ERNDIM number ---

Department of Clinical Chemistry and Neonatal Screening

Ms M Downing
Dr J R Bonham
Professor R J Pollitt
Dr R M Talbot

The Children's Hospital
Sheffield
S10 2TH
UK

Telephone **(+)44 114 271 7404**
Fax **(+)44 114 276 6205**

5th May 2009

ERNDIM QAP for qualitative urinary organic acid analysis

Annual Report 2008 (Sheffield)

Participation

Active participants (reporting on at least one set of samples in the year) are shown in Table 1. The number of participants continues to grow. 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 participants

	2008	*2007*	*2006*	*2005*	*2004*
Argentina	1	2	1	1	1
Australia	6	6	6	6	6
Belgium	5	5	4	6	6
Brazil	1	1	1	1	1
Canada	1	1	1	0	0
Democratic Republic of China	1	1	1	1	1
Finland	1	1	1	1	1
France	14	13	11	12	13
Germany†	1	1	1	1	1
Israel	2	2	2	2	2
Japan	1	1	1	0	0
Lebanon	1	1	1	1	1
Malaysia	3	2	2	1	1
New Zealand	1	2	2	1	0
People's Republic of China	6	6	4	4	4
Portugal	2	2	2	2	2
Republic of Korea	1	1	1	1	0
Republic of Ireland	1	1	1	1	1
Republic of Singapore	1	-	-	-	-
South Africa	1	-	-	-	-
Spain	5	5	5	5	5
Turkey	2	-	-	-	-
United Kingdom	20	20	21	21	21
USA	4	4	2	1	0
Venezuela	1	1	1	0	0
TOTAL	**83**	**79**	**72**	**69**	**67**

† Heidelberg laboratory

Samples and results

Three sets of three samples each (total 9; sample numbers 160-168) were dispatched together in April 2008. Seventy-six laboratories (92%) returned results for all three circulations, five returned for only two, and two laboratories made only a single return.

Instrumentation

Currently only one active participant is relying on gas-chromatography alone, the remainder performing their analyses wholly or in part by GC-MS.

Scoring of results

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

Satisfactory	2	Helpful but incomplete	1
Unhelpful	0	Slightly misleading	-1
Misleading	-2	Failing to return an individual result	0

Two points are deducted for transposed sample numbers.

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

Sample		Scores				
		-2	**-1**	**0**	**1**	**2**
160	Three months old, acidotic attack with hyperammonaemia, now well: Propionic acidaemia	2	2	6	-	69
161	Four-year-old boy, developing abnormal movements: Normal	5	1	3	-	70
162	Three weeks of age, unexplained episode of diarrhoea and vomiting: Methylmalonic semialdehyde dehydrogenase deficiency	10	-	18	15	36
163	18-year-old male. Muscle pain, myoglobinuria: Normal	3	1	1	1	73
164	35-year-old woman with three microcephalic children: Phenylketonuria	1	-	1	1	76
165†	2-year-old girl with frequent episodes of diarrhoea and vomiting, initially associated with hypoglycaemia: 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency	-	1	5	-	73
166	18-month-old boy. Very drowsy and not feeding: Maple syrup urine disease	5	-	-	3	71
167	Healthy 2-year old, consanguineous parentage. Cousin died of “Reye Syndrome” 2 years ago: 3-Methylcrotonyl-CoA carboxylase deficiency	-	2	1	1	75
168	Four-year-old boy, developmental regression: Normal	-	1	-	1	77

† Common sample with the Heidelberg scheme where 73 of 75 participants scored 2

Table 3: Cumulative scores for 2006 - 2008 (current Sheffield participants only)

