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Qualitative Organic Acids

Centre: Spain

Final Report 2023

prepared by
Dr. Judit García Villoria

Note: This annual report is intended for participants of the ERNDIM QLOU Barcelona scheme. The contents should not be used for any publication without permission of the Scientific Advisor. The fact that your laboratory participates in ERNDIM schemes is not confidential, however, the raw data and performance scores are confidential and will only be shared within ERNDIM for the purpose of evaluating your laboratories performance, unless ERNDIM is required to disclose performance data by a relevant government agency. For details please see the terms and conditions on page18 and the ERNDIM Privacy Policy on www.erndim.org.

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 Judit Garcia Barcelona Scheme in conjunction with CSCQ, the Swiss organisation for quality assurance in medical laboratories both appointed by and according to procedures laid down the ERNDIM Board.

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.

In 2023 78 laboratories from many different countries participated in the QLOU Barcelona scheme, without any educational participants (0 in 2022, 2 in 2021). 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.

[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.

Participants and new applicants will 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.

2. Geographical distribution of participants

There are 77 participants (1 lab withdrawn) with the followed geographic distribution:

Country	*Number of laboratories*		*Country*	*Number of laboratories*
France	21		Colombia	1
Italy	14		Cyprus	1
Spain	12		Greece	1
Hong Kong	5		Lebanon	1
India	5		Philippines	1
Argentina	3		Qatar	1
Brazil	2		Saudi Arabia	1
Germany	2		Singapore	1
Portugal	2		Turkey	1
Chile	1		Uruguay	1
China	1		TOTAL	78

3. Design and logistics of the scheme including sample information

The scheme has been designed and planned by Judit García Villoria as Scientific Advisor and coordinated by CSCQ, both appointed by and according to procedures laid down the ERNDIM Board. As usual, the samples used in 2021 were authentic human urine samples, 5 from affected patients and 1 from healthy individuals. In 2022 CSCQ dispatched the QLOU 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

Labelled copies of chromatograms can be uploaded on the CSCQ website.

2 surveys	Round 1: patients A, B and C
	Round 2: patients D, E and F

Origin of patients: Urine samples have been provided by the scheme organisers: Dr. Judit García Villoria (Hospital Clínic de Barcelona, Spain) and Mrs. Camilla Scott (Sheffield, UK), or donated by the following participants: Dr. Gerardo Perez (Hospital Son Espases Palma de Mallorca, Spain), Dr. María Machado (BPS Laboratorio de Pesquisa Neonatal, Montevideo, Uruguay)

All samples selected by the Scientific Advisor have been heat-treated and were tested for suitability in the Scientific Advisor's laboratory. Mailing: samples were sent by DHL; FedEx or the Swiss Post at room temperature.

To be able to continue this scheme we need a steady supply of new patient samples. Several laboratories have donated samples to the Urine QLOU 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 QLOU scheme in the following year

4. Tests

Required method is the determination of organic acids

5. Schedule of the scheme

- Febrary 8, 2023: shipment of samples of Survey 1 and Survey 2

- May 9, 2023: analysis start, clinical data available and submission availability in the website (Survey 1)
- May 30, 2023: deadline for result submission (Survey 1)
- August 15, 2023: interim report of Survey 1 available in the website
- August 29, 2023: analysis start, clinical data available and submission availability in the website (Survey 2)
- September 19, 2023: deadline for result submission (Survey 2)
- November 15, 2023: interim report of Survey 2 available in the website
- March, 2024: annual report

6. Results

	Survey 1	Survey 2
Receipt of results	75	74
No answer	3	4

7. Web site reporting

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

- Selection of tests: **don't 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 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.**
- 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.

8. Scoring and evaluation of results

Information regarding procedures for establishment of assigned values, statistical analysis, interpretation of statistical analysis etc. can be found in generic documents on the ERNDIM website.
The scoring system has been established by the International Scientific Advisory Board of ERNDIM. Two criteria are evaluated: 1) analytical performance, 2) interpretative proficiency also considering recommendations for further investigations.

A	Analytical performance	Correct results of the appropriate tests	2
		Partially correct or non-standard methods	1
		Unsatisfactory or misleading	0
I	Interpretative proficiency & Recommendations	Good (diagnosis was established)	2
		Helpful but incomplete	1
		Misleading or wrong diagnosis	0

The total score is calculated as a sum of these two criteria. The maximum to be achieved is 4 points per sample. The scores were calculated only for laboratories submitting results.

Scoring and certificate of participation: scoring is carried by a second assessor who changes every year as well as by the scientific advisor. The results of QLOU Barcelona 2022 have been also scored by Dr Joachim Janda, from QLOU Heidelberg. At the SAB meeting in 30th November and 1th Desember, the definitive scores have been finalized. The concept of critical error was introduced in 2014. A critical error

is defined as an error resulting from seriously misleading analytical findings and /or interpretations with serious clinical consequences for the patient. Thus labs failing to make a correct diagnosis of a sample considered as eligible for this category will be deemed not to have reached a satisfactory performance even if their total points for the year exceed the limit set at the SAB. For 2023, the SAB decided that sample A has to be considered as a critical error for the labs who failed to identify an increase of hexanoylglycine, suberylglycine and phenylpropionylglycine and not give the diagnosis of medium chain acyl-CoA dehydrogenase (MCAD) deficiency, and not provide any further recommendations to rule out it. Also SAB decided that sample D has to be considered as a critical error for the labs who failed to identify increase of 3-hydroxy-3-methylglutarate and the diagnosis of 3-hydroxy-3-methylglutaryl-CoA lyase deficiency, and not provide any further recommendations to rule out it. The sample E also was considered as critical error if no diagnosis of L-2-hydroxyglutaric aciduria was given and the diagnosis was reported as multiple acyl-CoA dehydrogenase without further recommendations to rule out it.

A certificate of participation will be issued for participation and it will be additionally notified whether the participant has received a performance support letter. This performance support letter is sent out if the performance is evaluated as unsatisfactory. Nine performance support letters will be sent by the Scheme Advisor for 2023. Any partial submitters will receive a letter from the ERNDIM Executive Administrator, Sara Gardner.

