QUALITY ASSURANCE IN LABORATORY TESTING FOR IEM

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Qualitative Blood Spot Acylcarnitine Scheme

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1. **Scheme Design**
   The scheme has been designed and planned by Dr Charles Turner and Prof Neil Dalton 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**
   All EQA materials are 30-50µl of lithium heparin anticoagulated whole blood dried as blood spots on Perkin Elmer (Ahlstrom) 226 paper. All samples are obtained following local ethical and consent guidelines.

3. **Shipment**
   Two circulations of 3 samples each (2015.01-.03 and 2015.04-06) were sent out to the 62 laboratories from 25 countries worldwide assigned to the London centre of the ERNDIM dried blood spot acylcarnitine scheme. One laboratory was an Educational Participant. The first circulation was sent out in June, with a return date of 8th August 2015 and the second in November with a return date of 31st December 2015.

4. **Receipt of results**
   Returns for circulation 2015.01-03 were received from 57 (93%); 55 of these arrived by the initial due date. For circulation 2015.04-06 valid returns were received from 56 (92%); 52 of these arrived before the due date. The educational participant is not included in the statistics; the laboratory reported results and would have had a satisfactory score.

   There were 2 laboratories who failed to make a return on either circulation. Three laboratories reported on circulation 2015.01-03 only, and two on circulation 2015.04-06 only.

5. **Scoring scheme**
   In the process of working towards accreditation for ERNDIM there is a need for harmonization of performance assessment within the qualitative schemes (see ERNDIM 'Newsletter Spring 2013' at www.erndim.org). In 2013 we changed the scoring system from the former scale (-2, -1, 0, +1, +2) to the four point system (+1, +2, + 3, +4) which is used also in the DPT schemes. In this system a maximum of two points is given each for analytical results and interpretation, with the latter including suggestions for further testing/actions. The total score achievable for a single circulation of three samples is twelve and twenty four for the whole sample set of six samples per year. Laboratories that participate only in one circulation are treated as non-submitters.

   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.

6. Results of samples and evaluation of reporting

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

Participants were asked to respond via email using a supplied report template, and to send a scan and/or table of quantitative results if possible. All laboratories responded by email except one who reported via fax.

All laboratories provided a suggested/differential diagnosis. Most suggested some form of appropriate follow-up testing to confirm a putative diagnosis. A summary of the samples sent and the number of respondents detecting the key acylcarnitine and/or suggesting the definitive diagnosis as part of their differential diagnosis is given in the table below.

Sample	Enzyme/transporter defect	Diagnostic Acylcarnitine	Respondents
2015.01	Multiple acyl CoA dehydrogenase deficiency (MADD OMIM 231680)	C8, C10, C5DC, C8/C10 ratio	55/57 ^C8,^C10 7/57 ^C5DC 35/57 MADD
2015.02	Isovaleryl CoA dehydrogenase deficiency (IVA OMIM 243500)	C5	57/57 ^C5 57/57 IVA
2015.03	Methylmalonyl CoA mutase deficiency (MMA OMIM 251000)	C3, C3 based ratios, C4DC, Low free carnitine	48/57 ^C3 or C3 ratio, 21/57 ^C4DC 51/57 MMA
2015.04	Very long chain acyl CoA dehydrogenase deficiency (VLCADD OMIM 201475),	C14:1, Low free carnitine	53/56 ^C14:1 53/56 VLCADD
2015.05	Beta-ketothiolase deficiency (BKT OMIM 203750),	C5OH, C5:1	56/56 ^C5OH 54/56 ^C5:1 54/56 BKT
2015.06	Riboflavin responsive Multiple acyl CoA dehydrogenase deficiency (MADD OMIM 231680	C8, C10, C12, C8/C10 ratio	52/56 ^ C8 & C10 36/56 ^C12 47/56 MADD

The profiles from patients with Isovaleric acidaemia (2015.02), Methylmalonic acidaemia (2015.03) Very Long chain acyl CoA dehydrogenase deficiency (2015.04), and Beta ketothiolase deficiency (2015.05) were characteristic of the disorders and were correctly assigned by almost all laboratories. The ERNDIM Scientific Advisory Board agreed that failure to identify the characteristic pattern in Sample 2015.02 (IVA) should be designated a critical error and it is encouraging that all laboratories correctly identified this disorder. It is however a concern that three laboratories failed to identify VLCADD (2015.04) particularly since acylcarnitine analysis is the first line test for detection of this disorder.

The samples from the patients with MADD (2015.01 & 2015.06) produced variation in interpretation between laboratories. All detected raised C8 carnitine but a number of laboratories interpreted this as indicating MCADD despite the raised C10 carnitine in both samples, the normal C8/C10 in both samples, the raised C5DC in sample 2015.01 and the raised C12 carnitine in sample 2015.06. Sample 2015.01 is not fully typical of the disorder. Previous samples on this patient were circulated in 2011 (sample 18a) and 2013 (sample 21a). Compared to previous circulations there was an increase in the proportion of respondents correctly identifying MADD and excluding MCADD on the basis of the C8/C10 ratio and relative amounts of C6 and C10:1. The profile in sample 2015.06 is more typical of MADD in that more acylcarnitine species are raised, although partial treatment with riboflavin meant that the elevations were modest. A higher proportion of respondents correctly identified the profile.

Proficiency per sample

Sample	No of returns	A (%)	I (%)	Total (%)
2015.01	57	98%	61%	80%
2015.02	57	100%	100%	100%
2015.03	57	92%	89%	90%
2015.04	56	95%	96%	95%
2015.05	56	98%	96%	97%
2015.06	56	100%	84%	92%

Cumulative Scores

The maximum score achievable was 24 points.

Total Score	No of labs (who submitted results for both rounds)
24	26
23	4
22	10
21	2
20	5
19	3
18	1
17	1
16	0
15	1
14	0
13	1
12	0
11	0
10	0
9	0
8	0
7	0
6	0
5	0
4	0
3	0
2	0
1	0
0	0

7. Donation of samples

Once again, we are extremely grateful to the centres that have provided informative material for circulation. If any participants can provide samples in the future it would enormously facilitate this scheme, providing, as it does, genuine clinically derived samples for assay and interpretation. 3-

4ml of lithium heparin anticoagulated whole blood or 70-80 30-50µl blood spots on Whatman (Schleicher & Schuell) 903 or Perkin Elmer 226 paper would provide sufficient material for one circulation. Samples for use in the scheme should be accompanied by a short clinical history and confirmation that informed consent/local ethical approval (as required in the referring centre) for use of the sample has been obtained.

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