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Acylcarnitines in dried blood spots

Centre: London United Kingdom

Final Report 2024

prepared by
Mrs Erin Emmett

Note: This annual report is intended for participants of the ERNDIM ACDB scheme. The contents should not be used for any publication without permission of the Scientific Advisor.

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1. Introduction

The ERNDIM Acylcarnitine in dried blood spots scheme offers dried blood spots obtained from confirmed patients with confirmed diagnoses to enable laboratories to gain or maintain experience to identify organoacidopathies and fatty acid β-oxidation defects. The scheme is organised by Mrs Erin Emmett (Synnovis, London UK) in conjunction with CSCQ, the Swiss organisation for quality assurance in medical laboratories.
As in previous years, samples were sent out to cover the spectrum of what is typically observed in the metabolic laboratory. A mix of clearly diagnostic profiles and some more challenging profiles were provided. No normal profiles were sent out this year, however the requirement to interpret a normal profile, as such, is as important as correctly identifying abnormal profiles. Correctly identifying a profile as normal can avoid unnecessary further investigation and distress to the patient and family.

2. Geographical distribution of participants

Participants and new applicants were distributed between the Heidelberg, London and Rome acylcarnitine in dried blood spots schemes which are run separately. The three organising laboratories each participate in the other's scheme by rotation.

[1] If this report is not Version 1 for this scheme year, go to APPENDIX 1 for details of the changes made since the last version of this document.

In 2024, 45 laboratories from many different countries participated in the ACDB London scheme. There were no educational participants in 2024. 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.

Country	Number of participants	Country	Number of participants
Australia	3	New Zealand	1
Brazil	2	Oman	1
Canada	4	Poland	2
Chile	1	Taiwan	1
Finland	1	Turkey	2
Ireland	1	United Kingdom	13
Italia	12	United States	1

3. Design and logistics of the scheme including sample information

The scheme has been designed and planned by Mrs Erin Emmett as Scientific Advisor and coordinated by CSCQ, the Swiss organisation for quality assurance in medical laboratories, both appointed by and according to procedures laid down by the ERNDIM Board. As usual, the samples used in 2024 were authentic human blood spot samples, all six from affected patients.
All samples selected by the Scientific Advisor are prepared from 25-50 µL of lithium heparin anticoagulated whole blood on Whatman (Schleicher & Schuell) 903™ paper. All samples are obtained following local ethical and consent guidelines.
In 2024 CSCQ dispatched the ACDB EQA samples to the scheme participants and provides a website for online submission of results and access to scheme reports. Existing QLOU, ACDB, DPT and Urine MPS scheme participants can log on to the CSCQ results submission website at: https://cscq.hcuge.ch/cscq/ERNDIM/Initial/Initial.php
Labelled copies of scan/chromatograms can be uploaded on the CSCQ website.

4. Schedule of the scheme

Time schedule in the 2024 ERNDIM ACDB London scheme:

	1st Submission Round	2nd Submission Round
Sample ID's	ACDB-UL-2024-A ACDB-UL-2024-B ACDB-UL-2024-C	ACDB-UL-2024-D ACDB-UL-2024-E ACDB-UL-2024-F
Shipment of samples	07 Feb 2024	
Start of analysis (clinical data available)	12 Mar 2024	03 Jun 2024
Reminder for result submission	26 Mar 2024	17 Jun 2024
Results submission deadline	02 Apr 2024	24 Jun 2024
Interim reports available on CSCQ website	May 2024	Aug 2024

To be able to continue this scheme we need a steady supply of new patient samples. Several laboratories have donated samples to the ACDB scheme in the past, for which they are gratefully acknowledged. If you have one or more samples available and are willing to donate these to the scheme, please contact us at admin@erndim.org.
Laboratories which donate samples that are used in the scheme are eligible for a 20% discount on their participation in the ACDB scheme in the following year.

Samples included in the 2024 ERNDIM ACDB London scheme:

Survey	Sample no.	Diagnosis
24-03-ACL	ACDB-UL-2024-A	Carnitine Palmitoyltransferase 1 (CPT1) deficiency (common sample)
	ACDB-UL-2024-B	No confirmed diagnosis – metabolic abnormalities resolved post-riboflavin
	ACDB-UL-2024-C	Glutaryl-CoA Dehydrogenase deficiency (Glutaric Aciduria type 1; GA1)
24-06-ACL	ACDB-UL-2024-D	Very Long Chain Acyl-CoA Dehydrogenase (VLCAD) deficiency
	ACDB-UL-2024-E	Propionyl-CoA carboxylase deficiency (Propionic Acidaemia; PA)
	ACDB-UL-2024-F	Medium Chain Acyl-CoA Dehydrogenase (MCAD) deficiency

The scheme format was kept identical to those of previous years. Samples were shipped by regular mail. Details regarding stability of samples are provided in the sample package.
Interim reports were generated by the evaluation program developed by CSCQ.

