



ERNDIM DPT Centre Basel

***University Children's Hospital
Paediatrics***

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***Diagnostic Proficiency Testing
Survey 2012***

Final Report

**prepared by
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1. **Geographical distribution of participants**

In 2012, 21 laboratories from 10 countries subscribed to the scheme. For the first survey 20 laboratories submitted results.

Country	Number of participants
Austria	1
Canada	4
China	1
Estonia	1
Germany	5
Norway	1
Sweden	2
Switzerland	2
UK	1
USA	3

2. **Samples and Shipment**

The samples contain a small amount of thiomersal and 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. The urine samples were distributed to participants on May 22nd at ambient temperature by CSCQ using the courier DHL. Delivery times of samples reported by the courier ranged from 1 to 5 days. There were discrepancies with times reported by participants suggesting possible internal delays.

3. **Tests**

Analyses of amino acids, organic acids, mucopolysaccharides, oligosaccharides and purines/pyrimidines were required in 2012.

4. **Schedule of the scheme in 2012**

Sample distribution	May 22 2012
Start of analysis of Survey 2012/1	June 04, 2012, Monday
Survey 2012/1 - Results submission	June 25, 2012, Monday
Survey 2012/1 - Reports	July 06, 2012, Friday
Start of analysis of Survey 2012/2	July 09, 2012, Monday
Survey 2012/2 – Results submission	July 30, 2012, Monday
Survey 2012/2 - Reports	August 15, 2012, Friday
Annual meeting of participants	Sept 04, 2012, in Birmingham at SSIEM
Annual Report 2012	December

Please note there was a delay in issuing reports for the surveys. This is because we have developed a programme for evaluation of results which enormously lightens the load of the scientific advisor and automatically produces individual reports for each participant. Since this is the first time we use this there are understandably some teething problems but nevertheless we expect to be able to issue the new types of results reports for all six samples before the end of August.

5. Receipt of samples and results

Receipt of samples (sent on May 22, 2012)

Receipt (days after shipment)	No. Labs	Delivery reported by DHL
1	8	
2	2	
3	4	
6	2	
9	3	

Date of reporting of results

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

6. Scoring system

Three criteria are evaluated: analytical performance, interpretative proficiency and 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 are still reported and summarised by the scheme organisers.

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	Good (diagnosis was established)	2	max 2
		Helpful but incomplete	1	
		Misleading or wrong diagnosis	0	
R	Recommendations	Helpful	1	max 1
		Unsatisfactory or misleading	0	

The **total score** is calculated as a sum of these three criteria. The maximum to be achieved is 5 points per sample. The scores were calculated only for laboratories submitting results.

7. Results of samples and evaluation of reporting

Sample A: Argininosuccinic aciduria due to argininosuccinate lyase deficiency

Patient details

Patient: this sample came from a 20 year old male patient with ASA who is under treatment with arginine. This urine was obtained in our hospital, Basel, Switzerland. Enzymatic or mutational analysis has not been performed but the plasma and urine amino acid profiles and clinical symptoms leave no doubt as to the diagnosis. This sample was also distributed in 2009.

Analytical performance: Two points were given for identification of ASA and/or its anhydrides. 18 of 20 labs identified key metabolites pointing to the correct diagnosis.

Interpretative proficiency: A correct diagnosis was judged to be arginino-succinic aciduria. 18 (90%) labs made the correct diagnosis.

Recommendations: Measurement of blood ammonia, plasma amino acids followed up by fibroblast enzyme studies of mutation analysis are all considered useful. 16 laboratories gave useful recommendations.

Overall impression: This sample was also distributed in 2009. Comparing analytical performance (90% now, 95% then); interpretation (90% now 95% then); follow up recommendations (80% now / 95% then) there is somewhat poorer overall performance that is rather unexpected. It is expected that all labs should be able to identify arginine-succinic acid and its anhydrides, this is especially easy with thin layer chromatography or electrophoresis. There appear to be some difficulties in identification on some amino acid analysers.