8.1. Score for satisfactory performance

At least 17 points from the maximum of 24 (71%).

If your laboratory is assigned poor performance and you wish to appeal against this classification please email the ERNDIM Administration Office (erndim@mft.nhs.uk), with full details of the reason for your appeal, within one month receiving your Performance Support Letter.

9. Results of samples and evaluation of reporting

9.1. Patient A

Medium chain acyl-CoA dehydrogenase (MCAD) deficiency

Patient details provided to participants

Patient under treatment, currently well and diagnosed by newborn screening.

Patient details

The urine sample is from a patient diagnosed of medium chain acyl-CoA dehydrogenase (MCAD) deficiency by newborn screening. Currently, the patient is 13 year old patient and is well. Pathological excretion of hexanoylglycine, suberylglycine and phenylpropionylglycine is observed in the organic acids profile, being a characteristic profile of MCAD deficiency.

Analytical performance

-75 laboratories of 78 active participants submitted results for sample A.
-Regarding key metabolites 84% of the participants detected high excretion of hexanoylglycine. 73 % of laboratories reported an increase of suberylglycine and only 63% of participants found elevated amounts of phenylpropionylglycine, for this reason the mass spectrum of phenylpropionylglycine is provided.
-One lab reported increased levels of propionylglycine and glycine.
-Four participants reported no alterations in the profile.

Diagnosis / Interpretative proficiency

-The 66 laboratories (88%) of the participants reported medium chain acyl-CoA dehydrogenase (MCAD) deficiency as the correct diagnosis.
-Two participants gave the diagnosis of multiple acyl-CoA dehydrogenase deficiency (MAD), but only one of them recommended analyzing acylcarnitines. MAD deficiency is considered unlikely because no other metabolites like ethylmalonic acid, isovalerylglycine, isobutyrylglycine, or 2-methylbutyrylglycine were found. In addition, the presence of phenylpropionylglycine is common in infantile/adults patients of MCAD.
-Two laboratories reported the diagnosis of propionic acidemia, one of them reported high levels of phenylpropionylglycine and the other high amounts of 3-hydroxiporionic acid.
- Five laboratories reported as normal sample.

Recommendations

The majority of participants recommended performing acylcarnitine analysis in DBS or plasma, and ACADM gene analysis. Many labs also suggest the measurement of MCAD activity in leukocytes.

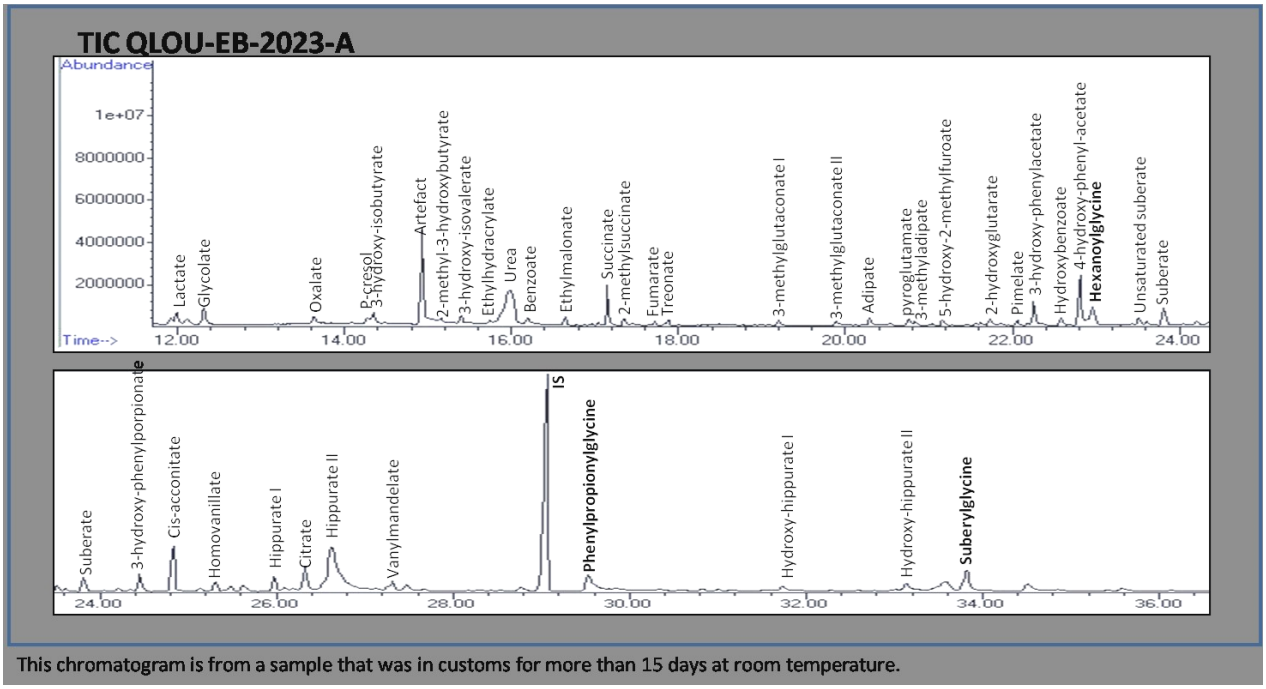
Scoring

- Analytical results: 2 points are given for the detection of at least two characteristic acylglycines. 1 point is given if only the increase of one acylglycine is reported.
- Interpretation of results: 2 points are given for the diagnosis of medium chain acyl-CoA dehydrogenase (MCAD) deficiency as first or alternative diagnosis. 1 point is given for MAD diagnosis and in the recommendations the study of acylcarnitines is specified.
- CRITICAL ERRORS: 4 labs that reported as normal sample without any recommendation.

Overall impression

The overall performance was 87%.

