



Scientific Coordination

ERNDIM

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Diagnostic Proficiency Testing Survey 2016 - Switzerland

Final Report

**prepared by
Brian Fowler**

1. Geographical distribution of participants

In 2016, 21 laboratories from 11 countries subscribed to the scheme. All laboratories submitted results for both sample batches.

Country	Number of participants
Australia	2
Austria	2
Canada	3
China	1
Estonia	1
Germany	3
Norway	1
Sweden	2
Switzerland	1
USA	4
UK	1

2. Samples and Shipment

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.

This year, in addition to the common sample and those originating from our own centre, **samples were donated by: K. Ounap, Tartu, Estonia; S. Scholl-Bürgi, Innsbruck, Austria,** to whom we express our gratitude.

The urine samples were distributed to participants on February 2nd at ambient temperature by CSCQ using the courier DHL. Delivery times of samples reported by the courier were all within a maximum of five days although 5 labs reported later receipt dates suggesting possible internal delays within the institution (see below).

3. Tests

Ability to analyse amino acids, organic acids, mucopolysaccharides, oligosaccharides and purines/pyrimidines was required in 2016.

4. Schedule of the scheme in 2016

Sample distribution	Feb 1 st 2016
Start of analysis of Survey 2016/1	Feb 22 nd , 2016
Survey 2016/1 - Results submission	March 14 th , 2016
Survey 2016/1 - Reports on website	May 15 th , 2016
Start of analysis of Survey 2016/2	May 23 rd , 2016
Survey 2016/2 – Results submission	June 6 th , 2016
Survey 2016/2 - Reports on website	July 31 st , 2016
Annual meeting of participants	SSIEM, Rome, September 6, 2016
Annual Report 2016	December 2016

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. Receipt of samples and results

Receipt of samples (sent on Feb 02, 2016)

Date after shipment	Delivery reported by courier	Delivery reported by participants
03 Feb	10	7
04 Feb	8	7
05 Feb	1	-
08 Feb	2	1
11 Feb		1
16 Feb		1
19 Feb		1
22 Feb		1
16 May !!		1
?		1

Discrepancies must be due to delays within the institution or incorrect recording on result submission. Specific details regarding your own sample are available on request.

Date of reporting of results

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

6. Scoring system

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. Results of samples and evaluation of reporting

Sample A: Hyperoxaluria type 2

Patient details provided

At the age of 5 years this boy was referred for the first time to a pediatric nephrologist, because of urolithiasis. At ages 7 and 10, again renal stones were found. At the time of the urine collection, he was 10 y old and in good health. He used no medication, had a normal diet and adequate renal function.

Further information

This was the common sample, distributed by the DPT centre in the Netherlands and came from a child with Hyperoxaluria type 2 due to glyoxylate reductase deficiency caused by mutations in the GRHPR gene.

Analytical performance:

The finding of increased glyceric acid (20 labs) and of oxalic acid (10 labs) each scored one point.

Interpretative proficiency

Glyceric aciduria due to hyperoxaluria was considered to be correct and scored two points (20 labs). The finding of no abnormality without a recommendation to measure oxalate was incorrect and received no point (1 lab).

Overall impression: High proficiency although half of labs did not find elevated oxalate, possibly related to organic acid extraction problems.

This sample was considered by the SAB to be eligible for critical error.

Analytical Details

Creatinine

n=21
median= 4.64
mean= 4.60
SD= 0.02
min, max= [4.31, 4.86]

pH

n=10
median= 6.25
mean= 6.25
SD= 0.06
min, max= [6.00, 6.50]

Spot tests

All negative.

Organic Acid Analysis

	n	points
Glyceric acid	20	1
Oxalic acid	10	1

Glyceric acid

n=11
median= 1000.00
mean= 915.10
SD= 785.34
min, max= [17.40, 2731.00]

Oxalic acid

n=5
median= 222.00
mean= 254.00
SD= 178.03
min, max= [11.00, 465.00]

Interpretation

	n	Points
Glyceric aciduria due to hyperoxaluria	20	2
No abnormality without rec. for oxalate measurement	1	0

Full details of the results of this common sample are to be found on the ERNDIM website with the following link:

<http://www.erndim.org/store/docs/ERNDIMDPTcommonsample201-ANUUFFEB114938-07-11-2016.pdf>

Sample B: HMG-CoA-lyase deficiency

Patient details provided:

Normal delivery, metabolic decompensation with acidosis at 2 days. Urine collected on treatment.

Further information

Normal delivery, metabolic decompensation with marked acidosis and hyperammonaemia at 2 days, muscular hypotonicity and general deterioration, poor feeding, tachydyspnea. Urine collected on treatment. Diagnosis confirmed by enzyme assay. Mutation analysis showed homozygosity for p.E37X.

Analytical performance:

The finding of increased 3-Hydroxy-3-methyl glutaric acid (20 labs) with or without associated metabolites was scored with two points.

Interpretative proficiency:

A diagnosis of 3-hydroxy-3-methylCoA lyase deficiency was correct and received two points.

Overall impression

There was very high proficiency of a straightforward sample.

This was considered by the SAB to be eligible for critical error.

