ERNDIM number

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ERNDIM QAP for qualitative urinary organic acid analysis

Annual Report 2017(Sheffield)

Participation

Active participants (reporting on at least one set of samples in the year) are shown in Table 1. The numbers of participants continues to increase. New applicants are distributed between the Sheffield and Heidelberg qualitative urinary organic acid schemes which are run separately. The two organising laboratories each participate in the other's scheme.

Table 1: Geographical distribution of registered participants

	2017	***2016***	***2015***	***2014***	***2013***	***2012***	***2011***
Argentina	3	4	3	3	2	2	2
Australia	6	6	6	6	6	6	6
Belgium	6	6	6	6	6	5	5
Brazil	2	2	2	2	2	2	2
Canada	1	1	1	1	1	1	1
Columbia	1	1	1	1	1	1	1
Chile	1	1	1	1	-	-	-
China	5	7	11	11	9	8	10
Finland	2	2	2	2	2	1	1
France	17	17	15	15	15	15	15
Germany†	1	1	1	1	1	1	1
Israel	3	3	3	3	3	3	3
Japan	2	2	2	2	1	1	1
Lebanon	1	1	1	1	1	1	1
Malaysia	3	3	3	3	3	3	3
New Zealand	1	1	1	1	1	1	1
Portugal	3	3	2	2	2	2	2
Hong Kong	5	-	-	-	-	-	-
Republic of Ireland	1	1	1	1	1	1	1
Republic of Singapore	1	1	1	1	1	1	1
South Africa	2	2	2	2	2	2	2
Spain	7	7	6	6	6	6	6
Turkey	9	10	7	3	3	3	3
United Kingdom	16	16	18	18	18	18	18
USA	6	6	5	5	5	3	3

Uruguay	1	1	1	1	-	-	-
Pakistan	1	1	-	-	-	1	1
TOTAL	**107**	**108**	**104**	**100**	**94**	**91**	**95**

† Heidelberg laboratory

Samples and results

Three sets of three samples (numbered 241-249) were dispatched together in spring 2017. Laboratories were asked to analyse the sets at intervals during the year as if they were separate circulations. One hundred and one laboratories returned results for all three sets; four participants returned two sets, two laboratories made no return. One participant is an educational participant.

Scoring of results

To enable data reduction the results were scored as shown below:

Satisfactory	4	Helpful but incomplete	3
Not helpful	2	Slightly misleading	1
Misleading	0		

Table 2: Distribution of scores for individual samples (laboratories making returns)

Sample	Scores				
	0	**1**	**2**	**3**	**4**
Sample 241 3 Month old hypoglycaemia, abnormal liver function, on treatment. Increased excretion of sebecate, suberate and adipate with a large peak of 7 hydroxy-octanoate. The pattern of sebecate >suberate >adipate along with excretion of 7 hydroxy-octanoante is consistent with treatment with medium chain triglyceride (MCT). It should be noted that a long chain fatty acid oxidation defect may be masked by treatment with MCT.	-	-	16	10	78
Sample 242 Developmental delay 2 year old. No significant abnormality	2	-	1	1	100
Sample 243 Metabolic acidosis and anaemia - 6 month old female. No significant abnormality	8	-	-	1	95
Sample 244 Muscle weakness, unwell, episodes of	4	2	19	9	67