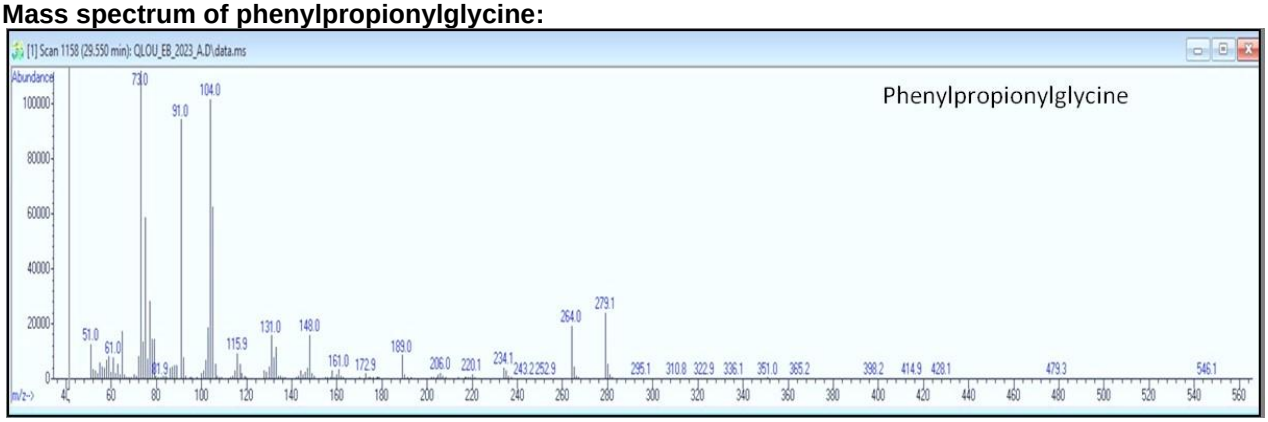
Chromatogram sample A:



This chromatogram is from a sample that was in customs for more than 15 days at room temperature.

Organic acids in urine were extracted with ethylacetate without oximation. After solvent evaporation TMS derivatization with bis-trimethylsilyl-trifluoroacetamide (BSTFA) was performed. The organic acids were analyzed by GC-MS using the 60 m x 0.25 mm ID HP-5MS capillary column.

Mass spectrum of phenylpropionylglycine:



9.2. Patient B

Normal sample

Patient details provided to participants

Autistic features. Actually pregnant

Patient details

The urine sample was collected from a voluntary individual. No abnormalities were detected in the organic acid profile.

Analytical performance

-75 laboratories of 78 active participants submitted results for sample B.
-98% of laboratories no specific abnormalities were detected in organic acid profile.
Only 22 laboratories reported the normal profile in the correct place in the key metabolite table.
-One laboratory detected high amounts of 3-hydroxipropionic and methyl-citric acids.

Diagnosis / Interpretative proficiency

-97% of participants reported as normal sample.
-One laboratory gave the diagnosis of propionic acidemia and another lab reported ketosis.

Recommendations

Most of the laboratories recommended measuring ammonia, amino acids, acylcarnitines, homocysteine, creatine and guanidinoacetate, purine and pyrimidines, and ruling out peroxisomal, lysosomal, and CDG defects.

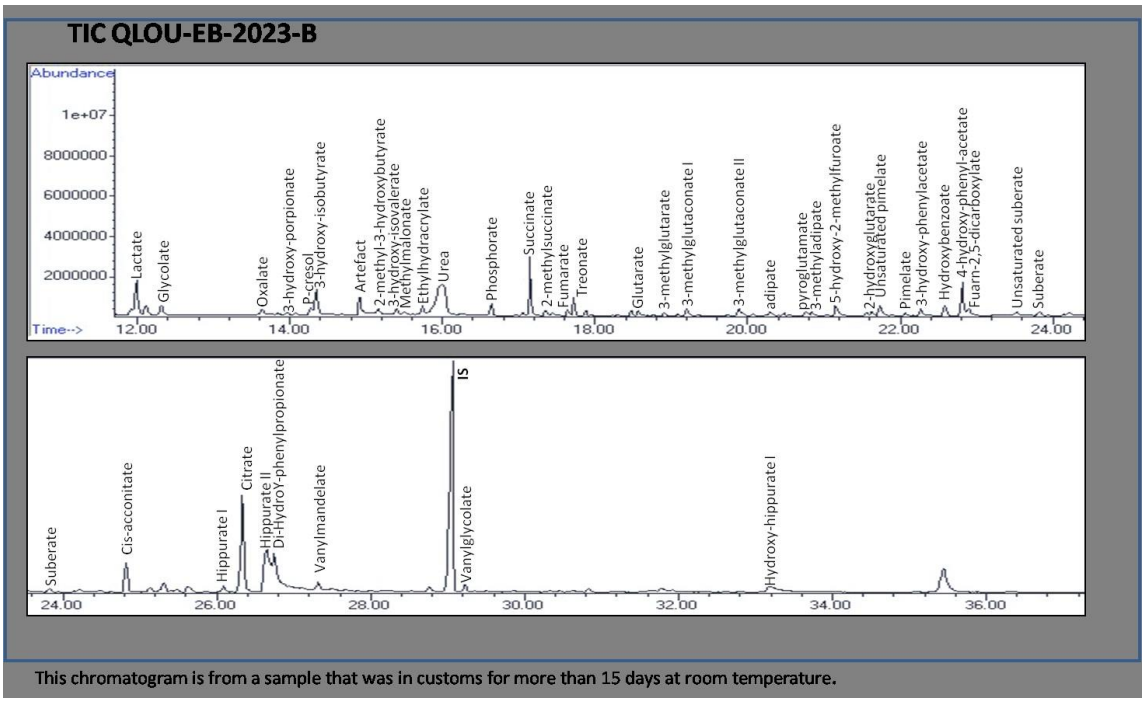
Scoring

- Analytical results: 2 points are given reporting normal profile
- Interpretation of results: 2 points are given for interpretation of normal sample.

Overall impression

The overall performance was 98%

Chromatogram sample B:



Organic acids in urine were extracted with ethylacetate without oximation. After solvent evaporation TMS derivatization with bis-trimethylsilyl-trifluoroacetamide (BSTFA) was performed. The organic acids were analyzed by GC-MS using the 60 m x 0.25 mm ID HP-5MS capillary column.

9.3. Patient C

Mevalonate kinase deficiency

Patient details provided to participants

Urine sample collected at 21 years old under treatment. Since the age of 2,5 years the patient began to experience recurrent episodes oh headache, hypotonia, vomiting, axial ataxia and vegetative symptoms.