Analytical Details

Creatinine

n=21
median= 2.79
mean= 2.75
SD= 0.01
min, max= [2.36, 2.95]

pH

n=10
median= 7.00
mean= 7.05
SD= 0.02
min, max= [7.00, 7.50]

Spot tests

All negative

Organic acid analysis

	n	points
3-Hydroxy-3-methyl glutaric acid	20	2
3-methylglutaconic acid	1	1

Quantitative data submitted

3-hydroxy-3-methylglutaric acid

n=7
median= 1163.00
mean= 1643.11
SD= 1303.35
min, max= [170.00, 4598.00]

3-methylglutaconic acid

n=8
median= 1127.45
mean= 1163.61
SD= 509.29
min, max= [413.00, 2093.00]

Quantitative data submitted continued

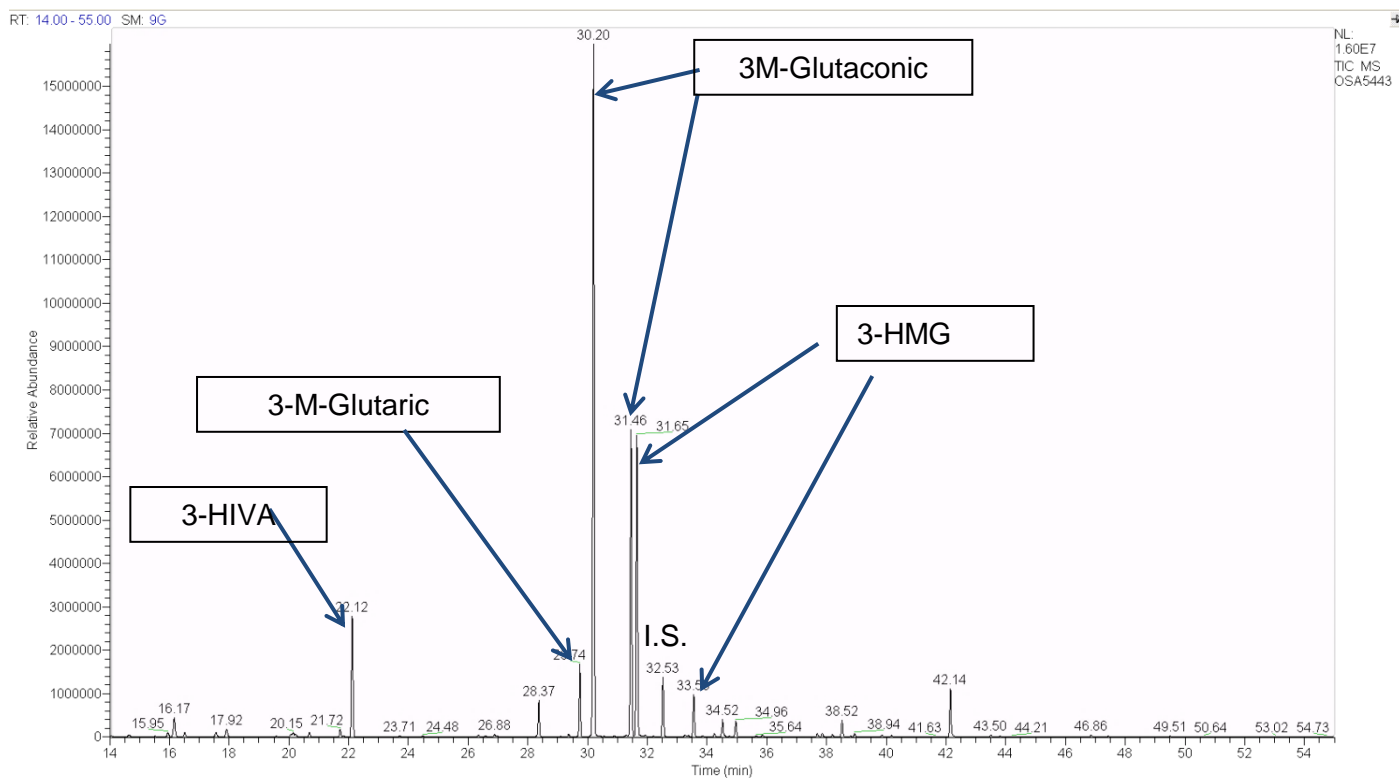
3-methylglutaric acid
 n=9
 median= 141.00
 mean= 156.21
 SD= 43.93
 min, max= [119.00, 270.00]

3-hydroxyisovaleric acid
 n=8
 median= 477.50
 mean= 700.70
 SD= 614.95
 min, max= [90.00, 2059.00]

Interpretation

	n	Points
HMGCoA lyase deficiency	20	2
3 methylglutaconylCoA hydratase deficiency	1	0

Organic acids - GC-MS



Sample C: Cystine / dibasic aminoaciduria

Patient details provided:

Asymptomatic sibling of older sister who initially presented at 2y with strange urine odour, otherwise unremarkable.

Further information

12 year old girl diagnosed at age 4 years, incidentally being asymptomatic, no mutation analysis, no complications while under treatment.

Analytical performance:

Increased cysteine and basic amino acids was scored with two points (19 labs).

Interpretative proficiency:

A diagnosis of cystinuria received two points, unspecified dibasic aminoaciduria was scored with one point.

Overall impression

A straightforward sample with high proficiency, if not as high as expected.

Sample from probable heterozygous cystinuria and considered by the SAB not to be eligible for critical error.

Analytical Details

Creatinine

n=21
median= 1.42
mean= 1.43
SD= 0
min, max= [1.27, 1.55]

pH

n=11
median= 9.00
mean= 9.00
SD= 0.15
min, max= [8.50, 10.00]

Spot tests

Two labs reported increased sulphides.

