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Qualitative Organic Acids

Centre: Germany

Final Report 2022

prepared by
Dr. J. Janda

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1. Introduction

The ERNDIM Qualitative Organic Acids in urine scheme offers urine samples obtained from confirmed patients with confirmed diagnoses to enable laboratories to gain or maintain experience to identify organic acid disorders. The scheme is organised by Dr Joachim Janda (Metabolic Center Heidelberg) in conjunction with Centre Suisse de Contrôle de Qualité (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.

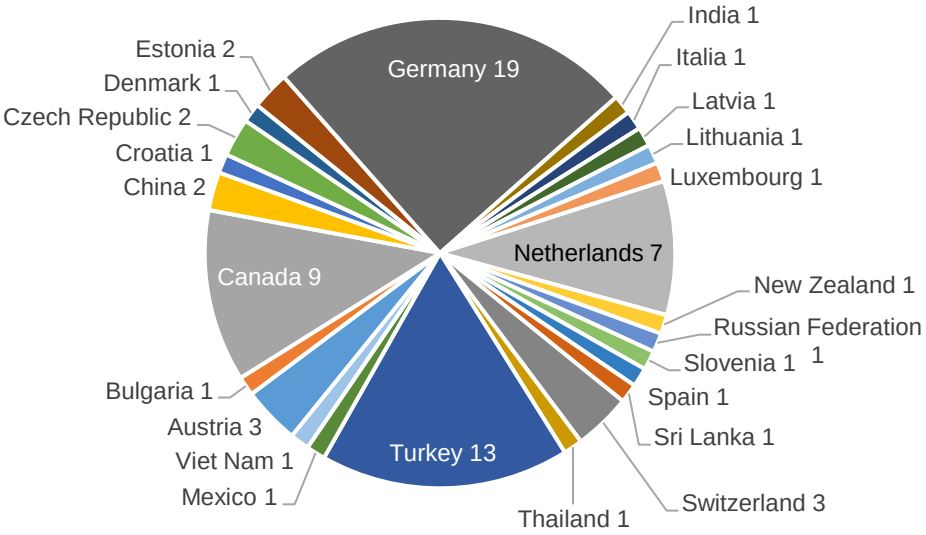
2. Geographical distribution of participants

In 2022, seventy-six laboratories from many different countries participated in the QLOU Heidelberg scheme. There were no educational participants in 2022 (none in 2021) - those take part in all aspects of the scheme and receive interim reports with scores. However, performance is not indicated on the ERNDIM certificate for educational participants.
Participants and new applicants are distributed between the Barcelona, Heidelberg and Sheffield qualitative urinary organic acid 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.

Country	Number of participants
Austria	3
Bulgaria	1
Canada	9
Croatia	1
Czechia	2
Denmark	1
Estonia	2
Germany	19
India	1
Italia	1
Latvia	1
Lithuania	1
Luxembourg	1

Country	Number of participants
Netherlands	7
New Zealand	1
People's Republic of China	2
Russian Federation	1
Slovenia	1
Spain	1
Sri Lanka	1
Switzerland	3
Thailand	1
Turkey	13
United States of America	1
Viet Nam	1



3. Design and logistics of the scheme including sample information

As usual, the samples used in 2022 were authentic human urine samples, five from affected patients and one from a healthy individual. All samples selected by the Scientific Advisor have been heat-treated and were tested for suitability in the Scientific Advisor's laboratory.
In 2022, CSCQ dispatched the QLOU 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

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 2022 ERNDIM QLOU Heidelberg scheme.

	1st Submission Round	2nd Submission Round
Sample IDs	QLOU-DH-2022-A QLOU-DH-2022-B QLOU-DH-2022-C	QLOU-DH-2022-D QLOU-DH-2022-E QLOU-DH-2022-F
Shipment of samples	February 02, 2022	
Start of analysis (clinical data available)	May 09, 2022	August 29, 2022
Reminder for result submission	May 23, 2022	September 12, 2022
Results submission deadline	May 30, 2022	September 19, 2022
Interim reports available on CSCQ website	July 27, 2022	October 25, 2022

Samples included in the 2022 ERNDIM QLOU Heidelberg scheme.

Survey	Sample	Diagnosis
22-05-OUH	QLOU-DH-2022-A	Normal control
	QLOU-DH-2022-B	5-Oxoprolinuria due to GSSD
	QLOU-DH-2022-C	Methylmalonic aciduria, mut(0) type
22-08-OUH	QLOU-DH-2022-D	Mevalonic aciduria
	QLOU-DH-2022-E	MAD deficiency
	QLOU-DH-2022-F	Combined malonic and methylmalonic aciduria

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: all urine samples have been provided by the scheme organizers or specified participants.

Patient A:	Normal control	Metabolic Center Heidelberg
Patient B:	5-Oxoprolinuria due to GSSD	
Patient C:	Methylmalonic aciduria, mut(0) type	
Patient D:	Mevalonic aciduria	
Patient E:	MAD deficiency	
Patient F:	Combined malonic and methylmalonic aciduria	Kindly provided by Dr. Jeannette Klein, Charité Universitätsmedizin Berlin

5. Results

Returned results in the 2022 ERNDIM QLOU Heidelberg scheme

	Survey 1	Survey 2
Receipt of results	73	71
No answer	3	5

6. Web site reporting

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

- **Selection of tests**
  Do not select a test if you will not perform it, otherwise the evaluation program includes it in the report.
- **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” window**, otherwise your results will not be included in the evaluation program.

- **Diagnosis**
  Do not enter the diagnosis in the “comments” window, otherwise it will not be included in the evaluation program.
- **Recommendations (= advice for further investigation).**
  - Scored together with the interpretative score.
  - Advice for treatment will not be scored.
  - **Do not 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 2022 samples were scored using the criteria given below. These criteria have been set by the Scientific Advisor, approved by the ERNDIM Scientific Advisory Board (SAB). The final decision on the scoring in the scheme is made by the SAB at its autumn meeting (November 25, 2022).

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’ (CE) has been 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 are 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 14, 2022.

Score for satisfactory performance

At least 17 points out of a maximum of 24 (71%) are required for satisfactory performance.

The ERNDIM Annual Certificate covers all ERNDIM schemes in which a laboratory has participated during the scheme year. For the ‘Qualitative Organic Acids in Urine’ scheme, “participation” is defined as requiring full returns for both surveys during the year. Failure to meet this requirement will result in the certificate of participation showing ‘non-submitter’ or ‘partial submitter’ rather than ‘satisfactory’ or ‘unsatisfactory’.

8. Results of samples and evaluation of reporting

8.1. Patient A

Normal control sample

Patient details provided to participants

10-year-old boy with behavioural problems and severe learning disabilities

This sample, which was taken from a healthy individual, shows a normal organic acid profile.

Analytical performance

In the first survey (samples A – C), 73 participants out of 76 submitted results.
Most laboratories reported the organic acids profile as normal. However, a few compounds were also reported as elevated or even highly elevated, such as 2-hydroxyisobutyric, 3-hydroxyphenyl-lactic, 3-hydroxyglutaric, citric, hippuric, homovanillic, malonic, methylmalonic, or succinic acid.

Evaluation criteria: Two points are awarded for reporting normal profiles. Analytical results (mis)leading to an IEM diagnosis result in a deduction of points.

Please consider the advice given in the "Scheme Instructions" in section 4.5 when submitting results for normal profiles: To facilitate the evaluation, "normal profile" should be stated in the key metabolite field.

