from the maximum of 24 (62%).

8. Results of samples and evaluation of reporting

8.1. Patient A

Dihydropyrimidine dehydrogenase (DPD) deficiency (thymine-uraciluria). OMIM # 274270

This was the common sample that was distributed to all five DPT schemes**.**

Patient details provided to participants
This female patient was referred at the age of 18 years with suspicion for multiple sclerosis based on MRI scan. Since the age of 5 years mental retardation and cognitive impairment was observed. Urine was collected at the age of 20 years.

Patient details
The diagnosis was confirmed by enzymatic and molecular genetic analyses. See ERNDIM website for more details (Meeting reports, Athens 2018).

Analytical performance
Organic acid analysis and/or purine and pyrimidine analysis was needed to detect the key metabolites, Uracil and Thymine. Finding of elevation of each received one point. Analytical proficiency was 95%.

Diagnosis / Interpretative proficiency
The correct diagnosis of dihydropyrimidine dehydrogenase was scored with two points. No point was given for one lab that recommended P/P analysis but specifically to rule out adenylo-succinate lyase deficiency. Interpretative proficiency was 98%.

Recommendations
Appropriate recommendations were:
Repeat analysis to carefully check for dihydrouracil and dihydrothymine in urine to exclude dihydropyrimidinase deficiency, measurement of DPD activity in fibroblasts and mutation analysis of the DPYD gene are all appropriate user recommendations. Avoidance of treatment with 5-fluorouracil is important.

Overall impression
Overall proficiency for this straightforward sample was very high at 97%

This sample was considered by the SAB to be eligible for critical error i.e. missing thymine/uracil. One lab missed elevated thymine and uracil and received CE for this sample.

Analytical Details

Creatinine
n=22
median= 5.38
mean= 5.40
SD= 0.31
min, max= [4.43, 5.84]

pH
n=11
median= 6.50
mean= 6.45
SD= 0.35
min, max= [6.00, 7.00]

Spot tests
All negative

Organic Acid, Purine/ Pyrimidine analysis

	n	points
Inc. Thymine (OA 13, P/P 14)	21	1
Uracil (OA 14. P/P 14)	21	1

Thymine (Purine/Pyrimidines)
n=11
median= 67
min, max= [46, 379]

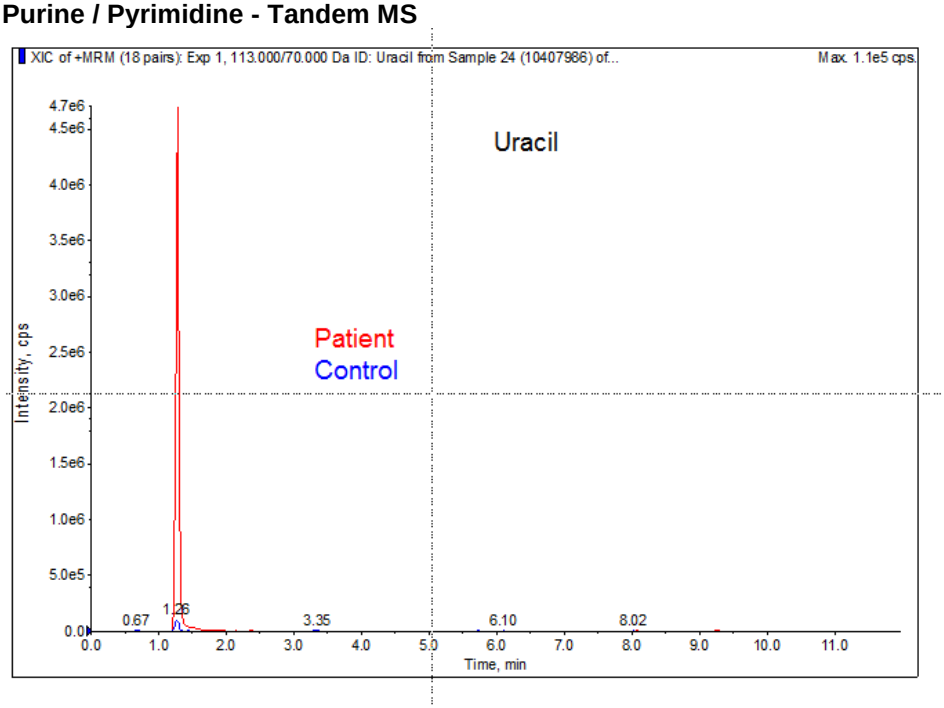
Uracil (Purine/Pyrimidines)
n=11
median= 152
min, max= [112 - 916]

