ERNDIM number

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QAP for qualitative urinary organic acid analysis

Annual Report (Amended) 2016(Sheffield)

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Changes: Data in table 3 was incorrect for 2015 & 2014 in the original report. This would have affected the total scores and the average scores. Please discard the original report dated 7th February 2017.

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

	2016	*2015*	*2014*	*2013*	*2012*	*2011*	*2010*
Argentina	4	3	3	2	2	2	2
Australia	6	6	6	6	6	6	6
Belgium	6	6	6	6	5	5	6
Brazil	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	-	-	-	-
China	7	11	11	9	8	10	7
Finland	2	2	2	2	1	1	1
France	17	15	15	15	15	15	13
Germany†	1	1	1	1	1	1	1
Israel	3	3	3	3	3	3	4
Japan	2	2	2	1	1	1	1
Lebanon	1	1	1	1	1	1	1
Malaysia	3	3	3	3	3	3	4
New Zealand	1	1	1	1	1	1	1
Portugal	3	2	2	2	2	2	2

Republic of Korea	-	1	1	1	1	1	1
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	6	6	6	6	6	6
Turkey	10	7	3	3	3	3	3
United Kingdom	16	18	18	18	18	18	19
USA	6	5	5	5	3	3	3
Uruguay	1	1	1	-	-	-	-
Pakistan	1	-	-	-	1	1	1
Kingdom of Saudi Arabia	1	-	-	-	-	-	-
Vietnam	1	1	1	1	1	1	-
TOTAL	**108**	**104**	**100**	**94**	**91**	**95**	**90**

† Heidelberg laboratory

Samples and results

Three sets of three samples (numbered 232-240) were dispatched together in April 2016. Laboratories were asked to analyse the sets at intervals during the year as if they were separate circulations. Ninety-nine laboratories returned results for all three sets; seven returned two, one laboratories made only a single return, and one made no return. Two participants are educational participants.

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		

One point was deducted for each transposed sample number

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

Sample	Scores				
	0	**1**	**2**	**3**	**4**
Sample 232 48 year old male with muscle weakness Nothing specifically diagnostic .	3	0	0	0	99
Sample 233 1 year old boy frequent vomiting and epilepsy Significantly increased excretion of malonic acid with increased methylmalonic acid. These results would be consistent with malonic	4	1	0	5	93

aciduria and the most likely defect would be Malonyl CoA decarboxylase deficiency.					
Sample 234 4 year old boy, unwell, drowsy and vomiting A large peak of 2-hydroxyisovalerate is present together with lesser amounts of 2-hydroxy-3-methylvalerate and 2-hydroxyisocaproate, consistent with a defect in branched-chain 2-oxoacid dehydrogenase activity. The clinical details suggest a mild or intermittent variant of Maple Syrup Urine Disease. Increased excretion of *p*-hydroxyphenyl-lactate indicates some degree of liver disorder.	5	3	1	1	93
Sample 235 3 year old microcephaly Nothing specifically diagnostic	23	0	1	2	76
Sample 236 39 year old woman. Mother of S235 Nothing specifically diagnostic	19	0	1	1	81
Sample 237 5 year old girl with recurrent kidney stones Significantly elevated peaks of glycolate and oxalate. Absence of glycerate. Results consistent with a diagnosis of Primary Hyperoxaluria Type1	9	1	3	0	89
Sample 238 9 month old girl, failure to thrive Increased orotic acid which may indicate an inborn error of metabolism, check plasma ammonia and urine and plasma amino acids as a matter of urgency. Discuss with a metabolic consultant.	17	0	0	0	87
Sample 239 6 year old female – mild dysmorphic features Increased excretion of 3-methylglutaconic acid and 3-methlyglutaric acid. Results indicative of 3-methlyglutaconic aciduria. Suggest further follow up tests to confirm and suggest discussion with a metabolic consultant.	13	0	4	8	79
Sample 240 35 year old female: Muscle weakness Increased excretion of 3-hydroxyisovaleric acid and 3-methylcrotonyl glycine. Results consistent with 3-Methylcrotonyl-CoA Carboxylase deficiency.	0	0	3	0	101

Table 3: Cumulative scores for 2014 - 2016 (current Sheffield participants only)