Diagnosis / Interpretative proficiency

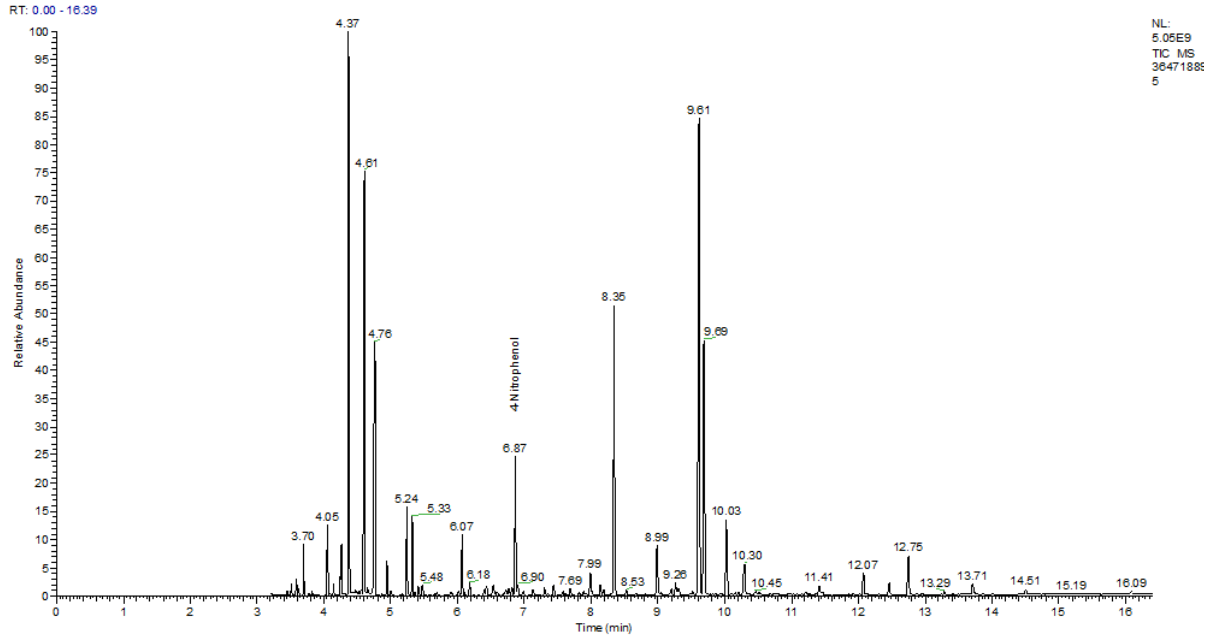
The majority of participants (n=70) stated that the sample is not indicative for an inborn metabolic error. Two laboratories voted for methylmalonic aciduria due to their analytical findings, and one lab was certain that it is combined malonic and methylmalonic aciduria.
Evaluation criteria: Results other than "normal profile" (or equivalent) taking also into account the stated reliability and given recommendations can result in a deduction of points.

Recommendations

In the recommendations for further investigation, most participants advised to continue the metabolic workup with urine or plasma analyses.

Overall impression

The participants performed very good achieving analytical and interpretational proficiencies of 96% and 96%, respectively.



Example chromatogram for sample A (4-Nitrophenol is internal standard).

8.2. Patient B

5-Oxoprolinuria due to glutathione synthetase deficiency (GSS)

Patient details provided to participants

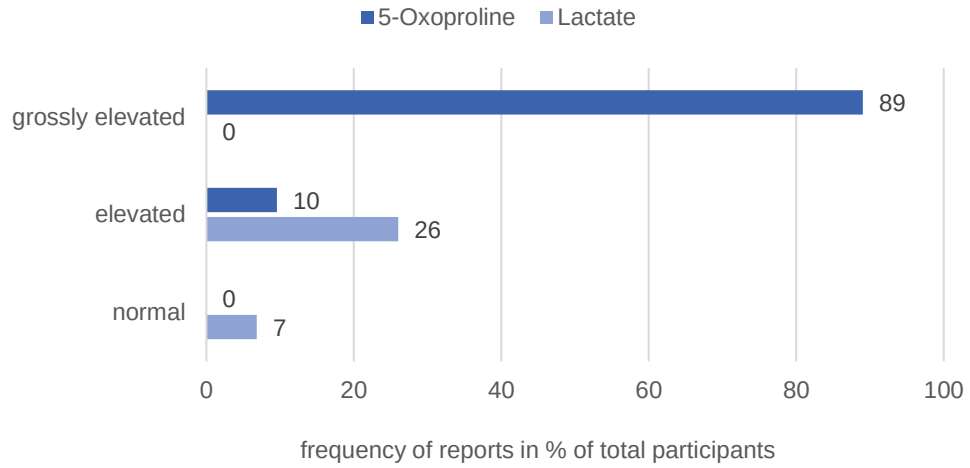
2-year-old male with anaemia and acute metabolic acidosis

The specimen was a preserved urine from a patient with confirmed glutathione synthetase (GSS) deficiency, which had also been distributed as part of the QLOU Heidelberg scheme in 2015.

Analytical performance

In the first survey (samples A – C), 73 participants out of 76 submitted results.
In the organic acid chromatogram, a clearly elevated peak for 5-oxoproline (pyroglutamic acid) can be detected and was reported as grossly elevated (n=65) or elevated (n=7) by 98.6% of the participants. Other analytes mentioned in the analytical results were elevated lactic (n=19), 3-hydroxybutyric (n=3), or pipecolic acid (n=2). Some participants also described the levels of 4-hydroxycyclohexylacetic (n=2) or 4-hydroxyphenylacetic acid (n=3) as normal in order to exclude Hawkinsinuria.

Evaluation criteria: Two points for 5-oxoproline reported as elevated or grossly elevated.



Frequency of the two most often mentioned metabolites

Diagnosis / Interpretative proficiency

GSS deficiency was given as primary diagnosis by 63 participants and indicated as alternative by five laboratories that opted for other primary diagnoses. 5-Oxoprolinase deficiency (OPLAHD) was second most frequently reported as primary diagnosis (n=11). Alternative diagnoses named were either OPLAHD (n=38) or the use of medication (n=21), e.g. paracetamol, to explain the high 5-oxoproline levels. Less frequently mentioned alternative IMD were Hawkinsinuria (n=3) or Stevens-Johnson syndrome (n=6).
One laboratory that had not detected 5-oxoproline reported an elevated level of lactate instead and described the sample as normal. This was considered a critical error by the SAB.