hypoglycaemia Increased 3 hydroxybutyrate, ethlylmalonate, 2 hydroxy glutarate and acylglycines. These results would be consistent with Glutaric Aciduria type 2 (GA2) also known as Multiple Acyl CoA dehydrogenase deficiency (MADD). Suggest check plasma acylcarnitines and repeat urine organic acids pre and post riboflavin. Confirmatory studies should be carried out on cultured fibroblasts. Urgent referral to a metabolic clinician required.					
Sample 245 Episodes of unresponsive hypoglycaemia 7 year old Increased excretion of suberyl, hexanoyl and phenylpropinoyl glycine. Results consist with Medium Chain Acyl CoA dehydrogenase (MCAD) deficiency. Suggest acylcarnitine analysis and mutation analysis of the ACADM gene to confirm. Urgent referral to a metabolic clinician required.	6	-	-	1	94
Sample 246 Autistic spectrum disorder 7 year old. No significant abnormality.	5	1	-	-	95
Sample 247 Epilepsy 5 year old. Increased excretion of N-(pyrrole-2-carboxyl) glycine diTMS and N-(pyrrole-2-carboxyl) glycine triTMS, along with metabolites of valproate. These results are suggestive of Hyperprolinaemia Type 2. Valproate metabolites consistent with treatment with valproate. Suggest check urine and plasma amino acids (for proline and hydroxyproline) and confirm with genetic studies. Suggest referral to metabolic consultant.	15	49	3	-	35
Sample 248 Fever – sample taken at time of fever 3 year old. Small but significant peak of mevalonolactone. In view of the clinical details results suggestive of Hyper IgD syndrome due to mevalonate kinase deficiency.	30	1	1	-	70
Sample 249 Same patient as 248 sample taken when well Trace of mevalonolactone in this sample. Please note the mevalonolactone may only be present during an episode of febrile attack. In view of the previous sample (248) and clinical details with this finding, results suggestive of Hyper IgD syndrome due to mevalonate kinase deficiency.	34	-	1	-	67

Table 3: Scores for 2015 - 2017 (current Sheffield participants only)

Laboratory number	Total score 2017**	Number of returns 2017	Total score 2016*	Number of returns 2016	Total score 2015*	Number of returns 2015
1	32	3	36	3		
2	32	3	32	3	36	3
3	24	3	32	3	36	3
4	23	3	32	3	34	3
5	32	3	32	3	36	3
6	31	3	32	3	34	3
7	31	3	36	3	34	3
8	32	3	32	3	35	3
9	32	3	32	3	36	3
10	23	3	32	3	36	3
11	32	3	36	3	36	3
12	32	3	32	3	32	3
13	32	3	36	3	34	3
14	24	3	26	3	30	3
15	30	3	36	3	36	3
16	30	3	32	3	28	3
17	32	3	29	3	36	3
18	32	3	36	3	36	3
19	28	3	28	3	36	3
20	32	3	35	3	36	3
21	26	3	32	3	36	3
22	32	3	36	3	36	3
23	28	3	35	3	36	3
24	32	3	36	3	32	3
25	32	3	36	3	36	3
26	24	3	36	3	35	3
27	32	3	28	3	36	3
28	30	3	36	3	34	3
29	30	3	36	3	35	3
30	28	3	36	3	36	3
31	32	3	36	3	36	3
32	32	3	36	3	35	3
33	32	3	22	3	32	3
34	32	3	32	3	36	3
35	32	3	34	3	12	1
36	32	3	28	3	36	3
37	32	3	32	3	35	3
38	31	3	32	3	36	3
39	30	3	32	3	36	3
40	31	3	36	3	36	3

41	32	3	28	3	36	3
42	28	3	36	3	36	3
43	32	3	36	3	36	3
44	24	3	36	3	36	3
45	32	3	32	3	36	3
46	32	3	32	3	36	3
47	32	3	32	3	36	3
48	31	3	35	3	36	3
49	20	2	36	3	36	3
50	32	3	27	3	32	3
51	32	3	35	3	35	3
52	24	3	35	3	36	3
53	21	3	31	3	24	2
54	32	3	28	3	35	3
55	32	3	34	2	36	3
56	24	3	29	3	36	3
57	21	3	28	3	30	3
58	Educational					
59	22	3	32	3	33	3
60	28	3	36	3	26	3
61	32	3	32	3	36	3
62	32	3	32	3	22	2
63	22	3	36	3	36	3
64	32	3	36	3	36	3
65	11	2	34	3	32	3
66	32	3	35	3		0
67	24	3	36	3	32	3
68	30	3	32	3	24	2
69	30	3	36	3	35	3
70	22	3	32	3	36	3
71	20	3	32	3	32	3
72	20	3	32	3	32	3
73	28	3	32	3	20	2
74	24	2	24	2	20	2
75	20	3	19	3	10	1
76	24	3	28	3	36	3
77	31	3	24	3	30	3
78	31	3	28	3	34	3
79	27	3	29	3	36	3
80	28	3	36	3	34	3
81	26	3	35	3	32	3
82	28	3	28	3	34	3
83	21	3	32	3	20	2
84	20	3	28	3	36	3