Patient details

The urine sample is from a patient diagnosed of mevalonate kinase deficiency at 7 years of age. The patient at 2.5 years of age began to experience recurrent episodes oh headache, hypotonia, vomiting, axial ataxia and vegetative symptoms. The sample was collected at 21 years of age, under carnitine and CoQ10 supplementation. The organic acid profile shows the typical pattern of this disease with elevated excretion of mevalonate lactone, mevalonate and unsaturated mevalonate. Molecular study revealed bi-allelic mutations in MVK gene.

Analytical performance

-76 laboratories of 78 active participants submitted results for sample C.
-All the participants, 76 (100%) , reported elevated excretion of mevalonate lactone or mevalonate. 93% detected high amounts of mevalonate lactone, 53% of laboratories reported increase of mevalonic acid levels and only the 8% identified increased unsaturated mevalonate levels. In order to differentiate between the 3 metabolites the mass spectra of them are included at the end of the report.

Diagnosis / Interpretative proficiency

-75 laboratories (99%) reported the correct mevalonate kinase deficiency diagnosis.
- One laboratory established the diagnosis of hyper-IgD syndrome without any other alternative diagnosis.

Recommendations

The majorty of participants recommended to perform analysis of MVK gene, measurement of the mevalonate kinase activity in fibroblasts, lymphocytes or lymphoblasts and measurement of serum immunoglobulins test (IgD AND IgA), transaminases, ck , cholesterol, leukotrienes, prostanoids, and ubiquinone.

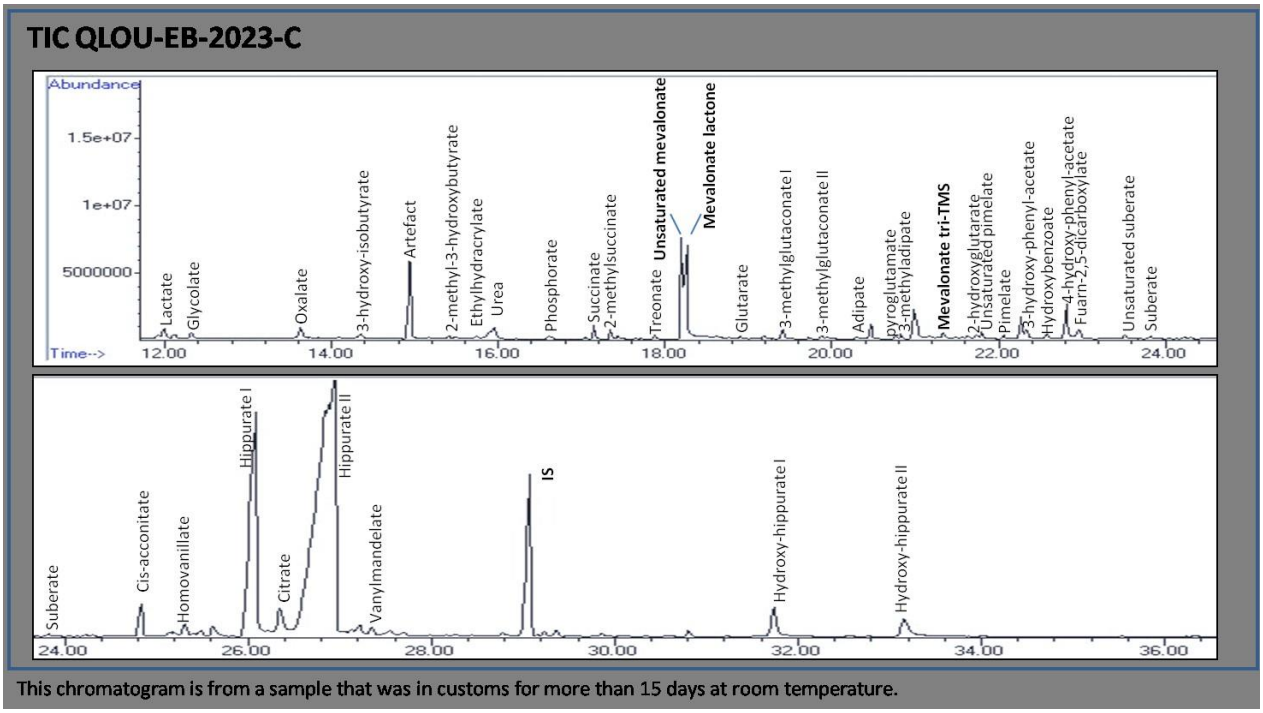
Scoring

- Analytical results: 2 points for the detection of the increase of mevalonate lactone and/or mevalonate
- Interpretation of results: 2 points for the correct diagnosis of mevalonate kinase deficiency or hyper-IgD syndrome and recommendation of MKV gene analysis.