Amino acid analysis

Cystine

n=19
median= 143.00
mean= 190.74
SD= 214.41
min, max= [43.00, 1093.00]

Lysine

n=19
median= 388.00
mean= 559.88
SD= 728.14
min, max= [110.00, 3629.00]

Arginine

n=17
median= 16.60
mean= 27.67
SD= 47.15
min, max= [7.00, 216.00]

Ornithine

n=19
median= 40.00
mean= 54.34
SD= 65.43
min, max= [13.00, 330.00]

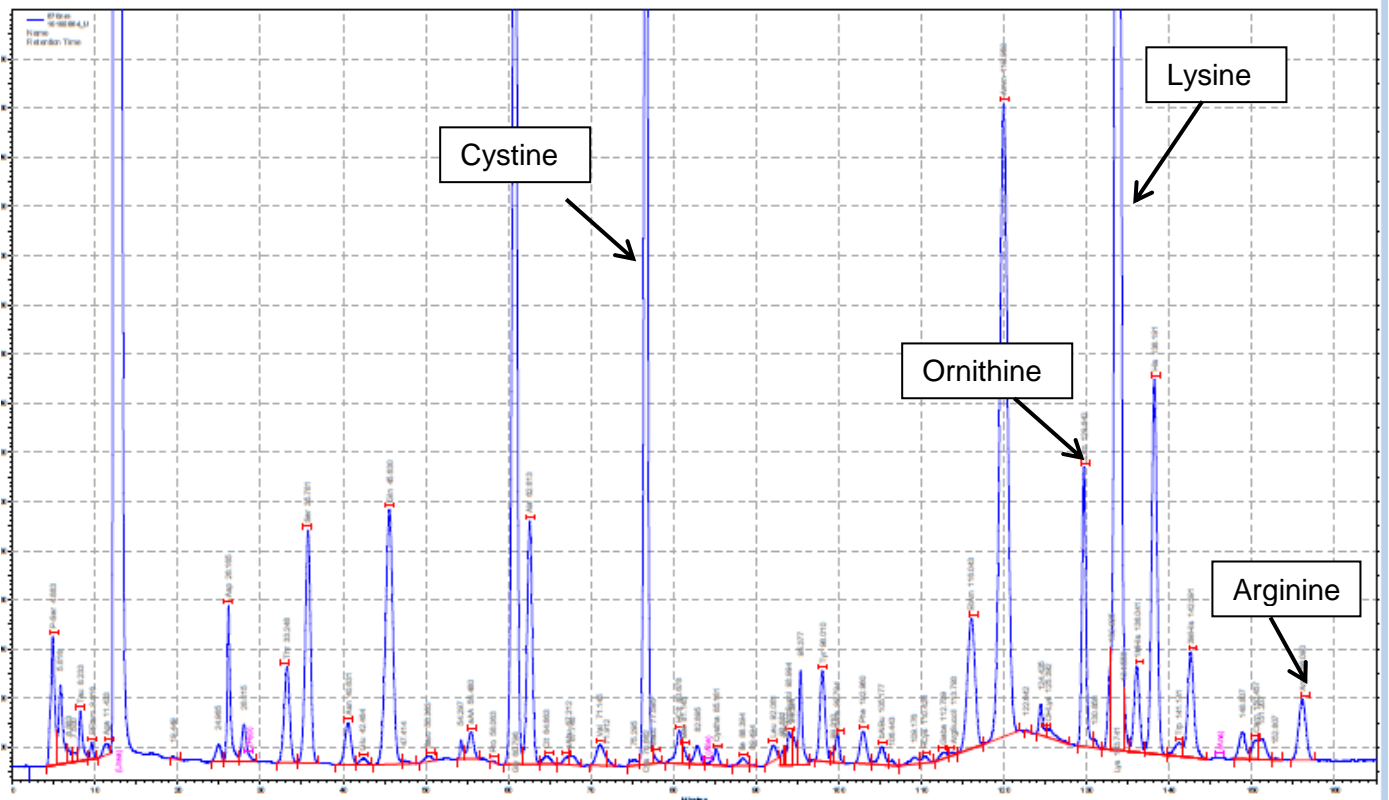
Amino acid analysis continued

	n	points
Cystine / Basic amino acids	19	2
No abnormality	2	0

Interpretation

	n	Points
Cystinuria	18	2
"dibasic aminoaciduria, unspecified"	1	1
Trimethylaminuria	1	0
No diagnosis given	1	0

Amino Acids – Ion Exchange



Sample D: Ornithine aminotransferase deficiency: OMIM 258870

Patient details provided:

16 year old male patient in good general condition and normal intellectual status with myopia since 5y. (urine collected on treatment).

Further information

16 year old male patient in good general condition and normal intellectual status with myopia which has been continually worsening since the age of 5. Two and a half year delay in bone age assessed at the age of 15. Ophthalmological examination shows myopic astigmatism and gyrate atrophy of the choroid and retina. Plasma ornithine 877 µmol/l. Homozygous mutation of the ornithine aminotransferase gene (c.498C>A in Exon 4, p.Tyr166Ter), treated with protein-restricted diet, vitamin B6 and creatine supplementation

Analytical performance:

The finding of increased ornithine (19 labs) was scored with two points.

Interpretative proficiency:

All labs that identified increased ornithine made the correct diagnosis of hyperornithinemia, scored with two points (19 labs). No diagnosis but recommendation to measure plasma amino acids received one point.

Overall impression:

There was high overall efficiency with this sample which showed a moderately, but not greatly elevated level of ornithine. Just two labs failed to report this and one of these gave a correct recommendation to check plasma amino acids.

