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ERNDIM QAP
for qualitative urinary organic acid analysis

Annual Report 2002

Participation

A further set of laboratories were transferred to the Heidelberg scheme this year. The two schemes are run separately, usually circulating different samples, but try to keep the same general philosophy and format. To assist this, the two organising laboratories each participate in the other's scheme. Active participants (reporting on at least one sample in the year) remaining in the Sheffield group are shown in Table 1.

Table 1: Geographical distribution of participants

	2002	*2001*	*2000*	*1999*	*1998*	*1997*	*1996*
United Kingdom	22	21	21	21	22	22	23
France	11	11	11	10	11	1	10
Italy	0	1	9	9	8	8	8
The Netherlands	9	8	8	8	8	6	6
Belgium	6	6	7	7	7	7	7
Germany	1†	1†	9	9	7	4	4
Australia	6	6	6	6	6	5	3
Spain	5	5	5	5	5	4	4
USA	0	5	5	5	5	5	5
Austria	0	0	3	3	3	3	3
Canada	0	3	3	3	3	3	2
Czech Republic	0	0	2	2	2	2	2
Denmark	0	2	2	2	2	2	2
Republic of China	3	3	2	2	2	1	0
Finland	0	1	1	1	2	1	1
Portugal	1	1	1	1	2	3	3
Sweden	0	2	2	2	2	2	2
Switzerland	0	0	2	2	2	2	2
Other countries*	6	11	14	14	12	10	10
TOTAL	**70**	**87**	**113**	**112**	**111**	**101**	**97**

† Heidelberg laboratory

* One participant from each country (2002): Argentina, Brazil, Eire, Israel, Lebanon and Taiwan

Samples and results

Three sets of three samples (total 9; sample numbers 106-114) were distributed in 2002. Fifty-seven laboratories returned results all three circulations.

Table 2: Receipt of results into the executive centre within the specified time period (approximately 6 weeks from dispatch) :

Number of returns in 2002	*Number of participants*				
	0 Late	*1 Late*	*2 Late*	*3 Late*	*Total*
1	1		-	-	1
2	6	4	2	-	12
3	31	14	12	0	57

Instrumentation

Information on method and workload was not systematically updated but examination of the returns showed that of the 70 active participants 64 used GC-MS and 6 used predominantly GC.

Scoring of results

Summary results for the individual returns were dispatched earlier. To enable data reduction and analysis of long-term performance the results were scored as shown below:

2	satisfactory
1	helpful but incomplete
0	unhelpful
-1	slightly misleading
-2	misleading.

A score of zero was given for failing to return an individual result.

Where samples were interchanged or misnumbered participants were penalised 2 points but otherwise given the best possible score that could be obtained by reassigning the results.

Table 3: Distribution of scores for individual samples (laboratories making returns)

Sample	**-2**	**-1**	**0**	**1**	**2**
#106 Fumarate hydratase deficiency	1	-	4	1	59
#107 Normal pattern	2	-	-	-	63
# 108 Tyrosinaemia type 1	5	1	13	9	37
#109 “Adult Reye syndrome” (see discussion)	3	2	2	5	51
#110 Medium-chain acyl-CoA dehydrogenase deficiency	-	-	1	4	58
#111 Normal pattern	-	-	2	4	57
#112 Normal pattern	1	-	-	-	66
#113 Patient of sample #109 in crisis	1	-	1	1	64
#114 Isovaleric acidaemia	-	-	-	-	67

Commentary

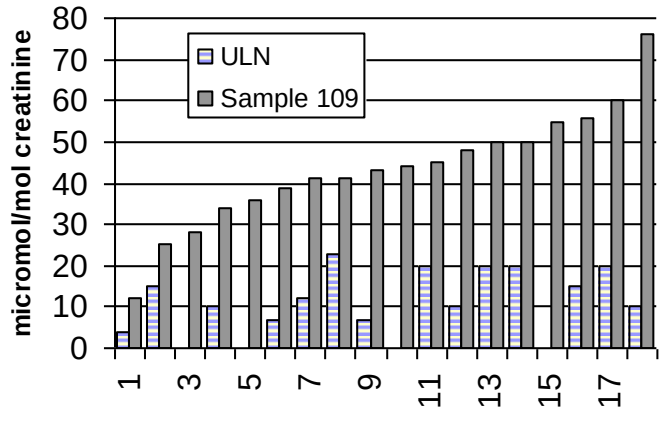
The results for the three normal samples and the three straight-forward pathological samples (fumarate hydratase deficiency, medium-chain acyl-CoA dehydrogenase deficiency and isovaleric acidaemia) were encouraging, with few returns causing concern.