Origin of patients: Five clinical samples were provided by the scheme organiser, and one clinical sample was donated by a participant laboratory.

5. Results

Returned results in the 2024 ERNDIM ACDB London scheme.

	Survey 1	Survey 2
Receipt of results	44	44
No answer	1	1

6. Website reporting

The website reporting system is compulsory for all centers. Please read carefully the following advice:

- Results
  - Give quantitative data as much as possible.
  - Enter the key metabolites with the evaluation **in the tables** even if you don't give quantitative data.
  - If the profile is normal: enter "Normal profile" in "Key metabolites".
  - **Don't enter results in the "comments" window**, **otherwise your results will not be included in the evaluation program.**
- Diagnosis
  - **Don't enter the diagnosis in the "comments" window**, **otherwise your results will not be included in the evaluation program.**
- Recommendations = **advice for further investigation**.
  - Scored together with the interpretative score.
  - Advice for treatment are not scored.
  - **Don't give advice for further investigation in "Comments on diagnosis"**: it will not be included in the evaluation program.

7. Scoring and evaluation of results

A scoring system was developed in 2012 and approved by the ERNDIM Scientific Advisory Board. Similar to other qualitative (proficiency testing) ERNDIM schemes, the maximum score for a sample is 4 points.
Qualitative results and diagnostic proficiency of the 2024 samples were scored using the criteria given below. These criteria have been set by the Scientific Advisor, approved by the Scientific Advisory Board.

The final decision about scoring of the scheme is made in the Scientific Advisory Board (SAB) during the Autumn meeting (November 29th, 2024).

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	1
	Incorrect: minimally required results not reported	0
Diagnostic proficiency	Correct according to criteria set for the sample	2
	Partially correct	1
	Unsatisfactory or misleading	0
	Maximum total score	**4**

Starting with the 2014 schemes the concept of 'critical error' is 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 29th, 2024.

7.1. Score for satisfactory performance

At least 17 points from the maximum of 24 (70%). In instances where the SAB agrees that a sample will be classed as an Educational Sample, the scores associated with the sample will be not included in the performance evaluation of the participating laboratories' overall scheme.
We are required to define "Participation" for the purpose of the ERNDIM Annual Certificate which covers all ERNDIM schemes. For this acylcarnitine in dried blood spots scheme we have defined "Participation" as requiring two returns during the year. Failure to meet this requirement will result in the certificate of participation showing 'non-submitter' rather than 'satisfactory' or 'unsatisfactory'.

8. Results of samples and evaluation of reporting

8.1. Patient A

Carnitine Palmitoyltransferase 1 (CPT1) deficiency due to mutation in the *CPT1A* gene, OMIM 255120.

Patient details provided to participants
Patient with hypoglycemic crises at 6 months of age. He currently has language and learning difficulties at school.

Patient details
This sample was taken from a 12 year old male who presented with hypoglycaemic crises at six months of age. He currently has language and learning difficulties at school. The sample was from a patient with CPT1 deficiency. This, the common sample for 2024, was circulated to all three sections of the ERNDIM ACDB scheme.

Analytical performance
Results were returned by 44/45 (98%) of participating laboratories.
This was a highly scoring sample with all participants who returned a result scoring two marks. All participants identified the elevated or grossly elevated free carnitine, and 86.4% of participants identified that C16 and C18 were decreased. Those that didn't mention the long chain acylcarnitines, or identified them as normal, scored full marks due to identification of increase in an appropriate ratio, such as C0/(C16+C18).

Diagnosis / Interpretative proficiency
All participants who returned a result identified carnitine palmitoyltransferase 1 (CPT1A) deficiency as the likely diagnosis.

Six participants included carnitine supplementation as an alternative diagnosis and two participants mentioned COASY protein-associated neurodegeneration (CoPAN).
Mutations in the gene for CoA synthase (COASY) have been identified as a cause of a subtype of neurodegeneration with brain iron accumulation - known as CoPAN. Increased free carnitine with decreased long-chain acylcarnitines and an increased C0/(C16+C18) ratio has been observed in bloodspots from patients with this disorder (but not in plasma). Therefore CoPAN should be considered, in light of the clinical presentation, in the differential diagnosis when this pattern is seen on bloodspot acylcarnitine analysis.
Christina Evers et al. Am J Med Genet A 2017 Jul;173(7):1878-1886.

