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ERNDIM QAP
for qualitative urinary organic acid analysis

Annual Report 2003 (Sheffield)

Participation

Active participants (reporting on at least one sample in the year) are shown in Table 1. A further set of laboratories, originally in the Sheffield scheme, transferred to Heidelberg in 2002. 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. Additionally, this year the two schemes circulated a common sample (see below).

Table 1: Geographical distribution of participants

	2003	***2002***	***2001***	***2000***	***1999***	***1998***	***1997***
United Kingdom	21	22	21	21	21	22	22
France	13	11	11	11	10	11	1
Italy	0	0	1	9	9	8	8
The Netherlands	10	9	8	8	8	8	6
Belgium	6	6	6	7	7	7	7
Germany	1†	1†	1†	9	9	7	4
Australia	6	6	6	6	6	6	5
Spain	5	5	5	5	5	5	4
USA	0	0	5	5	5	5	5
Austria	0	0	0	3	3	3	3
Canada	0	0	3	3	3	3	3
Czech Republic	0	0	0	2	2	2	2
Denmark	0	0	2	2	2	2	2
Republic of China	4	3	3	2	2	2	1
Israel	2	1	1	1	1	2	1
Portugal	2	1	1	1	1	2	3
Sweden	0	0	2	2	2	2	2
Switzerland	0	0	0	2	2	2	2
Other countries*	7	6	11	14	14	12	10
TOTAL	**77**	**71**	**87**	**113**	**112**	**111**	**101**

† Heidelberg laboratory; * One participant from each country (2003): Argentina, Brazil,

Finland, Republic of Ireland, Lebanon, Malaysia and Taiwan

Samples and results

Three sets of three samples (total 9; sample numbers 115-123) were distributed in 2003. Sixty-four laboratories returned results for 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 2003	*Number of participants*				
	0 Late	*1 Late*	*2 Late*	*3 Late*	*Total*
1	2	-	-	-	2
2	7	3	1	-	11
3	47	10	6	1	64

Instrumentation

Examination of the returns showed that of the 77 active participants 70 used GC-MS and 7 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	**Scores**				
	-2	**-1**	**0**	**1**	**2**
#115 Increased 3-hydroxyglutarate	22	3	2	1	45
#116 Malonic aciduria	4	-	-	-	69
#117 Normal pattern	4	-	-	-	69
#118 Complex syndrome with ?thiamine deficiency	-	-	-	-	-
#119 Anticonvulsant-induced carnitine deficiency	1	-	2	9	59
#120 Medium-chain acyl-CoA dehydrogenase deficiency	**7**	-	1	4	59
#121 Methylmalonic aciduria	-	-	2	10	52
#122 Normal pattern	1	3	-	-	60

#123 Urea cycle disorder, increased excretion of orotate	3	-	-	4	57

Commentary

Following the suggestion of the ERNDIM Scientific Advisory Board, this year we have provided structured response forms for each sample distributed. It was hoped that this would encourage participants to focus more clearly on the requirements of the referring physician and produce succinct reports that would address three main questions:

- what are the major analytical findings?
- what is the most likely diagnosis, how certain is it, and what, if any, are the possible alternatives?
- what further investigations are required to confirm or clarify the diagnosis?

Taking into account differing national perspectives on the respective functions of the physician and the laboratory specialist, advice on treatment was not included in the assessment.

Most participants used the form provided or adapted their reports to follow the same format. This was of considerable help in assessing the returns. Over 90% of participants also provided copies of their annotated chromatograms or total ion traces as requested. For some samples these gave useful information on the reasons for poor performance. Thus for samples #115 and #120 lack of analytical sensitivity (to 3-hydroxyglutarate and hexanoylglycine respectively) was the main problem and in some cases this was clearly due to poor chromatography, with trailing peaks suggestive of deterioration of the column or problems with the splitter.

In the case of sample #115, we departed from our normal practice in that this was urine from a healthy subject that had been enriched with synthetic 3-hydroxyglutarate. It was produced to investigate the sensitivity of routine qualitative organic acid analysis in the diagnosis of “non-excretor” glutaryl-CoA dehydrogenase deficiency. The concentration of 3-hydroxy- glutarate in this sample was many-fold greater than has been reported in the literature for such non-excretors but nevertheless 35% of respondents failed to detect the abnormality. This sample was also circulated to participants in the Heidelberg scheme with similar results, 59% of respondents failing to report the abnormality.

The other main causes of sub-optimal performance (as reflected in the number of participants scoring 1 for samples #119 or #120) were unclear or incomplete interpretations and failure to suggest appropriate follow-up investigations. Whilst it is unnecessary in all cases to confirm a diagnosis at the enzyme or DNA level, there are instances where additional laboratory information is required for differential diagnosis and appropriate management and the need for such follow-up should be indicated in the report.