Interpretation

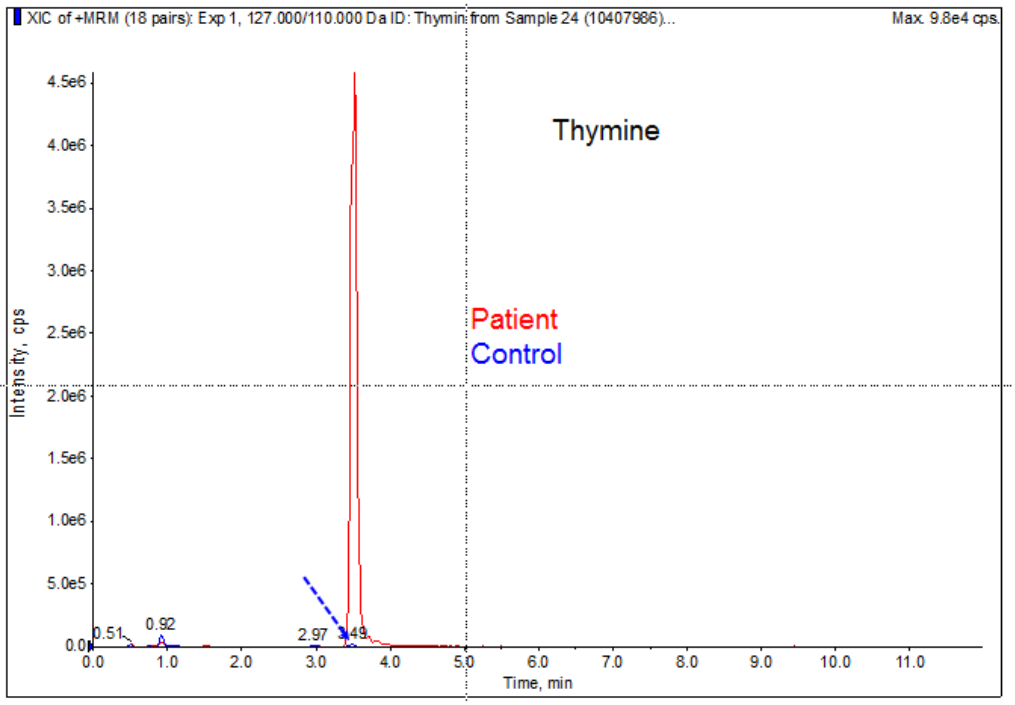
	n	Points
Dihydropyrimidine dehydrogenase deficiency	21	2
No specific diagnosis, P/P recommended for adenylo-succinate lyase deficiency	1	0

Full details of the results of this common sample are to be found on the ERNDIM website with the following link:
https://erndim.org/store/docs/ERNDIMDPTCommonsample201-GUKATEFE591813-27-09-2018.pdf

Purine / Pyrimidine - Tandem MS



Purine / Pyrimidine - Tandem MS contd



8.2. Patient B

Isovaleric Acidemia due to Isovaleryl-CoA Dehydrogenase Deficiency . OMIM 243500

Patient details provided to participants
Female presented at 6 days with poor feeding, movement abnormalities muscular hypotonia and seizures. Neutropenia and thrombocytopenia was observed. Sample collected on treatment at 25 years of age.

Patient details
A 6 day old female child presented with increasing feeding problems, reduced movement, muscular hypotonia and a left sided seizure together with neutropenia, thrombopenia and hyperammonaemia. The diagnosis of isovaleryl CoA dehydrogenase deficiency was confirmed by the finding of reduced fixation of label from [14C] isovalerate in fibroblasts and by mutation analysis.

Analytical performance
The key finding of elevated isovalerylglycine was scored with two points and was reported by all laboratories. Some other associated metabolites such as 3-hydroxyisovaleric acid and isovalerylglutamate were reported by a few labs.

Diagnosis / Interpretative proficiency
All labs made the correct diagnosis of isovalerylCoA dehydrogenase deficiency (two points).

Recommendations
Appropriate ones given were analysis of acyl carnitines (10 labs), enzyme assay (7 labs) or mutation analysis (13 labs). Other recommendations included acylglycine analysis (3),treatment monitoring (2), refer to specialist (6), gene not needed (1).