Analytical Details

Creatinine

n=20
median= 2.52
mean= 2.70
SD= 0.28
min, max= [2.00, 3.87]

pH

n=12
median= 6.50
mean= 6.58
SD= 0.17
min, max= [6.00, 7.00]

Spot tests

All negative

Aminoacid analysis (n=20)

	n	points
Arginino-succinic acid	17	2
Unusual peaks ?ASA	1	1
ASA anhydrides	5	

Amino acid quantitative/argininosuccinate

n=11

median= 3240.00

mean= 6528.09

SD= 7747.24

min, max= [126.00, 28693.00]

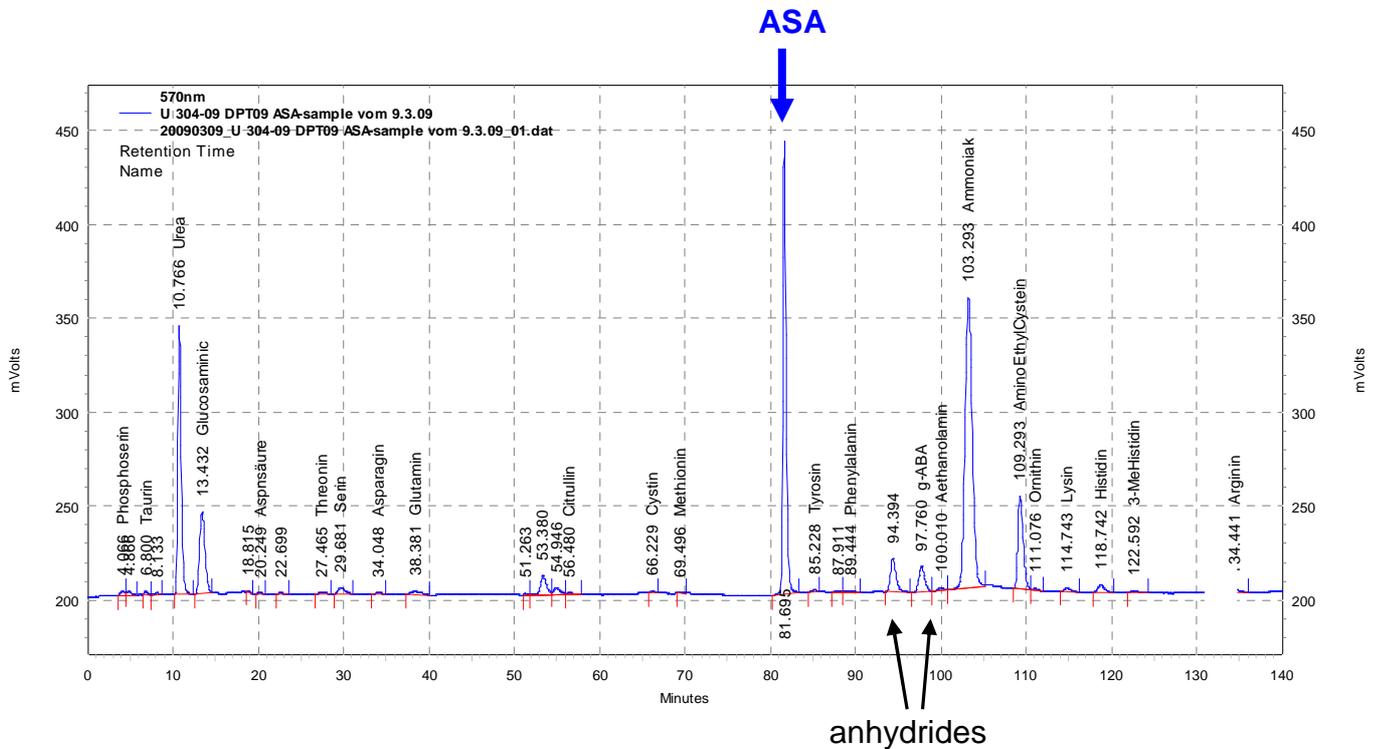
Interpretation

	n	Points
Argininosuccinic aciduria due to argininosuccinate lyase deficiency)	18	2
Hyperprolinaemia	1	0
VinylGABA therapy	1	0

Recommendations for further tests

	n	points
Ammonia	8	1
Plasma amino acids	7	1
Enzyme assay of (ASL)	10	1
Mutations (of ASL)	13 (5)	1
None	2	0
Contact metabolic centre	1	0

Amino acid analysis by Ion exchange chromatography



Sample B: Formiminoglutamic aciduria / formiminotransferase deficiency MIM229100

Patient:

This sample was also distributed in 2010 and was obtained from a 5 year old boy with delayed development and mild epilepsy in whom metabolic screening revealed clearly increased excretion of formimino-glutamic acid. Although the diagnosis has not been confirmed by molecular genetic analysis the finding of FIGLU-uria was confirmed in several urine samples and folate deficiency has been excluded. This urine was obtained in our hospital in Basel, Switzerland.

