ERNDIM
Acylcarnitines in DBS London
ANNUAL REPORT 2018

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1. Introduction

The ERNDIM Acylcarnitine in dried blood spots scheme offers dried blood spots from patients with known acylcarnitine disorders. The London scheme is organised by Charles Turner, Evelina London Children's Hospital in conjunction with CSCQ, the Swiss organisation for quality assurance in medical laboratories.

2. Participants

In 2018 42 laboratories from many different countries participated in the ACDB London. No laboratories were educational participants in 2018 (None in 2017). Educational participants take part in all aspects of the scheme and receive interim reports with scores, but performance is not indicated on the ERNDIM certificate of performance.

3. Design of scheme and logistics

The scheme has been designed and planned by Charles Turner as Scientific Advisor and distributed by Dr Xavier Albe as Scheme Organiser, both appointed by and according to procedures laid down by the ERNDIM Board.

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.

Six samples (2018.A- 2018.F) were sent out to the 42 laboratories from 14 countries worldwide assigned to the London centre of the ERNDIM dried blood spot acylcarnitine scheme. The samples were sent out on June 4th 2018, with a return date of July 18th 2018 for samples 2018.A – 2018.C and a second return date of September 17th 2018 for samples 2018.D – 2018.F.

Table 1. Samples included in the 2018 ERNDIM ACDB London scheme.

Samples, reporting deadline	Sample no.	Sample type (diagnosis)
2018-A – 2018-C, 18/7/2018	ACDB-UL-2018-A	Acute propionic acidaemia (PA)
	ACDB-UL-2018-B	Glutaric acidaemia type 1 (GA1)
	ACDB-UL-2018-C	Very long chain acyl CoA dehydrogenase deficiency (VLCADD)
2018-D – 2018-F, 17/9/2018	ACDB-UL-2018-D	Propionic acidaemia on treatment (PA)
	ACDB-UL-2018-E	Medium Chain acyl CoA dehydrogenase deficiency (MCADD)
	ACDB-UL-2018-F	Biotinidase deficiency on treatment

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 submit results online for the first time in 2018 using the result submission website: https://cscq.hcuge.ch/cscq/ERNDIM/Initial/Initial.php

4. Scoring of results

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. This increased to 17/24 for 2018. Laboratories that participate only in one circulation are treated as non-submitters. Since sample 2018-F was designated an educational sample, a satisfactory score was 14/20 for 2018.

Table 2. General criteria used to score results

Item	Description of scoring criteria	Score
Quantitative results	Correct classification of quantitative results (i.e. normal or increased) according to reference values	1
	Incorrect classification of quantitative results	0
Qualitative results	Correct results according to criteria set for the sample (Table 4)	1
	Incorrect: minimally required results not reported	0
Diagnostic proficiency	Correct according to criteria set for the sample (Table 5)	2
	Partially correct	1
	Unsatisfactory or misleading	0
	Maximum total score	4

From 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.

Returns for circulation 2018.A-C were received from 38 (90%); 37 of these arrived by the initial due date. For circulation 2018.D.-F valid returns were received from 39 (93%); all of these arrived before the due date.

There were 3 laboratories who failed to make a return on both circulations. 1 laboratory reported on circulation 2017.D.-F only.

Most 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.

Table 3. Criteria for scoring of diagnostic proficiency of 2018 samples.

Sample	Diagnoses (or combinations of possible diagnoses) scored as correct - 2 points	Combinations of possible diagnoses scored as partially correct - 1 point	Not correct - 0 points
ACDB-UL-2018-A	Propionic acidaemia in differential diagnosis	Raised C3 carnitine or C3 based ratio detected, PA not specifically mentioned	Raised C3 not detected or commented upon
ACDB-UL-2018-B	Glutaric acidaemia type 1 (GA1) in differential diagnosis	N/A	Increased Glutaryl carnitine not detected/commented upon
ACDB-UL-2018-C	Very long chain acyl CoA dehydrogenase deficiency (VLCADD)	Possible secondary carnitine depletion requiring further investigation	^C14:1 or C14:1 based ratio not detected, possibility of secondary carnitine depletion not mentioned
ACDB-UL-2018-D	Propionic acidaemia in differential diagnosis	Raised C3 carnitine or C3 based ratio detected, PA not specifically mentioned	Raised C3 not detected or commented upon
ACDB-UL-2018-E	Medium Chain acyl CoA dehydrogenase deficiency (MCADD)	Fatty acid oxidation defect MCADD not specified	Normal/no fatty acid oxidation defect
ACDB-UL-2018-F	Not scored: designated educational sample		

Starting with the 2014 schemes the concept of 'critical error' was introduced to the assessment of the qualitative schemes. Labs failing to make a correct diagnosis of a sample considered eligible for this category will be deemed not to have reached a satisfactory performance even if their total points for the year is sufficient according to the requirement set by the SAB. The classification of samples to be judged for critical error was undertaken at the SAB meeting held on November *28* 2018. Samples A, B, D and E were eligible for critical error. Amongst the reports of regular participants two critical errors were identified in 2018, one of these was also a partial submitter and the other was unsatisfactory by overall score.