Sample considered by the SAB not to be eligible for critical error.

Analytical Details

Creatinine

n=20
median= 12.11
mean= 11.96
SD= 0.91
min, max= [9.21, 13.29]

pH

n=10
median= 8.00
mean= 8.10
SD= 0.09
min, max= [8.00, 9.00]

Spot tests

All negative

Amino acid analysis (n= 21)

	n	points
Ornithine elevated	19	2
Amino acids normal	2	0

Amino acid analysis

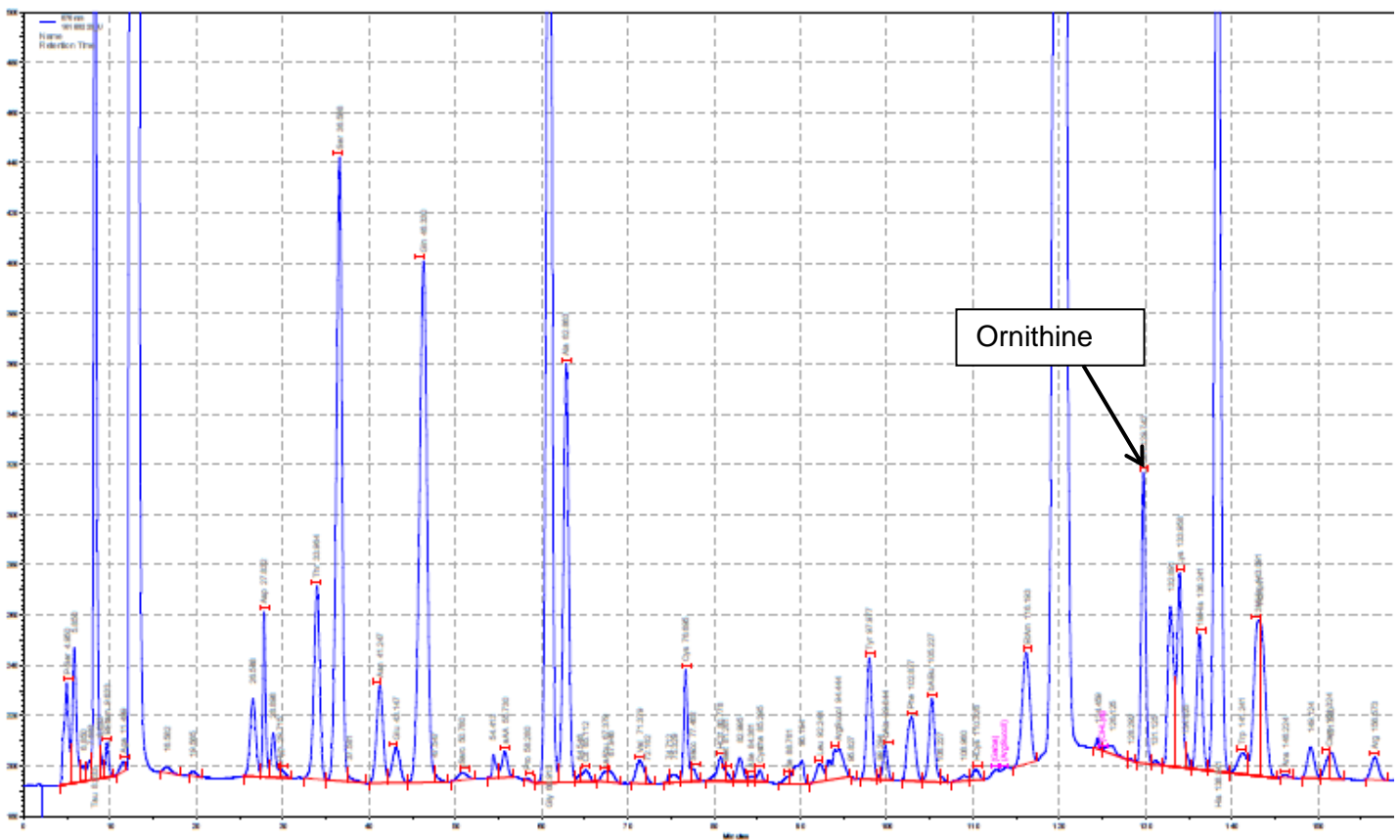
Ornithine

n=19
 median= 19.60
 mean= 25.74
 SD= 28.41
 min, max= [8.00, 145.00]

Interpretation

	n	Points
Hyperornithinemia	19	2
No diagnosis with recommendation to measure plasma amino acids	1	1
No diagnosis	1	0

Amino Acids – Ion exchange



Sample E: argininosuccinate lyase deficiency: OMIM 207900

Patient details provided:

Normal delivery, vomiting and somnolence at 3 days of age. Urine collected on treatment.

Further information

This is a treated case of ASuria confirmed by mutation analysis.
(p.Glu189Gly/p.Gly316Aspfs*24)

Analytical performance: The finding of elevated arginino-succinic acid was scored with two points (21 labs).

Interpretative performance

All labs made the correct diagnosis of argininosuccinic aciduria due to argininosuccinate lyase deficiency

Overall impression:

Excellent proficiency of 100%.

The SAB considered that this sample would have been eligible for critical error.