Overall impression
Excellent performance with 100% efficiency.

This was considered by the SAB to be eligible for critical error. No lab qualified for this sample

Analytical Details

Creatinine
n=22
median= 1.68
mean= 1.67
SD= 0.08
min, max= [1.51, 1.82]

pH
n=11
median= 7.00
mean= 6.77
SD= 0.60
min, max= [6.00, 8.00]

Spot tests
All negative

Organic acid analysis

	n	points
Isovaleryl glycine increase	22	2

Isovalerylglycine
n=11
median= 890.00
mean= 1214.81
SD= 755.87
min, max= [119.00, 2717.00]

Interpretation

	n	Points
IsovalerylCoA dehydrogenase deficiency	22	2

8.3. Patient C

Mucopolysaccharidosis type IV A
(N-acetylgalactosamine-6-sulfate sulfatase deficiency), OMIM # 253000

Patient details provided to participants
Female, Presented with short stature and pectus cranium, normal cognitive development. No treatment at point of collection.

Patient details
Now 21 years of age, cognitive development has been normal. Presently she is wheelchair bound, has contractures, deformity of the cervical spine and spinal MRI changes. The diagnosis has been confirmed by enzyme assay and enzyme replacement treatment has been started.

Analytical performance
Reporting increased keratan sulphate with differentiation of GAGs was scored with two points (12/22). Increased total GAGs were reported by 18/22 labs and when reported without the finding of keratan sulphate elevation received one point.

Diagnosis / Interpretative proficiency
A diagnosis of MPSIV based on abnormal analytical findings was scored with two points (11 labs). This diagnosis not based on correct specific analytical findings, a non-specific MPS disorder or recommendation to perform the correct analysis when this had not been done (11 labs) all received one point.

Recommendations
Following were given:

Relevant genetic analysis	(n=17)	N-AcGal-6 sulphatase	(n=14)
ß-galactosidase	(n=6)	GAG-analysis (rpt.), -diff-	(n=10)
Referral–centre/specialist	(n=3)	Spine X-Ray	(n=1)

Overall impression
Overall proficiency with this fairly straightforward sample was 72%. Nevertheless none of the labs would have missed the diagnosis.

This was considered to be eligible for critical error (no lab).

Analytical Details

Creatinine
n=22
median= 4.99
mean= 4.91
SD= 0.29
min, max= [4.18, 5.27]

pH
n=11
median= 7.00
mean= 7.18
SD= 0.56
min, max= [6.00, 8.00]

Spot tests
Nitrites 0 (3 labs); + (3 labs); ++ (3 labs); +++ (1 lab)

GAG quantitative n=17

	n	Points
Elevated	17	1
Normal/Not done	4	0

Glycosaminoglycans quantitative
n=17
median= 10.00
mean= 9.42
SD= 2.74
min, max= [4.59, 15.60]

Glycosaminoglycans fractionation

Keratan sulphate	n	Points
increased	12	1
Normal	1	0

Interpretation

	n	Points
MPSIV based on abnormal analytical findings	11	2
MPSIV with incorrect analytical findings	2	1
MPSIV with lacking analytical findings	7	1
Non-specific MPS disorder	2	1

8.4. Patient D

Hypoxanthine-Guanine Phosphoribosyltransferase Deficiency (Lesch-Nyhan Disease)OMIM No. 300332

Patient details provided to participants
Male child with developmental delay and muscular hypotonia since 1 year of life. Later dystonias and irritability developed. Urine collected at 6.5 years on treatment.

Patient details
The male patient presented with developmental delay and muscular hypotonia since 1 year of life. Later dystonias and irritability developed. Initial purine analysis gave borderline results but later results, Uric acid 864 µmol/mmol creat. (ref 157 – 821); Hypoxanthine 49 µmol/mmol creat. (ref 2 – 31); Xanthine 13 µmol/mmol creat. (ref 1 – 22), clearly pointed to HPRT deficiency. The diagnosis was confirmed by enzyme assay and mutation analysis. Currently 6.5 years old and treated with allopurinol.