Recommendations
100% of participating laboratories recommended genetic analysis of the *CPT1A* gene for confirmation of the suspected diagnosis.
There was a variety of other recommendations including repeat bloodspot and/or plasma acylcarnitines (19/44), enzyme analysis in fibroblasts (17), urine organic acid analysis (13), and a number of routine Chemistry tests (ammonia, liver function/coagulation, glucose, ketones, CK and blood gas).
17/44 participants provided recommendations on patient management, including referral to a specialist metabolic team and family testing.

Scoring
The scoring criteria were –
Analytical: 1 point for increased C0, and 1 point for decreased long chain acylcarnitines and/or increase in appropriate ratio such as C0/(C16+C18) (whether numerical or qualitative comment).
Interpretative: 2 points for CPT1 as the primary or secondary likely diagnosis, or 1 point for an alternative diagnosis with 1 point for appropriate recommendations (plasma acylcarnitines, genetics, enzyme analysis).

Overall impression
This was a high scoring sample with all participants who returned results scoring full marks for analysis and interpretation. 100% proficiency.

8.2. Patient B

Vitamin deficiencies including riboflavin; acylcarnitines normalised post-vitamin supplementation. Genetic results pending.

Patient details provided to participants
Weakness with subacute degeneration of spinal cord.

Patient details
This pre-treatment sample was obtained from a 33 year old female with a long complex clinical history, including chronic fatigue, deteriorating vision, sensory disturbance and an episode of metabolic acidosis. The hospital admission, during which this sample was obtained, was preceded by a significant worsening of symptoms over a few months including falls, weakness and inability to lift arms above her head. As well as subacute degeneration of the spinal cord, bilateral retinal ganglion pathology, peripheral neuropathy and proximal myopathy were also confirmed.
As well as the bloodspot acylcarnitine profile, the urine organic acid results could also not exclude riboflavin deficiency, a defect in riboflavin metabolism or transport, or multiple acyl-CoA dehydrogenase deficiency (MADD).
One week after supplementation with riboflavin, the bloodspot acylcarnitine and urine organic acid profiles had normalised.
At the time of this report, results from genetic investigations are still not available.

Analytical performance
Results were returned by 44/45 (98%) of participating laboratories.
42/44 participants identified non-specific increases in one or more acylcarnitine species, with elevated C14:1 being the most commonly identified abnormality (39/44) as well as increases in C10, C14, C16:1 and C18:1. One participant did not observe increases in any acylcarnitine species but identified increases in a number of acylcarnitine ratios. One participant did not identify any abnormalities.
Excluding one non-submitter, overall analytical proficiency for this sample was 96.6%.

Diagnosis / Interpretative proficiency
Two points were given to participants who included MADD and/or riboflavin deficiency, metabolism or transporter defect in their primary or alternative diagnosis list (36/44). 4/44 participants only included VLCADD in their differential diagnosis, however scored one point as appropriate recommendations were provided.
Other alternative diagnoses provided included other fatty acid oxidation defects (including SCAD, MCADD, CPT2, CACT, ACAD9 and TANGO2) (10/44), general B vitamin or vitamin B12 deficiency (9), nitrous oxide abuse (3), secondary mitochondrial dysfunction due to nutritional deficiencies and/or medication (3), EMA encephalopathy/Jamaican vomiting sickness (2) and CoQ10 deficiency (2), as well as other iatrogenic factors including sertraline (2) and MCT feed (1).
The long list of alternative diagnoses submitted by participants reflects the complex acylcarnitine profile and clinical picture.
Excluding one non-submitter, overall interpretative proficiency for this sample was 86.4%.

Recommendations
Again, reflecting the complicated acylcarnitine and clinical picture, a large and varied number of recommendations were made. Urine organic acid analysis for further investigation of MADD/riboflavin defects was the most common recommendation (35/44) followed by repeat bloodspot acylcarnitine analysis (plasma, bloodspot and/or urine) (26), and various genetic recommendations – *ETFA* / *ETFB* / *ETFDH* for MADD (15), *ACADVL* for VLCADD (14), *SLC52A2* / *SLC52A3* for riboflavin transporter defects (5) and other general genetic investigations including FAOD panels and WGS (13). 21/44 suggested analysis of one of more of plasma vitamin B12, folate, methylmalonate and total homocysteine and 14/44 recommended analysis of plasma riboflavin (vitamin B2) or riboflavin challenge. There were smaller numbers of participants who then suggested a wide variety of general Chemistry analyses including CK, ammonia, glucose, ketones, lactate, full blood count and assessment of liver function.
15/44 participants provided recommendations on patient management, including treatment with riboflavin and/or B vitamins, referral to a specialist metabolic team and family testing.

Scoring
The scoring criteria were –
Analytical: 2 points for any (non-specific) increase(s) in short, medium and/or long chain acylcarnitines.
Interpretative: 2 points for MADD, riboflavin deficiency or riboflavin transporter defect with appropriate recommendations. 1 point if only appropriate recommendations provided.
No critical errors were given for this sample as there is no obvious or confirmed diagnosis in this patient.