Analytical Details

Creatinine
n=20
median= 5.93
mean= 5.78
SD= 0.30
min, max= [3.99, 6.38]

pH
n=10
median= 8.00
mean= 8.30
SD= 0.17
min, max= [8.00, 9.00]

Spot tests

All negative

Amino acid analysis (n= 21)

	n	points
Elevated arginino-succinic acid	21	2

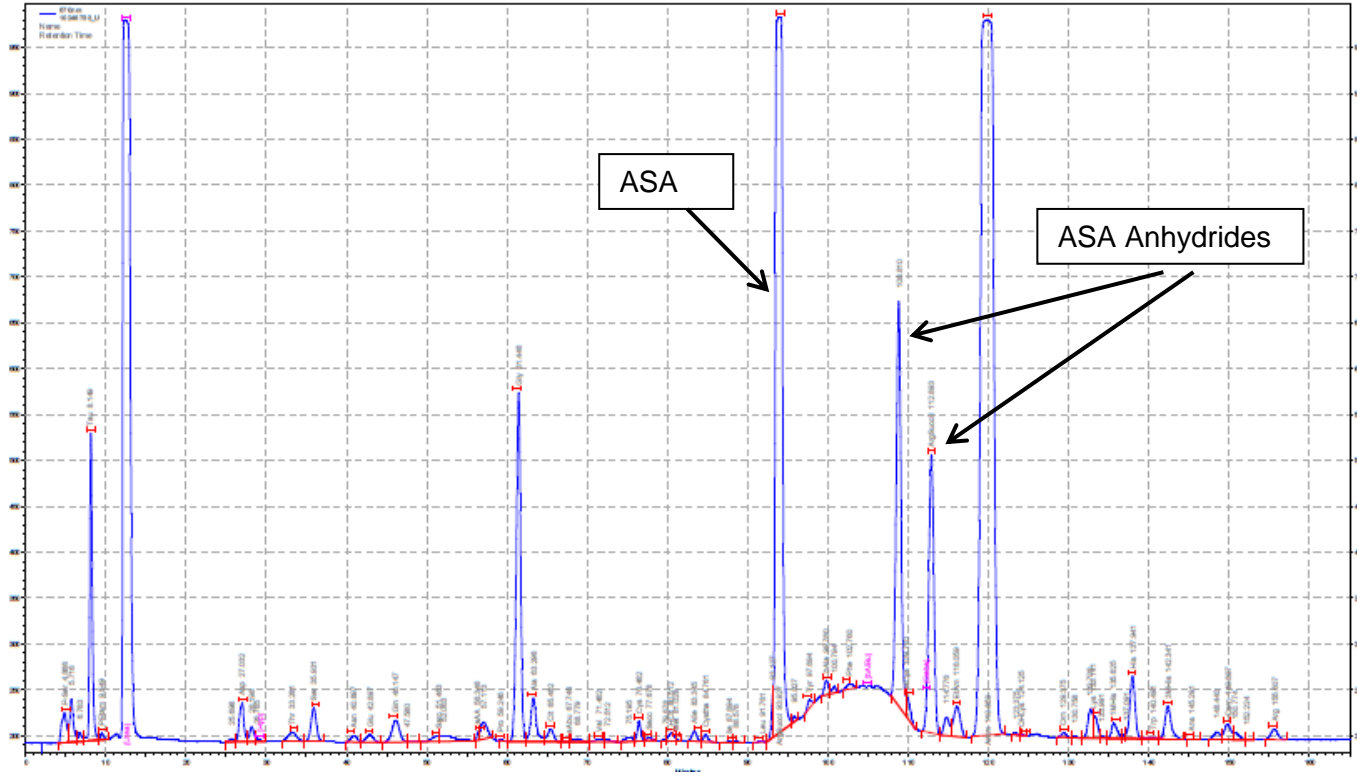
Arginino-succinic acid
n=13
median= 2300.00
mean= 2849.13
SD= 2610.12
min, max= [18.48, 9316.00]

ASA anhydrides
n=2
median= 1750.00
mean= 1750.00
SD= 450.00
min, max= [1300.00, 2200.0]

Interpretation

	n	Points
Arginino-succinic aciduria	21	2

Amino Acids – Ion Exchange



Sample F: Aromatic L-Aminoacid Decarboxylase (AADC) deficiency

Patient details provided:

Developmental delay and muscular hypotonia, no treatment

Further information

At 3 months showed developmental delay and muscular hypotonia. At 9 months hypotonia confirmed, brisk tendon reflexes and positive Babinski sign, not turning over or crawling, no head control. Diagnosed at 9.5 years with failure to thrive, and severe developmental delay, (lack of speech and spastic tetraparesis and dystonias evident).

Urinary DOPA was greatly elevated but vanillactate not dramatically elevated at 2.6 mmol/mol creatinine.

Diagnosis was confirmed by enzyme and molecular analysis.

This sample showed mildly increased excretion of vanillactate of 0.55 mmol/mol creatinine (normal in adults <0,08 mmol/mol creatinine).

Analytical performance:

Performance was low since the key metabolite for this disorder was reported to be increased by just three labs.

Interpretative proficiency:

Those three labs that found increased vanillactate made the correct diagnosis of aromatic L-Aminoacid Decarboxylase (AADC) deficiency.

Overall impression:

This was clearly a very difficult sample that will NOT be scored. Nevertheless it did contain a slightly increased level of the key metabolite, vanillic acid pointing to the need to look for this very carefully in organic acid analysis. Further, if quantitated. control values must be age matched.

