ERNDIM
Acylcarnitines in DBS
Heidelberg

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 scheme is organised by Dr Claus-Dieter Langhans (metabolic center Heidelberg) in conjunction with CSCQ, the Swiss organisation for quality assurance in medical laboratories.

2. Participants

In 2018 *41* laboratories from many different countries participated in the ACDB *Heidelberg*. *No* laboratories were educational participants in 2018 (*0* in 2017). They 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.

Table 1: Geographical distribution of participants

Country	Number of laboratories
Argentina	3
Austria	1
China	3
France	14
Germany	10
Hong Kong	2
Luxembourg	1
Netherlands	5
Turkey	1
UK	1

3. Design of scheme and logistics

The scheme has been designed and planned by Scientific Advisors name 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 Whatman (Schleicher & Schuell) 903™ paper. All samples are obtained following local ethical and consent guidelines.

Six samples (ACDB_DH_2018-A to ACDB_DH_2018-F) were sent out to the 41 laboratories from 10 countries worldwide assigned to the Heidelberg 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 ACDB_DH_2018-A to ACDB_DH_2018-C and a second return date of September 17th, 2018 for samples ACDB_DH_2018-D to ACDB_DH_2018-F.

Table 2. Samples included in the 2018 ERNDIM ACDB Heidelberg scheme.
One sample was donated by Dr Marie-Hélène Read from Caen, France.

Survey, reporting deadline	Sample no.	Sample type (diagnosis)
18-07-ACH, June 4th, 2018	ACDB_DH_2018-A	Cobalamin A deficiency
	ACDB_DH_2018-B	Glutaric aciduria type I (low excreter)
	ACDB_DH_2018-C	Propionic acidaemia
18-09-ACH, September 17th, 2018	ACDB_DH_2018-D	MAD deficiency
	ACDB_DH_2018-E	Normal
	ACDB_DH_2018-F	HMG-CoA lyase deficiency

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.

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 ACDB_DH_2018-A to ACDB_DH_2018-C were received from 38 (93%); 38 of these arrived by the initial due date. For circulation ACDB_DH_2018-D to ACDB_DH_2018-F valid returns were received from 37 (90%); 37 of these arrived before the due date.

There were 2 laboratories who failed to make a return on both circulations. 2 laboratories reported on circulation ACDB_DH_2018-A to ACDB_DH_2018-C only, and one on circulation ACDB_DH_2018-D to ACDB_DH_2018-F only.

A summary of the samples sent, and the number of respondents detecting the key acylcarnitines 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_DH_2018-A	33	2	3
ACDB_DH_2018-B	38	0	0
ACDB_DH_2018-C	34	1	3
ACDB_DH_2018-D	23	14	0
ACDB_DH_2018-E	32	2	3
ACDB_DH_2018-F	33	3	1

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 *29*, 2018. *Samples* ACDB_DH_2018-A *and* ACDB_DH_2018-C *were eligible for critical error. Amongst the reports of regular participants five critical errors were identified in 2018*.

5. Communication of results

Interim reports with diagnoses, summaries of the results submitted and interim scores were made available 05 October 2018 (ACDB_DH_2018-A to ACDB_DH_2018-C) and 13 February 2019 (ACDB_DH_2018-D to ACDB_DH_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.
4 Performance support letters will be sent for the 2018 surveys. *None* of these *4* participants have also received a performance support letter in *2017* or *2016*. 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, *36* participants submitted 2 reports including *no* educational participants. From the *41* ordinary (non-educational) participants *32* (*78*%) achieved satisfactory performance (score ≥*17*, no critical error). *9*

participants did not accomplish satisfactory performance, including *5* 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	Analytical performance A (%)	Interpretation I (%)	Total (%)
ACDB_DH_2018-A	38	89	87	81
ACDB_DH_2018-B	38	95	100	100
ACDB_DH_2018-C	38	84	89	84
ACDB_DH_2018-D	37	100	62	100
ACDB_DH_2018-E	37	100	86	86
ACDB_DH_2018-F	37	92	89	86

Table 5: Cumulative Scores. The maximum score achievable was 24 points.