Analytical performance
Increased hypoxanthine and xanthine (17 labs) was scored with two points. Only xanthine increase (one lab) was scored with one point. Low/normal uric acid, attributable to allopurinol treatment, was reported by 15 labs and 6 labs reported allopurinol derivative

Diagnosis / Interpretative proficiency

15 labs correctly interpreted the findings as due to Lesch-Nyhan disease (two points). One point was given for Xanthinuria (one lab) but no points were given for Mb-cofactor deficiency (2 labs, no sulphocysteine increase) or no diagnosis/abnormality.

Recommendations
Following were given: HPRT enzyme (6 labs), gene (12); treatment for Mb cofactor defect ((2); inappropriate mutation (3).
Definitive:
HPRT enzyme assay and mutation analysis.

Overall impression
Purine /pyrimidine analysis allowed diagnosis although one lab found the abnormalities with organic acid analysis reflecting their methodology.
Overall proficiency was fairly good for analytical findings (79%) but less so for interpretation (73%). This compares well with overall proficiency of 59% the last time a sample from a patient with this disorder was circulated in 2014 albeit from a different patient.

This sample was considered by the SAB not to be eligible for critical error.

Analytical Details

Creatinine
n=22
median= 2.30
mean= 2.27
SD= 0.12
min, max= [1.99, 2.51]

pH
n=12
median= 6.50
mean= 6.41
SD= 0.41
min, max= [6.00, 7.00]

Spot tests
All negative except positive nitrites reported by one lab.

Purines / Pyrimidines

	n	points
Increased hypoxanthine and xanthine	17	2
Only xanthine increase	1	1
Low/normal uric acid, *attributable to allopurinol*	15	-
allopurinol derivatives	6	-

Hypoxanthine
n=12
median= 735
Range 363-1109

Xanthine
N= 12
median 414
range 130 -593

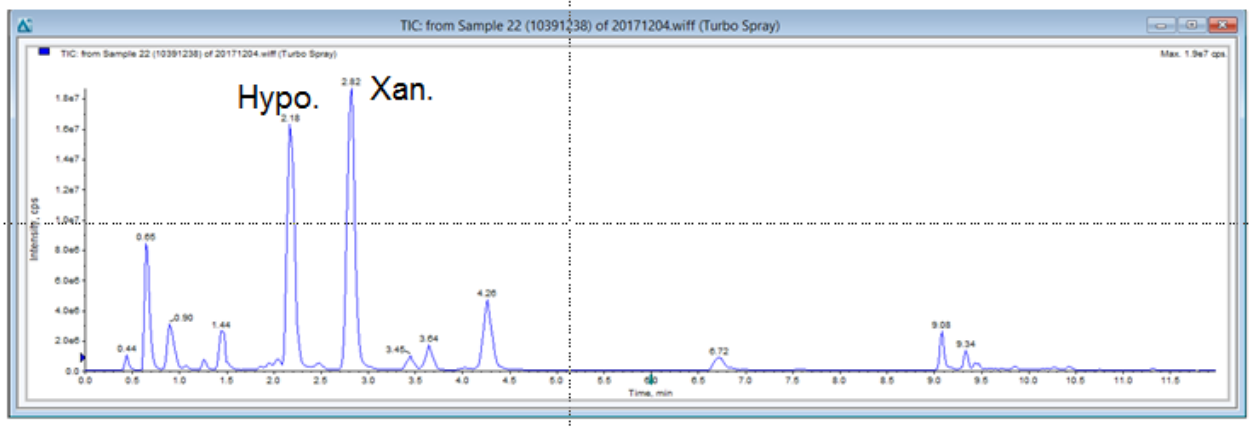
Uric acid
N= 4
median 99
range 93 -106

Allopurinol
N= 4
median 226
range 153 -306

Interpretation

	n	Points
Lesch-Nyhan disease	15	2
Xanthinuria	1	1
P/P analysis not done but recommended	1	1
Mb-cofactor deficiency (2) no sulphocysteine increase)	2	0
No diagnosis/abnormality	3	0

LC-MS



8.5. Patient E

Phenylketonuria, OMIM #261600

Patient details provided to participants
The female child was a recent immigrant presenting with psychomotor delay and skin lesions. Urine collected at 18 years on treatment.

Patient details
The clinical information given with the sample had been modified slightly.
In fact the sample was from an 18 year old female patient who had been detected on newborn screening and treated from early life. Classical PKU was confirmed by mutation analysis. The patient has developed normally although compliance to treatment has been poor during recent years.

Analytical performance
One point was scored for increased phenylalanine (22/22 labs) and one point for phenyl- and/or hydroxyphenyl-derivatives (20 labs).