5. Communication of results

Interim reports with diagnoses, summaries of the results submitted and interim scores were made available November 2018 (samples 2018.A – 2018.C) and February 2019 (samples 2018.D – 2018.F).

The annual report summarises scheme organisation and results.

ERNDIM provides a single certificate for all its schemes with details of participation and performance.
5 Performance Support letters will be sent for the 2018 surveys. 1 of these 5 participants have also received a performance support letter in 2017 or. Unsatisfactory performance (either due to overall score or due to critical error) within an EQA scheme for at least 2 out of 3 years that the participant has subscribed for will result in a notification letter of unsatisfactory performance to the quality manager or head of department.

6. Proficiency of the 2018 scheme

In 2018, 38 participants submitted 2 reports; there were no educational participants. From the 42 ordinary (non-educational) participants 37 (88%) achieved satisfactory performance (score ≥14/20, no critical error). 5 participants did not accomplish satisfactory performance, including 4 due to incomplete submission of results (i.e. no report or 1 survey report submitted instead of 2 reports).

Table 4: Proficiency per sample

Sample	No of returns	A (%)	I (%)	Total (%)
2018.01	37	98.6	93.2	95.9
2018.02	38	97.4	98.7	98.0
2018.03	38	71.1	52.6	61.8
2018.04	39	100.0	100.0	100.0
2018.05	39	94.9	93.6	94.2
2018.06	39	56.4	39.7	48.1

Table 5: Cumulative Scores. The maximum score achievable was 20 points.

Total Score	No of labs (who submitted results for both rounds)
20	14
18	6
17	12
16	4
15	1
13	1

7. Results of individual samples and evaluation of reporting

There were obviously difficulties experienced by some respondents as a result of the move to web based reporting, most obviously in the first round (samples 2018.A-C). Results were omitted from some sections of the report entry form, and some submissions were incomplete. However, most respondents submitted results, and the second set of submissions (samples 2018.D-F) were significantly less problematic.

ACDB-UL-2018-A. Acute propionic acidaemia (PA). All respondents correctly reported disproportionately elevated propionyl carnitine in this sample and the majority suggested a defect in propionate metabolism and described appropriate second line tests to refine the diagnosis.

ACDB-UL-2018-B. Glutaric acidaemia type 1 (GA1). All respondents found the appropriate abnormalities to diagnose glutaryl CoA dehydrogenase deficiency. Once again, most suggested appropriate tests to define the diagnosis

ACDB-UL-2018-C. Very long chain acyl CoA dehydrogenase deficiency (VLCADD). This sample presented major difficulties in interpretation to a large number of participants. A majority failed to recognise an elevation in C14:1 carnitine in a carnitine depleted patient and therefore did not suggest the diagnosis of VLCADD. This once again emphasises the importance of careful scrutiny of results when carnitine is low.

ACDB-UL-2018-D. Propionic acidaemia on treatment (PA). All respondents correctly reported the grossly elevated propionyl carnitine in this sample and the majority suggested a defect in propionate metabolism and described appropriate second line tests to refine the diagnosis.

ACDB-UL-2018-E. Medium Chain acyl CoA dehydrogenase deficiency (MCADD). Most respondents found the appropriate abnormalities to diagnose medium chain acyl CoA dehydrogenase deficiency. Once again, most suggested appropriate tests to define the diagnosis.

ACDB-UL-2018-F. Biotinidase deficiency on treatment. This sample presented major difficulties in interpretation. The elevations in C3 and C5OH carnitine were subtle, and there was a mild elevation of methylmalonyl carnitine (C4DC). It was not considered sufficiently diagnostic to constitute a fair test of laboratory performance, and was therefore designated as an "Educational Sample" and removed from the scoring.

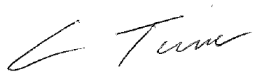
8. Preview of the scheme in 2019

The format of the ACDB 2019 scheme will be similar to that of 2018. Sample dispatch and reporting will be earlier in the year to facilitate reporting in a timely manner.

9. Donation of samples

Once again, we are extremely grateful to the centres that can provide 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 50-60 blood spots of 30-50µl 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.

Please contact the ERNDIM Administration office (admin@erndim.org) to discuss possible samples donations. Laboratories donating a sample that is used in the ACDB EQA scheme are eligible for a 20% discount of their participation costs in the ACDB scheme during the following year.



Charles Turner
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Note: *This annual report is intended for the participants of the Acylcarnitines in DBS scheme. The contents of this report or data derived from the use or analysis of ERNDIM EQA materials must not be used in written publications or oral presentations unless the explicit prior consent of ERNDIM has been granted*