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18th March 2016

QAP for qualitative urinary organic acid analysis

Annual Report 2015 (Sheffield)

1. Scheme Design

The scheme has been designed and planned by Mrs C Scott and Dr Jane Dalley as Scientific Advisor/Scheme Organiser and deputy Scientific Advisor/Scheme Organiser, respectively, both appointed by and according to procedures laid down by the ERNDIM Board.

2. Samples and shipment

All EQA materials are 2 ml of heat-treated urine. All samples are obtained following local ethical and consent guidelines. Three sets of three samples (numbered 223-231) were dispatched together in April 2015. Submission deadlines were 19th June (samples 223-225), 18th September (samples 226-228) and 18st November (samples 229-231).

3. Participation

Active participants (reporting on at least one set of samples in the year) are shown in Table 1 (page 2). The numbers of participants remain steady. 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.

4. Results

Laboratories were asked to analyse the sample sets at intervals during the year as if they were separate circulations. Eighty-eight laboratories returned results for all three sets; two returned only two, one laboratories made only a single return, and three made no return.

All submitted results are treated as confidential information and are only shared with ERNDIM approved persons for the purposes of evaluation and reporting

Table 1: Geographical distribution of registered participants

	2015	*2014*	*2013*	*2012*	*2011*	*2010*	*2009*
Argentina	3	3	2	2	2	2	2
Australia	6	6	6	6	6	6	6
Belgium	6	6	6	5	5	6	7
Brazil	2	2	2	2	2	-	1
Canada	1	1	1	1	1	1	1
Columbia	1	1	1	1	1	1	1
Chile	1	1	-	-	-	-	-
Czech Republic	-	-	-	-	1	-	-
Democratic Republic of China	1	1	1	1	2	2	1
Finland	2	2	2	1	1	1	1
France	15	15	15	15	15	13	13
Hong Kong	1	1	-	-	-	-	-
Germany†	1	1	1	1	1	1	1
Israel	3	3	3	3	3	4	3
Japan	2	2	1	1	1	1	1
Lebanon	1	1	1	1	1	1	1
Malaysia	3	3	3	3	3	4	3
New Zealand	1	1	1	1	1	1	1
People's Republic of China	9	9	9	8	10	7	7
Portugal	2	2	2	2	2	2	2
Republic of Korea	1	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	1
Spain	6	6	6	6	6	6	6
Turkey	7	3	3	3	3	3	2
United Kingdom	18	18	18	18	18	19	20
USA	5	5	5	3	3	3	4
Uruguay	1	1	-	-	-	-	-
Venezuela	-	-	-	1	1	1	1
Vietnam	1	1	1	1	1	-	-
TOTAL	**104**	**100**	**94**	**91**	**95**	**90**	**89**

† Heidelberg laboratory

5. 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

For the 2014 scheme onwards another criterion for satisfactory performance will be the absence of any "critical error" which is defined as an error resulting from seriously misleading analytical findings and /or interpretations with serious clinical consequences for the patient.

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

Sample	Scores				
	0	**1**	**2**	**3**	**4**
Sample 223 3 year old boy with dehydration vomiting, acidosis Gross excretion of methylmalonate with an excess of methylcitrate and slightly increased 3-hydroxypropionate indicates a primary or secondary deficiency of methylmalonyl-CoA mutase activity. The methylmalonic acid will be quantitated. Please send a sample for total homocysteine, vitamin B12 and full blood count.	-	-	5	-	89
Sample 224 15 year old boy admitted due to hypoglycaemia. Sample taken post recovery Increased excretions of hexanoyl-, suberyl- and phenylpropionylglycine, in the absence of an elevated dicarboxylic aciduria is indicative of medium chain acyl CoA dehydrogenase deficiency (MCADD), none crisis sample. Recommend further investigation, including plasma or dried blood spot acylcarnitine profile and mutational analysis of the ACDM (MCAD) gene.	11	-	1	1	81
Sample 225 10-year-old boy. Autistic spectrum disorder Nothing specifically diagnostic	4	-	-	-	90
Sample 226 15 year-old boy, intoxicated and unresponsive An extremely large peak of glycolic acid, prominent peaks of ethylene glycol and oxalate and moderately increased excretion of lactate and 3-hydroxybutyrate. Diagnostic of ethylene glycol ingestion.	1	-	3	1	96
Sample 227 5 year old girl with mental retardation, vomiting Increased excretion of fumarate and malate with no increase in lactate. Results would be consistent with a diagnosis of fumarate hydratase deficiency. Suggest a skin biopsy for enzymatic and molecular confirmation.	1	0	9	2	89
Sample 228 3 year-old girl with developmental delay Nothing specifically diagnostic	3	-	-	-	98
Sample 229 10 year-old boy, developmental delay Nothing specifically diagnostic	2	-	-	-	94