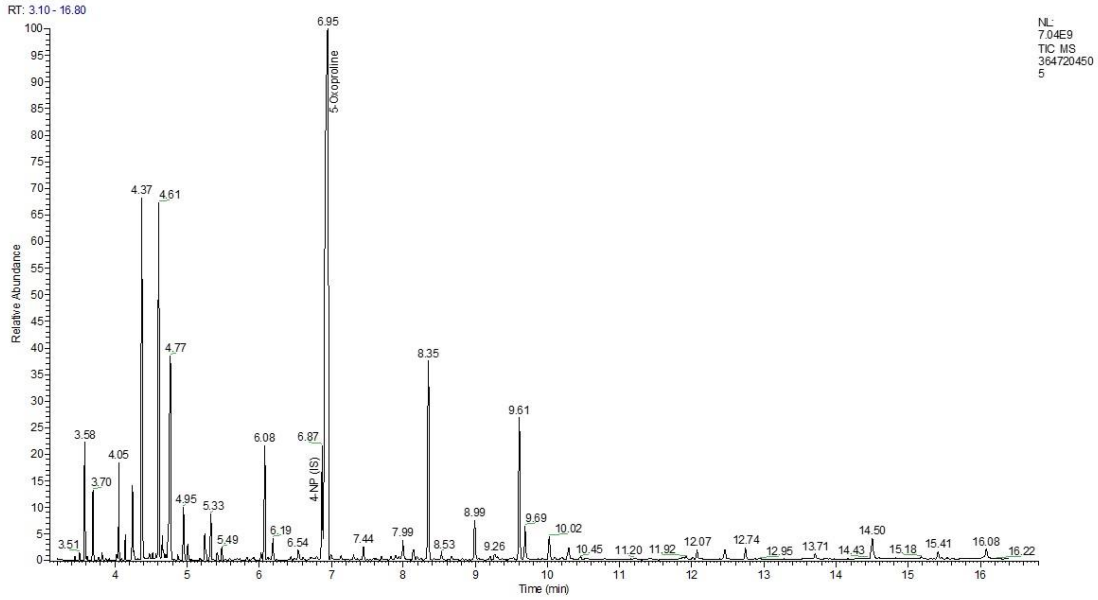
Evaluation criteria: Either GSS deficiency as principal diagnosis or as alternative providing recommendations suitable for differentiation results in 2 points.

Recommendations

In their recommendations, most participants focussed on methods to differentiate and/or support their findings. Molecular genetic analysis was most frequently mentioned (n=56) followed by measurement of enzymatic activity (n=42) and determination of glutathione in erythrocytes (n=24). Further lab tests suggested were amino acids in plasma or serum (n=7), determination of ammonia in blood (n=8), lactate in plasma (n=6 or paracetamol metabolites (n=2). Ten participants also gave recommendations on therapeutic measures.

Overall impression

The handling of this sample was straightforward for most laboratories resulting in very good analytical (99%) and interpretative (95%) proficiencies.



Example chromatogram for sample B

8.3. Patient C

Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency

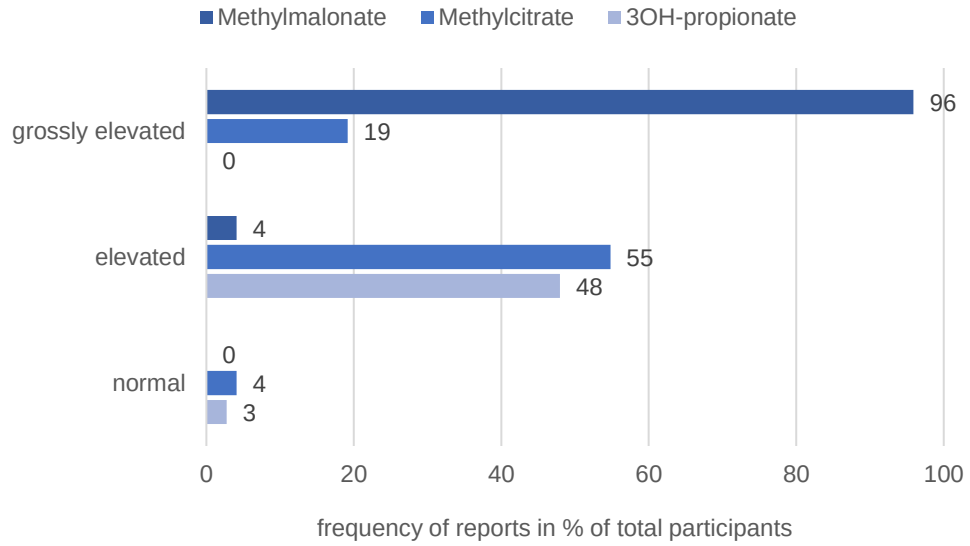
Patient details provided to participants

8-year old girl with impaired renal function after several episodes of metabolic decompensation

8-year-old girl with impaired renal function after several episodes of metabolic decompensation.
The sample originates from a patient who was diagnosed with methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency (MMA mut(0) type) as an infant in 2001. She was found to be compound heterozygous for two pathogenic variants in *MUT*.

Analytical performance

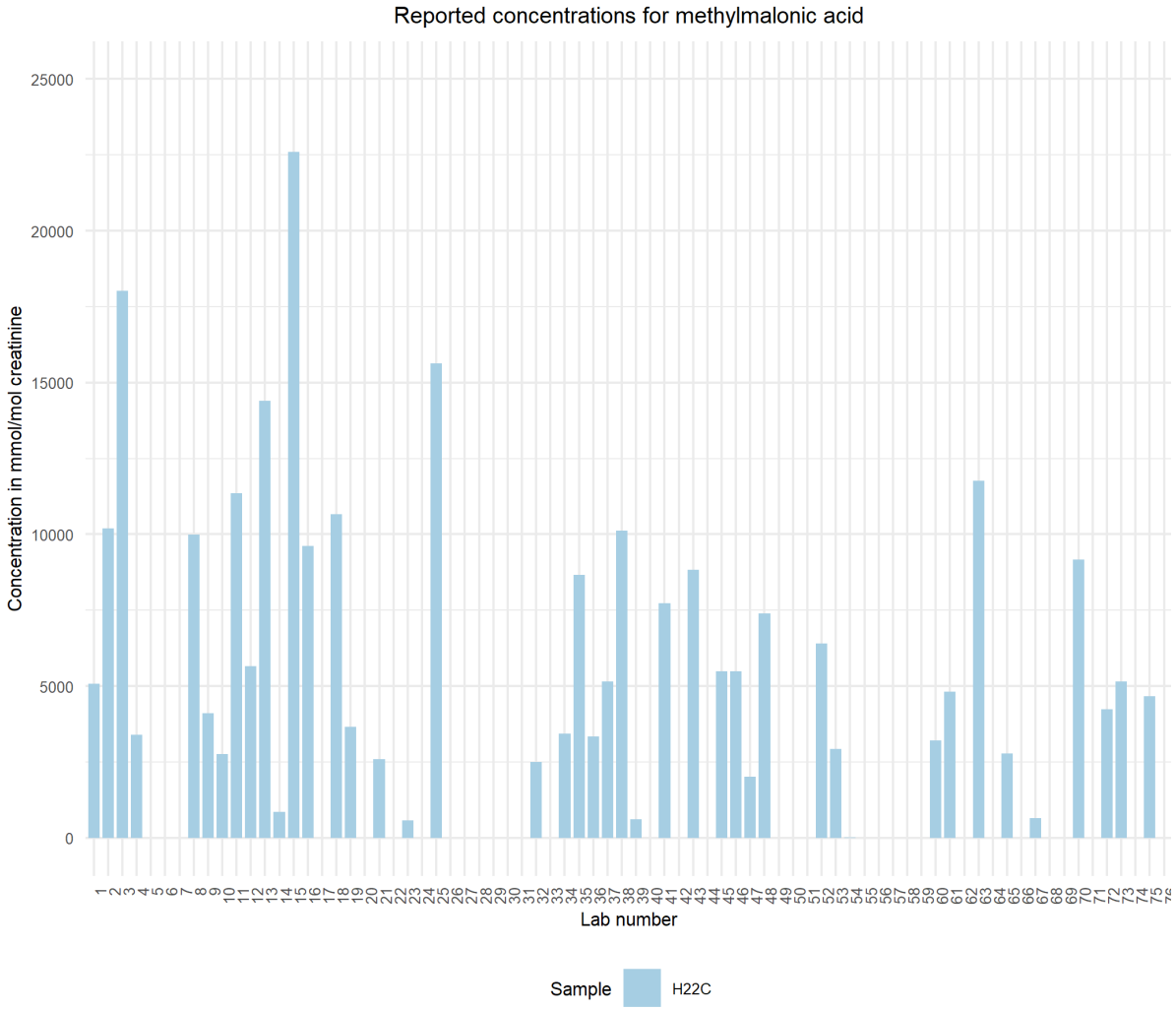
In the first survey (samples A – C), 73 participants out of 76 submitted results.
High concentrations of methylmalonic, methylcitric and 3-hydroxypropionic acids could be detected in this sample, which were also the most frequently reported analytes by the participants in this order: Methylmalonic acid (grossly elevated: n=70, elevated: n=3, 100% of participants), methylcitric acid (grossly elevated: n=14, elevated: n=40, 74% of participants), 3-hydroxypropionic acid (elevated: n=35, 47.9% of participants).