Overall impression

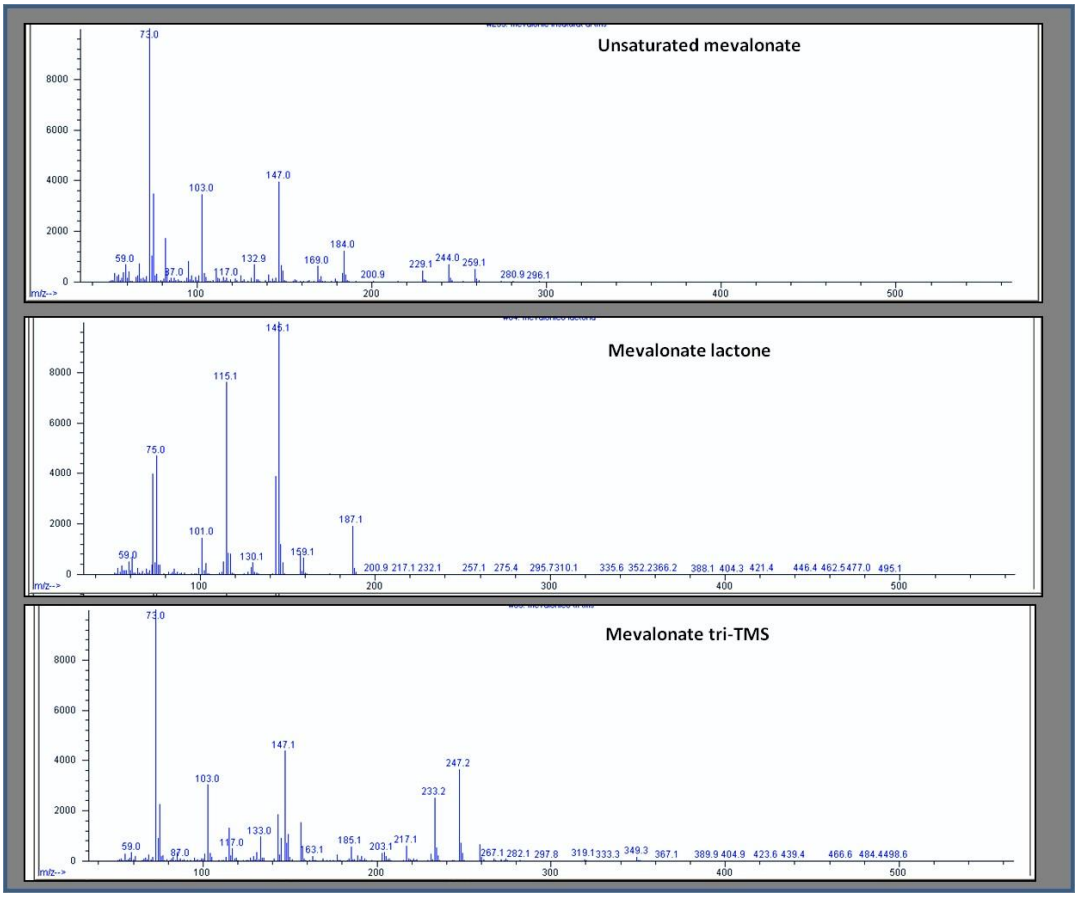
The overall performance was 99%.

Chromatogram sample C:



Organic acids in urine were extracted with ethylacetate without oximation. After solvent evaporation TMS derivatization with bis-trimethylsilyl-trifluoroacetamide (BSTFA) was performed. The organic acids were analyzed by GC-MS using the 60 m x 0.25 mm ID HP-5MS capillary column.

Mass spectrum forms of different forms of mevalonate:



9.4. Patient D

3-hydroxy-3-methylglutaryl-CoA lyase deficiency

Patient details provided to participants

Female diagnosed at 8 months of age when she had a severe viral infection, diarrhoea, vomiting, metabolic acidosis and hypoglycemia. At present she is under treatment.

Patient details

The sample was from a patient diagnosed of 3-hydroxy-3-methylglutaryl-CoA lyase deficiency at 8 months of age, when she had severe viral infection with diarrhea and vomiting. Metabolic acidosis and hypoglycemia without ketone bodies was detected on admission and the urine organic acid showed a profile consistent with this disease. On molecular study, two different pathogenic variants were identified in HMGCL gene. The sample was collected at 22 years of age under treatment.
The key metabolites were 3-hydroxy-3-methylglutarate, 3-methylglutaconate and 3-methylglutarate. Also an increase of 3-hydroxyisovalerate and 3-methylcronolylglycine was detected.

Analytical performance

-74 laboratories of 78 active participants submitted results for sample D.
-The majority of the laboratories reported the key metabolites. 71 labs (96%) detected increased 3-hydroxy-3- methylglutarate; 74 participants (100%) reported the increase of 3-methylglutaconate; 68 laboratories (92%) detected increased 3-methylglutarate. In addition, high amounts of 3-hydroxy-isovalerate and 3- methylcrotonilglycine were detected by 66 laboratories (89 %).

Diagnosis / Interpretative proficiency

-The majority of the laboratories, 71 (96%), reported 3-hydroxy-3-methylglutaryl-CoA lyase deficiency as correct diagnosis.
-Two labs reported the diagnosis of 3-methylcrotonylglicinuria.
-One lab gave the diagnosis of 3-methylglutaconic aciduria type I.

Recommendations

The majority of the participants recommended analysis of acylcarnitines and molecular studies of HMGCL gene. Less number of laboratories recommends measuring HMG-CoA Lyase activity in leukocytes or fibroblasts.

Scoring

- Analytical results: 2 points are given for the detection of 3-hydroxy-3-methylglutarate and other key metabolites. 1 point is given the detection of key metabolites without mention of the increase of 3-hydroxy-3-methylglutarate.
- Interpretation of results: 2 points are given for the diagnosis of 3-hydroxy-3-methylglutaryl-CoA lyase deficiency
- CRITICAL ERRORS: 3 labs that reported the diagnosis of 3-methylcrotonylglicinuria or 3-methylglutaconic aciduria type I and not identify the increase of 3-hydroxy-3-methylglutarate.

