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Published: 20 March 2024[1]

Acylcarnitines in Dried Blood Spots

Centre: Heidelberg-Germany

Final Report 2023

prepared by
Dr Joachim Janda

Note: This annual report is intended for participants of the ERNDIM Acylcarnitines in dried blood spots (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 ACDB scheme offers dried blood spots (DBS) 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 Dr Joachim Janda (Metabolic Center Heidelberg) 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. As in previous years normal profiles were also sent out. 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.

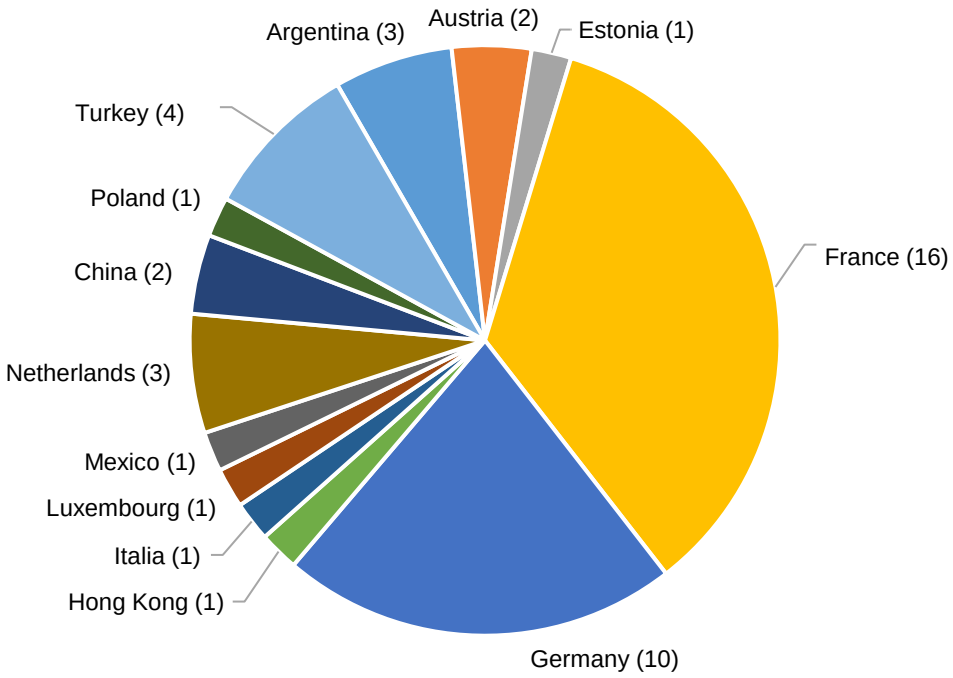
[1] If this report is not Version 1 for this scheme year, go to APPENDIX 1 for details of the changes made since the last version of this document.

2. Geographical distribution of participants

In 2023, 46 laboratories from many different countries participated in the ACDB Heidelberg scheme. There were no educational participants in 2023. Educational participants can 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.
Participants and new applicants will be distributed between the Heidelberg, London and Rome acylcarnitine in DBS schemes which are run separately. The three organising laboratories each participate in the other's scheme by rotation.

Country	Number of participants
Argentina	3
Austria	2
Estonia	1
France	16
Germany	10
Hong Kong	1
Italia	1

Country	Number of participants
Luxembourg	1
Mexico	1
Netherlands	3
People's Republic of China	2
Poland	1
Turkey	4



3. Design and logistics of the scheme including sample information

As in earlier ACDB schemes, the samples used in 2023 were authentic human DBS samples, five from affected patients and one from a healthy individual.

The scheme has been designed and planned by Joachim Janda 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.

All samples selected by the Scientific Advisor are typically prepared from 30-50 µL of lithium heparin (or EDTA) anticoagulated whole blood on Whatman (Schleicher & Schuell) 903™ paper. All samples are obtained following local ethical and consent guidelines.

In 2023 CSCQ dispatched the ACDB EQA samples to the scheme participants and provides a website for on-line 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

Participants are also encouraged to make use of the option to upload labelled copies of scans and/or chromatograms on the CSCQ website together with their analytical and interpretative results.

4. Schedule of the scheme

Time schedule in the 2023 ERNDIM ACDB Heidelberg scheme.

	1st Submission Round	2nd Submission Round
Sample IDs	ACDB-DH-2023-A ACDB-DH-2023-B ACDB-DH-2023-C	ACDB-DH-2023-D ACDB-DH-2023-E ACDB-DH-2023-F
Shipment of samples	February 8, 2023	
Start of analysis (clinical data available)	March 13, 2023	June 5, 2023
Reminder for result submission	March 27, 2023	June 19, 2023
Results submission deadline	April 3, 2023	June 26, 2023
Interim reports available on CSCQ website	May 23, 2023	July 26, 2023

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 2023 ERNDIM ACDB Heidelberg scheme.

Survey	Sample no.	Diagnosis
23-03-ACH	ACDB-DH-2023-A	Glutaric acidemia type 1 (common sample)
	ACDB-DH-2023-B	3-Methylglutaconic aciduria type I
	ACDB-DH-2023-C	normal control
23-06-ACH	ACDB-DH-2023-D	Propionic acidemia, PA
	ACDB-DH-2023-E	VLCAD deficiency
	ACDB-DH-2023-F	MMA cblC type

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 patient samples: All DBS samples in this year have been provided by the scheme organizers. The common sample for the ACDB schemes was provided by the ACDB centre Heidelberg

Prior to the distribution of the first round, a validation set of samples was returned from the CSCQ to the organising laboratory and re-analysed.

5. Results

Returned results in the 2023 ERNDIM ACDB Heidelberg scheme.

	Survey 1	Survey 2
Receipt of results	42	39
No answer	4	7

6. Web site reporting

The website reporting system is compulsory for all centres. The participants are reminded to carefully read and consider the following advice:

- **Results**
  - Give quantitative data as much as possible.
  - Enter the key metabolites with the evaluation **in the tables** even if you do not give quantitative data.
  - If the profile is normal: enter “Normal profile” in “Key metabolites”.
  - **Do not enter results in the “comments” field**, **otherwise your results will not be included in the evaluation program.**
- **Diagnosis**
  - **Do not 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 on treatment will not be scored.
  - **Do not give recommendations in “Comments on diagnosis” field**: 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 (SAB). Similar to other qualitative (proficiency testing) ERNDIM schemes, the maximum score for a sample is 4 points.
Qualitative results and diagnostic proficiency of the 2023 samples were scored using the criteria given below. These criteria have been set by the Scientific Advisor and approved by the SAB of ERNDIM. A second evaluation of this year's results was carried out by Dr. Charles Turner, scientific advisor of the ACDB London scheme. The final decision on scoring of the scheme has been made by the SAB during its autumn meeting (November 30, 2023).

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 13th, 2023.

Score for satisfactory performance
A minimum of 17 points out of a maximum of 24 is necessary for a satisfactory performance.

The ERNDIM Annual Certificate covers all ERNDIM schemes in which a laboratory has participated during the scheme year. For the ACDB scheme, “participation” is defined 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

Glutaryl-CoA dehydrogenase deficiency (GA 1)

Patient details provided to participants
30-year-old man presented in infancy with macrocephaly and dystonia. Today under treatment.

Patient details
30-year-old man presented in infancy with macrocephaly and dystonia. Today under treatment.
The sample originates from a patient of the Heidelberg Metabolic Laboratory, who had been diagnosed prenatally because of a positive family history.