Frequency of reporting of key metabolites for sample C

Other compounds were referred to less commonly and included tiglylglycine (elevated: n=7), lactic acid (elevated: n=4, normal: n=4), orotic acid (grossly elevated: n=1, elevated: n=8), propionylglycine (grossly elevated: n=1, elevated: n=2, normal: n=1), and 3-hydroxybutyric acid (elevated: n=5).

Evaluation criteria: Methylmalonic acid reported as elevated or grossly elevated: 1 point, methylcitric and/or 3OH-propionic acid reported: 1 point



Sample	H22C
Mean	6458.68
Median	5145
SD	4865.33

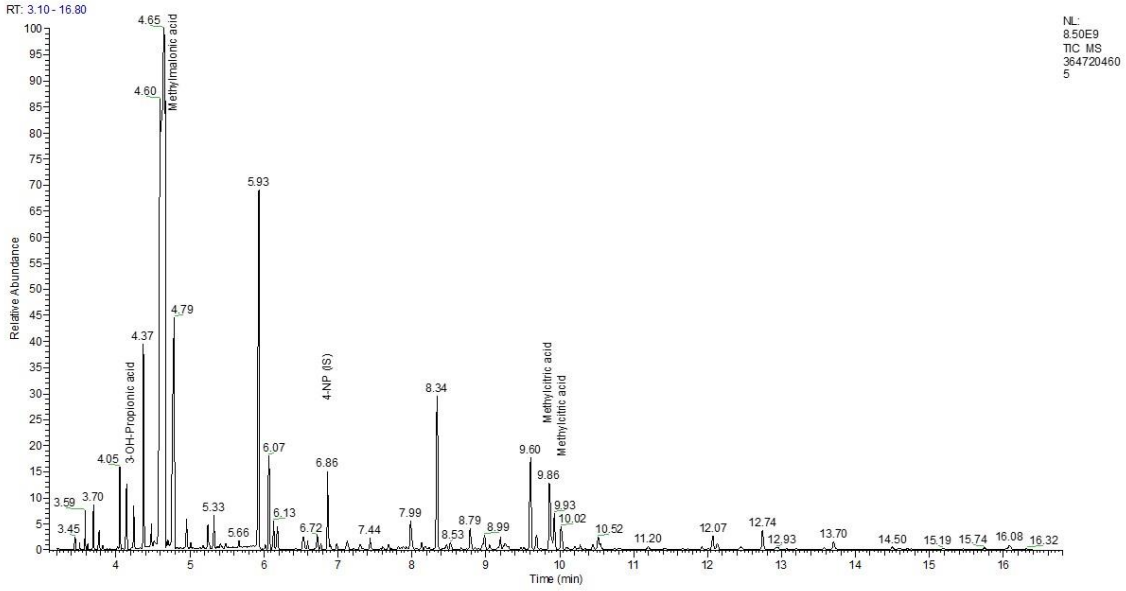
Distribution of concentrations reported by the participants for methylmalonic acid in sample C. Please note: Not all participants gave quantitative results for their findings.

Diagnosis / Interpretative proficiency
Almost all participants chose methylmalonic aciduria as their primary diagnosis and focused their recommendations on differentiating the type of MMA and on further supporting their findings.

Evaluation criteria: Either MMA as principal diagnosis or as alternative providing recommendations suitable for differentiation: 2 points

Recommendations
Consequently, the most recommended laboratory tests were molecular genetic testing (n=57), determination of homocysteine in plasma or dried blood (n=47), acyl carnitines in plasma or blood (n=43), cobalamin analysis (n=29), amino acids in plasma or serum (n=26), measurement of enzymatic activity (n=21), methylmalonic acid in plasma (n=20), basic diagnostics (n=15), and testing the patient's vitamin B_{12} responsiveness. In addition, 18 labs gave further advice on treating the patient.

Overall impression
Participants demonstrated a very good performance in the analytical (92%) and interpretative (100%) identification of MMA.



Example chromatogram for sample C

8.4. Patient D

Mevalonic aciduria due to mevalonate kinase (MVK) deficiency

Patient details provided to participants

3-year-old boy with hypotonia and cerebellar ataxia

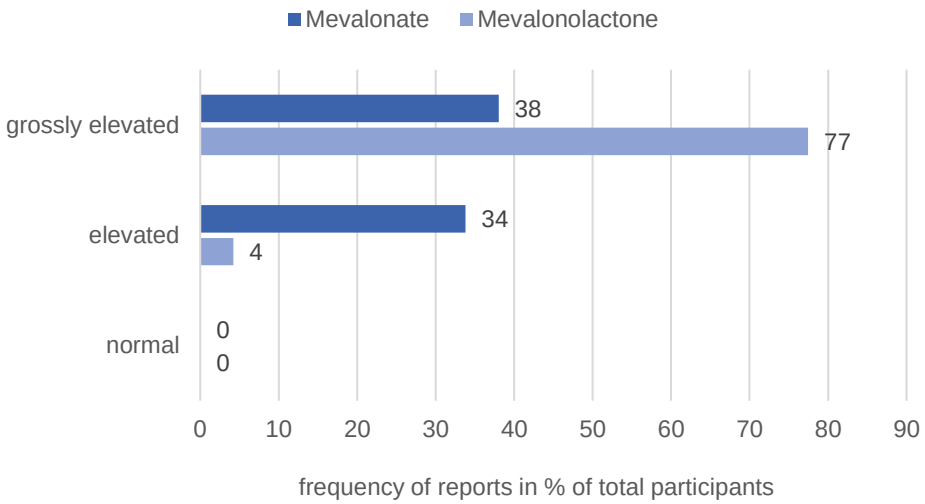
The sample originates from a patient with confirmed mevalonic aciduria. He is compound heterozygous for two variants in *MVK* and has severely reduced enzyme activity (< 1 %).

Analytical performance

In the second survey (samples D – F), 71 participants out of 76 submitted results.
The sample contains a high concentration of mevalonic acid (MVA) which can be assessed as free acid as well as in its lactone (MVAL) form.

Of the participants that submitted results, 51 reported MVA and 55 reported MVAL as elevated or grossly elevated. Here, an intersecting set of 38 labs reported for both forms of the marker.
Besides MVA and MVAL, several other substances were mentioned to be present in elevated concentrations, but less frequently, such as methylmalonic, methylglutaconic, glutaric or 3-methylglutaric acids. Malonic acid was reported as grossly elevated by one lab.

Evaluation criteria: Two points for reporting either MVA or MVAL as elevated at least.
This was achieved by all 71 labs submitting results for sample D.



Frequency of reported key metabolites for sample D
38 labs (50%) reported both forms of mevalonic acid.