Diagnosis / Interpretative proficiency
Phenylketonuria due to phenylalanine hydroxylase deficiency was the correct diagnosis scored with two points (22 labs). Fifteen labs also mentioned another hyperphenylalaninaemia as a possibilty (not scored).

Recommendations
Following were made: plasma amino acids (18 labs); phenylalanine hydroxylase gene (14); BH4 loading (11); pterins in urine (5); DHPR enzyme (7); dietary treatment (1).
Definitive:
Plasma amino acids and PAH mutation analysis. In a new patient testing for a biopterin disorder is appropriate.

Overall impression
Very high proficiency of 95% and 100% for analytical findings and interpretation respectively in a very straightforward sample.

The SAB considered that this sample was eligible for critical error (no lab).

Analytical Details

Creatinine
n=21
median= 3.43
mean= 3.40
SD= 0.17
min, max= [3.04, 3.72]

pH
n=12
median= 8.00
mean= 7.87
SD= 0.67
min, max= [7.00, 9.00]

Spot tests:
All negative

Amino acid analysis (n= 21)

	n	points
Phenylalanine increase	22	1

Phenylalanine
N= 19
median 136
range 110 - 161

Organic acid analysis

	n	points
Phenyl- OH-phenyl- derivatives increased	20	1

Phenylacetic acid
n= 4
median 116
range 33 - 133

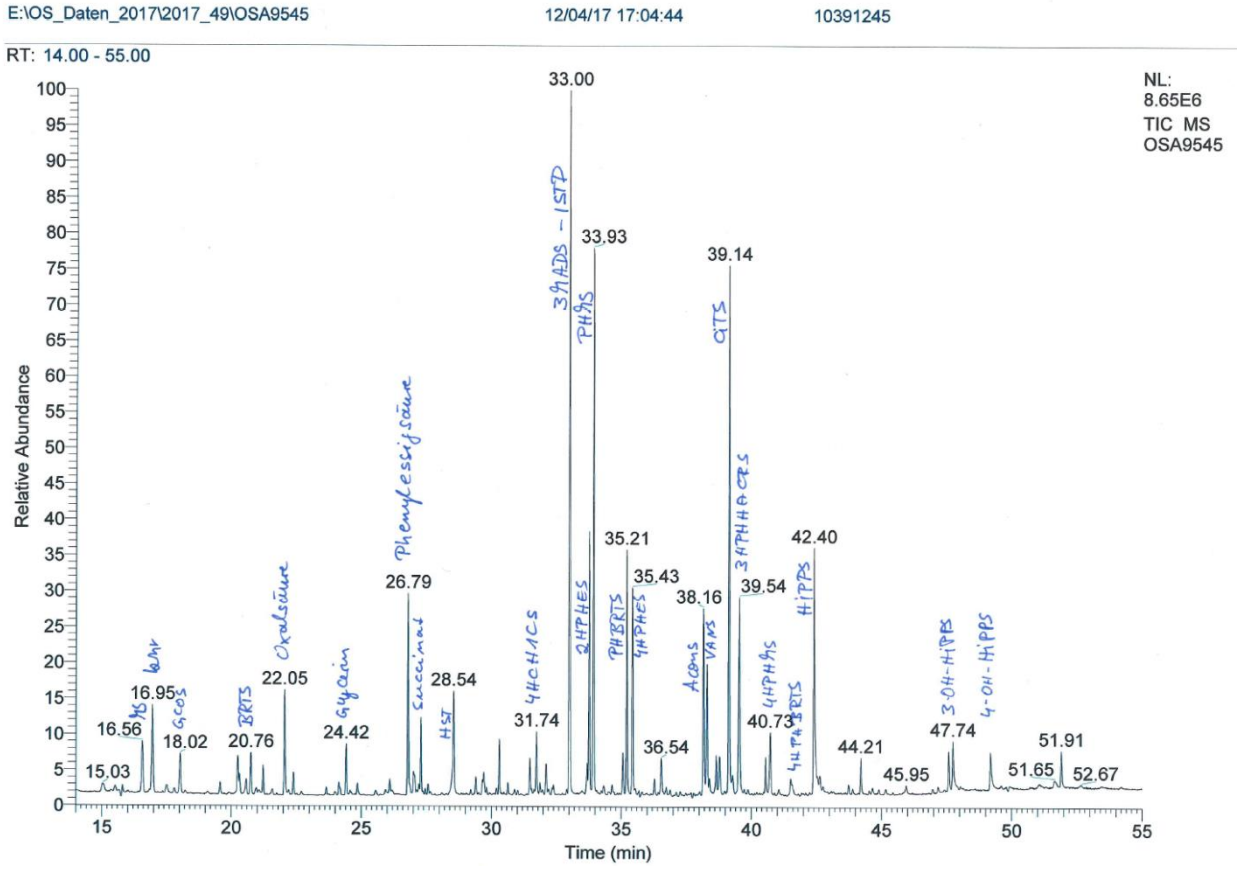
Phenyllactic acid
n= 6
median 86
range 60 -124