Overall impression
Despite the non-specific and complex acylcarnitine pattern, this was a high scoring sample with overall proficiency for participating laboratories of 91.5%.

8.3. Patient C

Glutaric aciduria type 1 (GA1); Glutaryl-CoA dehydrogenase deficiency due to mutation in the *GCDH* gene, OMIM 231670.

Patient details provided to participants
Seizures, hypotonia.

Patient details
This acute sample was obtained at presentation from a 9 month old male with seizures and hypotonia. His initial metabolic investigations were consistent with glutaric aciduria type 1 (GA1), and confirmed by genetic analysis. On retrospective review of the bloodspot newborn screening results, the C5DC concentration was just below the clinical cut-off.

Analytical performance
Results were returned by 44/45 (98%) of participating laboratories.
41/44 participants identified the increase in C5DC (many also mentioning increases in appropriate ratios such as C5DC/C8 or C5DC/C16) and scored full marks. One participant obtained a normal C5DC but identified an increase in a relevant ratio. Two participants did not identify any abnormalities.
Excluding one non-submitter, overall analytical proficiency for this sample was 95.5%.

Diagnosis / Interpretative proficiency
42/44 participants identified glutaric aciduria type 1 (GA1) as the likely or alternative diagnosis. Other diagnoses mentioned by participants included multiple acyl-CoA dehydrogenase deficiency (MADD) (3/44), maternal GA1 (2), renal impairment (2), carnitine uptake defect (1) and a secondary increase in isobaric C10OH due to dextrose.
Excluding one non-submitter, overall interpretative proficiency for this sample was 94.3%.

Recommendations
Of the 42 participants that identified GA1 as the likely diagnosis, 41 recommended urine organic acid analysis to follow up this patient and 39 recommended genetic analysis of the *GCDH* gene. There was a variety of other recommendations including repeat bloodspot, plasma and/or urine acylcarnitines (19/44), enzyme analysis in fibroblasts (13), plasma amino acids (3), assessment of renal function (2), liver function (1) and review of newborn bloodspot screening results (2).
19/44 participants provided recommendations on patient management, including referral to a specialist metabolic team and family testing.

Scoring
The scoring criteria were –
Analytical: 2 points for increased C5DC. Following second scoring, it was agreed to also award the full 2 points for increase in an appropriate ratio, such as C5DC/C8.
Interpretative: 2 points for GA1 as the primary or secondary likely diagnosis with appropriate recommendations (urine organic acids, genetics, enzyme analysis), or 1 point for GA1 without recommendations.

Overall impression
This was a high scoring sample with overall proficiency for participating laboratories of 94.9%. Two participants did not identify any abnormalities in this sample resulting in critical errors.

8.4. Patient D

Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency due to mutation in the *ACADVL* gene, OMIM 201475.

Patient details provided to participants
Sibling with metabolic disorder. On treatment.

Patient details
This sample was taken from a patient treated for VLCAD deficiency.
Following the death of a previous sibling with a diagnosis of VLCADD, a bloodspot for acylcarnitines was taken from this boy during the first month of life. This, and subsequent biochemical and genetic investigations, confirmed a diagnosis of VLCADD.
The current sample was taken at 11 years old, when the patient is doing well with no recent admissions or requirement to implement an emergency regimen. His diet is managed with supplementation including medium chain triglyceride feed and overnight cornstarch.

Analytical performance
Results were returned by 98% of participating laboratories.
Despite this sample showing only subtle abnormalities, an increased C14:1 and/or appropriate ratio(s), such as C14:1/C12:1, C14:1/C2 or C14:1/C16, were noted by 81.8% of participants (36/44). Three participants reported a normal profile and four participants noted abnormalities associated with CPT2 deficiency.
Excluding one non-submitter, overall analytical proficiency for this sample was 83.0%.

Diagnosis / Interpretative proficiency
Of the participants who returned a result for this distribution, 86.4% (38/44) suggested VLCADD as the primary or alternative diagnosis.
CPT2 deficiency was included in the differential diagnosis by 12/44 participants, CACT deficiency by 8 and heterozygous VLCAD by 4.
Two participants included TANGO2 deficiency in their potential diagnoses. Acylcarnitine abnormalities including, most commonly, increased C14:1 have been noted in acutely unwell patients with TANGO2

deficiency, first described in 2016. Clinical features common to both TANGO2 and VLCAD include cardiac dysfunction, hypoglycaemia and rhabdomyolysis. However TANGO2 additionally may also present with hypothyroidism and acute or chronic neurological defects including seizures. Ketosis is often present during hypoglycaemia.
Ref: J Schymick et al (2022), Am J Med Genet A, 188A, pg473-487.
Excluding one non-submitter, overall interpretative proficiency for this sample was 90.9%.