Diagnosis / Interpretative proficiency

Almost all participants, submitting results chose MVK deficiency as their main diagnosis (69/71). The most frequently mentioned alternative diagnosis was Hyper-IgD syndrome (30/71).
One lab, that reported a high level of malonic acid, suggested malonic aciduria as primary diagnosis. This was regarded as critical error by the SAB.

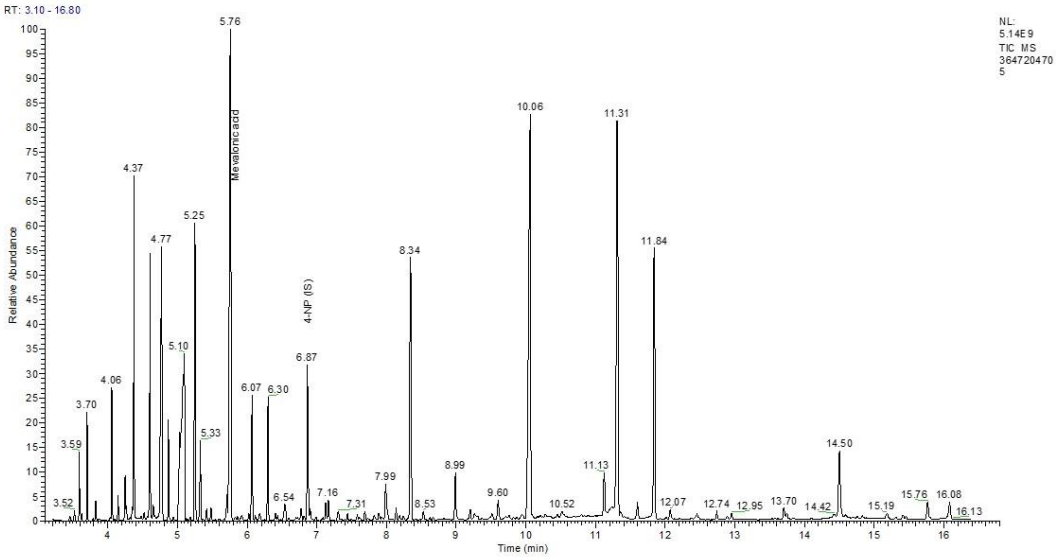
Evaluation criteria: Two points were awarded for mentioning MVK deficiency as diagnosis.

Recommendations

Most participants focused on further analyses to support their findings. They recommended e. g.: mutation analysis (*n*=62), measurements of mevalonate kinase activity (n=27), immunoglobulin D (n=24), creatine kinase (n=15), transaminases (n=14), cholesterol (n=14), or leukotrienes / prostanoides (n=11). Nine participants also recommended therapeutic measures.

Overall impression

The participants performed excellent with this sample achieving 100% analytical and 98% interpretative proficiency.



Example chromatogram for sample D

8.5. Patient E

Multiple acyl-CoA dehydrogenase (MAD) deficiency, late onset

Patient details provided to participants

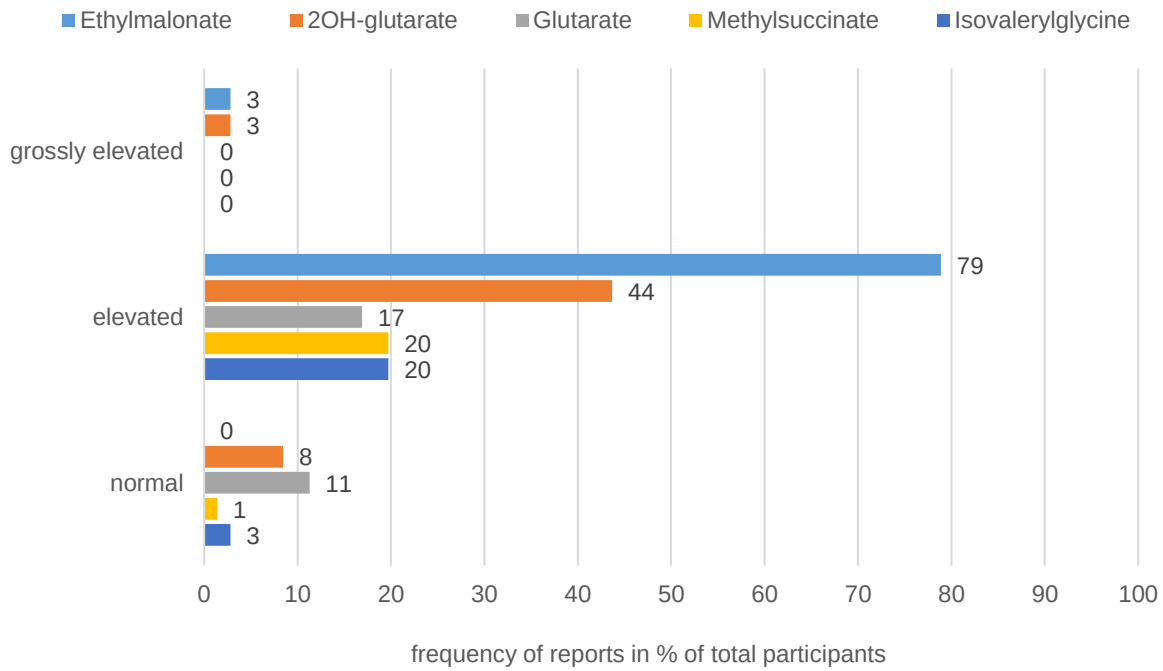
Male patient, presented at the age of 30 years with unclear myopathy. Urine collected whilst on treatment

MAD deficiency with late onset has been confirmed in this patient by genetic analysis (homozygosity for pathogenic variant in ETFDH).

Analytical performance

In the second survey (samples D – F), 71 participants out of 76 submitted results.
In this sample, only slightly elevated concentrations of indicative markers are detectable (e. g. ethylmalonic and 2-hydroxyglutaric acids), posing a challenge to the participants.
Seventy-one labs reported results. The metabolites most often mentioned by them as elevated or grossly elevated were ethylmalonic (n=58), 2-hydroxyglutaric (n=31), methylsuccinic (n=14) and glutaric acids (n=12), isobutyryl (n=14) and isovaleryl glycine (n=10).

Evaluation criteria: Reporting of ethylmalonic acid at least as elevated resulted in two points. Reporting of other relevant markers as elevated or grossly elevated yielded one point each.