Overall impression

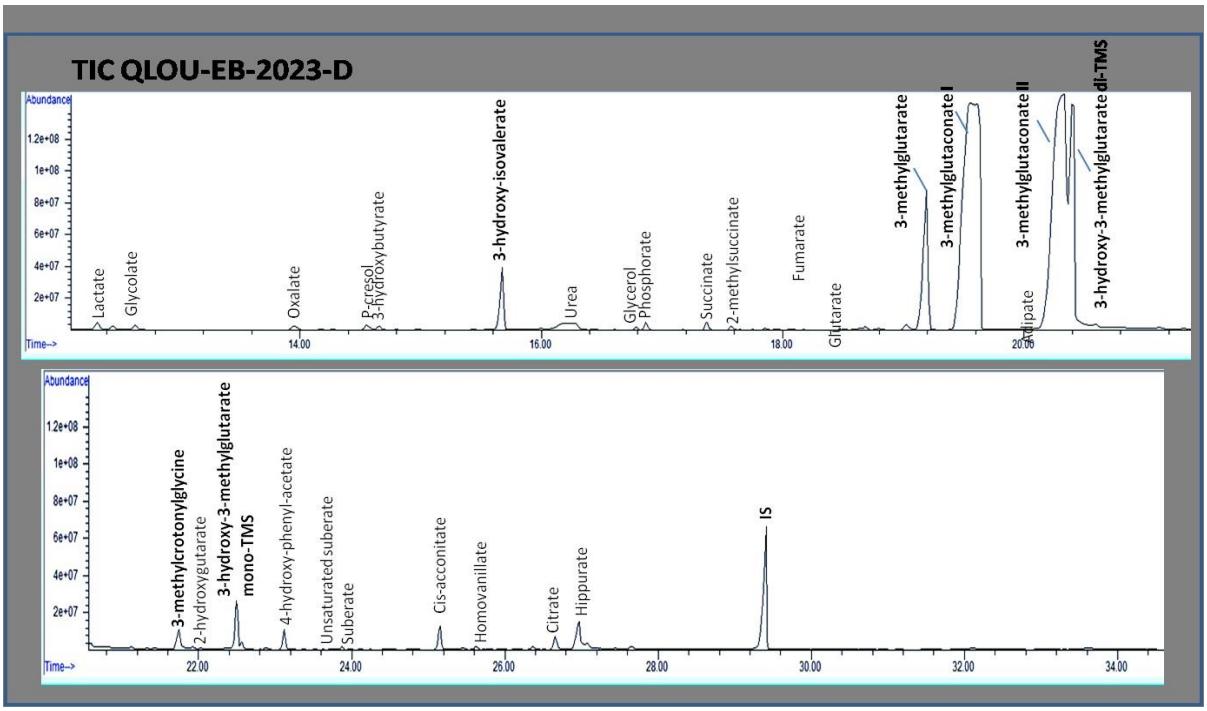
The overall performance was 97%.

Multiple distributions of similar samples

Similar proficiency was obtained in other circulation in 2020.

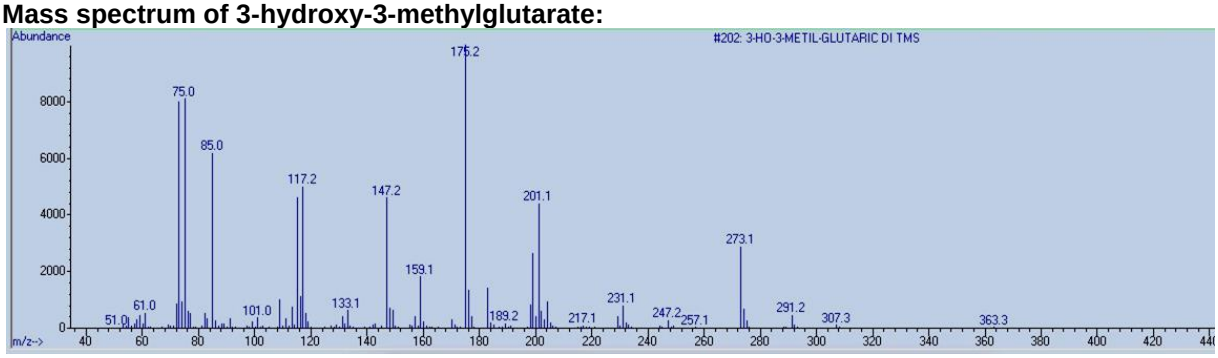
Circulation	2020
Overall performance	96%

Chromatogram sample D:



Organic acids in urine were extracted with ethylacetate without oximation. After solvent evaporation TMS derivatization with bis-trimethylsilyl-trifluoroacetamide (BSTFA) was performed. The organic acids were analyzed by GC-MS using the 60 m x 0.25 mm ID HP-5MS capillary column.

Mass spectrum of 3-hydroxy-3-methylglutarate:



9.5. Patient E

L-2-hydroxyglutaric aciduria

Patient details provided to participants

Female that at 4 years of age presented with development delay, mild mental retardation, tremor and ataxia. Diagnosed at 43 years of age.

Patient details

Female born from consanguineous parents. Patient with development delay and mild mental retardation (IQ 59). Parents noticed tremor when she was 4 years of age, after, ataxia was evident. Bilaterally symmetrical subcortical WM abnormalities were present since the first MR (29 years). 4 years latter involvement of both dentate nuclei was evident. There have been no clinical progression. Ammonia, lactic acid, amino acids were normal. At 43 years of age, qualitative urine organic acid profile showed high level of 2 hydroxyglutaric acid. At this age, epilepsy started. Because the clinical picture and MRI findings, sequencing of the L2HGA gene was performed. It was find a known pathogenic variant.
The key metabolites were 2-hydroxyglutarte and 2-hydroxyglutarate lactone. Keppra derivated metabolites are present.

Analytical performance

-74 laboratories of 77 active participants submitted results for sample E.
-All the laboratories, 74 (100%), reported correctly the increase of 2-hydroxyglutarate. One lab specified the increase of D-2-hydroxyglutarate, but the increased metabolite should be the L-2-hydroxyglutarate.
-30 laboratories (41%) also reported the increase of 2-hydroxyglutarate lactone, another key metabolite of the disease, and 25 laboratories (34%) detected the presence of keppra derivates due to the treatment.

Diagnosis / Interpretative proficiency

-The majority of the laboratories, 72(97%), reported the 2-hydroxyglutaric aciduria as correct diagnosis.
-One lab gave the diagnosis of D-2-hydroxyglutaric aciduria.
-One lab reported multyple acyl-CoA dehydrogenase deficiency.

Recommendations

The majority of the participants recommend:
-Chiral metabolite analysis to distinguish L/D forms.
-Perform genetic analysis of L2HGDH gene and D2HGDH, less laboratories mentioned the analysis of IDH2 and SLC25A1 genes.

Scoring

- Analytical results: 2 points are given for the detection of 2-hydroxyglutarate without specification or L-2-hydroxyglutarate.
- Interpretation of results: 2 points are given for the diagnosis of 2-hydroxyglutaric aciduria without specify the type but with recommendation of chiral analysis, or for L-2-hydroxyglutaric aciduria as most likely or alternative diagnosis. 1 point was given for only D-2-hydroxyglutaric aciduria, without additional recommendations.
- CRITICAL ERROR: 1 laboratory reported the diagnosis of multyple acyl-CoA dehydrogenase deficiency without information regarding neither alternative diagnosis nor recommendation.