Recommendations
36/44 participants recommended genetic analysis of the *ACADVL* gene for confirmation of the suspected diagnosis, 11 suggested VLCAD enzyme studies in leukocytes or fibroblasts, and 3 others suggested general FAO flux studies.
The most commonly suggested biochemical recommendations were urine organic acids (22/44) and plasma acylcarnitines (21/44).
16/44 participants provided recommendations on patient management, including referral to a specialist metabolic team and family testing.

Scoring
The scoring criteria were –
Analytical: 2 points for increased C14:1 and/or appropriate ratio.
Interpretative: 2 points for VLCADD as the primary or secondary likely diagnosis with appropriate recommendations (plasma acylcarnitines, genetics, enzyme analysis). 1 point for VLCADD without recommendations or 1 point if VLCADD not mentioned but appropriate recommendations provided that could identify VLCADD as the likely diagnosis.
No critical errors were given for this sample as the profile was deemed too subtle following discussion at the Scientific Advisory Board meeting.

Overall impression
Despite this sample showing only mild abnormalities, overall proficiency for participating laboratories was 86.9%. This sample highlights the importance of including ratios when assessing samples with subtle abnormalities such as this one. A similar sample from a different patient with VLCADD was distributed by this scheme in 2023 with a lower overall proficiency of 72.8%.

8.5. Patient E

Propionic acidaemia (PA); Propionyl-CoA carboxylase deficiency due to mutation in the *PCCA* gene, OMIM 606054.

Patient details provided to participants
Ketotic hypoglycaemia following vomiting illness. Diagnosed age 4, now on treatment.

Patient details
This sample was taken from a patient with genetically confirmed propionic acidaemia.
This young girl had metabolic investigations when she presented with ketotic hypoglycaemia following a vomiting illness at age 4. Prior to this episode, she had the usual childhood vomiting illnesses and three febrile convulsions, but was developmentally normal and meeting all childhood milestones. Genetic analysis confirmed that the patient is compound heterozygous for one likely pathogenic and one pathogenic variant in the *PCCA* gene.
Based on the clinical history and presenting symptoms, this is being treated as a mild form of PA. The sample was taken six months after diagnosis, when the patient was well and on carnitine supplementation but not on formal protein restriction.

Analytical performance
Results were returned by 98% of participating laboratories.
All 44 participants noted an increased C3 with some also commenting on increased ratios such as C3/C2 and C3/C16. Of those who noted C4DC in their results, all said it was normal in this sample.
Excluding one non-submitter, overall analytical proficiency for this sample was 100%.

Diagnosis / Interpretative proficiency
Two points were given to 40/44 participants (90.9%) who included propionic acidaemia as the primary or alternative diagnosis, plus provision of appropriate recommendations that would identify the correct

diagnosis of PA. Many noted that a normal C4DC does not exclude methylmalonic acidaemia, and as PA and MMA cannot always be distinguished by acylcarnitine analysis alone, additional investigations are required.
The list of differential diagnoses provided in addition to PA included methylmalonic acidaemia (due to *MMUT* deficiency), a disorder of cobalamin metabolism, SUCLA2 deficiency, MMA-CoA epimerase deficiency, holocarboxylase synthetase deficiency and vitamin B12 deficiency or uptake defect.
Excluding one non-submitter, overall interpretative proficiency for this sample was 94.3%.

Recommendations
A large number of recommendations were provided, reflecting the long list of potential diagnoses that could result in the acylcarnitine abnormalities observed. Most commonly suggested (by 40/44 participants) was urine organic acids, with genetic confirmation recommended by 37/44 (genes mentioned include *PCCA* and *PCCB*, *MMUT*, and MMA-gene panels). Other recommendations included plasma total homocysteine (24), plasma or serum amino acids (17), vitamin B12 (17), repeat and/or plasma acylcarnitines (16), plasma MMA (14) and ammonia (12). Enzyme analysis of propionyl-CoA carboxylase was suggested by 8 participants.
19/44 participants provided recommendations on patient management, including referral to a specialist metabolic team, treatment suggestions and family testing.

Scoring
The scoring criteria were –
Analytical: 2 points for increased C3 and/or appropriate ratio.
Interpretative: 2 points if PA included in the primary or secondary likely diagnosis with appropriate recommendations (urine organic acids, plasma MMA, total homocysteine, vitamin B12, genetics, enzyme analysis). 1 point for PA without recommendations or 1 point for only MMA but with appropriate recommendations.

Overall impression
This was a high scoring sample with overall proficiency for participating laboratories of 97.2%. One participant did not identify the correct abnormalities in this sample and provided misleading recommendations, resulting in a critical error.