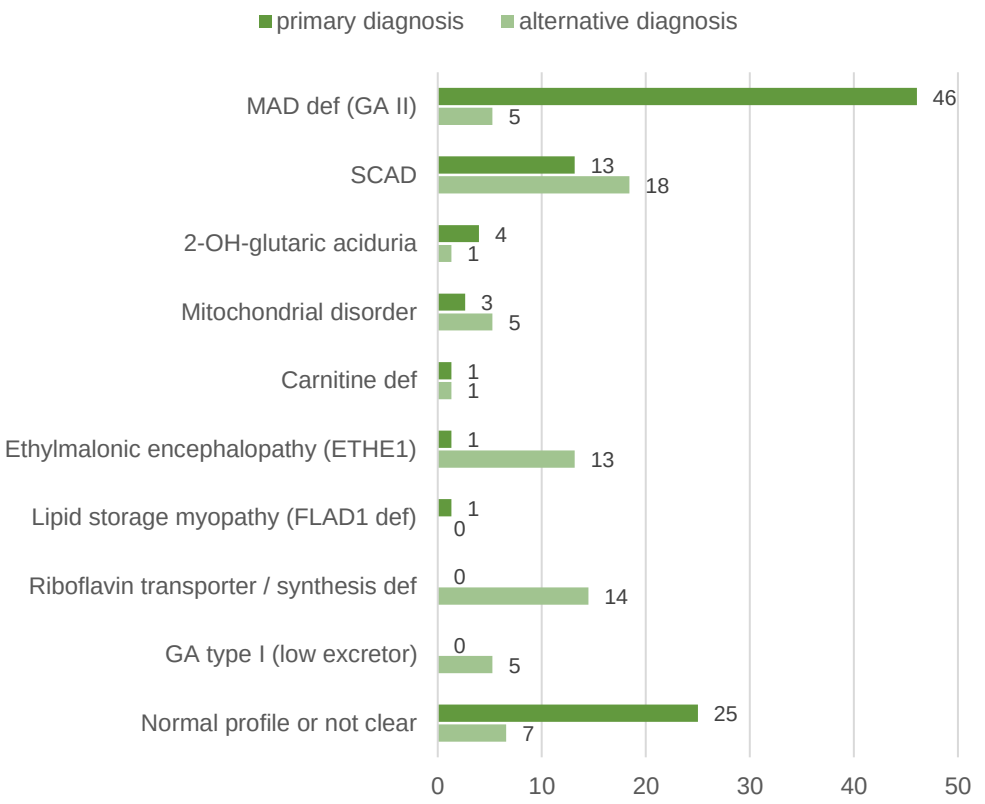


Frequency of the five most often mentioned metabolites for sample E

Diagnosis / Interpretative proficiency

Of the 71 participating labs which submitted results, roughly the half (n=35) decided for MAD deficiency as the primary diagnosis and four laboratories as alternative diagnosis. Other frequently mentioned primary or alternative diagnoses were short-chain acyl-CoA dehydrogenase deficiency (SCAD, n=24), ethylmalonic encephalopathy (EE, n=11), or riboflavin-related defects (n=11). A high share of laboratories (n=14) considered the sample not to represent a metabolic defect.

Evaluation criteria: Two points were awarded, if MAD deficiency was reported as primary diagnosis or if a diagnosis pointing to a mitochondrial disorder was considered including a recommendation for an analysis suitable to find the correct diagnosis.



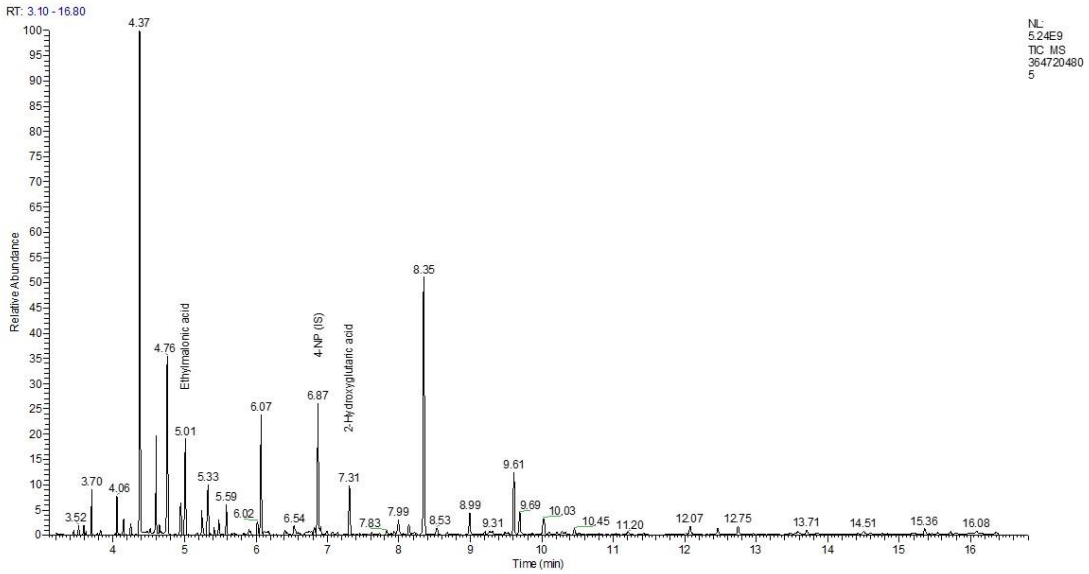
Frequency of reported primary and alternative diagnoses for sample E in % of participants

Recommendations

Most participants who opted for MAD deficiency focussed on supporting their findings with acylcarnitine analyses in plasma or dried blood (n=31) and/or mutation analysis targeting ETF genes (n=31).
Even overall, acylcarnitine (n=45) and mutation analyses (n=49) were most frequently recommended, followed by repetition of urinary organic acids (n=15), determination of amino acids in plasma or serum (n=5), and measurement of enzymatic activity (n=5). Eleven participants gave recommendations on therapeutic measures.

Overall impression

This sample was difficult because it contained only low concentrations of indicative metabolites, which moreover are individually not specific for MAD deficiency. Nevertheless, many participants suggested the correct diagnosis. The analytical and interpretative proficiencies were 85% and 74%, respectively.



Example chromatogram for sample E

8.6. Patient F

Combined malonic and methylmalonic aciduria (CMAMMA) due to Acetyl-CoA-synthase 3 (ACSF3) deficiency

Patient details provided to participants

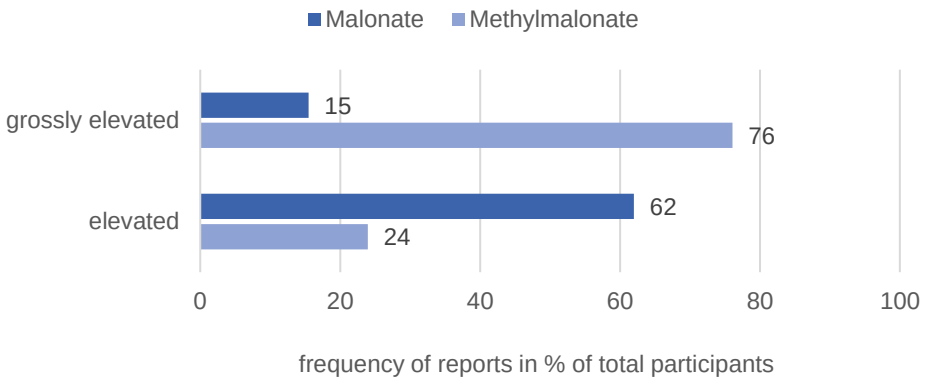
5-year old girl admitted due to global developmental delay

The sample contains considerably increased concentrations of malonic (MA) and methylmalonic acid (MMA).

Analytical performance

In the second survey (samples D – F), 71 participants out of 76 submitted results.
All participants submitting results reported MMA concentrations as elevated or grossly elevated. The MA concentrations, however, were classified as elevated or grossly elevated only by 55 laboratories. Some laboratories also mentioned methylcitric acid in their submissions and characterized its concentrations as elevated (n=3) or normal (n=6).

Evaluation criteria:
One point each is given for MA or MMA if reported (at least) as elevated.



Frequency of reported key metabolites for sample F.
Normal or low concentrations were not reported for either metabolite.

Diagnosis / Interpretative proficiency

CMAMMA was given as primary diagnosis by 49 participants and by three participants as alternative diagnosis. Even though MA was detected and reported as elevated by 55 labs, three of them did not consider CMAMMA.
The second-most mentioned primary diagnoses were variants of MMAuria (n=16).
Alternative diagnoses frequently indicated by the laboratories were other MMAurias (n=18), vitamin B_{12} dependent deficiencies (n=18) or malonyl-CoA decarboxylase deficiency (n=15).