Analytical performance: One point was given for identification of FIGLU (9 labs) and one for hydantoin-5-propionic acid (8 labs). Overall analytical proficiency was 45%.

Interpretative proficiency: A diagnosis of figlu-uria was considered correct (10 labs).

Recommendations: Ruling out folate deficiency, histidine loading and mutation analysis of the FTCD gene were considered helpful. Useful recommendations were given by each lab except one that correctly identified the metabolic disorder (9 labs, 40%).

Overall impression

Overall proficiency was 46% compared with around 33%, so an improvement but not as much as hoped for.

Analytical Details

Creatinine

n=20
median= 2.48
mean= 2.43
SD= 0.06
min, max= [1.90, 2.84]

pH

n=12
median= 6.50
mean= 6.29
SD= 0.29
min, max= [5.00, 7.00]

Spot tests

All negative except

Glucose (11)	Trace 1	+ 5
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Amino acid analysis (n=20)

	n	points
Figlu	9	1

Amino acid quantitative/formiminoglutamic acid

n=1
median= 1473.00
mean= 1473.00
SD= 0.00
min, max= [1473.00, 1473.00]

Organic acid analysis (n= 20)

	n	points
Hydantoin-5- propionate	8	1

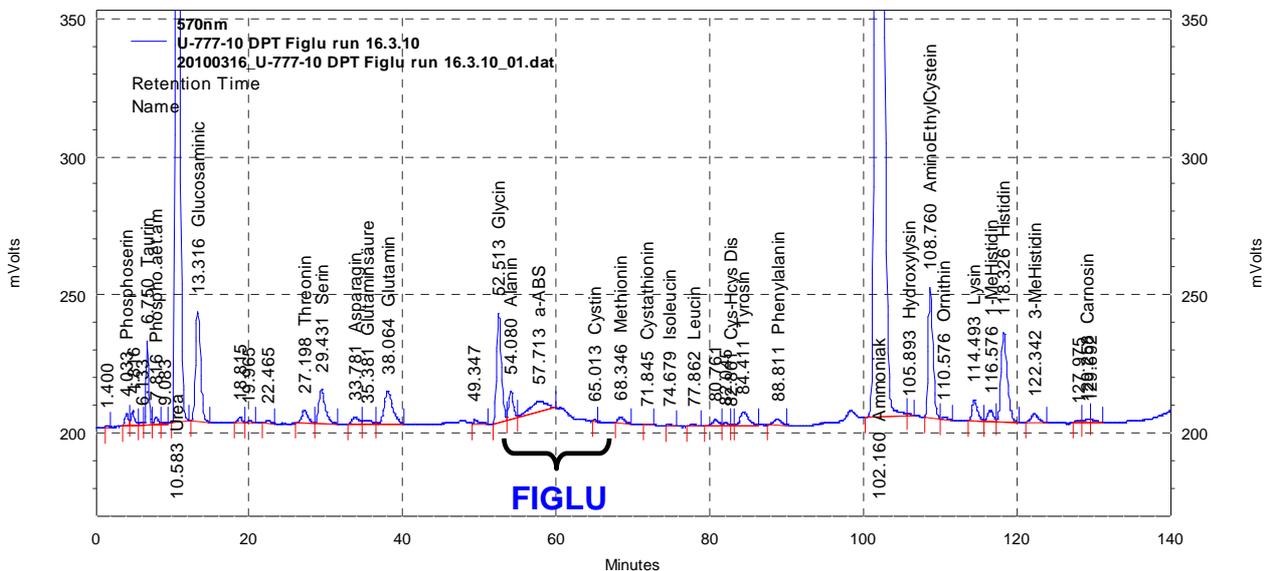
Interpretation

	n	Points
Formiminoglutamic aciduria	10	2
Normal, no IEM	9	0
SCAD deficiency	1	0

Recommendations for further tests

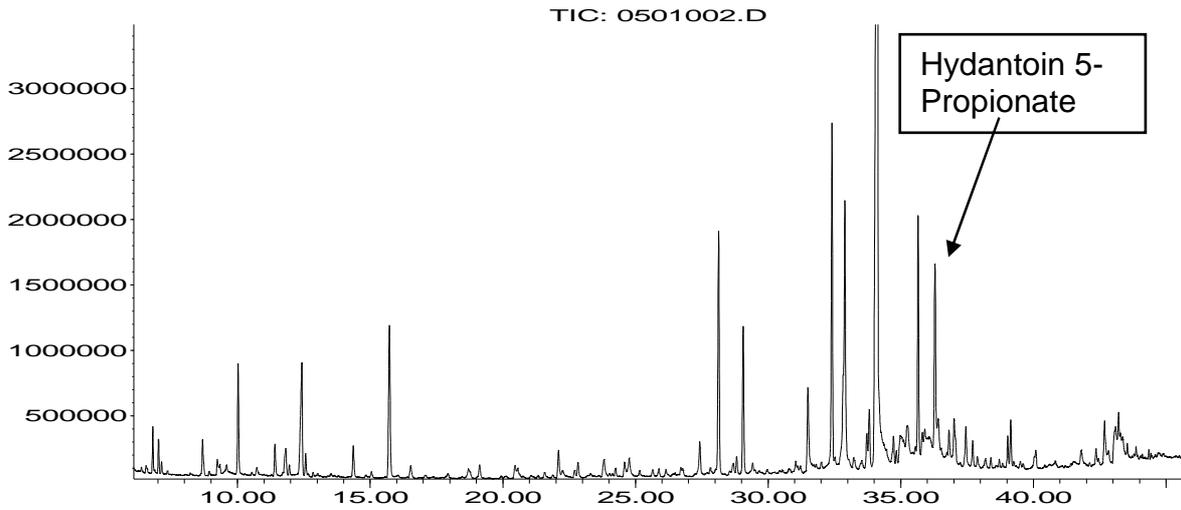
	n	points
Ruling out folate deficiency	7	1
Histidine loading	5	1
mutation analysis (of the FTCD gene)	8(6)	1
Repeat for FIGLU	1	1
Repeat for other analyte	9	0
None	2	0

Amino acid analysis: ion exchange



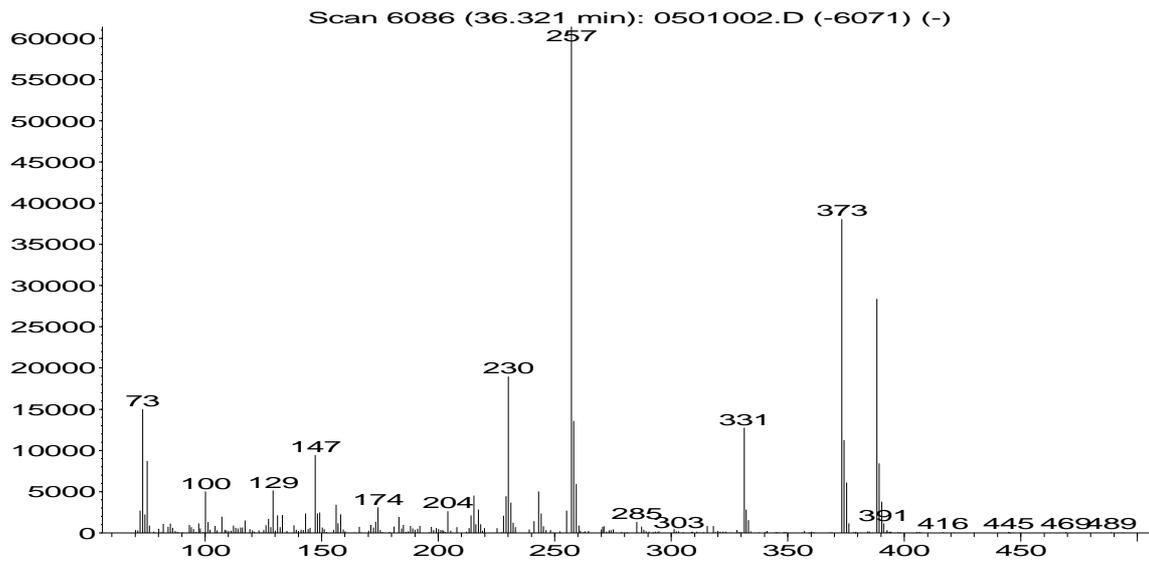
Organic acid analysis

Abundance



Hydantoin 5-Propionate: Mass Spectrum

Abundance



Sample C: Intermittent branched chain aminoaciduria due to branched chain ketoacid decarboxylase deficiency

Patient:

6 year old male, recurrent unexplained ataxia.