85	22	3	36	3	10	1
86	28	3	31	3	26	3
87	25	3	30	3	20	3
88	26	3	20	3	36	3
89	17	3	10	3	36	3
90	No return					
92	20	2				
93	14	3				
94	14	3				
95	30	3	34	3	36	3
96	22	3	20	2	33	3
97	32	3	33	3	35	3
98	17	3				
99	32	3	35	3	36	3
100	32	3	36	0	30	3
101	24	3	24	2	28	3
102	24	3	32	3	24	3
103	11	3	26	3		
104	21	3	36	3	36	3
105	15	3	28	3		
108	23	3	36	3		
109	No return					

* Maximum total score is 36 for three returns and 24 for two returns 2016 & 2015
** Maximum total score is 32 for three returns 2017 (sample 247 not scored).

Please note to maintain confidentiality you are assigned a laboratory number in the above table. This is different from your ERNDIM number.

Your Laboratory OA Number in the above Table is

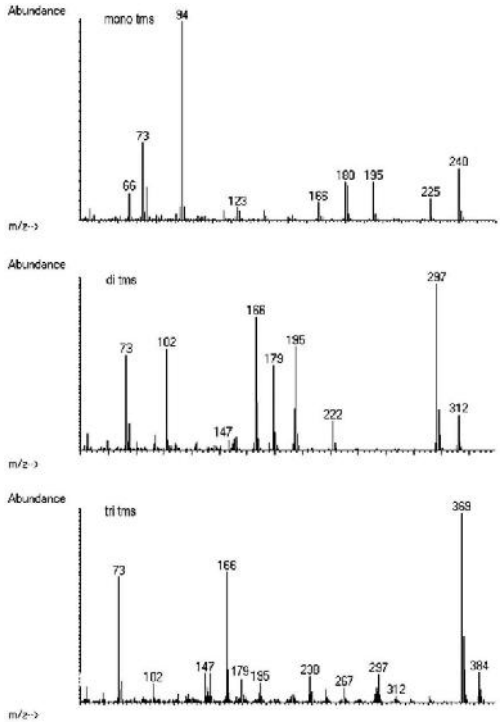
Please use your ERNDIM number in all communication with the scientific advisors, laboratory numbers are only used for the purpose of this table.

Commentary

As in previous years, samples were sent out to cover the spectrum of what is typically observed in the metabolic laboratory. A mix of clearly diagnostic profiles and some more challenging profiles were provided. As in previous years normal profiles were also sent out. The requirement to interpret a normal profile, as such, is as important as correctly identifying abnormal profiles. Correctly identifying a profile as normal can avoid unnecessary further investigation and distress to the patient and family

The most problematic samples sent out in 2017 included the Hyperprolinaemia Type 2 and the two samples from the patient with Hyper IgD syndrome.

Hypeprolinaemia type 2 (Pyrroline-5-carboxylate dehydrogenase deficiency) is associated with epilepsy. N-(pyrrole-2-carboxyl) glycine TMS derivatives produce the following ion spectra (for BSTFA derivitised GC/MS methods)



Literature source: Walker V and Mills G. **2009** N-(pyrrole-2-carboxyl) glycine a diagnostic marker of hyperprolinaemia type II: Mass spectra of trimethylsilyl derivatives. *Clinica Chimica Acta* **405**:153–154

This sample was discussed in depth at the Scientific Board meeting in November and due to the low number of participants identifying the key metabolites it was decided that this sample would be scored as educational. An educational sample does not count towards the final score and is not included when assessing overall performance. It is important that this metabolite is added to participants libraries because in future distributions this condition will be scored.

Samples 248 and 249 were from a patient with confirmed Hyper IgD syndrome. Mevalonolactone is excreted usually in lower amounts in Hyper IgD syndrome and larger amounts along with mevalonic acid in classical mevalonic aciduria. Hyper IgD syndrome is associated with recurrent febrile attacks. It is important to note that the mevalonolactone may only be detectable at times of febrile attack. Excretion can be very low between febrile episodes. The scoring of these samples was also discussed at the Scientific Board in November and it was agreed that these should be scored because the mevalonolactone levels reflected a typical Hyper IgD presentation. The clinical details provided should have prompted the participants to specifically look for the mevalonolactone.