Lab Number	Total Score 2016*	Number of returns 2016	Total Score 2015*	Number of returns 2015	Total Score 2014*	Numb er of returns 2014	**Total Score over 3 years (max 108)**	Average score per year (max 36)
1	36	3	-	-	-	-	**36**	36
2	32	3	36	3	36	3	**104**	35
3	32	3	36	3	31	3	**99**	33
4	32	3	34	3	35	3	**101**	34
5	32	3	36	3	36	3	**104**	35
6	32	3	34	3	36	3	**102**	34
7	36	3	34	3	36	3	**106**	35
8	32	3	35	3	36	3	**103**	34
9	32	3	36	3	32	3	**100**	33
10	32	3	36	3	36	3	**104**	35
11	36	3	36	3	36	3	**108**	36
12	32	3	32	3	35	3	**99**	33
13	36	3	34	3	36	3	**106**	35
14	26	3	30	3	23	3	**79**	26
15	36	3	36	3	30	3	**102**	34
16	32	3	28	3	4	1	**64**	21
17	29	3	36	3	35	3	**100**	33
18	36	3	36	3	36	3	**108**	36
19	28	3	36	3	27	3	**91**	30
20	35	3	36	3	34	3	**105**	35
21	32	3	36	3	35	3	**103**	34
22	36	3	36	3	36	3	**108**	36
23	35	3	36	3	35	3	**106**	35
24	36	3	32	3	36	3	**104**	35
25	36	3	36	3	35	3	**107**	36
26	36	3	35	3	36	3	**107**	36
27	28	3	36	3	36	3	**100**	33
28	36	3	34	3	24	2	**94**	31
29	36	3	35	3	36	3	**107**	36
30	36	3	36	3	24	2	**96**	32
31	36	3	36	3	35	3	**107**	36
32	36	3	35	3	36	3	**107**	36

33	22	3	32	3	34	3	**88**	29
34	32	3	36	3	33	3	**101**	34
Lab Number	Total Score 2016*	Number of returns 2016	Total Score 2015*	Number of returns 2015	Total Score 2014*	Numb er of returns 2014	**Total Score over 3 years (max 108)**	Average score per year (max 36)
35	34	3	12	1	36	3	**82**	27
36	28	3	36	3	36	3	**100**	33
37	32	3	35	3	34	3	**101**	34
38	32	3	36	3	35	3	**103**	34
39	32	3	36	3	36	3	**104**	35
40	36	3	36	3	36	3	**108**	36
41	28	3	36	3	36	3	**100**	33
42	36	3	36	3	35	3	**107**	36
43	36	3	36	3	36	3	**108**	36
44	36	3	36	3	36	3	**108**	36
45	32	3	36	3	32	3	**100**	33
46	32	3	36	3	34	3	**102**	34
47	32	3	36	3	35	3	**103**	34
48	35	3	36	3	35	3	**106**	35
49	36	3	36	3	36	3	**108**	36
50	27	3	32	3	36	3	**95**	32
51	35	3	35	3	33	3	**103**	34
52	35	3	36	3	36	3	**107**	36
53	31	3	24	2	26	3	**81**	27
54	28	3	35	3	36	3	**99**	33
55	34	2	36	3	36	3	**106**	35
56	29	3	36	3	33	3	**98**	33
57	28	3	30	3	28	3	**86**	29
58	(edu) 12	2	-	-	-	-	**12**	12
59	32	3	33	3	31	3	**96**	32
60	36	3	26	3	31	3	**93**	31
61	32	3	36	3	35	3	**103**	34
62	32	3	22	2	35	3	**89**	30
63	36	3	36	3	32	3	**104**	35
64	36	3	36	3	34	3	**106**	35
65	34	3	32	3	33	3	**99**	33
66	35	3	-	-	31	3	**66**	33
67	36	3	32	3	34	3	**102**	34
68	32	3	24	2	36	3	**92**	31
69	36	3	35	3	31	3	**102**	34
70	32	3	36	3	28	3	**96**	32