Analytical performance: One point was given for increased leucine or allo-isoleucine (19 labs) and one for increased 2-hydroxy isovaleric with or without other branched chain amino acid metabolites (20 labs).

Interpretative proficiency: Reporting MSUD was considered correct. 18 of 20 labs gave this and one gave this as an alternative diagnosis (95%)

Recommendations: Plasma amino acid analysis followed up by assay of BCKDH enzyme complex or mutation analysis of the BCKDH gene was considered useful. Useful recommendations were given by 19 of 20 labs (95%).

Overall impression

Analytical Details

Creatinine

n=20

median= 2.89

mean= 141.21

SD= 382852.41

min, max= [2.48, 2770.00]

pH

n=12

median= 7.00

mean= 7.04

SD= 0.56

min, max= [5.00, 8.00]

Spot tests

Glucose

0: 1

Trace: 0

+: 1

++: 1

+++: 9

Total = 12

Amino Acid analysis (n=20)

		n	points
Leucine	elevated	14	1
Iso leucine	elevated	9	1
Allo-isoleucine	elevated	13	1
Valine	elevated	3	

Organic Acid analysis (n=20)

		n	points
2-hydroxyisovaleric acid	elevated	20	1
2-hydroxy-3-methylvaleric acid	elevated	8	
2-hydroxyisocaproic acid	elevated	5	
2-ketoisocaproic acid	elevated	1	
2-keto-3-methylvaleric acid	elevated	1	

2-hydroxyisovaleric acid

n=9

median= 155.00

mean= 157.82

SD= 54.85

min, max= [36.00, 227.00]

Interpretation

	n	Points
MSUD (intermittent or mild))	18 (6)	2
Citrullinaemia (alternative MSUD)	1	1
Hyperornithinemia-Hyperammonemia-Homocitrullinuria-syndrome under Citrulline-therapy	1	0

Recommendations for further tests

	n	points
Plasma amino acid analysis	15	1
enzyme assay (BCKDH complex)	10(5)	1
mutation analysis (BCKDH gene)	11(4)	1
contact a metabolic centre	2	0

Sample D: Homogentisic aciduria due to homogentisic acid oxidase deficiency

Patient:

The urine was collected from a 39 y old male who was investigated because of arthralgia. There was no treatment. This sample was provided by Prof. Johannes Häberle, Children's Hospital, Zürich

Analytical performance: Two points were given for finding increased homogentisic acid (18 of 20 labs).

Interpretative proficiency: Two points were given diagnosing alcaptonuria (18/20 labs).

Recommendations: Repeat urine analysis, mutation analysis or management suggestions related to the disorder were considered helpful (15).

Overall impression: The level of HGA was very high in this sample so that finding of small or no increase may indicate destruction during extraction e.g. by alkali treatment.

Analytical Details

Creatinine

n=20
median= 2.36
mean= 2.33
SD= 0.55
min, max= [0.80, 3.38]

pH

n=11
median= 5.50
mean= 5.50
SD= 0.25
min, max= [5.00, 6.00]

Spot tests

Glucose

0: 11
Trace: 0
+: 0
++: 0
+++: 0
Total = 11

Organic acid analysis (n= 20)

	n	points
Homogentisic acid elevated	18	2

Homogentisic acid]

n=5
median= 1600.00
mean= 1899.20
SD= 1316.38
min, max= [220.00, 4120.00]

Interpretation

	n	Points
Alcaptonuria	18	2
No disorder	2	0

Recommendations for further tests

	n	points
Repeat urine analysis for HGA	3	1
mutation analysis (specific gene)	8 (7)	1
management suggestions related to the disorder	7	1
Referral to a metabolic specialist	2	0
Other tests	2	0
None	1	0

Sample E: Combined malonic and methylmalonic aciduria due to mutations in the ACSF3 gene.