We have not allocated any scores for sample #118 which, as described previously, presented a considerable diagnostic challenge. The key metabolite was 2-hydroxyvalerate. The majority (60%) of participants correctly identified the peak but only half of these mentioned it in their report, an interesting question of interpretational sensitivity.

Supply of samples

The tendency towards more “difficult” samples noted last year has continued. To some extent this reflects the maturity of the scheme and the fact that the vast majority of participants no longer find difficulty in diagnosing the more common disorders from “typical” urine samples.

We need to keep stretching the limits if the scheme is to continue being useful. However, again as noted last year and echoed in the annual report from Heidelberg, the lack of suitable samples from the less common conditions is increasingly becoming a constraint. **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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Principal Biochemist	Consultant Biochemist	Consultant Biochemist

Scheme organisers

TABLE 4: CUMULATIVE SCORES FOR 2003 AND THE FIVE PRECEDING YEARS (CURRENT SHEFFIELD PARTICIPANTS ONLY)

Year	2003			2002	2001	2000	1999	1998
Lab ID no	Number of returns	Late returns	Total score	Total score	Total score	Total score	Total score	Total score*
3	3	0	16	12	13	10	10	12
4	3	0	14	17	12	15	18	11
5	3	0	12	15	17	18	18	4.5
6	3	1	13	18	17	14	18	16.5
7	3	0	16	18	18	14	18	15
9	3	1	9	18	18	18	18	7.5
10	3	0	16	14	15	15	10	12
11	3	0	12	18	18	18	14	15
12	3	0	16	14	18	18	18	17
13	3	0	12	12	17	18	18	12
14	2	2	10	13	17	8	16	16.5
15	3	1	16	11	17	17	18	13
17	3	0	13	14	11	12	18	15
18	3	0	16	18	17	14	17	15
19	3	0	16	18	15	13	18	17
21	3	0	16	12	12	16	18	17
24	3	0	12	18	17	18	18	14
25	3	0	14	16	17	18	18	17
26	3	0	16	18	17	18	18	17
27	3	2	1	4	-1	11	7	2
28	3	0	4	14	15	14	18	12
29	3	0	16	14	15	18	17	13.5
31	3	0	16	18	17	17	17	15
32	3	1	16	18	12	18	18	15
35	3	0	16	18	17	18	18	18
37	3	0	15	17	18	18	18	17
38	3	0	16	18	18	18	15	17
42	3	0	16	18	18	18	18	16.5
43	3	1	11	17	18	16	14	17
44	3	0	15	18	15	14	18	17
48	2	1	8	16	10	14	18	15
49	3	2	11	15	18	14	18	9
51	3	1	12	18	18	17	14	16.5
52	3	0	13	10	18	18	18	17
57	3	0	10	17	17	18	13	7
59	3	0	9	17	18	14	17	14
60	3	1	9	18	18	18	6	13.5
65	3	0	16	16	14	18	18	15
66	3	0	14	14	17	18	18	17
69	2	1	5	4	2	8	12	-4.5
70	3	0	11	17	18	12	18	16.5
74	3	0	16	16	18	16	17	15
76	3	0	13	18	16	18	6	12
77	3	1	6	18	14	18	18	16
78	3	3	9	6	17	18	8	12

79	3	2	14	17	11	13	18	15

TABLE 4 (CONTINUED)

Year	2003			2002	2001	2000	1999	1998
Lab ID no	Number of returns	Late returns	Total score	Total score	Total score	Total score	Total score	Total score*
83	3	0	16	15	17	18	18	17
85	3	2	12	16	17	18	14	13.5
86	3	0	12	11	17	14	15	13
88	2	0	5	8	10	18	11	15
90	3	0	15	11	11	17	12	12
92	3	0	16	17	17	12	12	17
93	3	1	16	18	17	14	18	13
94	3	0	6	14	13	11	16	15
96	2	0	10	12	17	6	18	13
98	3	1	16	17	18	16	18	12
101	3	0	16	16	18	18	18	15
102	3	0	13	17	16	18	18	17
104	2	0	12	16	17	14	11	16.5
106	2	0	10					
107	3	0	16	16	17	18	12	18
108	3	0	12	16	8	10	14	13
111	2	0	9	18	17	18	18	16.5
113	1	1	0	10	12	7	6	
114	3	0	7	6	17	14	13	
119	3	0	12	18	17	6		
120	3	2	8	16	10			
121	3	0	12	11	12			
125	3	0	11	18				
126	3	0	15					
128	2	1	4					
129	3	0	16					
130	3	0	16					
131	2	0	9					
132	3	0	8					
133	1	1	5					
134	2	0	9					
Maximum score	3		16	18	18	18	18	18

*Adjusted to equivalent score for 3 circulations a year