Analytical performance
Forty-two of the total 46 participants submitted results for this sample.
The primary diagnostic marker for glutaric acidemia type 1 is glutarylcarnitine (C5DC). The acylcarnitine profile of this sample contains a clearly elevated signal for this AC species. Several diagnostic ratios, which can be used to substantiate the analytical result, such as C5DC/C8, C5DC/C16, or C5DC/C0, are also elevated.
All participants submitting results, except one, referred to the C5DC concentration and mostly categorized it as elevated (n=21) or even grossly elevated (19). Many participants also mentioned diagnostic ratios in their reports, e. g., C5DC/C8 (elevated: n=5, grossly elevated: n=9) or C5DC/C16 (elevated: n=7, grossly elevated: n=6). Free carnitine was reported as normal (n=11) or as decreased (n=10).

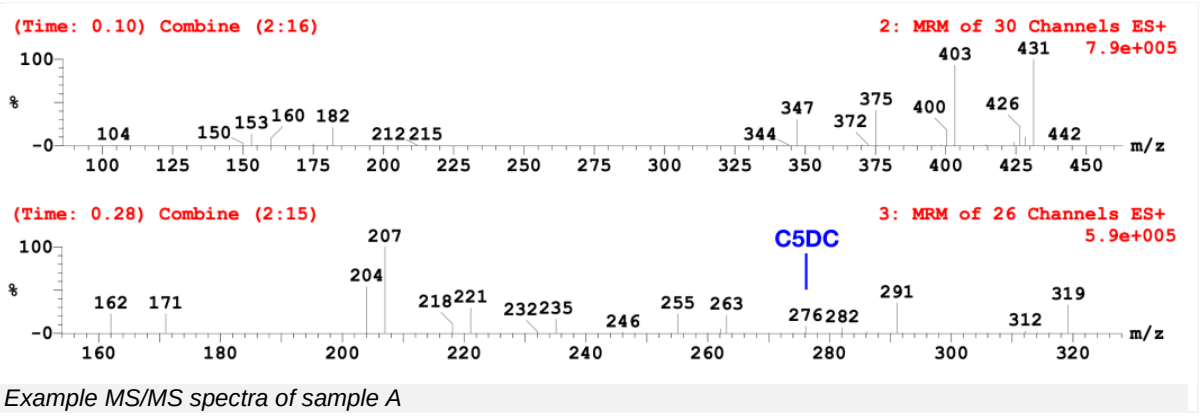
Evaluation criteria: Reporting of an increased C5-DC concentrations and/or a corresponding ratio at least as elevated gives 2 pts.

Diagnosis / Interpretative proficiency
Forty participants clearly interpreted their results as GA 1. One participant only stated “elevation of glutarylcarnitine” as the interpretation. Another participant who did not report C5DC or a related ratio did not report any diagnosis which was considered a critical error.

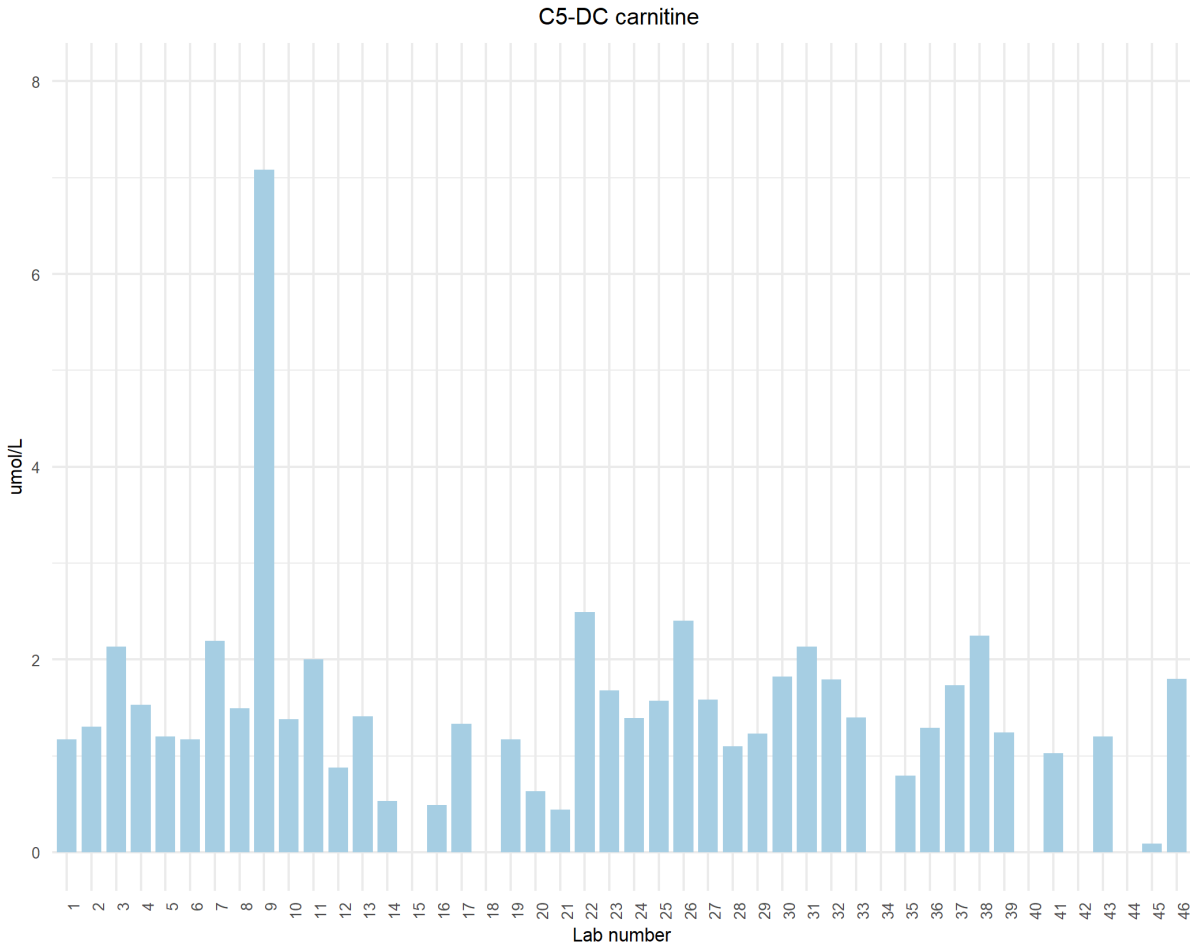
Evaluation criteria: Glutaric acidemia type 1 needs to be reported to achieve 2 points. If it is stated as alternative with a different primary diagnosis, recommendations have to be given that may lead to the correct diagnosis.

Recommendations
In the recommendations for further investigation, the participants focused on confirmation of their findings. Methods recommended for this were organic acids in urine (n=36), molecular genetic testing (n=34), measurement of enzymatic activity (n=17), and acylcarnitines in plasma or urine (n=7). Fifteen participants gave additional recommendations on therapeutic measures.

Overall impression
This was a straightforward sample for the participants resulting in excellent (98% analytical and 96% interpretative) proficiency.



Example MS/MS spectra of sample A



Sample	H23A
Mean	1.54
Median	1.38
SD	1.04

8.2. Patient B

3-Methylglutaconyl-CoA hydratase deficiency (MGA1)

Patient details provided to participants

17-year-old teenager with global developmental delay in infancy, now moderate intellectual disability.

Patient details

17-year-old teenager with global developmental delay in infancy, now moderate intellectual disability. For this patient, further diagnostic was performed at the age of 6 years after elevated 3-OH isovaleric acid and 3-methylglutaconate in urine had been detected. Activity of 3-methylglutaconyl-CoA hydratase in lymphocytes was clearly reduced. Subsequently a homozygous deletion of exons 5-6 in the *AUH* gene confirmed the diagnosis.