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

Analytical Details

Creatinine

n=20
median= 12.90
mean= 12.95
SD= 0.30
min, max= [11.74, 13.83]

pH

n=10
median= 6.00
mean= 5.70
SD= 0.28
min, max= [5.00, 6.50]

Spot tests

All negative

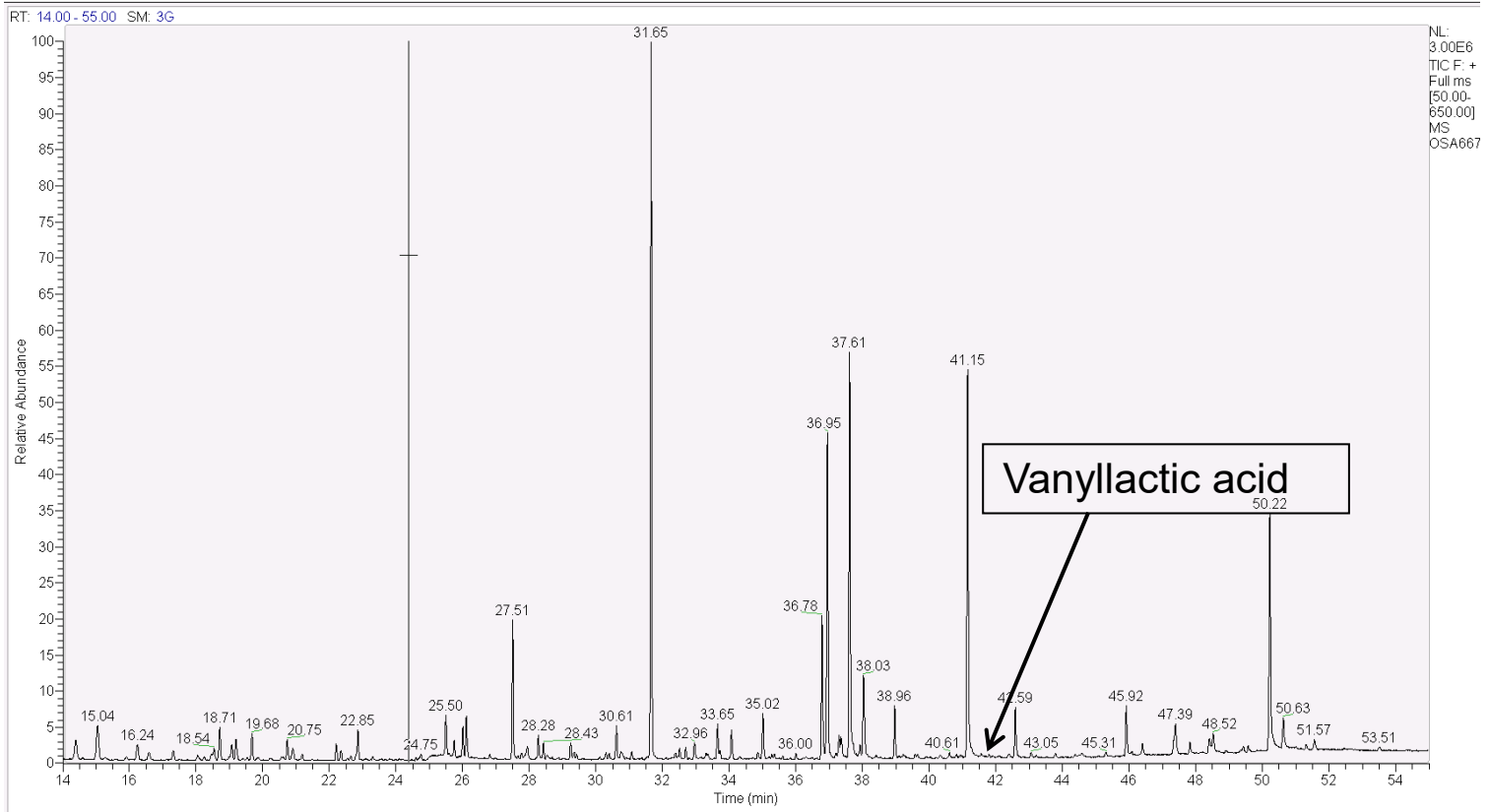
Organic acid analysis

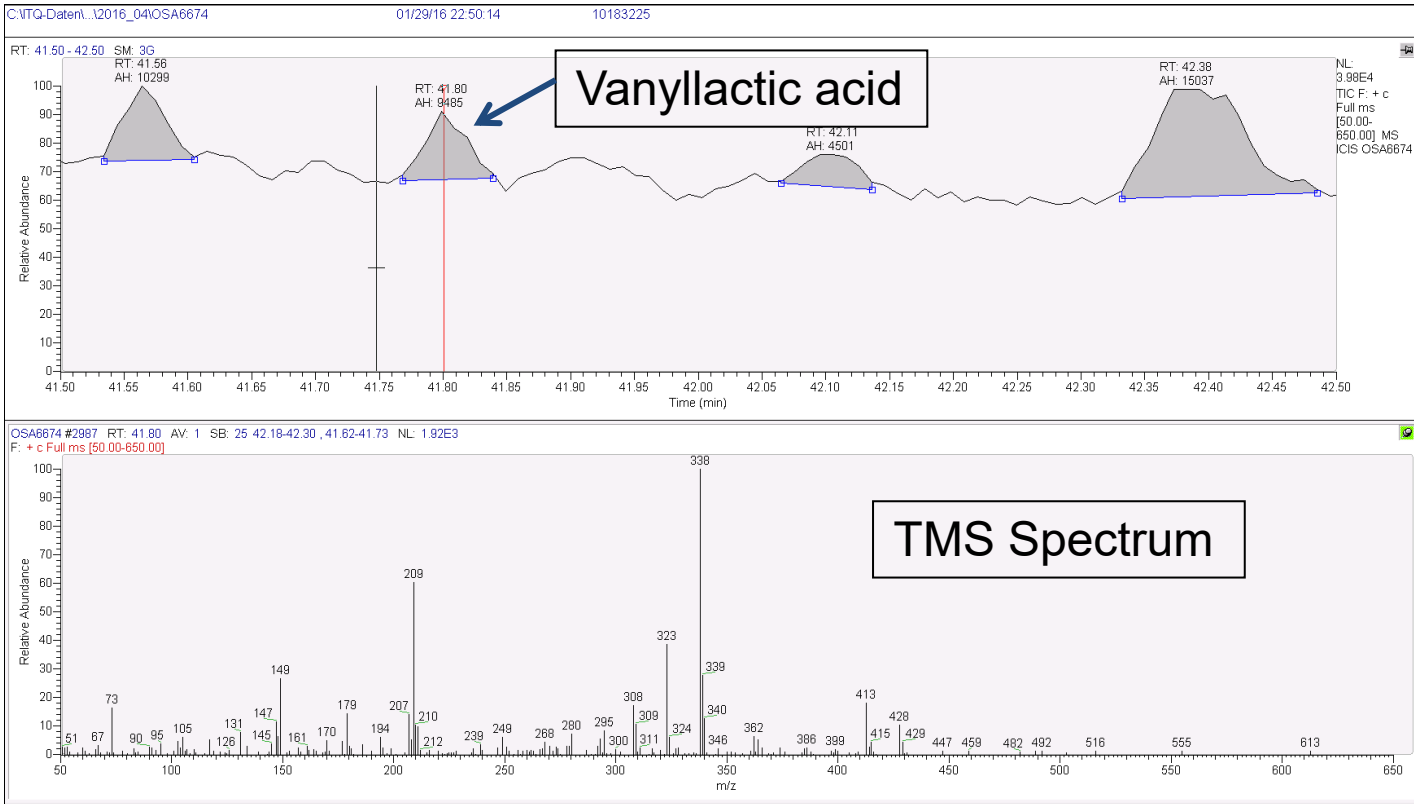
	n	points
Vanillic acid elevated	3	2

Interpretation

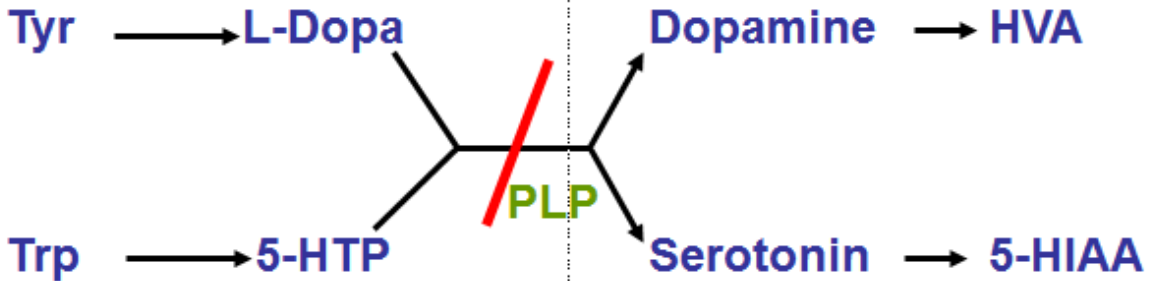
	n	Points
aromatic L-Aminoacid Decarboxylase (ADC) deficiency	3	2
No abnormality / Normal	13	0
Pu/Py disorder	2	0
Biotinidase deficiency	1	0
CDG Syndrome	1	0
MPS III	1	0

Organic acids - GC-MS





Aromatic Amino Acid Decarboxylase Deficiency



Clinical features resemble those of recessive BH4 deficiency; hypotonia, oculogyric crises, ptosis and paucity of spontaneous movement. Can be fatal

Urine: Vanill-lactic acid (Organic acid analysis)

CSF: Low HVA + 5-HIAA, but *normal* pterin profile and accumulation of 3-O-methyldopa. Enzymatic analysis possible on plasma.