2-OH-phenylacetic acid
n= 9
median 25
range 5 - 53

Interpretation

	n	Points
Phenylketonuria (phenylalanine hydroxylase deficiency	22	2
Other hyperphenylalaninaemia	15	-

Organic acids – GCMS



8.6. Patient F

GM1-gangliosidosis # 230500.

Patient details provided to participants
Male patient presented at the age of one month due to oedema associated with hepato-splenomegaly. Urine collected at 10 months of age.

Patient details
A male patient who came to attention at the age of one month due to ödema associated with hepatosplenomegaly. Blood film showed unspecific storage vacuoles in lymphocytes. Subsequently showed signs of neurodegeneration and skin abnormalities. Beta-Galactosidase deficiency found in leucocytes. Urine collected at 10 months, receiving symptomatic treatment. This sample was also circulated in 2013.

Analytical performance
Analysis of oligosaccharides was essential to make a diagnosis in this sample. 14 labs reported results with 13 clearly abnormal (2 points). One lab reported borderline findings (one point). Regarding MPS abnormalities please note that glycosaminoglycans quantitative levels (n=16, median= 29.58, range 13.90 - 92.00) were not dramatically high and note the low creatinine. Of those reporting differentiation, 6 found a normal profile, 1 borderline and only one an abnormal profile (indication of MPSIV).

Diagnosis / Interpretative proficiency
All thirteen labs that found abnormal oligosaccharides made the correct diagnosis of GM1-gangliosidosis (two points). Two labs included this as a possible diagnosis (one point) and two labs that did not perform the analysis made a recommendation for appropriate testing (one point).

Recommendations
Following were made: Beta-galactosidase enzyme (13 labs) and gene (12); vaculated lymphocytes (1); Oligosaccharide analysis when not performed (2); Lysosomal enzyme screening (2); MPS enzymes / genes (4); GAGs in urine (2): purine/pyrimidine analysis (1).
Definitive:
Beta-galactosidase enzyme assay and mutation analysis, search for storage disease if oligosaccharide analysis not available.

Overall impression
Overall proficiency of 67%, reflecting absence of the availability of oligosaccharide analysis in some labs. When this sample was circulated in 2013 proficiency was 59%.

This sample was considered by the SAB to be eligible for critical error. One participant failed to detect increased GAGs and did not recommend oligosaccharide testing and therefore received a critical error

Analytical Details

Creatinine
n=21
median= 0.56
mean= 0.54
SD= 0.07
min, max= [0.30, 0.62]

pH
n=12
median= 7.00
mean= 7.16
SD= 0.65
min, max= [6.00, 8.00]

Spot tests
All negative

Oligosaccharide analysis (n= 21)

	n	points
Clear abnormality	13	2
Borderline findings	1	1

GAG quantitative n=16

	n	Points
Elevated	9	0
Normal/Not done	7	0

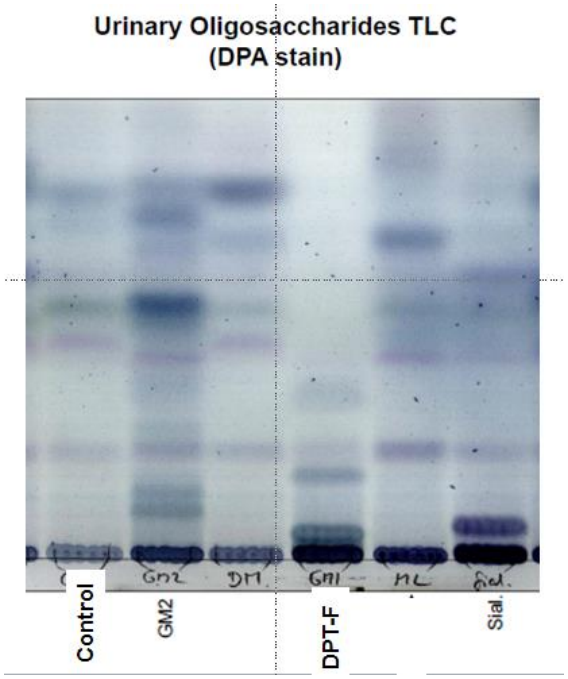
Glycosaminoglycans quantitative
n=16
median= 29.6, mean= 37.3
SD= 20.7 min, max= [13.9, 92]