Analytical performance

Forty-two of the total 46 participants submitted results for this sample.
The acylcarnitine (AC) profile contains an elevated signal for hydroxyisovalerylcarnitine (C5OH) which can be supported by corresponding ratios, e. g. C5OH/C2.
Depending on the analytical method used, the targeted analyte is isobaric with several other ACs, e. g., 2-methyl-3-hydroxybutyrylcarnitine, methylmalonylcarnitine, or succinylcarnitine. Due to this analytical challenge and also the diagnostic ambiguity of C5OH, more acylcarnitine markers such as C3, C5:1, and C6-DC should be taken into consideration as additional key metabolites for this sample.
Of the 42 participants who submitted results in this survey, forty (95%) reported elevated concentrations of C5OH (or C4DC). However, the ACs useful for differential diagnosis were reported less frequently: C3 (n=15; 36%) was reported as normal or low, C5:1 (n=11; 26%) was reported mostly as normal and once as elevated, C6DC (n=14; 33%) was mostly reported as normal, once as elevated, and once as low.
Two participants did not report any ACs as elevated.

Evaluation criteria: 2 pts for reporting C5-OH carnitine (and/or indicative ratios)

Diagnosis / Interpretative proficiency

As C5OH carnitine can be also elevated in case of other IEMs, acylcarnitine markers such as C3, C5:1, and C6-DC – at normal concentrations here - should be considered to rule out particular hypotheses. Since an increased C5OH concentration in itself does not clearly indicate a specific disease, it is important to consider (and also mention) potential alternative diagnoses in the interpretation of this sample.
3-Methylglutaconic aciduria was reported as main (n=5) or alternative (n=15) diagnosis by 20 participants (48%). Most participants opted for 3-methylcrotonyl-CoA carboxylase deficiency (3MCCD, n=24) as their diagnosis, followed by 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG CLD, n=5). Diagnoses that were frequently reported as alternatives included deficiencies of HMG CL (n=22), multiple carboxylase (biotinidase or holocarboxylase, n=18), beta-ketothiolase (n=14), 2-methyl-3-hydroxybutyryl-CoA dehydrogenase (n=9), or 3-MCC (n=8). Some participants who interpreted the analytical result as C4DC instead of C5OH mentioned methylmalonic acidemia or succinyl-CoA ligase deficiency in their diagnoses.
The two participants who did not report elevated ACs also did not report a diagnosis, which was considered a critical error.

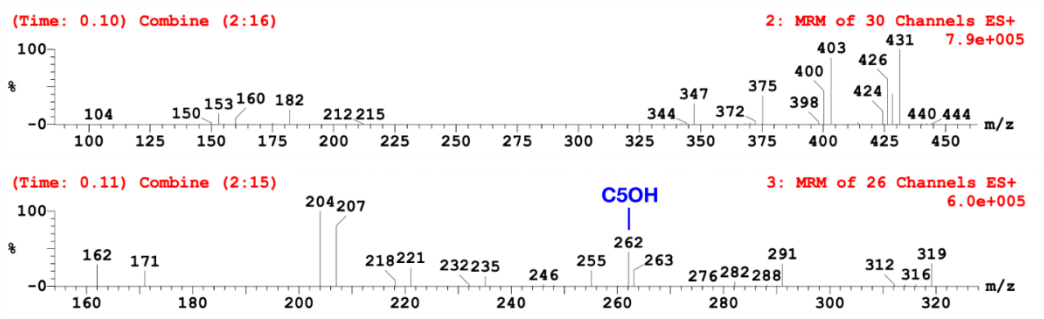
Evaluation criteria: Two points are given either for reporting 3-methylglutaconic aciduria as the most likely diagnosis or for reporting as alternative diagnosis with additional recommendation to analyse urinary organic acids.

Recommendations

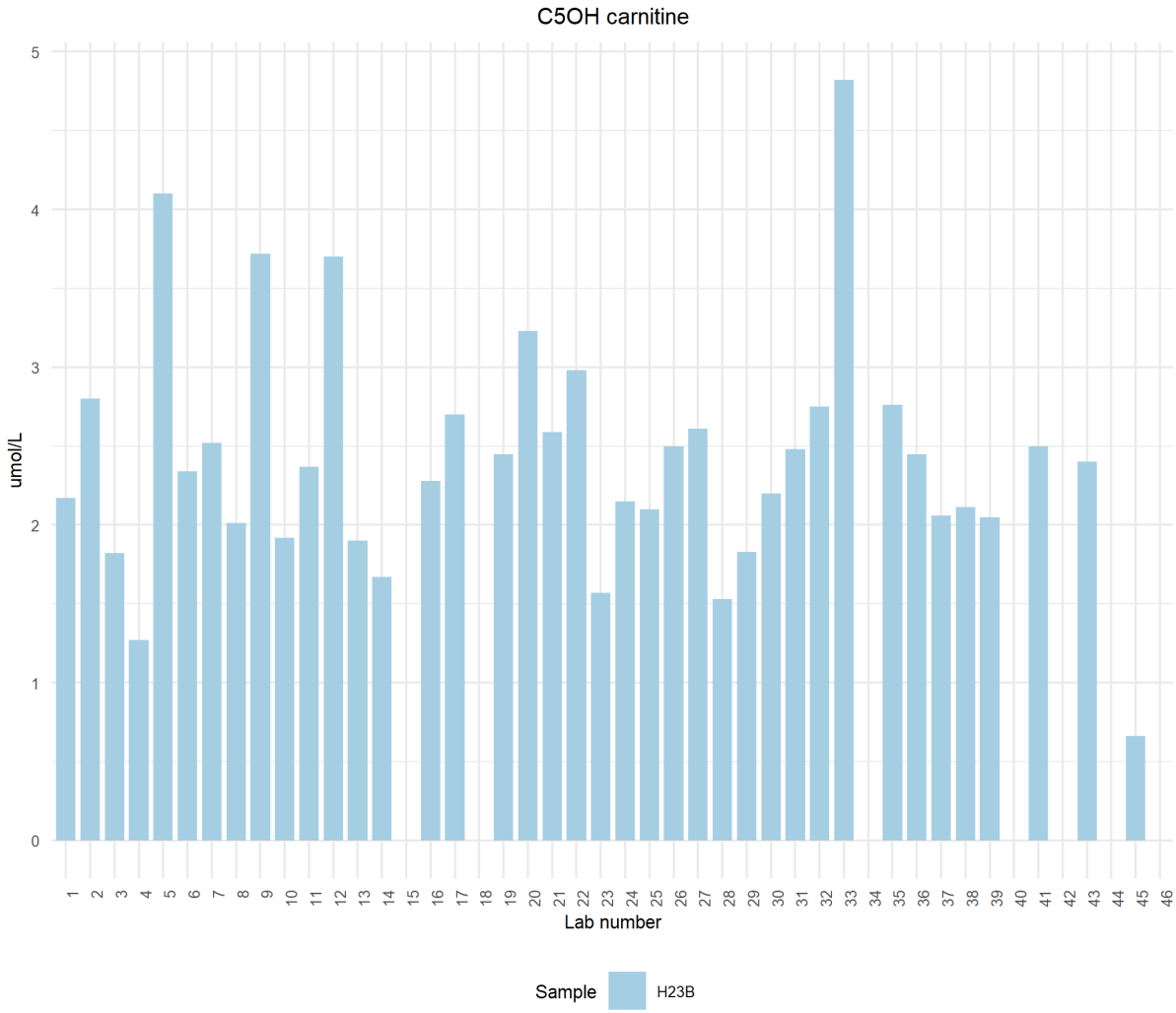
In their recommendations, the participants focused on differentiation by analysis of urinary organic acids (n=40). Other frequent recommendations were molecular genetic variant analysis (n=27) and determination of enzymatic activity (n=21). However, only a minority of participants directly mentioned the *AUH* gene or 3-methylglutaconyl-CoA hydratase specifically – many participants recommended to select the analytical targets depending on the results of organic acid analyses.