	2008			2007		2006		2006-8
Laboratory OA Number	No of returns	Late returns	Total score	No of returns	Total score	No of returns	Total score	Average score*
3	3	0	14	3	16	3	18	1.85
4	3	0	14	3	16	3	17	1.81
5	3	0	16	3	10	3	18	1.69
6	3	0	18	3	16	3	18	2.00
7	3	0	14	3	16	3	17	1.81
9	3	0	15	3	16	3	17	1.85
10	3	0	16	3	16	3	15	1.81
11	3	0	14	3	16	3	17	1.81
12	3	0	18	3	16	3	18	2.00
13	3	0	16	3	16	3	18	1.92
14	3	1	18	3	16	3	18	2.00
15	3	0	14	3	16	3	14	1.69
17	3	0	18	3	15	3	10	1.65
18	3	1	18	3	16	3	16	1.92
19	3	0	16	2	10	3	18	1.91
21	3	2	18	3	16	3	18	2.00
24	3	0	18	3	16	3	16	1.92
25	3	0	14	3	16	2	11	1.78
26	3	0	18	3	15	3	14	1.81
27	3	0	16	3	16	3	10	1.62
28	3	1	6	3	13	3	8	1.04
29	3	0	17	3	14	3	18	1.88
31	3	0	16	3	14	2	12	1.83
32	3	0	15	3	16	3	18	1.88
35	3	0	16	3	16	3	18	1.92
38	3	0	18	3	16	3	18	2.00
42	3	0	18	3	16	3	18	2.00
44	3	1	18	3	15	3	15	1.85
48	3	1	16	3	16	3	18	1.92
49	3	0	18	3	16			2.00
51	3	2	17	3	16	3	18	1.96
52	3	0	18	3	15	3	15	1.85
65	3	1	18	3	16	3	18	2.00
66	3	0	18	3	16	3	17	1.96
83	3	0	15	3	16	3	17	1.85
85	2	1	12	3	16	3	18	2.00
86	3	0	18	3	16	2	7	1.78
88	3	1	17	3	16	2	12	1.96
92	3	0	18	3	11	3	15	1.69
93	3	2	14	3	16	3	17	1.81
94	3	0	17	3	16	3	17	1.92
96	3	0	18	3	16	2	11	1.96
98	3	1	17	3	16	3	17	1.92
101	3	0	17	3	16	3	18	1.96
102	3	0	18	3	13	3	18	1.88
104	3	0	18	2	10	3	12	1.74
106	3	0	18	3	16	3	18	2.00

	2008			2007		2006		2006-8
Laboratory OA Number	No of returns	Late returns	Total score	No of returns	Total score	No of returns	Total score	Average score*
108	3	0	12	3	14	3	18	1.69
111	3	0	16	3	16	3	14	1.77
113	3	1	14	3	10	3	13	1.42
114	3	1	8	3	10	3	16	1.31
119	3	0	17	3	16	3	18	1.96
120	3	0	16	3	10	3	16	1.62
121	3	0	14	3	12	3	18	1.69
126	3	1	14	3	11	3	15	1.54
128	1	0	2	2	5	3	15	1.29
130	3	0	17	3	16	2	12	1.96
132	3	0	16	3	16	3	18	1.92
133	3	3	17	3	14	3	15	1.77
134	3	0	15	3	16	3	18	1.88
135	3	0	17	3	14	2	8	1.70
137	3	0	18	3	16	3	18	2.00
138	2	0	10	3	15	3	13	1.65
139	3	0	16	3	14	3	15	1.73
140	3	0	18	3	14	3	14	1.77
141	2	0	4	3	14	3	15	1.43
142	3	0	13	3	16	3	16	1.73
143	3	0	13	3	11	2	10	1.48
144	3	0	18	3	14			1.88
146	3	0	13	2	8			1.50
147	3	0	9	3	16			1.47
148	3	0	13	2	10			1.64
149	3	0	11	3	16			1.59
150	2	0	10	3	12			1.57
151	1	0	4	3	16			1.82
152	3	1	14	3	5			1.12
153	2	0	11	2	10			1.91
154	3	0	11					
155	3	0	17					
156	3	0	14					
157	3	1	8					
158	3	1	12					
159	3	0	16					

*The average score is **per sample reported**. The maximum score for 2007 was 16. For 2006 and 2008 the maximum scores were 18. The distribution of these scores is shown graphically in Figure 1 on the next page. Those with the best scores have the lowest rankings.