GAG differentiation

	n	points
Normal profile	6	Not scored
borderline	1	Not scored
abnormal profile, indication of MPSIV	1	Not scored

Interpretation

	n	Points
Abnormal oligosaccharides - GM1-gangliosidosis	13	2
GM1-gangliosidosis possibility	2	1
Recommendation for appropriate testing	2	1



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 Dihydropyrimidine DeH deficiency			Patient B IsovalerylCoA dehydrogenase deficiency			Patient C MPS IV			
	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	0	1	1	9
4	2	2	4	2	2	4	1	1	2	10
5	2	2	4	2	2	4	2	2	4	12
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	0	1	1	9
9	2	2	4	2	2	4	1	1	2	10
10	2	2	4	2	2	4	2	2	4	12
11	2	2	4	2	2	4	1	1	2	10
12	2	2	4	2	2	4	1	1	2	10
13	0	1	1	2	2	4	2	2	4	9
14	2	2	4	2	2	4	1	1	2	10
15	2	2	4	2	2	4	2	2	4	12
16	2	2	4	2	2	4	2	2	4	12
17	2	2	4	2	2	4	1	1	2	10
18	2	2	4	2	2	4	2	2	4	12
19	2	2	4	2	2	4	1	1	2	10
20	2	2	4	2	2	4	0	1	1	9
21	2	2	4	2	2	4	1	1	2	10
22	2	2	4	2	2	4	2	2	4	12

Detailed scores – Round 2

Lab n°	Patient D Lesch-Nyhan, HPRT deficiency			Patient E Phenylketonuria			Patient F GM1 gangliosidosis			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	2	4	2	2	4	2	2	4	12
2	1	0	1	2	2	4	2	2	4	9
3	2	2	4	2	2	4	2	2	4	12
4	2	2	4	2	2	4	2	2	4	12
5	2	2	4	2	2	4	2	2	4	12
6	2	2	4	2	2	4	1	1	2	10
7	2	2	4	2	2	4	0	1	1	9
8	2	2	4	2	2	4	2	2	4	12
9	2	2	4	1	2	3	0	0	0	7
10	2	2	4	1	2	3	2	2	4	11
11	2	2	4	2	2	4	0	0	0	8
12	2	2	4	2	2	4	2	2	4	12
13	0	0	0	2	2	4	0	0	0	4
14	0	0	0	2	2	4	2	2	4	8
15	2	2	4	2	2	4	2	2	4	12
16	2	1	3	2	2	4	2	2	4	11
17	2	0	2	2	2	4	0	0	0	6
18	0	1	1	2	2	4	0	1	1	6
19	2	2	4	2	2	4	0	0	0	8
20	0	0	0	2	2	4	0	1	1	5
21	2	2	4	2	2	4	2	2	4	12
22	2	2	4	2	2	4	2	2	4	12

Total scores

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Critical error
1	4	4	4	4	4	4	24	100	
2	4	4	4	1	4	4	21	88	
3	4	4	1	4	4	4	21	88	
4	4	4	2	4	4	4	22	92	
5	4	4	4	4	4	4	24	100	
6	4	4	4	4	4	2	22	92	
7	4	4	4	4	4	1	21	88	
8	4	4	1	4	4	4	21	88	
9	4	4	2	4	3	0	17	71	
10	4	4	4	4	3	4	23	96	
11	4	4	2	4	4	0	18	75	
12	4	4	2	4	4	4	22	92	
13	1	4	4	0	4	0	13	54	CE
14	4	4	2	0	4	4	18	75	
15	4	4	4	4	4	4	24	100	
16	4	4	4	3	4	4	23	96	
17	4	4	2	2	4	0	16	67	CE
18	4	4	4	1	4	1	18	75	
19	4	4	2	4	4	0	18	75	
20	4	4	1	0	4	1	14	58	
21	4	4	2	4	4	4	22	92	
22	4	4	4	4	4	4	24	100	

The scores proposed by us were evaluated by a second advisor and confirmed at the Scientific Advisory Board meeting in November 2018. At this meeting the cut off point for satisfactory performance was set (see below). Labs failing to reach this mark or making a critical error will receive a performance advice letter.