Overall impression

This was a tricky sample. Most participants reported the elevated C5OH metabolite achieving 95% analytical proficiency. On the other hand, more than half of the participants did not consider MGA1 when interpreting their results and the given patient details, leading to an interpretational proficiency of 48% only.



Example MS/MS spectra of sample B



Sample	H23B
Mean	2.41
Median	2.37
SD	0.75

8.3. Patient C

No diagnosis (normal control sample)

Patient details provided to participants

Woman aged 54 years with recurrent muscle weakness.

Patient details

Woman aged 54 years with recurrent muscle weakness.
The sample was from a healthy colleague with no known metabolic disorder.

Analytical performance

Forty-two of the total 46 participants submitted results for this sample.
The AC profile taken for sample validation does not contain any elevated AC concentrations. Most of the participants submitting results (n=37) also characterised their analytical results as normal AC profiles, with a few exceptions. Five participants reported increased C3 of which one classified the concentration found as grossly elevated. Concentrations of C4DC classified as elevated or even grossly elevated were reported by four participants. Other AC species reported as elevated were C4 and C5 carnitines (both n=2).

Evaluation criteria: Two points are awarded, when a “normal profile” is reported.

Diagnosis / Interpretative proficiency

As stated above, the majority of participants interpreted their results as normal. Other diagnoses reported were of the group of methylmalonic acidemias, with or without relation to vitamin B_{12} deficiency (n=4), and 2-methylbutyryl-CoA dehydrogenase deficiency (n=1).

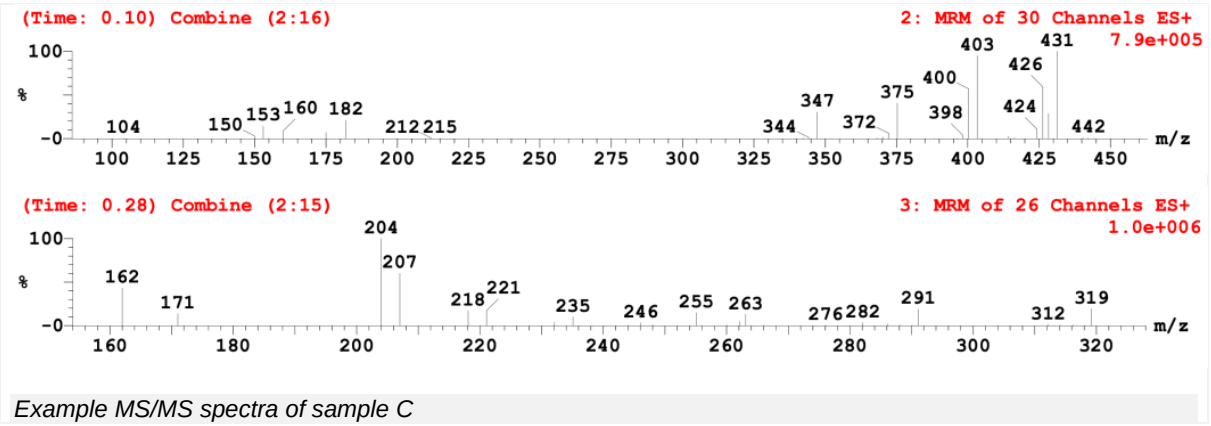
Evaluation criteria: Two points are awarded, when “no metabolic disorder” is considered.

Recommendations

The recommendations for further testing included organic acids in urine (n=21), repetition of acylcarnitines with a sample taken during a stress episode (n=12), and amino acids in plasma (n=10). Some participants recommended investigations regarding the indicated muscle weakness, such as assessment of lactate/pyruvate ratios or measurement of creatine kinase.

Overall impression

Most participants clearly identified the sample as a normal control, leading to a total proficiency of 88%. However, the same sample has been circulated in the 2022 ACDB-DH scheme with a better result (ACDB-DH-2022-F, 100% proficiency).



Example MS/MS spectra of sample C

8.4. Patient D

Propionyl-CoA carboxylase deficiency

Patient details provided to participants

12-year old patient referred due to ketoacidosis, ataxia and dystonia. On treatment with carnitine.

Patient details

12-year-old patient referred due to ketoacidosis, ataxia, and dystonia. On treatment with carnitine. The sample originates from a patient with propionic acidemia (PA) confirmed by molecular analysis. Depending on the lab's reference concentrations, the propionyl (C3) carnitine concentration in this sample may be borderline or only slightly elevated. Free carnitine is in the upper normal range or slightly elevated due to carnitine supplementation. The indicative ratio C3/C2 is clearly elevated, as may be the C3/C16 ratio. Second-tier metabolites 3-OH propionate and methylcitrate are increased, while methylmalonate is normal.

Analytical performance

Thirty-nine participants out of a total of 46 submitted results for this sample. Most of these reported C3 carnitine to be elevated or even grossly elevated (n=32). Three participants classified the C3 concentration as normal but reported elevated or grossly elevated C3/C2 and C3/C16 ratios. In total, indicative ratios were reported to be at least elevated by 19 (C3/C2) and 11 (C3/C16) participants, respectively. In addition, 39% of the participants (n=15) reported normal concentrations of C4DC carnitine, 44% (n=17) reported that C2 carnitine concentrations were decreased, and 49% of the participants reported free carnitine concentrations to be increased (n=19) or normal (n=7).
Four participants did not report on either C3 or indicative ratios for PA.
One participant did not report any ACs but gave results on amino acids instead.

Evaluation criteria: Reporting of C3 carnitine with at least elevated concentration and/or indicative ratios will be evaluated with 2 pts.

Diagnosis / Interpretative proficiency

Twenty-five participants chose PA as the primary diagnosis for this sample, while four participants mentioned it in as alternative. The second-most reported diagnoses were variants of MMA (principal: n=5, alternative: n=17). Two participants stated the acylcarnitine profile not to be representative for an organoaciduria or fatty acid metabolism defect, and once each, biotinidase deficiency, pyruvate dehydrogenase deficiency, carnitine uptake deficiency, CPT II, and mitochondrial respiratory chain disorder were chosen as primary diagnosis. One participant reported several numeric concentrations but did not categorize the findings or give a diagnosis.

Three participants were assigned critical errors with this sample.

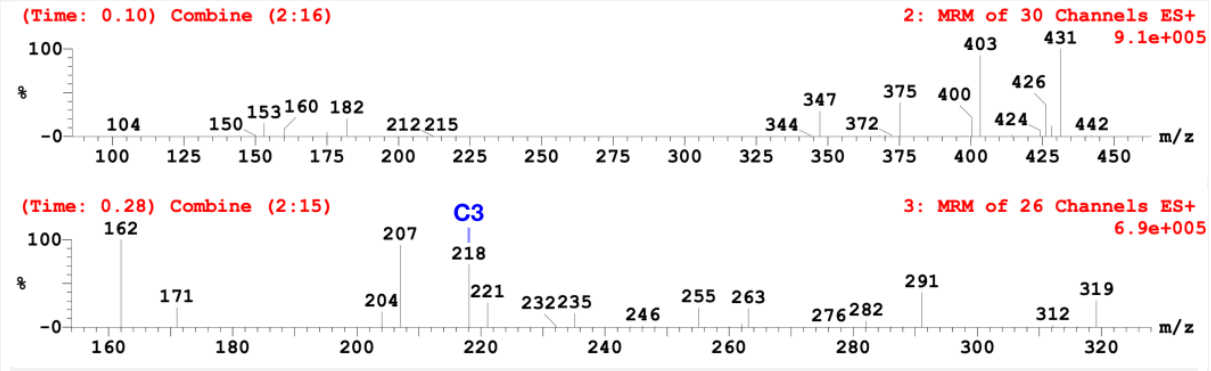
Evaluation criteria: Stating PA as the principal diagnosis is scored as two points. If PA is indicated as an alternative diagnosis, the recommendations must also specify a method enabling to find the correct diagnosis.