71	32	3	32	3	36	3	**100**	33
72	32	3	32	3	12	1	**76**	25
73	32	3	20	2	35	3	**87**	29
Lab Number	Total Score 2016*	Number of returns 2016	Total Score 2015*	Number of returns 2015	Total Score 2014*	Numb er of returns 2014	**Total Score over 3 years (max 108)**	Average score per year (max 36)
74	24	2	20	2	24	2	**68**	23
75	19	3	10	1	34	3	**63**	21
76	28	3	36	3	36	3	**100**	33
77	24	3	30	3	30	3	**84**	28
78	28	3	34	3	34	3	**96**	32
79	29	3	36	3	-	-	**65**	33
80	36	3	34	3	34	3	**104**	35
81	35	3	32	3	30	3	**97**	32
82	28	3	34	3	34	3	**96**	32
83	32	3	20	2	21	3	**73**	24
84	28	3	36	3	36	3	**100**	33
85	36	3	10	1	16	2	**62**	21
86	31	3	26	3	-	-	**57**	29
87	30	3	20	3	-	-	**50**	25
88	20	3	36	3	22	3	**78**	26
89	10	3	36	3			**46**	23
90	36	3	32	3	36	3	**104**	35
91	24	3	-	-	-	-	**24**	24
92	-	-	31	3	31	3	**62**	31
93	18	3	22	2	-	-	**40**	20
94	8	1	32	3	34	3	**74**	25
95	34	3	36	3	35	3	**105**	35
96	20	2	33	3	32	3	**85**	28
97	33	3	35	3	35	3	**103**	34
98	22	3	-	-	-	-	**22**	22
99	35	3	36	3	35	3	**106**	35
100	36	3	30	3	34	3	**100**	33
101	24	2	28	3	31	3	**83**	28
102	32	3	24	3	-	-	**56**	28
103	26	3	-	-	-	-	**26**	26
104	36	3	36	3	-	-	**72**	36
105	28	3	-	-	-	-	**28**	28
106	17	2	-	-	-	-	**17**	17
107	(edu)	-	-	-	-	-	**-**	-
108	36	3	-	-	-	-	**36**	36

* Maximum total score is 36 for three returns and 24 for two returns. Maximum scores over 3

years = 108 and is only applicable if all three returns have been received over the previous three years.

Your Laboratory OA Number in the above Table is 0

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. For the samples sent out in 2016 the majority of participants correctly assigned the normal profile however as in previous years there are still a significant proportion of participants who over interpret based on clinical details. This was clearly the case with samples 236 & 237 which were donated by an unaffected mother and child. Participants, in view of the clinical picture, appropriately looked for metabolites associated with phenylketonuria however even in the absence of any metabolites a number still incorrectly assigned the disorder without any biochemical evidence. It is useful to be guided by clinical details but the likely diagnosis should only be suggested in view of the biochemical evidence. In contrast, highlighting the complexity of the role of metabolic interpretation, the hyperoxaluria type 1 case (237) had strong clinical details; 5 year old girl with recurrent kidney stones. The majority of participants correctly identified increase in both glycolate and oxalate. Some participant's identified increased glycolate only. Which is not uncommon, as oxalate extraction for organic acids is problematic and highly variable, given this knowledge and clinical details further testing such as quantitative method for oxalate measurement would be expected.

Of the abnormal samples, two proved particularly challenging; the orotic acid (sample 238) and the sample with 3-methylglutaconic aciduria (sample 239). Over the past few years the detection and identification of orotic acid has continued to be challenging for a number of laboratories. The detection of orotic acid is crucial in the diagnosis of inherited defects of metabolism and laboratories need to have internal procedures in place to ensure this peak is not missed.

The detection of a slightly increased 3-methylglutaconic acid also proved to be challenging. The significance of a persistently elevated excretion of this metabolite in the absence of a known protein defect is open to debate, but generally it is agreed this finding requires further follow up and investigation. The majority of laboratories agreed and did identify this as abnormally increased and suggested appropriate follow up. Traditionally in Sheffield we have used the numerical classification for the classification of type IV methlyglutaconic acid. However, we draw the attention of

our participants to manuscript of Saskia Wortmann on an updated classification. For reporting purposes one should distinguish between primary 3-methylglutaconic aciduria (previously known at type I) due to deficiency of 3-methylglutaconyl-CoA Hydratase deficiency and secondary 3-methlyglutaconic aciduria. The secondary group should be identified by the defective protein or historical name (e.g. TAZ or Barth syndrome, SERAC1 defect or MEGDEL syndrome, OPA3 defect or Costeff syndrome, DNAJC19 defect or DCMA syndrome and TMEM70 defect). The remaining patients that do not fit the above criteria should be referred to as not otherwise specified (NOS) 3-methylgutaconic aciduria. The full classification can be found in J Inherit Metab Dis (2013) 35:923-928. This sample (239) was donated from a patient with NOS 3-methylgutaoconic aciduria.

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 three returns a score of 22/36 and for two returns a score of 15 or more. On this basis four 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 <u>any</u> 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 will be discussed at the Spring meeting of the Scientific Advisory Board (SAB) and all proposed critical errors will need to be ratified by the SAB before being confirmed.

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 & Dr Jane Dalley
Scheme organisers