Sample #108, from a patient with tyrosinaemia type 1, contained much less succinylacetone than we anticipated, though a partially reduced derivative (hydroxyoxoheptanoate)was present in clear excess. As described in the report for that circulation, the suggestions for further investigation weighed heavily in determining the score for returns which left the diagnosis in doubt. This reflects the fact that, in terms of patient care, the way findings are reported can be as important as the analytical results themselves. We are including structured response forms with the circulations for 2003 in the hope that this will encourage a more rigorous approach. to the post-analytical phase.

Samples #109 and 113 presented a somewhat different challenge. For obvious reasons we circulated them in reverse order, the post-crisis sample first. The exercise was not completely artificial: in real life it is not that unusual to receive only a non-crisis urine, collected as an afterthought. The main question for sample #109 was whether, bearing in mind the clinical history, the modest increase in ethylmalonic acid was likely to have any significance. The majority of participants thought that it probably had, and the scoring scheme was based on this majority view, fortified by the benefit of hindsight. One participant wrote querying whether this was justified in that an isolated moderate ethylmalonic aciduria is of no diagnostic significance. There is indeed much conflicting information in the literature and the relationships between mutations in the SCAD gene, ethylmalonic aciduria, and increased susceptibility to otherwise minor biochemical anomalies remain to be properly elucidated. Nevertheless, in some instances (and this one in particular) increased excretion of ethylmalonic acid is an indicator of a treatable disorder and should be reported as such, with the appropriate caveats.

Another participant reported that the ethylmalonate in sample #109 was within their laboratory's reference range, and therefore was not reported. Most participants produce essentially qualitative reports but the few who did supply quantitative data (18 out of the 63 respondents) showed a large variation in both quantitative measurements and reference ranges (Figure 1, ULN = upper limit of normal). It is clear that there is tremendous variation in both the absolute amounts reported and in laboratory reference ranges.

Figure 1: Ethylmalonic acid in sample #109



Quantitation has only a limited role in diagnostic investigation of urinary organic acids: (1) as the ERNDIM quantitative organic acid scheme has shown, there is a great deal of. Inter-laboratory variation; (2) for some disorders, fatty acid oxidation defects in particular, it is the overall pattern that is diagnostic, the individual metabolites may well be within “normal” limits for a hospital population.

Sample #113 was more obviously abnormal but was inconsistent with any of the well-recognised disorders of fatty acid oxidation. Almost all respondents placed the disorder amongst the multiple-acyl-CoA dehydrogenation defects despite the puzzling lack of acylglycines in the urine. The gratifying conclusion from this case is that sometimes one can suggest a life-saving treatment without fully understanding the biochemical basis of the problem.

Supply of samples

One of our long-standing participants has commented adversely on the quality of the samples recently supplied, drawing attention particularly to the fact that several have contained drug metabolites. He writes "at present we appear to be learning more from the EQA scheme about degradation products and artefacts than metabolic disorders and the value of the ERNDIM EQA programme is diminishing". He has a point in that samples containing drug metabolites, or partially degraded through improper storage or during transport cause a great deal of additional work and may give misleading results. However, such samples are, unfortunately, part of the every-day fare of most routine laboratories. The spectra of many of the offending compounds, particularly drug metabolites and food additives, are not recorded in the generally-available mass spectral databases. Do we really need to be able to identify such peaks? Though it may not always seem like that, the core business of a clinical organic acid service is the identification of known, well-characterised metabolic disorders. In their recent paper Kumps *et al* (Kumps A, Duez P, Mardens Y. Metabolic, nutritional, iatrogenic, and artifactual sources of urinary organic acids: A comprehensive table. *Clinical chemistry* 2002; **48**: 708-717) list about 125 compounds that are relevant to this task. As long as we can recognise these, and a few others that could be usefully added to the list (see sample #108 in the previous circulation for example), we fulfil our task.

It must be admitted that the tendency towards more “difficult” samples is partly due to increasing difficulty in finding suitable urine samples of sufficient volume for the EQA scheme. This is partly because patients are being treated more rapidly and to greater effect than previously. It is also a result of the increasing emphasis on obtaining consent before samples are used for anything other than primary diagnosis and the difficulty of broaching this issue with the parents of a deceased or seriously ill child. **Participants are urged to submit samples that would be suitable for inclusion in the scheme**, particularly those from patients with rarer conditions which other participants might meet only occasionally. Please let us know what you have (volume, clinical details, and a copy of the chromatogram). If the sample is suitable we will reimburse transport costs.