Overall impression

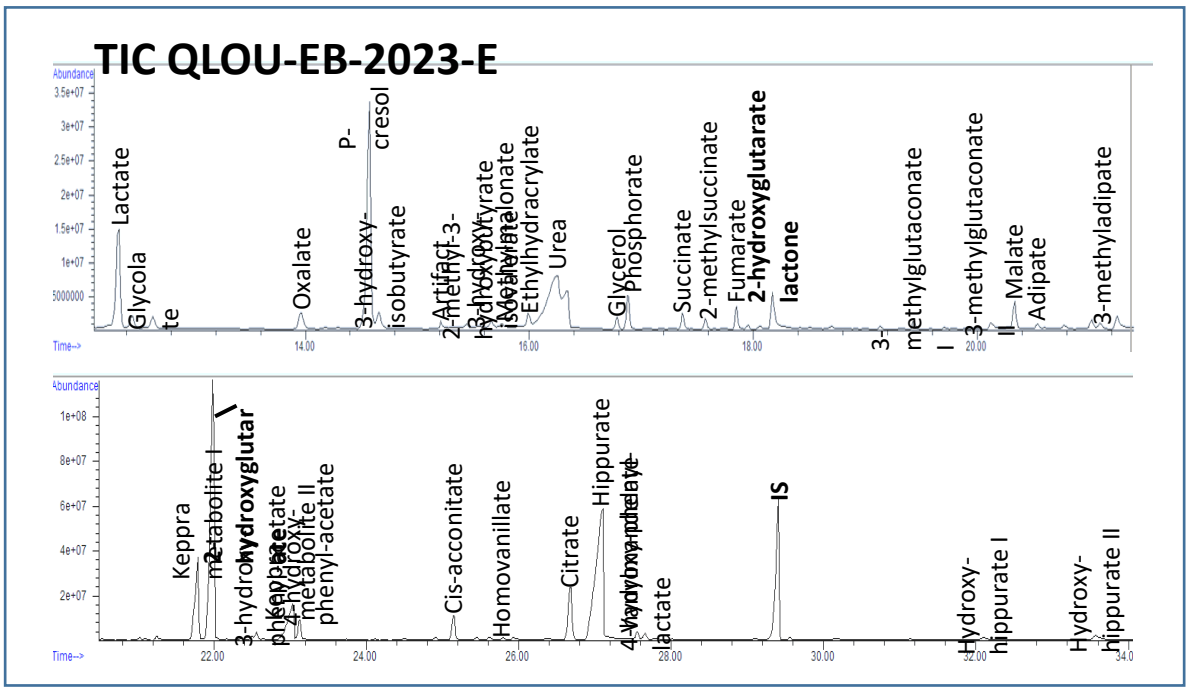
The overall performance was 97%.

Multiple distributions of similar samples

Similar proficiency was obtained in other circulation in 2020.

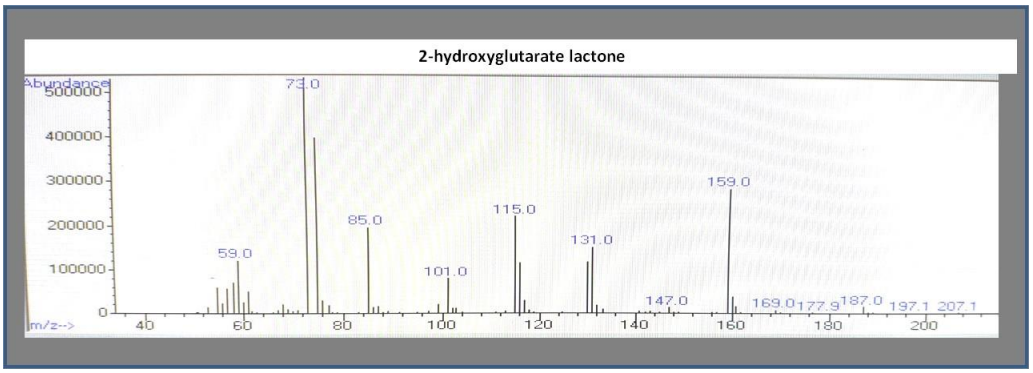
Circulation	2020
Overall performance	98 %

Chromatogram sample E:



Organic acids in urine were extracted with ethylacetate without oximation. After solvent evaporation TMS derivatization with bis-trimethylsilyl-trifluoroacetamide (BSTFA) was performed. The organic acids were analyzed by GC-MS using the 60 m x 0.25 mm ID HP-5MS capillary column.

Mass spectrum of 2-hydroxyglutarate lactone:



9.6. Patient F

Citrullinemia type I

Patient details provided to participants

Male with developmental delay, hiperamonemia episodes. Currently under treatment and MRI and physical examination were normal.

Patient details

4 years-old boy that presented with a picture of hepatic encephalopathy with Reye-like symptoms. The subsequent evolution was marked by the slow recovery from encephalopathy. The biochemical and genetic studies revealed a Citrullinemia Type I. The sample was collected at 28 years old under treatment. He attends a special education school, he has some widely spaced and short-lived epileptic seizures, and language delay.
The key metabolites were uracil, cyclic derivate of citrulline and benzoate, a slight increase of orotic acid can be detected.

Analytical performance

-73 laboratories of 77 active participants submitted results for sample F.
-46 laboratories (63%) reported the increase of cyclic derivate of citrulline (mass spectrum shown at the end of the report), 20 participants (27%) detected increased uracil, 23 labs (32%) reported increase of benzoate and 24 laboratories (33%) detected an increase of orotic acid.

Diagnosis / Interpretative proficiency

-46 laboratories (63%) reported citrullinemia type I as correct diagnosis and as first or alterative option.
-7 labs give the diagnosis of ornithine transcarbaliase (OTC) or other urea cycle disorders.
-11 participants reported as normal sample.
-4 laboratories reported the diagnosis of methylmalonic aciduria or cobalamin deficiency.
-Other individual diagnoses given were pipecolic oxidase deficiency, fenorbabital or bacterial interference

Recommendations

The majority of the laboratories recommended:
- Measure ammonia
- Perform analysis of amino acids in plasma
- Perform mutation analysis of ASS1 gene or other genes related to urea cycle disorders.

