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 (numbers 23 & 24) of 3 samples each were sent out to the 66 laboratories assigned to the London centre of the ERNDIM dried blood spot acylcarnitine scheme. Two laboratories were Educational Participants. The first circulation was sent out in June, with a return date of 8th August 2014 and the second in November with a return date of 15th December 2014.

4. Receipt of results

Returns for circulation 23 were received from 59 (89%); 51 of these arrived by the initial due date. For circulation 24 valid returns were received from 53 (80%); all but one of these arrived before the due date. The two educational participants are not included in the statistics; one reported results and would have had a satisfactory score.

There were 5 laboratories who failed to make a return on either circulation. One of these submitted no results in 2013 or 2012, and one submitted only 1 circulation in 2013. Seven laboratories reported on Circulation 23 only (one of these withdrew from the scheme before circulation 24), and one on Circulation 24 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.

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
23a	Medium chain acyl CoA dehydrogenase deficiency MCADD MIM 201450	C8, C6, C10:1, C8/C10 ratio	58/58 ^C8 58/58 MCADD
23b	Propionyl CoA carboxylase deficiency (PA MIM 606054)	C3, normal C4DC	58/58 ^C3 58/58 PA
23c	Very long chain acyl CoA dehydrogenase deficiency (VLCADD MIM 201475)	C14:1	57/58 ^C14:1 56/58 VLCADD
24a	Long chain hydroxyacyl CoA dehydrogenase deficiency (LCHADD MIM 609016),	C14OH, C16OH, C16:1OH, C18OH, C18:1OH	51/52 ^LCOH 51/52 LCHADD
24b	Normal individual		32/52 Normal
24c	Carnitine Palmitoyl Transferase II deficiency (CPT II MIM 255110)	Low C2, C0 Long Chain/Short chain ratio	26/52 ^ ratio 26/52 low C2 36/52 CPT II

The profiles from patients with MCADD (23a), Propionyl CoA carboxylase deficiency (23b), VLCADD (23c) and LCHADD were very characteristic of the disorders and were correctly characterized by almost all laboratories. The ERNDIM Scientific Advisory Board agreed that failure to identify the characteristic pattern in Sample 23c (VLCADD) should be designated a critical error, particularly since acylcarnitine analysis is the first line test for detection of this disorder.

The sample from the normal individual produced variation in interpretation between laboratories due to the borderline raised C5OH acylcarnitine. This introduced the possibility of 3-methyl crotonylCoA carboxylase deficiency or biotin insufficiency and therefore a range of further testing suggestions depending on the cut-offs for C5OH used.

Sample 24c was from a patient with carnitine palmitoyl transferase II deficiency (CPT II) deficiency, with a typical history of rhabdomyolysis. A sample from a patient with this disorder was circulated in 2013 and only 19/51 respondents suggested the disorder. There was an increase in the reporting of ratios, in particular (C16+C18:1)/C2, and an increase in the proportion (36/52) suggesting the diagnosis. The C2 was slightly lower in this sample which may also have provided a

diagnostic clue, but the increase in the proportion of laboratories identifying the disorder suggests enhanced awareness both of the disorder and of the utility of ratios in making the diagnosis.

Proficiency per sample

Sample	No of returns	A (%)	I (%)	Total (%)
23a	58	100%	99%	100%
23b	58	100%	100%	100%
23c	58	98%	97%	97%
24a	52	99%	98%	99%
24b	52	98%	98%	98%
24c	52	65%	66%	66%

Cumulative Scores

The maximum score achievable was 24 points.

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