Yours sincerely

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Scheme organisers

TABLE 4: CUMULATIVE SCORES FOR 2001 AND THE FOUR PRECEDING YEARS (CURRENT SHEFFIELD PARTICIPANTS ONLY)

Year	2002			2001	2000	1999	1998	1998-2002
Lab ID no	Number of returns	Late returns	Total score	Total score	Total score	Total score	Total score*	Average score
3	2	0	12	13	10	10	12	11.4
4	3	0	17	12	15	18	11	14.6
5	3	1	15	17	18	18	4.5	14.5
6	3	0	18	17	14	18	16.5	16.7
7	3	0	18	18	14	18	15	16.6
9	3	0	18	18	18	18	7.5	15.9
10	3	1	14	15	15	10	12	13.2
11	3	0	18	18	18	14	15	16.6
12	3	0	14	18	18	18	17	17.0
13	2	0	12	17	18	18	12	15.4
14	3	2	13	17	8	16	16.5	14.1
15	2	0	11	17	17	18	13	15.2
16	3	1	18	17	18	18	17	17.6
17	3	1	14	11	12	18	15	14.0
18	3	0	18	17	14	17	15	16.2
19	3	2	18	15	13	18	17	16.2
21	2	1	12	12	16	18	17	15.0
24	3	0	18	17	18	18	14	17.0
25	3	0	16	17	18	18	17	17.2
26	3	2	18	17	18	18	17	17.6
27	3	1	4	-1	11	7	2	4.6
28	3	0	14	15	14	18	12	14.6
29	3	0	14	15	18	17	13.5	15.5
31	3	0	18	17	17	17	15	16.8
32	3	1	18	12	18	18	15	16.2
35	3	0	18	17	18	18	18	17.8
37	3	0	17	18	18	18	17	17.6
38	3	0	18	18	18	15	17	17.2
42	3	0	18	18	18	18	16.5	17.7
43	3	1	17	18	16	14	17	16.4
44	3	0	18	15	14	18	17	16.4
48	3	1	16	10	14	18	15	14.6
49	3	2	15	18	14	18	9	14.8
51	3	1	18	18	17	14	16.5	16.7
52	2	1	10	18	18	18	17	16.2
57	3	0	17	17	18	13	7	14.4
59	3	0	17	18	14	17	14	16.0
60	3	0	18	18	18	6	13.5	14.7
65	3	2	16	14	18	18	15	16.2
66	3	0	14	17	18	18	17	16.8
69	2	2	4	2	8	12	-4.5	4.3
70	3	0	17	18	12	18	16.5	16.3
74	3	0	16	18	16	17	15	16.4
76	3	0	18	16	18	6	12	14.0
77	3	2	18	14	18	18	16	16.8
78	3	2	6	17	18	8	12	12.2
79	3	2	17	11	13	18	15	14.8

TABLE 4 (CONTINUED)

Year	2002			2001	2000	1999	1998	1998-2002
Lab ID no	Number of returns	Late returns	Total score	Total score	Total score	Total score	Total score*	Average score
83	3	2	15	17	18	18	17	17.0
85	3	2	16	17	18	14	13.5	15.7
86	3	0	11	17	14	15	13	14.0
88	2	0	8	10	18	11	15	12.4
90	2	0	11	11	17	12	12	12.6
92	3	1	17	17	12	12	17	15.0
93	3	0	18	17	14	18	13	16.0
94	3	0	14	13	11	16	15	13.8
96	2	1	12	17	6	18	13	13.2
98	3	2	17	18	16	18	12	16.2
101	3	0	16	18	18	18	15	17.0
102	3	1	17	16	18	18	17	17.2
104	3	1	16	17	14	11	16.5	14.9
107	3	2	16	17	18	12	18	16.2
108	3	0	16	8	10	14	13	12.2
111	3	0	18	17	18	18	16.5	17.5
113	2	2	10	12	7	6		8.8
114	1	0	6	17	14	13		12.5
119	3	1	18	17	6			13.7
120	3	1	16	10				13.0
121	2	0	11	12				11.5
125	3	0	18					
127	2	1	1					

*Adjusted to equivalent score for 3 circulations a year

This Table has been extensively revised following the transfer of another group of participants to the Heidelberg scheme. Please let us know if any inaccuracies have crept in during the process