Table 3: Cumulative scores for 2013 - 2015 (current Sheffield participants only)

The maximum scores for all 3 years 2013, 2014 & 2015 were 36

Lab Number	No of returns in 2015	Total score 2015 out of 36 for 3 returns	Number of returns 2014	Total score 2014 out of 36 for 3 returns	Number of returns 2013	Total score 2013 out of 36 for 3 returns	**Total score Over 3 years*.**
1	3	36	3	36	3	36	108
2	3	35	3	36	3	35	106
3	3	36	3	32	3	36	104
4	3	34	3	34	3	36	104
5	3	36	3	36	3	35	107
6	3	34	3	36	3	36	106
7	3	34	3	36	3	36	106
8	3	35	3	36	3	36	107
9	3	36	3	34	3	34	104
10	3	36	3	36	3	35	107
11	3	36	3	36	3	35	107
12	3	32	3	34	3	36	102
13	3	34	3	36	3	36	106
14	3	30	3	22	3	30	82
15	3	36	3	32	3	36	104
16	3	28	1	4	3	32	64
17	3	36	3	34	3	34	104
18	3	36	3	36	3	36	108
19	3	36	3	26	3	34	96
20	3	36	3	34	3	34	104
21	3	36	3	34	3	36	106
22	3	36	3	36	3	35	107
23	3	36	3	34	3	36	106
24	3	32	3	36	3	36	104
25	3	36	3	34	3	36	106
26	3	35	3	36	3	36	107
27	3	36	3	36	3	36	108
28	3	34	2	24	3	36	96
29	3	35	3	36	3	36	107
30	3	36	3	36	3	34	106
31	3	36	3	36	3	36	108
32	3	35	3	36	3	35	106
33	3	32	3	32	3	36	100
34	3	36	3	33	3	28	97
35	1	12	3	36	3	28	-
36	3	36	3	36	3	36	108
37	3	35	3	34	3	36	105
38	3	36	3	34	-	-	-
39	3	36	3	36	3	36	108
40	3	36	3	36	3	36	108
41	3	36	3	36	3	36	108
42	3	36	3	34	3	36	106

Lab Number	No of returns in 2015	Total score 2015 out of 36 for 3 returns	Number of returns 2014	Total score 2014 out of 36 for 3 returns	Number of returns 2013	Total score 2013 out of 36 for 3 returns	**Total score Over 3 years*.**
43	3	36	3	36	3	36	108
44	3	36	3	36	3	36	108
45	3	36	3	32	3	36	104
46	3	36	3	36	3	34	106
47	3	36	3	36	3	36	108
48	3	36	3	34	3	35	105
49	3	36	3	36	3	36	108
50	3	32	3	36	3	36	104
51	3	35	3	33	3	36	104
52	3	36	3	36	3	35	107
53	2	24	3	18	3	28	70
54	3	35	3	36	3	36	107
55	3	36	3	36	3	36	108
56	3	36	3	30	3	32	98
57	3	30	3	28	3	30	88
58	3	36	3	36	3	36	108
59	3	33	3	30	3	36	99
60	3	26	3	32	3	36	94
61	3	36	3	36	3	36	108
62	2	22	3	34	3	36	92
63	3	36	3	32	3	34	102
64	3	36	3	32	3	36	104
65	3	32	3	32	1	8	72
66	0	0	3	28	3	36	64
67	3	32	3	32	3	36	100
68	2	24	3	36	3	32	92
69	3	35	3	30	3	36	101
70	3	36	3	25	3	36	97
71	3	32	3	36	3	36	104
72	3	32	1	12	3	36	80
73	2	20	3	36	0	0	56
74	2	20	1	12	2	24	56
75	1	10	3	36	2	22	68
76	3	36	3	36	3	36	108
77	3	30	3	24	3	32	86
78	3	34	3	32	3	35	101
79	3	36	-	-	-	-	-
80	3	34	3	34	3	33	101
81	3	32	3	32	3	36	100
82	3	34	3	33	3	36	103
83	2	20	3	15	3	34	-
84	3	36	3	36	3	36	108
85	1	10	3	24	3	32	-
86	3	26	-	-	-	-	-
87	2	20	-	-	-	-	-