The majority of participants were able to identify the key metabolites associated with the Medium Chain Acyl CoA Dehydrogenase deficiency patient (MCADD). A significant proportion of participants failed to differentiate the Medium Chain Triglyceride (MCT) profile and the Glutaric Aciduria Type 2 (GA2) profile from an MCADD profile. Because of the importance of identifying a typical MCADD profile it was decided by the Scientific Board that failure to identify MCADD constitutes a critical error.

It is appreciated that in all the cases the urine organic acid profile is only part of the diagnostic investigation and where the organic acid profile does not give a clear diagnosis the further investigations box is key when it comes to scoring. The 'Further investigations' box should indicate any additional investigations you consider necessary to interpret or confirm conclusions based on the analytical results. The 'Additional comments' box may also be used for caveats or to suggest other lines of investigation based on the clinical presentation rather than the analytical findings. Suggestions should follow a logical hierarchy with simple group investigations such as amino acid chromatography or blood-spot acylcarnitine profiling (if indicated) taking precedence over much more specific investigations such as gene sequencing.

We are somewhat limited in the samples we send out by the volume of sample required and the number of participants within our scheme. We are also limited by the number of samples with appropriate amounts of abnormal metabolites in. We appeal to any of our participants to donate samples for inclusion in our scheme or any of the other ERNDIM schemes.

Certificates of Participation and Performance

We are required to define "Participation" and "Satisfactory Performance" for the purpose of the ERNDIM Annual Certificate which covers all ERNDIM schemes. For this urinary organic acid scheme we have defined "Participation" as requiring at least two returns during the year. Defining "Satisfactory Performance" is more problematical as in some years there are more difficult samples than in others.

The criteria for satisfactory performance for 2017 for three returns is a score of 19/32. On this basis six laboratories were deemed to fall below the satisfactory criteria. Satisfactory Performance" criteria are always somewhat arbitrary and in practice even a single missed or wrong diagnosis can be highly damaging. Thus the reason(s) for

failure to correctly report on any of the samples in the scheme should be investigated locally and appropriate remedial action taken.

A critical error is an error that would be unacceptable to the majority of labs and would have a serious adverse effect on patient management. The introduction of critical error is on the advice of the Genetic Services Quality Committee (GSQC) of the European Society of Human Genetics (ESHG), which wants to see harmonisation across all European genetic EQA providers. A confirmed critical error will mean automatic classification as a poor performer. The final scoring of all qualitative schemes was discussed at the November meeting of the Scientific Advisory Board (SAB) and all proposed critical errors have been ratified by the SAB before being confirmed. For 2017 the only critical error ratified was for the Sheffield organic acid qualitative scheme was MCADD. Participants that failed to identify the MCADD profile in sample 248 were awarded a critical error regardless of overall total score. Four laboratories received notification of critical error.

Changes for 2018

In 2018 there will be three providers for the qualitative organic acid scheme instead of two.

Results should be submitted electronically via the ERNDIM website rather than by email/fax or post. Details will be sent with the 2018 samples.

The satisfactory performance score will also change from 61% to 70% which equates to 25/36 for 3 returns and 17/24 for two returns. The labelling of samples will also change from numerical to alphabetical e.g. s250 will next year be labelled QLOU-SH-2018A

Finally and very importantly it is with great sadness that I have to inform participants that we sadly lost our Scientific Advisor, Dr Jane Dalley, after a short but courageous battle to leukaemia in 2018. Dr Dalley was a passionate scientist who had been working as the Scientific Advisor for the Sheffield Organic Acid Scheme since 2014. She will be greatly missed by all who knew her and worked with her.

We thank Lynne Wolstenholme for administering our participant database and dealing with the returns, and Jennifer Watkinson for preparing the samples. We hope that you continue to find this scheme useful.

Yours sincerely

Mrs Camilla Scott & Miss Sharon Colyer
Scheme organisers