8.6. Patient F

Medium chain acyl-CoA dehydrogenase (MCAD) deficiency due to mutation in the *ACADM* gene, OMIM 201450.

Patient details provided to participants
Encephalopathy and respiratory distress. Metabolic acidosis, hypoglycaemia, high ketones.

Patient details
This acute sample was obtained at presentation from a newborn who was taken to the Emergency department at day 4 of age as he was cold, not feeding and increasingly sleepy/unrousable. Metabolic acidosis and hypoglycaemia were noted at admission and he was encephalopathic and in respiratory distress. Blood ketones were significantly increased. It was during this acute stage that this sample was obtained.
The initial metabolic investigations included acylcarnitine and urine organic acid analysis, which were both consistent with a diagnosis of MCADD and showed evidence of ketosis/ketonuria. A referral for MCADD was also made by Newborn Screening a few days later.

Analytical performance
Results were returned by 98% of participating laboratories, and 43/44 scored the full two marks for analytical performance. The most commonly identified abnormalities were increased C8, C6 and C8/C10 ratio.
Excluding one non-submitter, overall analytical proficiency for this sample was 98.9%.

Diagnosis / Interpretative proficiency
41/44 participants gave MCADD as the primary diagnosis and the remaining three labs suggested MADD, with two of these mentioning MCADD as an alternative diagnosis.

21/44 participants included MADD in their alternative diagnoses, with others suggesting treatment with TPN/MCT/SMOF (3), “other FAOD” (1), GA1 (1) and “CPT” (1).
In the returns for samples E and F, some participants noted that the clinical details did not align with the abnormalities observed and queried a mix-up of the clinical details. The clinical details provided are correct and reflect two inherited metabolic diseases with less common clinical presentations – a later-onset and mild form of PA without hyperammonaemia (sample E) and a very severe early-onset MCADD with ketotic hypoglycaemia (sample F). MCADD presenting with ketotic hypoglycaemia is unusual but not impossible and a fatty acid oxidation defect should not be excluded in a patient solely on the basis of the presence of ketones.
Excluding one non-submitter, overall interpretative proficiency for this sample was 97.7%.

Recommendations
Of the 41 participants that identified MCADD as the likely diagnosis, all recommended genetic analysis of the *ACADM* gene and 39 suggested urine organic acid analysis. Assessment of enzyme activity (of either the MCAD enzyme specifically or more general FAO flux studies) was recommended by 8 participants. 25/44 suggested repeat and/or plasma acylcarnitines. A number of other suggestions were made for routine Biochemistry tests including liver function tests (7), CK (5), ammonia (4) and glucose (4).
23/44 participants provided recommendations on patient management, including referral to a specialist metabolic team, treatment suggestions and family testing.

Scoring
The scoring criteria were –
Analytical: 2 points for increased C8, C6 and/or appropriate ratio such as C8/C10.
Interpretative: 2 points for MCADD as the primary or secondary likely diagnosis or 1 point for an alternative diagnosis (such as MADD) with recommendations (urine organic acids, genetics, enzyme analysis).

Overall impression
This was a high scoring sample with overall proficiency for participating laboratories of 98.3%. Although some participants commented on the unusual clinical presentation, the clinical details provided of ‘high ketones’ and the increased C4OH in the sample did not deter most participants from suggesting a potential fatty acid oxidation defect, with 43/44 participants scoring full marks.
One participant provided an incorrect diagnosis and misleading recommendations, resulting in a critical error.

9. Scores of participants

All data transfer, the submission of data as well as the request and viewing of reports proceed via the CSCQ results website. The results of your laboratory are confidential and only accessible to you (with your username and password). The anonymous scores of all laboratories are accessible to all participants and only in your version is your laboratory highlighted in the leftmost column.

If your laboratory is assigned poor performance and you wish to appeal against this classification, please email the ERNDIM Administration Office (admin@erndim.org), with full details of the reason for your appeal, within one month receiving your Performance Support Letter. Details of how to appeal poor performance are included in the Performance Support Letter sent to poor performing laboratories.