Treatment; B6, MAOI & dopamine agonists.

8. Scores

Overall proficiency

Sample	Diagnosis	A (%)	I (%)	total (%)
A	Hyperoxaluria type 2	74	95	85
B	HMG-CoA-lyase deficiency	98	95	96
C	Cystine / dibasic aminoaciduria	90	88	89
D	Ornithine aminotransferase deficiency	90	93	92
E	argininosuccinate lyase deficiency	100	100	100
F	Aromatic L-Aminoacid Decarboxylase (AADC) deficiency	14	14	14

Total scores

Lab No	Survey 1			Survey 2			Total (F not scored)
	A	B	C	D	E	F	
1	4	4	4	4	4	0	20
2	4	4	4	4	4	0	20
3	3	4	4	4	4	0	19
4	4	4	4	4	4	0	20
5	3	4	4	4	4	0	19
6	4	1	4	4	4	0	17
7	4	4	4	4	4	0	20
8	4	4	4	4	4	0	20
9	3	4	0	4	4	0	15
10	4	4	0	0	4	0	12
11	3	4	3	4	4	0	18
12	3	4	4	4	4	4	19
13	0	4	4	4	4	0	16
14	3	4	4	4	4	0	19
15	3	4	4	1	4	0	16
16	3	4	4	4	4	0	19
17	4	4	4	4	4	4	20
18	4	4	4	4	4	0	20
19	4	4	4	4	4	0	20
20	3	4	4	4	4	0	19
21	4	4	4	4	4	4	20

The scores proposed by us were evaluated by a second advisor and confirmed at the Scientific Advisory Board meeting in November 2016. 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.