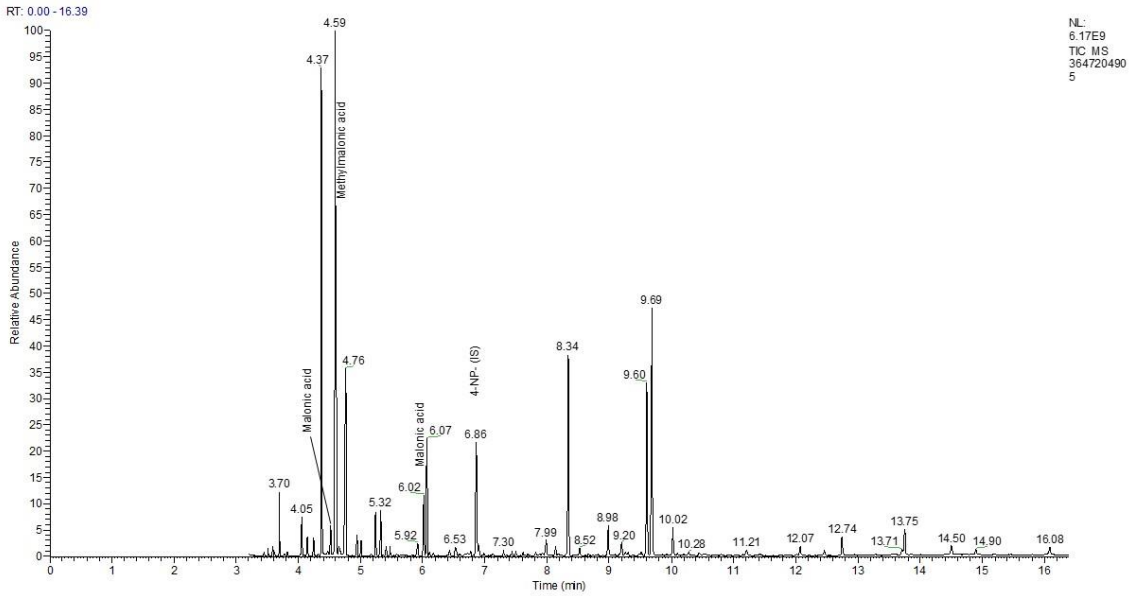
Evaluation criteria:
Two points are awarded for reporting CMAMMA as the primary diagnosis or if given as alternative diagnosis including a recommendation suitable to identify the correct diagnosis.

Recommendations

To support their findings, most participants recommended to analyse acylcarnitines (n=41) or perform genetic testing (n=54). Further specific investigations mentioned were for homocysteine (n=24), vitamin B_{12} (n=20), or MMA (n=15) in plasma.

Overall impression

The majority of laboratories clearly detected both key metabolites. However, it seems that several participants had problems with characterizing the malonic acid concentration, which misdirected their interpretation. The analytical proficiency was 89% while the interpretative proficiency resulted in 80%.



Example chromatogram for sample F

9. Scores of participants

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

9.1. Detailed scores – Round 1

Lab n°	Patient A Normal control			Patient B 5-Oxoprolinuria due to GSSD			Patient C Methylmalonic aciduria, mut(0) type			
	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	2	4	2	2	4	12
3	2	2	4	0	0	0	2	2	4	8
4	2	2	4	2	2	4	1	2	3	11
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	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
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	2	2	4	2	2	4	12
22	2	2	4	2	2	4	1	2	3	11
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	2	4	2	2	4	12

Lab n°	Patient A Normal control			Patient B 5-Oxoprolinuria due to GSSD			Patient C Methylmalonic aciduria, mut(0) type			
	A	I	Total	A	I	Total	A	I	Total	Total
28	2	2	4	2	2	4	2	2	4	12
29	2	2	4	2	2	4	2	2	4	12
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	2	4	2	2	4	12
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	2	4	2	2	4	12
38	0	0	0	2	2	4	1	2	3	7
39	2	2	4	2	2	4	2	2	4	12
40	2	2	4	2	2	4	1	2	3	11
41	2	2	4	2	2	4	2	2	4	12
42	0	0	0	2	2	4	2	2	4	8
43	2	2	4	2	2	4	2	2	4	12
44	2	2	4	2	2	4	2	2	4	12
45	2	2	4	2	2	4	2	2	4	12
46	2	2	4	2	1	3	1	2	3	10
47	2	2	4	2	2	4	1	2	3	11
48	2	2	4	2	2	4	1	2	3	11
49	2	2	4	2	2	4	2	2	4	12
50	2	2	4	2	0	2	2	2	4	10
51	2	2	4	2	2	4	2	2	4	12
52	2	2	4	2	2	4	2	2	4	12
53	2	2	4	2	2	4	2	2	4	12
54	2	2	4	2	2	4	2	2	4	12
55	2	2	4	2	2	4	1	2	3	11
56	2	2	4	2	2	4	2	2	4	12
57	2	2	4	2	2	4	2	2	4	12
58	2	2	4	2	2	4	2	2	4	12
59	2	2	4	2	2	4	2	2	4	12

Lab n°	Patient A Normal control			Patient B 5-Oxoprolinuria due to GSSD			Patient C Methylmalonic aciduria, mut(0) type			
	A	**I**	**Total**	**A**	**I**	**Total**	**A**	**I**	**Total**	**Total**
60	2	2	4	2	1	3	1	2	3	10
61	2	2	4	2	1	3	1	2	3	10
62	2	2	4	2	2	4	2	2	4	12
63	2	2	4	2	2	4	2	2	4	12
64	2	2	4	2	2	4	2	2	4	12
65	0	0	0	2	2	4	1	2	3	7
66	--	--	--	--	--	--	--	--	--	0
67	2	2	4	2	2	4	2	2	4	12
68	2	2	4	2	2	4	1	2	3	11
69	2	2	4	2	2	4	2	2	4	12
70	2	2	4	2	2	4	2	2	4	12
71	2	2	4	2	2	4	2	2	4	12
72	2	2	4	2	2	4	2	2	4	12
73	2	2	4	2	2	4	2	2	4	12
74	--	--	--	--	--	--	--	--	--	0
75	2	2	4	2	2	4	2	2	4	12
76	--	--	--	--	--	--	--	--	--	0

9.2. Round 2

Lab n°	Patient D Mevalonic aciduria			Patient E MAD deficiency			Patient F Combined malonic and methylmalonic aciduria			
	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	1	3	2	0	2	9
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	--	--	--	--	--	--	--	--	--	0
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	1	1	2	1	0	1	7
13	2	2	4	2	2	4	1	1	2	10
14	2	2	4	2	2	4	2	2	4	12
15	2	2	4	0	0	0	2	2	4	8
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	0	0	0	2	2	4	8
20	2	1	3	2	2	4	2	2	4	11
21	2	2	4	2	2	4	1	1	2	10
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	1	1	2	10
25	2	2	4	2	2	4	2	2	4	12
26	2	2	4	2	1	3	2	2	4	11
27	2	2	4	0	0	0	1	0	1	5
28	2	2	4	2	2	4	2	2	4	12
29	2	2	4	2	2	4	1	1	2	10
30	2	2	4	2	0	2	2	2	4	10