Total Score	No of labs (who submitted results for both rounds)
24	12
23	12
22	3
21	3
20	2
18	1
16	2
15	1

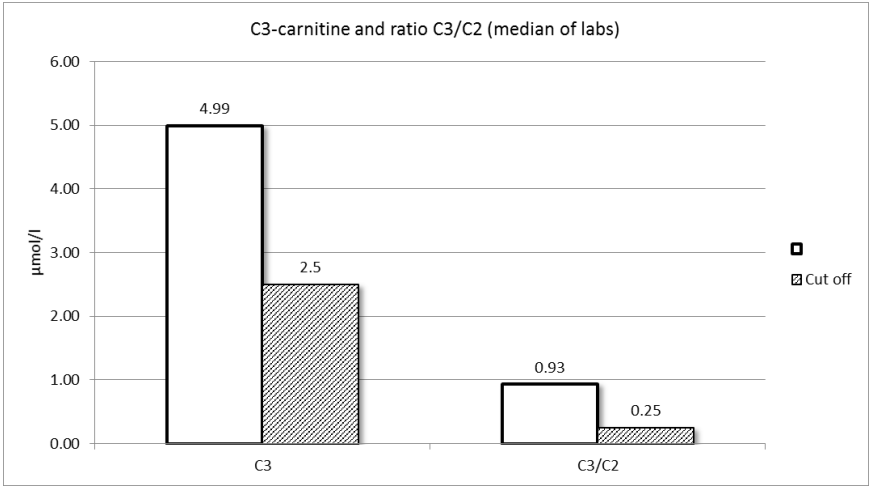
7. Results of individual samples and evaluation of reporting

Sample ACDB_DH_2018-A:

Patient details: 6-year old boy presented with failure to thrive and acute ataxia

Known diagnosis: Cobalamine A deficiency

Analytical details: This sample showed elevated propionylcarnitine (C3) which was detected by 87% of the participants (31/38). The ratio C3/C2 was also increased, and this was reported by 26% (10/38).



Interpretation: Participants diagnosed methylmalonic acidaemia or propionic acidaemia.
The overall diagnostic performance was 81%.

This sample was considered by the SAB to be eligible for critical error, as is the case with 3 participants who reported "normal" without further recommendations.

Sample ACDB_DH_2018-B:

Patient details: 3-year old girl with macrocephaly and psychomotor retardation

Known diagnosis: glutaric aciduria type I (low excretor)

Analytical details: 95% of the participants (36/38) reported elevated glutarylcarnitine or glutarylcarnitine/3-hydroxyhexanoylcarnitine (C5DC+C6OH).

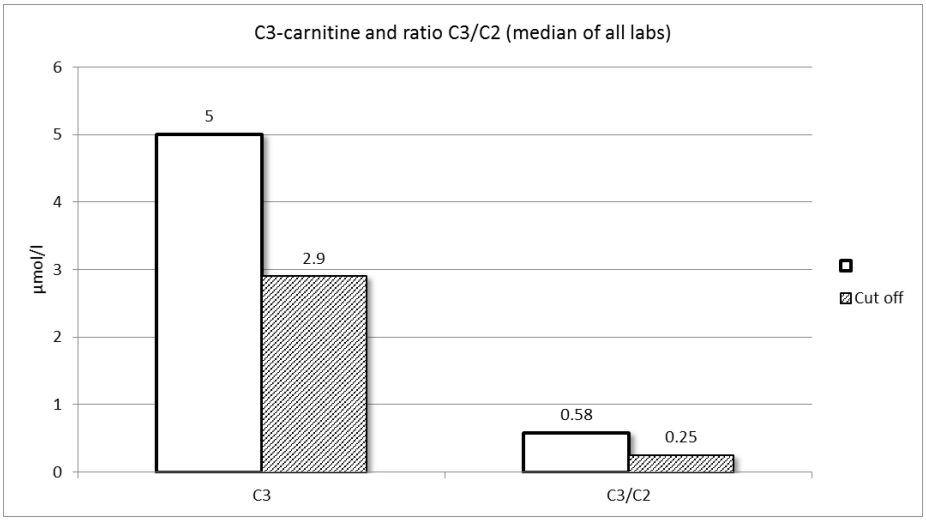
Interpretation: All participants diagnosed glutaric aciduria type I (GA I).
This was a straightforward sample with a very high proficiency of 100%.