Your Laboratory OA Number in the above Table is --

Commentary

Certificates of Participation

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 difficult. This year a substantial number of

participants experienced problems with sample # 162 from a case of (methyl)malonic semialdehyde dehydrogenase deficiency (OMIM +603178). This was circulated partly as an educational exercise as few laboratories have had experience of the disorder though it does appear to be relatively common in some Middle-Eastern ethnic groups. In view of the large number of low scores for this sample we have retained the same criteria for "Satisfactory Performance" as in 2007: when one of the nine samples circulated proved to be unstable and was not scored. Thus a score of 11 or more based on three returns (maximum possible score 18), or of 7 or more where only two returns have been received (maximum possible score 12) has been classed as satisfactory. We will be sending individual letters, drawing attention to areas that appear particularly problematical, to laboratories failing these formal "Satisfactory Performance" criteria. However, such 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.

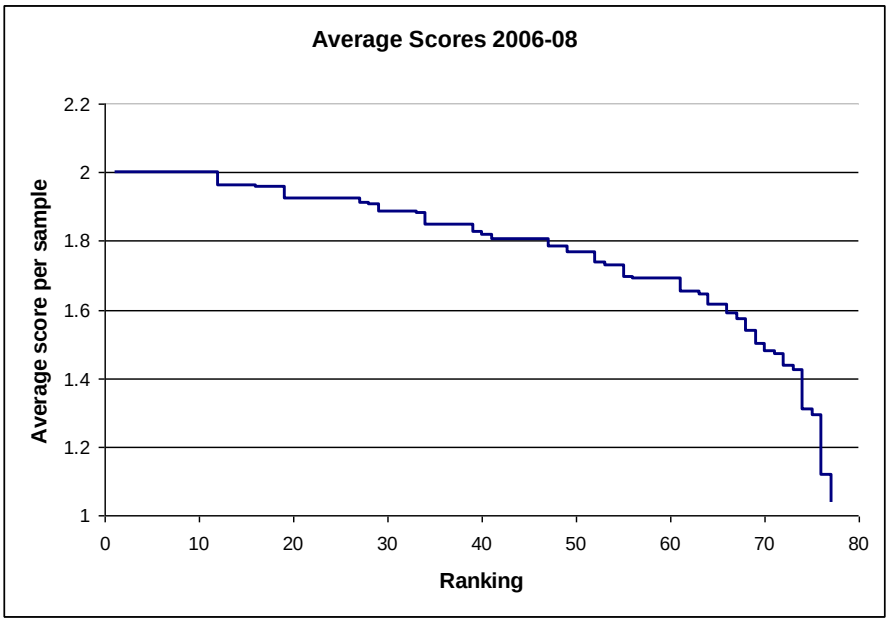

Figure 1: Distribution of average scores per sample, 2006-2008.

Review of long-term performance data

The quality of analytical performance in the ERNDIM quality assurance schemes, together with the scope and organisation of the various schemes, has recently been reviewed (Fowler B, Burlina A, Kovich V, Vianey-Saban C. Quality of analytical performance in inherited metabolic disorders: the role of ERNDIM. *J Inherit Metab Dis* 2008; **31**: 680-689). In a related article (Peters V, Garbade SF, Langhans CD et al. Qualitative urinary organic acid analysis: Methodological approaches and performance. *J Inherit Metab Dis* 2008; **30**: 690-696) data for 50 samples circulated in the Sheffield scheme were examined to determine the underlying reason for any individual score of 0 or less. It was found that the most frequent problem was failure to detect minor peaks of diagnostic significance. This type of failure was strongly clustered: 19 on a sample from a case of tyrosinaemia type 1, 11 on a sample from a case of succinic semialdehyde dehydrogenase deficiency (4-hydroxybutyric aciduria) and 11 on a sample from an adult with well-compensated medium-chain acyl-CoA dehydrogenase deficiency. Another sample from compensated medium-chain acyl-CoA dehydrogenase deficiency resulted in 6 such failures, fumarate hydratase deficiency (two circulations of the same sample) 8, and ornithine