Lab n°	Patient D Mevalonic aciduria			Patient E MAD deficiency			Patient F Combined malonic and methylmalonic aciduria			
	A	I	Total	A	I	Total	A	I	Total	Total
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	1	1	2	10
34	2	2	4	2	2	4	2	2	4	12
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	2	4	2	2	4	12
38	2	2	4	2	0	2	2	2	4	10
39	2	2	4	2	2	4	2	2	4	12
40	2	2	4	0	0	0	1	0	1	5
41	2	2	4	2	2	4	2	2	4	12
42	2	2	4	2	0	2	2	2	4	10
43	2	2	4	1	0	1	2	2	4	9
44	2	2	4	2	1	3	2	2	4	11
45	2	2	4	2	1	3	2	2	4	11
46	2	2	4	0	0	0	1	1	2	6
47	2	2	4	0	0	0	1	0	1	5
48	2	2	4	1	2	3	1	1	2	9
49	2	2	4	2	0	2	2	2	4	10
50	2	2	4	2	2	4	2	2	4	12
51	2	2	4	2	2	4	1	0	1	9
52	2	2	4	2	2	4	2	2	4	12
53	2	2	4	2	2	4	2	2	4	12
54	2	2	4	0	0	0	2	2	4	8
55	2	2	4	2	2	4	2	2	4	12
56	2	2	4	2	2	4	2	2	4	12
57	2	2	4	2	2	4	2	2	4	12
58	--	--	--	--	--	--	--	--	--	0
59	2	2	4	1	1	2	2	2	4	10
60	2	2	4	2	2	4	2	2	4	12
61	2	2	4	2	2	4	2	2	4	12
62	2	2	4	2	0	2	1	0	1	7

Lab n°	Patient D Mevalonic aciduria			Patient E MAD deficiency			Patient F Combined malonic and methylmalonic aciduria			
	A	I	Total	A	I	Total	A	I	Total	Total
63	2	2	4	0	0	0	2	0	2	6
64	2	2	4	2	2	4	2	2	4	12
65	2	0	2	2	2	4	2	2	4	10
66	--	--	--	--	--	--	--	--	--	0
67	2	2	4	2	2	4	2	2	4	12
68	2	2	4	2	2	4	2	2	4	12
69	2	2	4	2	1	3	2	2	4	11
70	2	2	4	2	2	4	2	2	4	12
71	2	2	4	2	2	4	1	0	1	9
72	2	2	4	0	0	0	1	0	1	5
73	2	2	4	2	2	4	1	1	2	10
74	--	--	--	--	--	--	--	--	--	0
75	2	2	4	2	2	4	2	2	4	12
76	--	--	--	--	--	--	--	--	--	0

9.3. Total scores

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score in %	Critical error
1	4	4	4	4	4	4	24	100	
2	4	4	4	4	3	2	21	88	
3	4	0	4	4	4	4	20	83	CE
4	4	4	3	4	4	4	23	96	
5	4	4	4	4	4	4	24	100	
6	4	4	4	4	4	4	24	100	
7	4	4	4	4	4	4	24	100	
8	4	4	4	4	4	4	24	100	
9	4	4	4	--	--	--	12	50	
10	4	4	4	4	4	4	24	100	
11	4	4	4	4	4	4	24	100	
12	4	4	4	4	2	1	19	79	
13	4	4	4	4	4	2	22	92	
14	4	4	4	4	4	4	24	100	
15	4	4	4	4	0	4	20	83	
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	0	4	20	83	
20	4	4	4	3	4	4	23	96	
21	4	4	4	4	4	2	22	92	
22	4	4	3	4	4	4	23	96	
23	4	4	4	4	4	4	24	100	
24	4	4	4	4	4	2	22	92	
25	4	4	4	4	4	4	24	100	
26	4	4	4	4	3	4	23	96	
27	4	4	4	4	0	1	17	71	
28	4	4	4	4	4	4	24	100	
29	4	4	4	4	4	2	22	92	
30	4	4	4	4	2	4	22	92	
31	4	4	4	4	4	4	24	100	
32	4	4	4	4	4	4	24	100	
33	4	4	4	4	4	2	22	92	

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score in %	Critical error
34	4	4	4	4	4	4	24	100	
35	4	4	4	4	4	4	24	100	
36	4	4	4	4	4	4	24	100	
37	4	4	4	4	4	4	24	100	
38	0	4	3	4	2	4	17	71	
39	4	4	4	4	4	4	24	100	
40	4	4	3	4	0	1	16	67	
41	4	4	4	4	4	4	24	100	
42	0	4	4	4	2	4	18	75	
43	4	4	4	4	1	4	21	88	
44	4	4	4	4	3	4	23	96	
45	4	4	4	4	3	4	23	96	
46	4	3	3	4	0	2	16	67	
47	4	4	3	4	0	1	16	67	
48	4	4	3	4	3	2	20	83	
49	4	4	4	4	2	4	22	92	
50	4	2	4	4	4	4	22	92	
51	4	4	4	4	4	1	21	88	
52	4	4	4	4	4	4	24	100	
53	4	4	4	4	4	4	24	100	
54	4	4	4	4	0	4	20	83	
55	4	4	3	4	4	4	23	96	
56	4	4	4	4	4	4	24	100	
57	4	4	4	4	4	4	24	100	
58	4	4	4	--	--	--	12	50	
59	4	4	4	4	2	4	22	92	
60	4	3	3	4	4	4	22	92	
61	4	3	3	4	4	4	22	92	
62	4	4	4	4	2	1	19	79	
63	4	4	4	4	0	2	18	75	
64	4	4	4	4	4	4	24	100	
65	0	4	3	2	4	4	17	71	CE
66	--	--	--	--	--	--	0	0	
67	4	4	4	4	4	4	24	100	

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score in %	Critical error
68	4	4	3	4	4	4	23	96	
69	4	4	4	4	3	4	23	96	
70	4	4	4	4	4	4	24	100	
71	4	4	4	4	4	1	21	88	
72	4	4	4	4	0	1	17	71	
73	4	4	4	4	4	2	22	92	
74	--	--	--	--	--	--	0	0	
75	4	4	4	4	4	4	24	100	
76	--	--	--	--	--	--	0	0	

Performance

	Number of labs	% total labs
Satisfactory performers (≥ 71 % of adequate responses)	66	87
Unsatisfactory performers (< 71 % adequate responses and/or critical error)	5	7
Partial and non-submitters	5	7

Overall Proficiency

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Total (%)
QLOU-DH-2022-A	Normal control	96	96	96
QLOU-DH-2022-B	5-Oxoprolinuria due to GSSD	99	95	97
QLOU-DH-2022-C	Methylmalonic aciduria, mut(0) type	92	100	96
QLOU-DH-2022-D	Mevalonic aciduria	100	98	99
QLOU-DH-2022-E	MAD deficiency	85	74	79
QLOU-DH-2022-F	Combined malonic and methylmalonic aciduria	89	80	85

10. ERNDIM certificate of participation

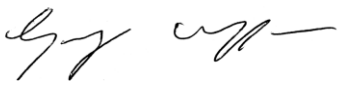
A combined certificate of participation covering all EQA schemes will be provided to all participants who take part in any ERNDIM scheme. For the QLOU scheme this certificate will indicate if results were submitted and whether satisfactory performance was achieved in the scheme.

Date of report, 2023-07-20
Name and signature of Scientific Advisor

Dr. J. Janda
Scientific Advisor
Laboratory of Metabolic Diseases

Prof. Dr. V. Peters

Laboratory of Metabolic Diseases



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

To be able to continue this scheme, we need a steady supply of new patient samples. Several laboratories have donated urine samples to the QLOU scheme in the past, for which they are gratefully acknowledged. If you are able to collect one or more samples 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 QLOU scheme in the following year.

Please note:
This annual report is intended for participants of the ERNDIM QLOU 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	27 March 2023	2022 annual report published

END