Patient: The sample was provided by Dr. Elisabeth Holme, Gothenburg, and is from a woman born 1976 who is essentially healthy. At around 20 years of age she was investigated for bowel problems and serum methylmalonate was 11 $\mu\text{mol/L}$. No anemia or macrocytosis was present and she was treated with B12 and folate without any effect on methylmalonate. Urinary organic acid analysis in 2006 showed methylmalonate, 73 mmol/mol creatinine and malonate, 13 mmol/mol creatinine. A DNA sample was saved and after the publications on combined malonic and methylmalonic aciduria the 1672C>T, p. Arg558Trp mutation and a novel c.781G>T P.Gly261X mutation in the ACSF3 gene were identified.

Analytical performance: The finding of increased methylmalonic acid was scored with one point (20 labs) and increased malonic acid with one point (10 labs).

Interpretative proficiency: The correct diagnosis was considered to be combined malonic acid and methylmalonic aciduria scoring two points (9 labs). Other diagnoses based on finding methylmalonic acid alone were scored with 0 points.

Recommendations: Mutation analysis of the correct gene was considered helpful (8 labs). Follow up tests pursuing a vitamin B12 or mild MMA defect were not considered correct.

Overall impression: This was a fairly difficult sample but it was clearly possible to detect increased malonic acid as reported by ten labs pointing to the correct diagnosis.

Analytical Details

Creatinine

n=20
median= 5.70
mean= 5.65
SD= 0.11
min, max= [5.00, 6.14]

pH

n=12
median= 5.25
mean= 5.41
SD= 0.21
min, max= [5.00, 6.00]

Spot tests

Almost all negative

Organic acid analysis (n= 20)

	n	points
Methylmalonic acid and Malonic acid elevated	10	2
Methylmalonic acid only elevated	10	1

methylmalonic acid

n=15
median= 89.00
mean= 89.83
SD= 36.26
min, max= [0.08, 160.00]

malonic acid

n=5
 median= 34.00
 mean= 36.40
 SD= 5.85
 min, max= [32.00, 48.00]

Interpretation

	n	Points
Combined malonic and methylmalonic aciduria	9	2
Malonic aciduria	1	0
Mild MMA/B12 deficiency	10	0

Recommendations for further tests

Mutation analysis (of ACSF3 gene)	7 (6)	1
Further tests for MMA	10	0
None	1	0

Sample F: Mucopolysaccharidosis type II (Hunter) due to iduronate sulphate sulphatase deficiency

Patient: A 4.5 year old boy, recently arrived in this country, with restricted movement, hepatosplenomegaly and mild mental retardation. This sample was obtained from a 4.5 year old boy suffering from mucopolysaccharidosis type II (Hunter). This urine was obtained in our hospital, Basel, Switzerland. The diagnosis had been confirmed by the finding of severe iduronate sulphate sulphatase deficiency in serum and leucocytes (Prof. B. Steinmann, Zurich, Switzerland). This sample was also distributed in 2010..

Analytical performance: Elevated total GAG scored one point (19 labs) and differentiation of GAGs pointing to a diagnosis including MPS II scored an additional point (16 labs).

Interpretative proficiency: A diagnosis of MPS including mention of MPSII scored two points (18 labs) while an unspecified MPS disorder scored one point (one lab).

Recommendations: Most labs recommended enzyme assay and / or mutation analysis, some without specifying the enzyme or gene. Strictly this should be mentioned but points were not deducted in this case on this occasion. On this basis 16 labs gave useful recommendations.

Overall impression:

Importantly, all labs that performed GAG analysis correctly identified an MPS disorder although one made the incorrect diagnosis of MPS three. Overall proficiency was 89%, a distinct improvement compared with last time (about 80%).

Analytical Details

Creatinine

n=20
median= 4.98
mean= 4.84
SD= 0.23
min, max= [3.86, 5.60]

pH

n=12
median= 6.00
mean= 6.12
SD= 0.27
min, max= [5.00, 7.00]

Spot tests

GAG screening (n=4)	n	points
+ - +++	4	1

GAG analysis (n=17)

GAG quantitative	n	points
elevated	17	1

Glycosaminoglycans quantitative

n=17
median= 45.60
mean= 55.70
SD= 1097.71
min, max= [29.10, 139.90]

GAG differentiation	n	points
Dermatan sulphate	16	1
Heparan Sulphate	1	1

Interpretation

	n	Points
Mucopolysaccharidosis type II (Hunter).	6	2
MPS I or II	6	2
MPS I or II or VI.	4	2
MPS I or II or VI or VII	1	2
MPS I or II or VII	1	2
MPS III	1	0
No diagnosis by urine amino or urine organic acid analysis. Clinical description suggests mucopolysaccharidosis	1	0