Recommendations

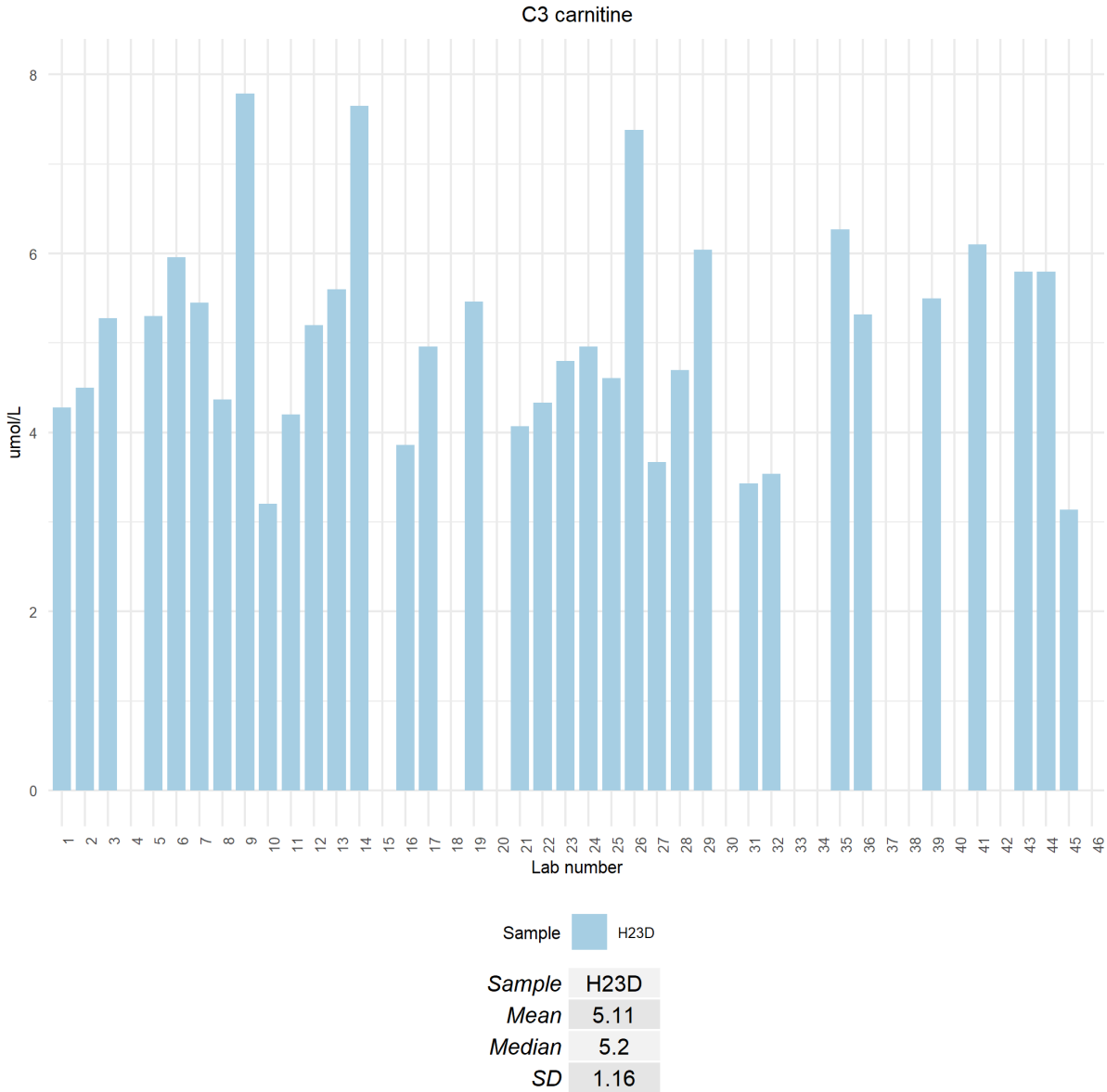
In their recommendations, most participants focussed on differential diagnostic measures and confirmation. The most frequently recommended additional tests to perform were organic acids in urine (n=36), molecular genetics (n=25), as well as plasma amino acids (n=17), total homocysteine (n=14), and methylmalonic acid (n=8). Six participants gave recommendations on further treatment.

Overall impression

Compared to earlier circulations of PA specimens, this sample seemed to pose a challenge for some participants. The analytical proficiency was 91%, while the diagnostic proficiency resulted in 74%.



Example MS/MS spectra of sample D



Sample	H23D
Mean	5.11
Median	5.2
SD	1.16

8.5. Patient E

Very long-chain acyl CoA dehydrogenase (VLCAD) deficiency

Patient details provided to participants

32-year-old woman, first referred at the age of 23 years with recurrent generalized myalgia.

Patient details

32-year-old woman, first referred at the age of 23 years with recurrent generalized myalgia.
VLCAD was confirmed by reduced enzyme activity (10 %) and molecular analysis which showed two pathogenic variants in *ACADVL*.
MS/MS analysis reveals elevated C14:1 carnitine and correspondingly elevated indicative ratios, such as C14:1/C4, C14:1/C6, or C14:1/C8. Depending on the lab internal reference ranges, other C14-, C16-, or C18-derived analytes may be detected in elevated concentrations.

Analytical performance

Seven of the 46 participants in the scheme did not submit results for this sample, so the data from 39 participants are considered in the scoring. The analytical parameters most frequently reported with elevated or even grossly elevated concentrations or values were C14:1 (GE: 13, E: 24), C14:0 (GE: 2, E: 20), C14:2 (GE: 0, E: 18), and C16:1 (GE: 9, E: 2) carnitines and the ratios C14:1/C12:1 (GE: 3, E: 8) and C14:1/C4 (GE: 3, E: 1). Other potential markers for VLCAD such as C16:2 carnitine, C14:1/C6 ratio, C14:1/C8 ratio, or C14:1/C16 ratio were reported less frequently, but in most cases at least as elevated.

Evaluation criteria: Two points are given for reporting C14(:1)-, C16-, or C18 carnitine derived analytes (non-hydroxylated) or corresponding indicative ratios as at least elevated.

Diagnosis / Interpretative proficiency

All of the participants who returned results for this sample, except for two, decided for VLCAD as the primary diagnosis. Several participants mentioned alternative diagnoses, such as CPT II (n=3) or MADD (n=5).
One participant commented on slightly elevated C14 carnitine but categorized it as not relevant for a pathologic condition and opted for a normal acylcarnitine profile. Another participant reported several numeric concentrations for various acylcarnitines but did not categorize the findings or give a diagnosis. Both cases were considered critical errors.