carbamoyltransferase deficiency 5. In some cases the underlying problem seemed to be poor chromatography. In others there appeared to be no system in place to look specifically for the compounds in question (succinylacetone, acylglycines, 4-hydroxybutyrate, orotic acid) even though it is well-recognised that even small amounts may be significant. Related issues were failure to identify a reasonably prominent abnormal peak (10 returns) or failure to recognise the significance of such a peak that had been correctly labelled (23 returns). In 52 returns the wrong disorder was diagnosed, fairly evenly spread through the samples but particularly on samples from cases of 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (6) and DOPA administration (10). A sample from a teenager who has ingested gamma-butyrolactone as a recreational drug was interesting in that succinic semialdehyde dehydrogenase deficiency was diagnosed in 11 returns despite an obviously inappropriate clinical presentation. Overall, 172 of 2418 (7.1%) of returns on abnormal samples were considered unhelpful or misleading.

The converse situation, where a sample from a healthy child was given a possible or definite diagnosis was less frequent, 37 of 1086 returns (3.4%). Another problem identified in this survey was misidentification of samples, either transposition within the EQA samples or confusion with other samples being processed at the time. In all there were 12 examples of this in the 17 circulations surveyed (1.03% per three-sample return).

Assessing suggestions for further investigation

The response form sent out with the urine samples asks for "Further investigations required to confirm/clarify the diagnosis". Participants interpret this request in a great variety of ways. With some samples a simple "none" would suffice, with others a variety of alternative diagnoses need to be considered; a doubtful or borderline abnormality may require further samples or some alternative approach for verification. The organisers of the qualitative diagnostic proficiency schemes have noted that their participants' recommendations for further investigation tend to lack focus and perspective, bringing problems when scoring this aspect of the report. Some participants in the present scheme show similar tendencies, with suggestions covering every possible angle but no clear sense of priority. Given that the report is destined to a hypothetical "non-specialist paediatrician in a distant general hospital" a structured approach is required. As an example, when reporting a urine sample with a suspiciously prominent peak of lactate the next step would be determination of plasma lactate, possibly more than once if the clinician deemed this appropriate, and only then, with lactic acidaemia confirmed, would any of the numerous more specialist investigations be appropriate. Context is also important in that a clinician faced with an acutely ill baby may well regard suggestions involving fibroblast culture or determination of gene sequence as not immediately helpful. Indeed if the metabolite results are sufficiently clear investigation at enzyme or gene level may not be required to establish the diagnosis.

Caveats (relating to the transitory nature of organic acid findings in some of the fatty acid oxidation defects for example) or suggestions for other lines of laboratory investigation based on the clinical presentation rather than the analytical findings should be placed in the "Additional comments" box. However, in some countries there is a very clear line between "biologists" and "clinicians" and care is needed here not to trespass into issues of patient management.

Communication

For 2008 we sent the entire set of nine urine samples as a single consignment, to be analysed and reported in three sets. We sent out E-mail reminders to participants whose reports were outstanding after the closing dates. This revealed that a small number of returns had indeed gone missing in the mail and that a slightly larger number of laboratories had overlooked the closing date or lost their response forms – a disadvantage of sending all the samples out together.

We are repeating this procedure with the 2009 samples. The samples were dispatched during the first week in April and we also sent advisory E-mails. In return we received a number of 'Mail Delivery Failed' notices. If you did not receive this E-mail please send your current E-mail address to rodney.pollitt@sch.nhs.uk giving also your ERNDIM number.

****

We thank Elaine Singleton for administering our participant database and dealing with the returns, and Joyce Allen for preparing and dispatching the samples. We hope that you continue to find this scheme useful.

Yours sincerely

Dr J R Bonham Ms M Downing Professor R J Pollitt Dr R M Talbot

Scheme organisers