Recommendations for further tests

	n	points
Enzyme assay in leucocytes or fibroblasts	16	1
Mutation analysis	8	1
GAG differentiation if not done in own lab	1	1
None	1	0

8. Scores

Overall proficiency

Sample	Diagnosis	A (%)	I (%)	R (%)	total (%)
A	Argininosuccinic aciduria due to argininosuccinate lyase deficiency	87.5	90	80	87
B	Formiminoglutamic aciduria	45	50	40	46
C	Intermittent branched chain aminoaciduria due to branched chain ketoacid decarboxylase deficiency	97.5	95	95	96
D	Homogentisic aciduria due to homogentisic acid oxidase deficiency	90	90	75	87
E	Combined malonic and methylmalonic aciduria due to mutations in the ACSF3 gene.	75	42.5	40	54
F	Mucopolysaccharidosis type II (Hunter) due to iduronate sulphate sulphatase deficiency	90	92.5	80	89

Total scores

Lab No	Survey 1			Survey 2			Total
	A	B	C	D	E	F	
1	5	0	4	4	1	3	17
2	5	0	2	5	1	4	17
3	0	5	5	5	1	5	21
4	5	5	5	5	5	5	30
5	4	4	5	4	5	5	27
6	5	0	5	5	1	5	21
7	4	0	5	5	2	5	21
8	5	5	5	0	3	1	19
9	5	5	5	5	5	5	30
10	5	0	5	4	1	4	19
11	5	5	5	5	1	5	26
12	4	0	5	0	5	5	19
13	5	5	5	5	5	5	30
14	5	0	5	5	1	5	21
15	0	0	5	5	1	5	16
16	5	0	5	5	5	5	25
17	5	5	5	5	1	2	23
18	5	0	5	5	5	5	25
19	5	3	5	5	1	5	24
20	5	4	5	5	4	5	28
21	-	-	-	-	-	-	-

*This year the scores proposed by us have been evaluated by a second advisor and confirmed at the Scientific Advisory Board meeting in November. In the case of differences in scoring the decision of the second advisor is taken unless this would lead to a lack of satisfactory

performance in which case the final decision is made at the SAB. **Appeals** against allocated scores should be sent to the scientific advisor within two weeks of receipt of this report.

Detailed Scores: A,B,C

Lab no	Sample A ASAuria				Sample B FIGLUuria				Sample C MSUD				Total
	A	I	R	Total	A*	I	R	Total	A	I	R	Total	
1	2	2	1	5	0	0	0	0	2	2	0	4	9
2	2	2	1	5	0	0	0	0	1	0	1	2	7
3	0	0	0	0	2	2	1	5	2	2	1	5	10
4	2	2	1	5	2	2	1	5	2	2	1	5	15
5	2	2	0	4	2	2	0	4	2	2	1	5	14
6	2	2	1	5	0	0	0	0	2	2	1	5	10
7	2	2	0	4	0	0	0	0	2	2	1	5	9
8	2	2	1	5	2	2	1	5	2	2	1	5	15
9	2	2	1	5	2	2	1	5	2	2	1	5	15
10	2	2	1	5	0	0	0	0	2	2	1	5	10
11	2	2	1	5	2	2	1	5	2	2	1	5	15
12	1	2	1	4	0	0	0	0	2	2	1	5	9
13	2	2	1	5	2	2	1	5	2	2	1	5	14
14	2	2	1	5	0	0	0	0	2	2	1	5	10
15	0	0	0	0	0	0	0	0	2	2	1	5	5
16	2	2	1	5	0	0	0	0	2	2	1	5	10
17	2	2	1	5	2	2	1	5	2	2	1	5	15
18	2	2	1	5	0	0	0	0	2	2	1	5	10
19	2	2	1	5	1	2	0	3	2	2	1	5	13
20	2	2	1	5	1	2	1	4	2	2	1	5	14
21	-	-	-	-	-	-	-	-	-	-	-	-	-
ratio	35/40	36/40	16/20	87/100	18/40	20/40	8/20	46/100	39/40	38/40	19/20	96/100	
%	87.5	90	80	87	45	50	40	46	97.5	95	95	96	