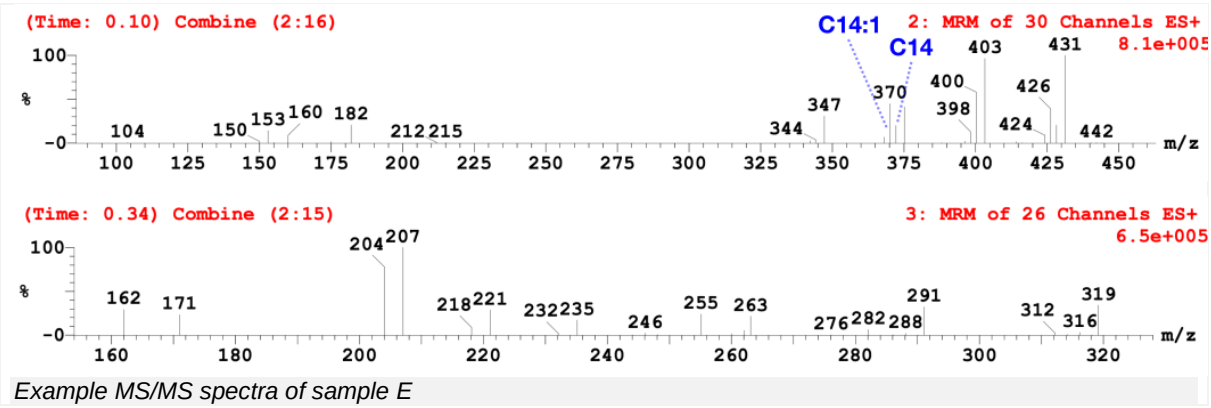
Evaluation criteria: Two points are assigned if VLCAD is mentioned as a diagnosis.

Recommendations

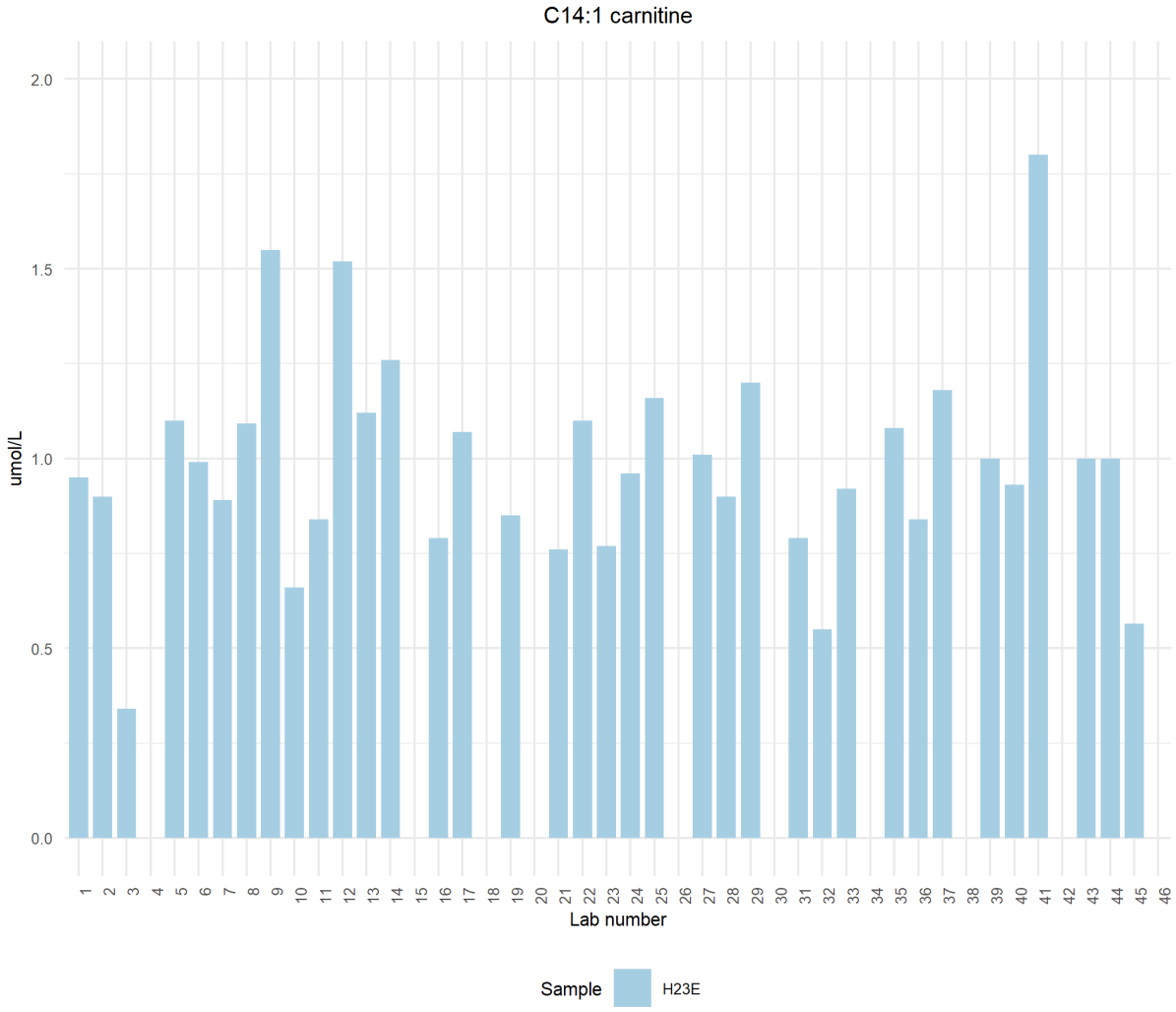
Aiming to support their hypotheses, the participants frequently recommended to analyse organic acids in urine (n=19), measure enzymatic activity (n=19), repeat acylcarnitines in plasma (n=10) and/or perform a molecular genetic analysis (n=33).

Overall impression

This was a straightforward sample for most participants, achieving excellent analytical (97%) and diagnostic (95%) proficiency.



Example MS/MS spectra of sample E



Sample	H23E
Mean	0.98
Median	0.98
SD	0.27

8.6. Patient F

Methylmalonic aciduria with homocystinuria, type cblC

Patient details provided to participants

20-year-old female with cognitive impairment, gingival hyperplasia and areflexia of lower extremities.

Patient details

20-year-old female with cognitive impairment, gingival hyperplasia and areflexia of lower extremities. On the 5th day of life, she presented with muscular hypotonia and mild hyperammonemia. Metabolic screening showed elevated urinary methylmalonate and plasma homocysteine. A homozygous pathogenic variant in *MMACHC* was detected by molecular analysis and confirmed CblC deficiency.

This sample contains a C3 carnitine concentration in the upper normal range and a slightly elevated C3/C2 ratio. Second tier analysis shows clearly elevated concentrations of methylmalonate and homocysteine.

Analytical performance

Thirty-nine participants reported results for this sample. Most participants referenced C3 carnitine (n=32) with elevated (n=27) and normal (n=5) concentrations. The C3/C2 ratio was mentioned to be elevated (n=9) or normal (n=2) as well as the C3/C16 ratio (6 elevated, 1 normal). Several participants also gave results for C4DC carnitine (6 elevated, 4 normal).

Due to the indeterminate profile, many participants also reported on other acylcarnitines, such as C2 (3 elevated, 6 normal), C4 (5 elevated, 3 normal), C16 (2 elevated, 2 normal), C16:1 (2 elevated), C18:1 (7 elevated), or C18:2 (3 elevated), in addition to various individual mentions of analytes.

Evaluation criteria: Two points are awarded, when either C3 or one of the indicative C3-based ratios or C4DC is reported as elevated.