Lab Number	No of returns in 2015	Total score 2015 out of 36 for 3 returns	Number of returns 2014	Total score 2014 out of 36 for 3 returns	Number of returns 2013	Total score 2013 out of 36 for 3 returns	**Total score Over 3 years*.**
88	3	36	3	24	-	-	-
89	3	36	-	-	-	-	-
90	3	32	3	36	3	36	104
91	3	28	3	38	3	30	96
92	3	31	3	29	3	31	91
93	2	22	-	-	-	-	-
94	3	32	3	34	3	36	102
95	3	36	3	34	-	-	-
96	3	33	3	32	3	32	93
97	3	35	3	36	2	20	91
98	2	22	-	-	-	-	-
99	3	36	3	36	-	-	-
100	3	30	3	32	-	-	-
101	3	28	3	36	-	-	-
102	3	24	-	-	-	-	-
103	2	24	-	-	-	-	-
104	3	36	-	-	-	-	-

* Maximum score is 108 over 3 years for 3 returns per year. The maximum score is only valid if all 3 returns over 3 years have been received.

Your Laboratory OA Number in the above Table is

Please note: for the purpose of this table you have a new laboratory numbers from previous years. Your ERNDIM number has not changed, please use your ERNDIM number in all communication with the scientific advisors.

6. Commentary

This year's 2015 samples were received and scored well this year compared to 2014, with 53% of participants achieving maximum scores compared to only 36% in 2014. In the first triplet of urine specimens, sample 224 proved slightly more challenging with a number of laboratories failing to identify acylglycines in a 'none crisis sample'. Many laboratories have developed targeted selective ion searches (macros) that scan automatically in every sample and some laboratories include heptonylglycine internal standard reflecting the potential inefficiency of acylglycine extraction. If your laboratory has a concern, please note, Sheffield Children's Hospital provide heptanoylglycine Internal Standards (Charge = 100mg/£1.00 – 1g minimum order). The second distribution, samples 226-228 happily providing little challenge to most participants.

In the final distribution, sample 230 was the most contentious, with 80% (71/96) obtaining full marks. This sample was from a patient with genetically confirmed short chain acyl Co A dehydrogenase (SCADD) deficiency. They are compound heterozygous for the c.310_312del, p.(Glu104del) pathogenic mutation in exon 3 and the c.1138C>T, p.(Arg380Trp) pathogenic mutation in exon 10 of the ACADS gene. Both mutations have been described previously in affected individuals and shown in vitro to abolish enzyme activity (Corydon et al. (2001) Pediatr

Res 49:18-23, Bok et al. (2003) Pediatr 112:1152-1155 and Pedersen et al. (2008) Hum Genet 124:43-56). Analysis by organic acid profiling cannot fully distinguish (SCADD) or ethylmalonic encephalopathy (EME) although the age of the patient and clinical details would have strongly favoured SCADD. The scoring reflects this. Full marks were awarded if SCADD was identified, or both EME and SCADD identified as either most likely diagnosis or secondary diagnosis. A point was deducted for EME only or if multiple acyl dehydrogenase deficiency or mitochondrial dysfunction was considered the most likely diagnosis. This was to award those who correctly included SCADD into their report.

It is appreciated that in all the cases the urine organic acid profile is only part of the diagnostic profile 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.

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 under the new scoring system, and for two returns a score of 15 or more. On this basis all participating laboratories, that returned greater then two returns, were deemed satisfactory. 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. Starting with the 2014 schemes the concept of 'critical error' was introduced to the assessment of the qualitative urinary organic acid scheme.

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 Darwin 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,

Dr Jane Dalley	Professor J R Bonham	Mrs Camilla Scott
Deputy Scientific Advisor		Scientific Advisor

Scheme organisers