Sample ACDB_DH_2018-C:

Patient details: 7-month old boy presented with a 3-day history of poor feeding and lethargy

Known diagnosis: propionic aciduria

Analytical details: The key finding in this sample was also elevated propionylcarnitine (C3). 87% of the participants (33/38) detected this. However the increase of the ratio C3/C2 was lower than in sample ACDB_DH_2018_A but was noticed by 11 participants (29%).



Interpretation: Propionic acidaemia and methylmalonic acidaemia was suggested by the majority of the participants as the main diagnosis.
In detail 47 % of the participants gave preference to propionic acidaemia (18/38) and 32% to methylmalonic acidaemia (12/38) or any of its subgroups. Two responders did not decide upon one of these two options and suggested methylmalonic aciduria or propionic aciduria.
Two points for interpretation were awarded for a diagnosis pointing PA or MMA.
For any other diagnosis one point was given for recommending at least organic acid analysis.
Overall performance for the differential diagnosis PA/MMA was 84%

This sample was considered by the SAB to be eligible for critical error, as is the case with 3 participants who reported "normal" without further recommendations.

Sample ACDB_DH_2018-D:

Patient details: 49-year old woman, history of episodic myalgia and limb weakness

Known diagnosis: multiple acyl CoA dehydrogenase deficiency (MADD, GA 2)

Analytical details: This sample showed clearly elevated amounts of decanoylcarnitine (C10) and octanoylcarnitine (C8). The analytical performance was 100%.

Interpretation: As expected either multiple acyl-CoA dehydrogenase deficiency (MADD) or medium chain acyl-CoA dehydrogenase deficiency (MCADD) were the preferred diagnoses suggested by 49% each.
One lab pointed to riboflavin transporter deficiency
Overall proficiency was 100%.
For scoring recommendations for further investigations were taken into account.
MADD as main diagnosis scored 4 points.
Four points were awarded for MCADD with the alternative MADD and/or recommending organic acid analysis in urine.
Riboflavin transporter deficiency scored with 4 points as well.
Three points were given for diagnosing MCADD without pointing to MADD and not recommending organic acid analysis in urine.

Sample ACDB_DH_2018-E:

Patient details: 58-year-old male with intermittent episodes of ataxia

Known diagnosis: normal profile

Analytical details: 32% of the participants reported some suspicious findings, mostly propionylcarnitine (C3), methylmalonyl carnitine (C4DC) or C5-carnitine.

Interpretation: Most of the participants found this sample to be normal (32/37) which result in an overall proficiency of 86%.
One or two points were subtracted for any other diagnosis depending on the recommendations for further investigations.

Sample ACDB_DH_2018-F:

Patient details: 10-year-old girl with frequent episodes of vomiting

Known diagnosis: 3-hydroxy-3-methylglutaric aciduria (3-hydroxy-3-methylglutaryl-CoA lyase deficiency, 3-HMG)

Analytical details: this sample showed a typical acyl carnitine profile with elevated 3-hydroxyisovaleryl-carnitine (C5OH) and 3-methylglutaryl-carnitine (C6DC) concentrations. Thirty-four participants identified either of these carnitine species (92%) Reporting elevated C5OH and /or C6DC scored two points for analytical proficiency.

Interpretation: 70% of the participants diagnosed 3-HMG (26/37) and 16% 3-methyl-crotonyl-CoA-carboxylase deficiency (16/37).
Two points were given for reporting 3-HMG as main diagnosis or as alternative. Diagnosing 3-methyl-crotonyl-CoA-carboxylase deficiency without mentioning 3-HMG scored 1 point.
Thirty-three participants scored two points for interpretation (89%).
Thirty-two participants got full points for analytic and interpretation.
Overall proficiency for this sample was 86%

8. Preview of the scheme in 2019

The format of the ACDB 2019 scheme will be similar to that of previous years.

Changes planned for 2019:
Interim reports are intended to be produced automatically by a software developed by CSCQ.
This is already working in the proficiency testing schemes and has to be adopted to the ACDB requirements.

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.

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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*