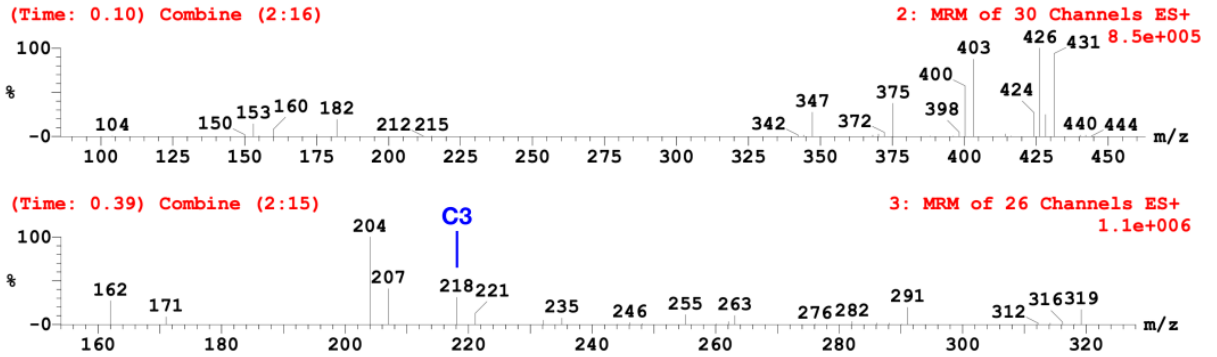
Diagnosis / Interpretative proficiency
The most frequently mentioned diagnoses for this sample were variants of MMA with or without relation to cobalamin-metabolism (taken together: n=28) followed by propionic acidemia (n=10). Six participants opted for a normal profile. Less frequently mentioned diagnoses were MADD (n=1), LCHAD (n=1), or mitochondrial trifunctional protein deficiency (n=2) apart from comments referring to lysosomal diseases.

Evaluation criteria: Two points are awarded for MMA variants or disorders related to cobalamin metabolism. If given as alternative diagnosis, an additional recommendation suitable to find the correct diagnosis is required to achieve two points.

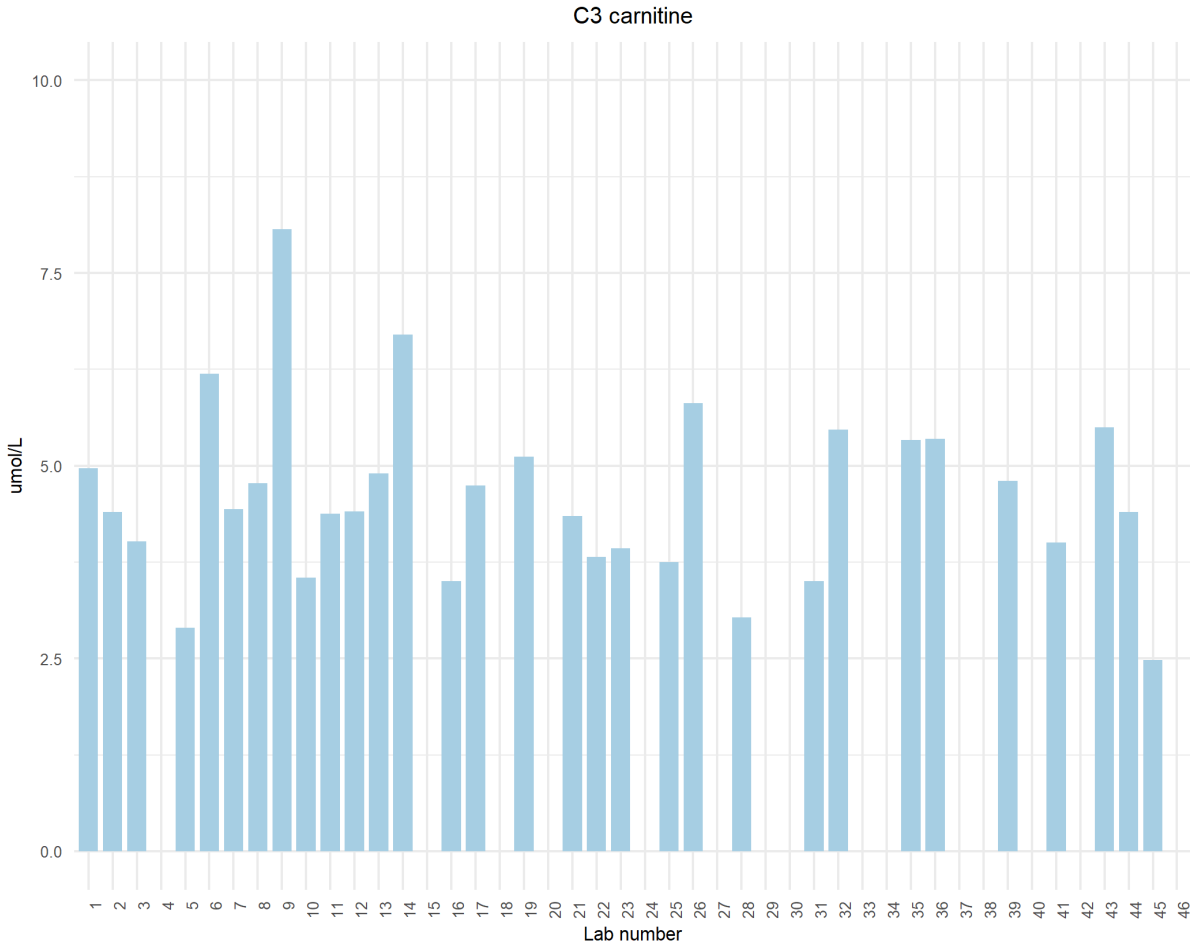
Recommendations
In their recommendations for further testing, the participants focused on differentiation. Most frequently mentioned additional tests were organic acids in urine (n=32), determination of total homocysteine in plasma (n=21), Vitamin B_{12} status (n=18), plasma amino acids (n=16), methylmalonic acid in plasma (n=12), and repetition of acylcarnitines (n=11).

Scoring
The sample was normally scored, but due to its difficulty, the SAB agreed not to assign any critical errors.

Overall impression
This was a difficult sample, but the participants achieved good analytical (80%) and satisfying interpretive (71%) proficiency.



Example MS/MS spectra of sample F



Sample	H23F
Mean	4.58
Median	4.41
SD	1.12

9. Scores of participants

All data transfer, the submission of data as well as the request and viewing of reports proceed via the ACDB-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.

9.1. Detailed scores – Round 1

Lab n°	Patient A Glutaric acidemia type 1			Patient B 3-Methylglutaconic aciduria type I			Patient C normal control			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	2	4	2	2	4	2	2	4	12
2	2	2	4	2	0	2	2	2	4	10
3	2	2	4	2	2	4	2	2	4	12
4	2	2	4	2	0	2	2	2	4	10
5	2	2	4	2	2	4	0	0	0	8
6	2	2	4	2	0	2	2	2	4	10
7	2	2	4	2	0	2	2	2	4	10
8	2	2	4	2	0	2	2	2	4	10
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	0	2	2	2	4	10
12	2	2	4	2	0	2	2	2	4	10
13	2	2	4	2	0	2	2	2	4	10
14	2	2	4	2	2	4	2	2	4	12
15	--	--	--	--	--	--	--	--	--	0
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	0	0	0	8
19	2	2	4	2	2	4	2	2	4	12
20	2	2	4	2	2	4	0	0	0	8
21	2	2	4	2	2	4	2	2	4	12
22	2	2	4	2	2	4	2	2	4	12
23	2	2	4	2	0	2	2	2	4	10
24	2	2	4	2	0	2	2	2	4	10