Detailed scores – Round 1

	Patient A			**Patient B**			**Patient C**			
Lab no.	**CPT1 (common sample)**			**Vitamin deficiencies including riboflavin**			**GA1**			
	A	**I**	**Total**	**A**	**I**	**Total**	**A**	**I**	**Total**	**Total**
1	2	2	4	2	1	3	2	2	4	11
2	2	2	4	2	2	4	2	2	4	12
3	2	2	4	2	2	4	2	2	4	12
4	2	2	4	2	2	4	2	2	4	12
5	2	2	4	2	2	4	2	2	4	12
6	2	2	4	2	2	4	2	2	4	12
7	2	2	4	2	2	4	2	2	4	12
8	2	2	4	2	2	4	2	2	4	12
9	2	2	4	2	2	4	2	2	4	12
10	2	2	4	2	1	3	2	2	4	11
11	2	2	4	2	2	4	2	2	4	12
12	2	2	4	2	1	3	0	0	0	7
13	2	2	4	2	2	4	2	2	4	12
14	2	2	4	2	2	4	2	2	4	12
15	2	2	4	2	2	4	2	2	4	12
16	2	2	4	2	2	4	2	2	4	12
17	2	2	4	2	2	4	2	2	4	12
18	2	2	4	2	2	4	2	2	4	12
19	2	2	4	2	2	4	2	2	4	12
20	2	2	4	2	2	4	2	2	4	12
21	2	2	4	0	0	0	2	2	4	8
22	2	2	4	2	2	4	2	2	4	12
23	2	2	4	2	2	4	2	2	4	12
24	2	2	4	2	2	4	2	2	4	12
25	2	2	4	2	2	4	2	2	4	12
26	2	2	4	2	2	4	2	2	4	12
27	2	2	4	2	0	2	2	2	4	10
28	2	2	4	2	2	4	2	2	4	12
29										

	Patient A			Patient B			Patient C			
Lab no.	CPT1 (common sample)			Vitamin deficiencies including riboflavin			GA1			
	A	I	Total	A	I	Total	A	I	Total	Total
30	2	2	4	2	2	4	2	2	4	12
31	2	2	4	2	2	4	2	2	4	12
32	2	2	4	2	2	4	2	2	4	12
33	2	2	4	2	2	4	2	2	4	12
34	2	2	4	2	1	3	2	2	4	11
35	2	2	4	2	2	4	2	2	4	12
36	2	2	4	2	2	4	2	2	4	12
37	2	2	4	2	1	3	2	2	4	11
38	2	2	4	2	2	4	2	2	4	12
39	2	2	4	2	2	4	2	2	4	12
40	2	2	4	2	2	4	2	2	4	12
41	2	2	4	1	1	2	2	1	3	9
42	2	2	4	2	2	4	2	2	4	12
43	2	2	4	2	0	2	0	0	0	6
44	2	2	4	2	2	4	2	2	4	12
45	2	2	4	2	2	4	2	2	4	12

Detailed scores – Round 2

	Patient D			Patient E			Patient F			
Lab no.	VLCADD			PA			MCADD			
	A	I	Total	A	I	Total	A	I	Total	Total
1	0	0	0	2	2	4	2	2	4	8
2	2	2	4	2	2	4	2	2	4	12
3	2	2	4	2	2	4	2	2	4	12
4	2	2	4	2	2	4	2	2	4	12
5	0	1	1	2	2	4	2	2	4	9
6	2	2	4	2	2	4	2	2	4	12
7	0	1	1	2	0	2	2	2	4	7
8	2	2	4	2	2	4	2	2	4	12
9	2	2	4	2	2	4	2	2	4	12
10	2	2	4	2	2	4	2	2	4	12
11	2	2	4	2	2	4	2	2	4	12
12	2	2	4	2	2	4	2	2	4	12
13	2	2	4	2	2	4	2	2	4	12
14	2	2	4	2	2	4	2	2	4	12
15	2	2	4	2	2	4	2	2	4	12
16	2	2	4	2	2	4	2	2	4	12

	Patient D			Patient E			Patient F			
Lab no.	VLCADD			PA			MCADD			
	A	I	Total	A	I	Total	A	I	Total	Total
17	2	2	4	2	2	4	2	2	4	12
18	2	2	4	2	2	4	2	2	4	12
19	2	2	4	2	2	4	2	2	4	12
20	2	2	4	2	2	4	2	2	4	12
21	0	1	1	2	2	4	2	2	4	9
22	2	2	4	2	2	4	2	2	4	12
23	2	2	4	2	2	4	2	2	4	12
24	0	1	1	2	2	4	2	2	4	9
25	2	2	4	2	2	4	2	2	4	12
26	2	2	4	2	2	4	2	2	4	12
27	2	2	4	2	2	4	2	2	4	12
28	0	2	2	2	2	4	2	2	4	10
29	2	2	4	2	2	4	2	2	4	12
30	0	1	1	2	2	4	2	2	4	9
31										
32	2	2	4	2	2	4	2	2	4	12
33	2	2	4	2	2	4	2	2	4	12
34	2	2	4	2	2	4	2	2	4	12
35	2	2	4	2	1	3	2	2	4	11
36	2	2	4	2	2	4	2	2	4	12
37	2	2	4	2	2	4	2	2	4	12
38	2	2	4	2	2	4	2	2	4	12
39	2	2	4	2	2	4	2	2	4	12
40	2	2	4	2	2	4	2	2	4	12
41	2	1	3	2	1	3	1	0	1	7
42	2	2	4	2	2	4	2	2	4	12
43	1	2	3	2	2	4	2	2	4	11
44	2	2	4	2	1	3	2	2	4	11
45	2	2	4	2	2	4	2	2	4	12