Performance

	Number of labs	% total labs
Satisfactory performers (≥ 60 % of adequate responses)	19	86
Unsatisfactory performers (< 60 % adequate responses and/or critical error)	3	14
Partial and non-submitters	0	0

Overall Proficiency

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Total (%)
Sample 2018-A	Dihydropyrimidine DeH deficiency	95	98	97
Sample 2018-B	IsovalerylCoA dehydrogenase deficiency	100	100	100
Sample 2018-C	MPS IV	68	75	72
Sample 2018-D	Lesch-Nyhan, HPRT deficiency	80	73	76
Sample 2018-E	Phenylketonuria	95	100	98
Sample 2018-F	GM1 gangliosidosis	61	68	65

10. Assessment of performance

The Scientific Advisory Board of ERNDIM sets the level of good performance within a proficiency scheme. Letters of support to those laboratories with clear poor performance will be issued. The level for satisfactory performance for this year was set at the SAB meeting in November. The concept of **critical error** was introduced in 2014**.** 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 2018 samples **A, B, C, E and F** qualified as possible critical errors.
Sample D was scored normally but not considered to be valid for critical error. No samples were considered to be educational.
The level set for **satisfactory performance is fifteen points** and below this is evaluated as unsatisfactory.
Note to educational samples: Samples may be classed as 'educational' in exceptional cases, e.g. when the metabolite pattern in a sample is particularly challenging and diagnosis is hard to reach or when non-standard methods are required. The Scientific Advisory Board decides whether a sample is classed as educational. When a sample, that has been classed as educational in an earlier survey, is circulated again it will be scored routinely and cannot be educational for a second time.

11. Annual meeting of participants

The annual meeting of participants of this DPT centre took place, alongside those of the other four centres. during the SSIEM annual symposium in Athens on September 4th. This was attended by 21 participants representing 13 centres. The agenda included:

- Organisational aspects, samples, delivery, reporting improvements?
- Reports on individual samples performance
- Overall performance and scores
- Critical error samples
- Perspectives / Discussion
    - How to improve performance for certain types of disorder
    - Do our current EQA schemes meet emerging needs e.g. due to technology changes
- DPT meeting in 2019: this is planned to be held at the SSIEM annual symposium in Rotterdam, September 3rd.

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.

12. 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 29 and 30 April 2019 near Zurich. The program for biochemists includes:
        - Glycogen Storage Disorders
        - CDG Syndromes
        - Mitochondrial Disease
        - Neurotransmitters disorders
    - 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!). Annex 1 gives the list of the urine samples we already sent.

  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. Then aliquot the sample in 10 ml plastic tubes (minimum 48 tubes), add stoppers and freeze. Be careful to constantly homogenize the urine while aliquoting the sample. Send the aliquots on dry ice by rapid mail or express transport to:

  Brian Fowler / Matthias Baumgartner
  Stoffwechselabteilung
  Kinderspital Zürich
  Steinwiesstrasse 75
  8032 Zürich
  phone: ++41 61 704 2826
  E-mail: brian.fowler@ukbb.ch

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

13. Reminders

We remind you that to participate to the DPT-scheme, you must perform at least:

- Amino acids
- Organic acids
- Oligosaccharides
- Mucopolysaccharides

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.

14. Tentative schedule and fee in 2018

Sample distribution	5 February 2019
Start of analysis of Survey 2019/1 Website open	March 4th 2019
Survey 2019/1 - Results submission	March 25th 2019
Survey 2019/1 - Reports	May 20th, 2019
Start of analysis of Survey 2019/2	June 3rd, 2019
Survey 2019/2 – Results submission	June 24th, 2019
Survey 2019/2 - Reports	August 5th, 2019
Annual meeting of participants	Sept 3rd, 2019, Rotterdam SSIEM
Annual Report 2019	December 2019

Fee was set at €459.

15. 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, 2019-04-09
Name and signature of Scientific Advisor

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