Lab n°	Patient A Glutaric acidemia type 1			Patient B 3-Methylglutaconic aciduria type I			Patient C normal control			
	A	I	Total	A	I	Total	A	I	Total	Total
25	2	2	4	2	0	2	0	0	0	6
26	2	2	4	2	0	2	2	2	4	10
27	2	2	4	2	0	2	0	0	0	6
28	2	2	4	2	2	4	2	2	4	12
29	2	2	4	2	0	2	2	2	4	10
30	2	2	4	2	2	4	2	2	4	12
31	2	2	4	2	0	2	2	2	4	10
32	2	2	4	2	0	2	2	2	4	10
33	2	2	4	2	2	4	2	2	4	12
34	--	--	--	--	--	--	--	--	--	0
35	2	2	4	2	2	4	2	2	4	12
36	2	2	4	2	0	2	2	2	4	10
37	2	2	4	2	0	2	2	2	4	10
38	2	2	4	2	2	4	2	2	4	12
39	2	2	4	2	0	2	2	2	4	10
40	--	--	--	--	--	--	--	--	--	0
41	2	2	4	2	0	2	2	2	4	10
42	--	--	--	--	--	--	--	--	--	0
43	2	2	4	2	2	4	2	2	4	12
44	0	0	0	0	0	0	2	2	4	4
45	2	2	4	2	2	4	2	2	4	12
46	2	0	2	0	0	0	2	2	4	6

9.2. Detailed scores – Round 2

Lab n°	Patient D Propionic acidemia, PA			Patient E VLCAD deficiency			Patient F MMA cblC type			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	0	2	2	2	4	2	2	4	10
2	2	2	4	2	2	4	2	2	4	12
3	2	2	4	2	2	4	2	0	2	10
4	--	--	--	--	--	--	--	--	--	0
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	0	2	2	2	4	2	0	2	8
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	0	0	0	8
12	2	2	4	2	2	4	2	2	4	12
13	2	2	4	2	2	4	2	0	2	10
14	2	2	4	2	2	4	2	2	4	12
15	--	--	--	--	--	--	--	--	--	0
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	--	--	--	--	--	--	--	--	--	0
21	2	2	4	2	2	4	2	2	4	12
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	0	0	0	8
25	2	2	4	2	2	4	2	0	2	10
26	2	2	4	0	0	0	2	2	4	8
27	0	0	0	2	2	4	2	2	4	8
28	2	2	4	2	2	4	2	2	4	12
29	2	2	4	2	2	4	0	0	0	8
30	--	--	--	--	--	--	--	--	--	0
31	2	0	2	2	2	4	2	2	4	10

Lab n°	Patient D Propionic acidemia, PA			Patient E VLCAD deficiency			Patient F MMA cblC type			
	A	**I**	**Total**	**A**	**I**	**Total**	**A**	**I**	**Total**	**Total**
32	2	2	4	2	2	4	2	2	4	12
33	0	0	0	2	2	4	0	0	0	4
34	--	--	--	--	--	--	--	--	--	0
35	2	2	4	2	2	4	2	2	4	12
36	2	2	4	2	2	4	2	2	4	12
37	2	0	2	2	2	4	0	0	0	6
38	2	2	4	2	2	4	0	0	0	8
39	2	0	2	2	2	4	2	2	4	10
40	0	0	0	2	2	4	0	0	0	4
41	2	2	4	2	2	4	2	2	4	12
42	--	--	--	--	--	--	--	--	--	0
43	2	0	2	2	2	4	2	2	4	10
44	2	0	2	2	0	2	2	0	2	6
45	2	2	4	2	2	4	2	2	4	12
46	--	--	--	--	--	--	--	--	--	0

9.3. Total scores

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Critical error
1	4	4	4	2	4	4	22	92	
2	4	2	4	4	4	4	22	92	
3	4	4	4	4	4	2	22	92	
4	4	2	4	--	--	--	10	42	
5	4	4	0	4	4	4	20	83	
6	4	2	4	4	4	4	22	92	
7	4	2	4	4	4	4	22	92	
8	4	2	4	2	4	2	18	75	
9	4	4	4	4	4	4	24	100	
10	4	4	4	4	4	4	24	100	
11	4	2	4	4	4	0	18	75	
12	4	2	4	4	4	4	22	92	
13	4	2	4	4	4	2	20	83	
14	4	4	4	4	4	4	24	100	
15	--	--	--	--	--	--	0	0	
16	4	4	4	4	4	4	24	100	
17	4	4	4	4	4	4	24	100	
18	4	4	0	4	4	4	20	83	
19	4	4	4	4	4	4	24	100	
20	4	4	0	--	--	--	8	33	
21	4	4	4	4	4	4	24	100	
22	4	4	4	4	4	4	24	100	
23	4	2	4	4	4	4	22	92	
24	4	2	4	4	4	0	18	75	
25	4	2	0	4	4	2	16	67	
26	4	2	4	4	0	4	18	75	CE
27	4	2	0	0	4	4	14	58	CE
28	4	4	4	4	4	4	24	100	
29	4	2	4	4	4	0	18	75	
30	4	4	4	--	--	--	12	50	
31	4	2	4	2	4	4	20	83	
32	4	2	4	4	4	4	22	92	
33	4	4	4	0	4	0	16	67	

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Critical error
34	--	--	--	--	--	--	0	0	
35	4	4	4	4	4	4	24	100	
36	4	2	4	4	4	4	22	92	
37	4	2	4	2	4	0	16	67	
38	4	4	4	4	4	0	20	83	
39	4	2	4	2	4	4	20	83	
40	--	--	--	0	4	0	4	17	CE
41	4	2	4	4	4	4	22	92	
42	--	--	--	--	--	--	0	0	
43	4	4	4	2	4	4	22	92	
44	0	0	4	2	2	2	10	42	CE
45	4	4	4	4	4	4	24	100	
46	2	0	4	--	--	--	6	25	CE

9.4. Performance

	Number of labs	% total labs
Satisfactory performers (≥ 70 % of adequate responses)	32	70
Unsatisfactory performers (< 70 % adequate responses and/or critical error)	6	13
Partial and non-submitters	8	17

9.5. Overall Proficiency

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Total (%)
ACDB-DH-2023-A	Glutaric acidemia type 1	98	95	96
ACDB-DH-2023-B	3-Methylglutaconic aciduria type I	95	48	71
ACDB-DH-2023-C	normal control	88	88	88
ACDB-DH-2023-D	Propionic acidemia, PA	92	74	83
ACDB-DH-2023-E	VLCAD deficiency	97	95	96
ACDB-DH-2023-F	MMA cblC type	82	69	76

10. Tentative 2024 schedule

Sample distribution	8th February 2024
Start of analysis of Survey 2024/1 Website open	13th March 2024
Survey 2024/1 - Results submission	2rd April 2024
Survey 2024/1 - Reports	April/May 2024
Start of analysis of Survey 2024/2 Website open	5th June 2024
Survey 2024/2 – Results submission	19th June 2024
Survey 2024/2 - Reports	July/August 2024
Annual Report 2024	January 2025

11. ERNDIM certificate of participation

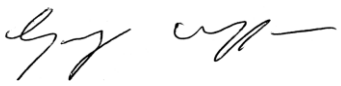
A combined certificate of participation covering all EQA schemes will be provided to all participants who take part in any ERNDIM scheme. For the ACDB scheme this certificate will indicate if results were submitted and whether satisfactory performance was achieved in the scheme.

12. Questions, Comments and Suggestions

If you have any questions, comments or suggestions please address to the Scientific Advisor of the scheme, Dr. Joachim Janda (Joachim.Janda@med.uni-heidelberg.de) and/or to the ERNDIM Administration Office (admin@erndim.org)

Date of report, 2024-03-11
Name and signature of Scientific Advisor

Dr J. Janda
Scientific Advisor
Laboratory of Metabolic Diseases



Prof. Dr. G. F. Hoffmann
Director
Department of General Paediatrics

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	20th March 2024	2023 annual report published

END