Detailed Scores: D,E,F

Lab no	Sample D Homogentisic aciduria				Sample E Malonic/Methylmalonic aciduria				Sample F MPS II				Total
	A	I	R	Total	A*	I	R	Total	A	I	R	Total	
1	2	2	0	4	1	0	0	1	1	2	0	3	8
2	2	2	1	5	1	0	0	1	2	2	0	4	10
3	2	2	1	5	1	0	0	1	2	2	1	5	11
4	2	2	1	5	2	2	1	5	2	2	1	5	15
5	2	2	0	4	2	2	1	5	2	2	1	5	14
6	2	2	1	5	1	0	0	1	2	2	1	5	11
7	2	2	1	5	2	0	0	2	2	2	1	5	12
8	0	0	0	0	2	1	0	3	1	0	0	1	4
9	2	2	1	5	2	2	1	5	2	2	1	5	15
10	2	2	0	4	1	0	0	1	2	2	0	4	9
11	2	2	1	5	1	0	0	1	2	2	1	5	11
12	0	0	0	0	2	2	1	5	2	2	1	5	10
13	2	2	1	5	2	2	1	5	2	2	1	5	15
14	2	2	1	5	1	0	0	1	2	2	1	5	11
15	2	2	1	5	1	0	0	1	2	2	1	5	11
16	2	2	1	5	2	2	1	5	2	2	1	5	15
17	2	2	1	5	1	0	0	1	0	1	1	2	8
18	2	2	1	5	2	2	1	5	2	2	1	5	15
19	2	2	1	5	1	0	0	1	2	2	1	5	11
20	2	2	1	5	2	2	0	4	2	2	1	5	14
21	-	-	-	-	-	-	-	-	-	-	-	-	-
ratio	36/40	36/40	15/20	87/100	30/40	17/40	8/20	54/100	36/40	37/40	16/20	89/100	
%	90	90	75	87	75	42.5	40	54	90	92.5	80	89	

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. At this year's meeting the cut off point for satisfactory performance was set at a minimum of 18 points. Labs failing to reach this mark will receive a performance advice letter.

A special meeting of scientific advisors was held in November to consider how to harmonise scoring within all our qualitative schemes and the question of introducing critical errors in our schemes.

10. Annual meeting

The annual meeting of participants of the 5 DPT centres took place during the SSIEM symposium in Birmingham on Tuesday, September 3rd, 9:00.

11. Changes planned for 2013

No changes to the distribution and reporting arrangements in place for 2012 are envisaged. This means that again you will be required to submit results online to our website. The samples for the Basel scheme will again be distributed by the CSCQ but we will remain responsible for the scientific and evaluation aspects of the scheme. The reports will be produced by us using the newly developed evaluation of results programme as tested in 2012.

Scoring changes:

Scoring of recommendations

At a special meeting of the Scientific Advisory Board in November it was agreed that from 2013 onwards the qualitative schemes will all adopt the same scoring system of two points for analytical results and two points for interpretation. Thus for the DPT scheme, there will no longer be an additional point for suggested further actions or testing. This will be included as part of the interpretation. This will also reduce the total score achievable to twenty four (with six samples) and at the present time acceptable performance will be achieved by scoring at least fourteen points.

Critical Error

The Scientific Advisory Board is now discussing the definition of 'critical error' since presently labs can completely miss two straightforward diagnoses and still reach overall satisfactory performance. Also this will bring us into line with the EQA schemes for the other genetic disciplines. All participants will be informed on how this will affect the scoring. In principle this is a category of error that would be unacceptable to the majority of labs and would have a serious adverse effect on patient management. Critical error for any sample deemed appropriate for this category will prevent achievement of satisfactory performance for that year regardless of total points scored. We are hoping to be able to institute this for 2014.

12. **Tentative schedule and fee in 2013**

Provisional

Sample distribution	April 2013
Start of analysis of Survey 2013/1	May 13, 2013
Survey 2013/1 - Results submission	June 3, 2013
Survey 2013/1 - Reports	June 24, 2013
Start of analysis of Survey 2013/2	July 1, 2013
Survey 2013/2 – Results submission	July 22, 2013
Survey 2013/2 - Reports	August 16, 2013
Annual meeting of participants	ICIEM, Barcelona, September 3, 2013
Annual Report 2013	December 2013.

The fee for the DPT scheme for 2013 is €341, a rise of just 2% compared with 2012.

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, December 2012

Brian Fowler
Scientific advisor

Marianne Zaugg
Scheme organiser