Detailed Scores: A,B,C

Lab no	Sample A Hyperoxaluria II			Sample B HMG CoA lyase ef.			Sample C Cystinuria			Total
	A	I	Total	A	I	Total	A	I	Total	
1	2	2	4	2	2	4	2	2	4	12
2	2	2	4	2	2	4	2	2	4	12
3	1	2	3	2	2	4	2	2	4	11
4	2	2	4	2	2	4	2	2	4	12
5	1	2	3	2	2	4	2	2	4	11
6	2	2	4	1	0	1	2	2	4	9
7	2	2	4	2	2	4	2	2	4	12
8	2	2	4	2	2	4	2	2	4	12
9	1	2	3	2	2	4	0	0	0	7
10	2	2	4	2	2	4	0	0	0	8
11	1	2	3	2	2	4	2	1	3	10
12	1	2	3	2	2	4	2	2	4	11
13	0	0	0	2	2	4	2	2	4	8
14	1	2	3	2	2	4	2	2	4	11
15	1	2	3	2	2	4	2	2	4	11
16	1	2	3	2	2	4	2	2	4	11
17	2	2	4	2	2	4	2	2	4	12
18	2	2	4	2	2	4	2	2	4	12
19	2	2	4	2	2	4	2	2	4	12
20	1	2	3	2	2	4	2	2	4	11
21	2	2	4	2	2	4	2	2	4	12
ratio	31/42	40/42	71/84	41/42	40/42	81/84	38/42	37/42	75/84	
%	74	95	85	98	95	96	90	88	89	

Detailed Scores: D,E,F

Lab no	Sample D Hyperornithinaemia			Sample E ASAuria			Sample F AADC def.			Total
	A	I	Total	A	I	Total	A	I	Total	
1	2	2	4	2	2	4	0	0	0	8
2	2	2	4	2	2	4	0	0	0	8
3	2	2	4	2	2	4	0	0	0	8
4	2	2	4	2	2	4	0	0	0	8
5	2	2	4	2	2	4	0	0	0	8
6	2	2	4	2	2	4	0	0	0	8
7	2	2	4	2	2	4	0	0	0	8
8	2	2	4	2	2	4	0	0	0	8
9	2	2	4	2	2	4	0	0	0	8
10	0	0	0	2	2	4	0	0	0	4
11	2	2	4	2	2	4	0	0	0	8
12	2	2	4	2	2	4	2	2	4	12
13	2	2	4	2	2	4	0	0	0	8
14	2	2	4	2	2	4	0	0	0	8
15	0	1	1	2	2	4	0	0	0	8
16	2	2	4	2	2	4	0	0	0	8
17	2	2	4	2	2	4	2	2	4	12
18	2	2	4	2	2	4	0	0	0	8
19	2	2	4	2	2	4	0	0	0	8
20	2	2	4	2	2	4	0	0	0	8
21	2	2	4	2	2	4	2	2	4	12
ratio	38/42	39/42	77/84	42/42	42/42	84/84	6/42	6/42	12/84	
%	90	93	92	100	100	100	14	14	14	

9. Assessment of performance

Steps have been taken within the Scientific Advisory Board of ERNDIM to set 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. A special meeting of scientific advisors took place in November 2012 to consider how to harmonise scoring within all our qualitative schemes and the question of introducing critical errors in our schemes. Here it was decided to incorporate recommendations into interpretation giving a 2 plus 2 scoring system. Also 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.

This year samples **A, B** and **E** qualified as possible critical error.

Sample F was judged to be educational and its scores were not included in assessment of overall performance. Thus the level set for **satisfactory performance is twelve points** and below this is evaluated as unsatisfactory.

10. Annual meeting

The annual meeting of participants of this DPT centre took place, alongside those of the other four centres. during the SSIEM symposium in Rome on Tuesday, September 6th, 09.00. This was attended by 31 participants representing 14 centres. The agenda included:

- Discussion of organisational aspects, samples, delivery problems, and any requests for reporting improvements.
- Results of the individual samples, consensus on scoring and participants' performance.
- Overall performance and scores.
- Proposals for critical error samples.
- Future perspectives.
- DPT meeting in 2017: since there will be no SSIEM meeting in 2017 but the ICIEM in Brazil it is planned to hold an extended ERNDIM meeting which will also include the DPT meetings in late 2017 (it is envisaged that this will take place on November 21/22 2017).

11. Changes planned for 2017

No changes are envisaged

12. Tentative schedule and fee in 2017

Sample distribution	February 6 th , 2017
Start of analysis of Survey 2017/1	February 20 th , 2017
Survey 2017/1 - Results submission	March 13 th , 2017
Survey 2017/1 - Reports	May 15 th , 2017
Start of analysis of Survey 2017/2	May 22 nd , 2017
Survey 2017/2 – Results submission	June 12 th , 2017
Survey 2017/2 - Reports	July 31 st , 2017
Annual meeting of participants	ERNDIM meeting November 21/22 2017
Annual Report 2017	December 2017

Fee was set at €416.

13. 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.

Basel / Zürich, January 2017

Brian Fowler
Scientific advisor