Total scores

Lab no.	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Critical error
1	4	3	4	0	4	4	19	79	
2	4	4	4	4	4	4	24	100	
3	4	4	4	4	4	4	24	100	
4	4	4	4	4	4	4	24	100	
5	4	4	4	1	4	4	21	88	
6	4	4	4	4	4	4	24	100	

Lab no.	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Critical error
7	4	4	4	1	2	4	19	79	Y
8	4	4	4	4	4	4	24	100	
9	4	4	4	4	4	4	24	100	
10	4	3	4	4	4	4	23	96	
11	4	4	4	4	4	4	24	100	
12	4	3	0	4	4	4	19	79	Y
13	4	4	4	4	4	4	24	100	
14	4	4	4	4	4	4	24	100	
15	4	4	4	4	4	4	24	100	
16	4	4	4	4	4	4	24	100	
17	4	4	4	4	4	4	24	100	
18	4	4	4	4	4	4	24	100	
19	4	4	4	4	4	4	24	100	
20	4	4	4	4	4	4	24	100	
21	4	0	4	1	4	4	17	71	
22	4	4	4	4	4	4	24	100	
23	4	4	4	4	4	4	24	100	
24	4	4	4	1	4	4	21	88	
25	4	4	4	4	4	4	24	100	
26	4	4	4	4	4	4	24	100	
27	4	2	4	4	4	4	22	92	
28	4	4	4	2	4	4	22	92	
29				4	4	4	12	50	
30	4	4	4	1	4	4	21	88	
31	4	4	4				12	50	
32	4	4	4	4	4	4	24	100	
33	4	4	4	4	4	4	24	100	
34	4	3	4	4	4	4	23	96	
35	4	4	4	4	3	4	23	96	
36	4	4	4	4	4	4	24	100	
37	4	3	4	4	4	4	23	96	
38	4	4	4	4	4	4	24	100	
39	4	4	4	4	4	4	24	100	
40	4	4	4	4	4	4	24	100	
41	4	2	3	3	3	1	16	67	Y
42	4	4	4	4	4	4	24	100	
43	4	2	0	3	4	4	17	71	Y
44	4	4	4	4	3	4	23	96	
45	4	4	4	4	4	4	24	100	

Performance

	Number of labs	% total labs
Satisfactory performers (≥ 70 % of adequate responses)	39	87
Unsatisfactory performers (< 70 % adequate responses and/or critical error)	4	9
Partial and non-submitters	2	4

Overall Proficiency

(excluding non-submitters)

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Total (%)
ACDB-UL-2024-A	CPT1 (common sample)	**100**	**100**	**100**
ACDB-UL-2024-B	Vitamin deficiencies including riboflavin	**96.6**	**86.4**	**91.5**
ACDB-UL-2024-C	GA1	**95.5**	**94.3**	**94.9**
ACDB-UL-2024-D	VLCADD	**83.0**	**90.9**	**86.9**
ACDB-UL-2024-E	PA	**100**	**94.3**	**97.2**
ACDB-UL-2024-F	MCADD	**98.9**	**97.7**	**98.3**

10. Preview of the scheme in 2025

Sample distribution	5th February 2025
Start of analysis of Survey 2025/1 - Website open	17th March 2025
Survey 2025/1 - Results submission	7th April 2025
Survey 2025/1 - Reports	20th May 2025
Start of analysis of Survey 2025/2 - Website open	2nd June 2025
Survey 2025/2 – Results submission	23rd June 2025
Survey 2025/2 - Reports	4th August 2025
Annual Report 2025	Jan-Mar 2026

11. ERNDIM certificate of participation

A combined certificate of participation covering all EQA schemes will be provided to all participants who take part in any ERNDIM scheme. For the ACDB scheme this certificate will indicate if results were submitted and whether satisfactory performance was achieved in the scheme.

12. Questions, Comments and Suggestions

If you have any questions, comments or suggestions please address to the Scientific Advisor of the scheme, Mrs Erin Emmett (erin.mozley@nhs.net) and/or to the ERNDIM Administration Office (admin@erndim.org)

Date of report, 2025-03-27
Name and signature of Scientific Advisor

Erin Emmett

Mrs Erin Emmett
Scientific Advisor

Please note:
This annual report is intended for participants of the ERNDIM ACDB scheme. The contents should not be used for any publication without permission of the scheme advisor.

APPENDIX 1. Change log (changes since the last version)

Version Number	Published	Amendments
1	27th March 2025	2024 annual report published

END