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 (2016.A-C and 2016.D-F) were sent out to the 61 laboratories from 23 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 August, with a return date of 31st September 2016 and the second in November with a return date of 16th December 2016.

4. Receipt of results

Returns for circulation 2016.A-C were received from 57 (94%); 54 of these arrived by the initial due date. For circulation 2016.D-F valid returns were received from 56 (93%); 53 of these arrived before the due date. The educational participant is not included in the statistics; the laboratory did not report results.

There were 2 laboratories who failed to make a return on either circulation. Two laboratories reported on circulation 2016.A-C only, and one on circulation 2016.D-F 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. To obtain satisfactory performance a score of 16 or more should be achieved on two returns. In 2016 sample 2016.D was considered an educational sample: an acceptable score was defined as 14/20. Laboratories that participate only in one circulation are treated as non-submitters.

For the 2014 scheme onwards another criterion for satisfactory performance is 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
2016.A	Medium chain acyl CoA dehydrogenase deficiency MCADD (MIM 201450),	C8, C10:1, C6, C8/C10 ratio	57/57 ^C8, 41/57 ^C10:1 57/57 MCADD
2016.B	Normal (rhabdomyolysis due to recreational drugs)		35/57 Normal AC profile 42/57 normal
2016.C	Cobalamin C defect Cbl C (MIM 277400)	C3, C3 based ratios, C4DC, Low free carnitine	42/57 ^C3 or C3 ratio, 27/57 ^C4DC 53/57 MMA/Cbl
2016.D	Carnitine palmitoyl transferase type 2 deficiency CPT2 (MIM 600649),	Low (C2) acetyl carnitine. Raised (C16+C18:1)/C2 ratio	27/56 ^{V} C2 14/56 ^ ratio 27/56 normal
2016.E	Glutaryl CoA dehydrogenase deficiency GA1 (MIM 231670),	^C5DC and C5DC ratios	56/56 ^C5DC 11/56 ^ratios 56/56 GA1
2016.F	Propionyl CoA carboxylase deficiency PA (MIM 606054)	C3, C3 based ratios Normal C4DC	56/56 ^ C3 10/56 normal C4DC 56/56 PA

The profiles from patients with medium chain acyl CoA dehydrogenase deficiency (2016.A), Glutaryl CoA dehydrogenase deficiency (2016.E) and Propionyl CoA carboxylase deficiency (2016.F) were characteristic of the disorders and were correctly assigned by all laboratories who submitted results. Almost all laboratories also correctly identified the sample from the patient with methylmalonic acidaemia due to a Cobalamin C defect. The ERNDIM Scientific Advisory Board agreed that failure to identify the characteristic pattern in Sample 2016.A (MCADD) and 2016.E (GA1) would have been designated as critical errors and it is encouraging that all laboratories correctly identified these disorders. The sample from the patient with rhabdomyolysis due to non-metabolic cause (2016.B) caused some problems of interpretation, but a fat oxidation defect was ruled out by most respondents. The sample that caused the most difficulty was that from a patient with CPT2 deficiency (2016.D) as the metabolite disturbance was mild (the patient was well at the time of sampling) and the presentation given, although it specified that the patient had presented in childhood, was uncharacteristic for an adult patient with this disorder. The sample was correctly identified by a minority of respondents and was therefore classified as "educational" and excluded from the overall score for the year.

Proficiency per sample

Sample	No of returns	A (%)	I (%)	Total (%)
2016.A	57	100.0%	99.1%	99.6%
2016.B	57	84.2%	82.5%	83.3%
2016.C	57	95.6%	93.9%	94.7%
2016.D	56	52.7%	38.4%	45.5%
2016.E	56	100.0%	100.0%	100.0%
2016.F	56	100.0%	100.0%	100.0%

Cumulative Scores

The maximum score achievable was 20 points.

Total Score	No of labs (who submitted results for both rounds)
20	34
19	9
18	3
17	3
16	5
15	0
14	0
13	1

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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