Scoring

- Analytical results: 2 points are given for the detection of cyclic derivate of citrulline. 1 point is given if only one or two key metabolites are reported without the cyclic derivate of citrulline
- Interpretation of results: 2 points are given for the diagnosis of citrullinemia type I as first or alternative option, and for other urea cycle disorder and recommendation of amino acid analysis. 1 point is given for recommendation of amino acid analysis and for other UCD without amino acid analysis recommendation.

Overall impression

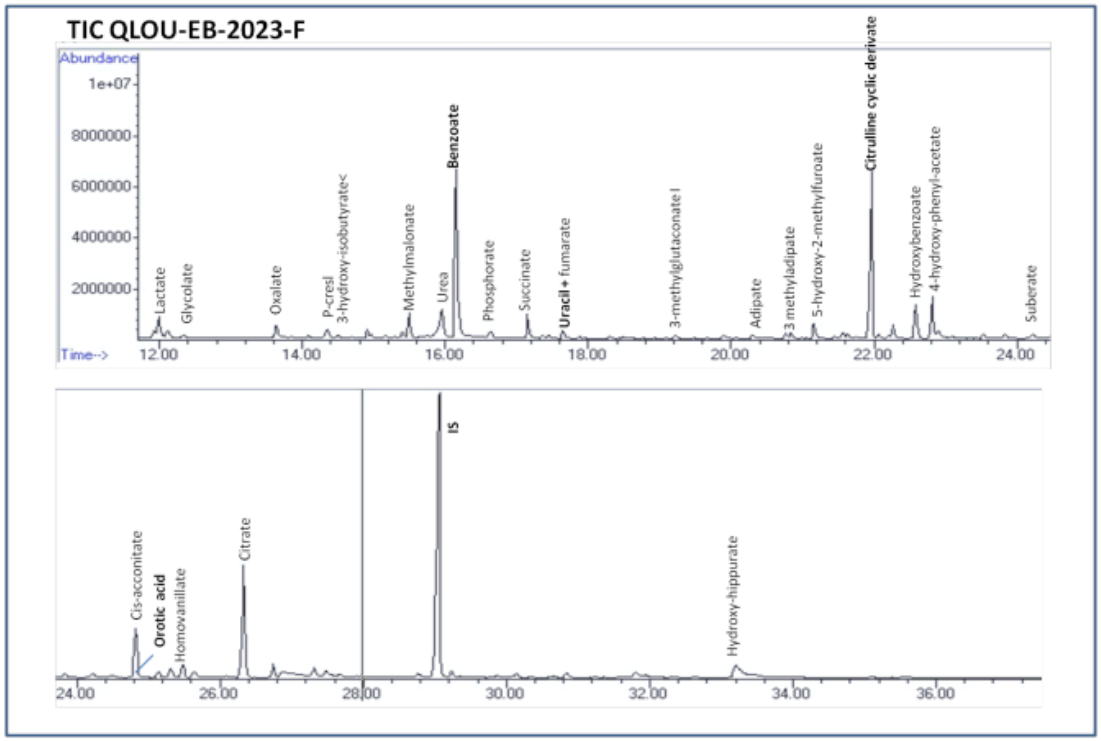
The overall performance was 72%.

Multiple distributions of similar samples

A lower proficiency was obtained in other circulation in 2020.

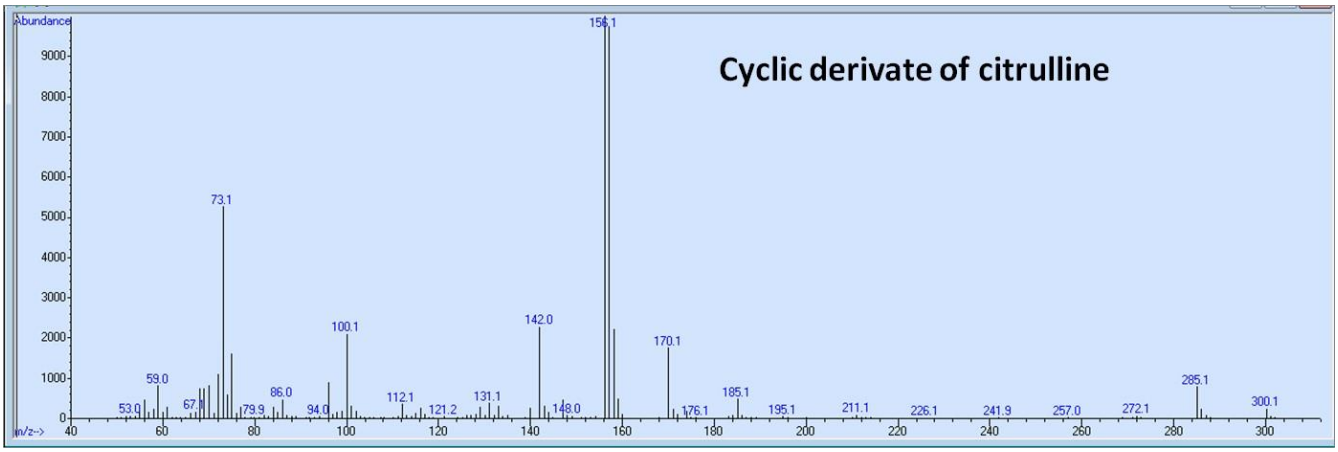
Circulation	2020
Overall performance	64 %

Chromatogram sample F:



Organic acids in urine were extracted with ethylacetate without oximation. After solvent evaporation TMS derivatization with bis-trimethylsilyl-trifluoroacetamide (BSTFA) was performed. The organic acids were analyzed by GC-MS using the 60 m x 0.25 mm ID HP-5MS capillary column.

Mass spectrum of cyclic derivate of citrulline:



10. 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.

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

Lab n°	Patient A Medium chain acyl-CoA dehydrogenase deficiency (MCADD)			Patient B Normal sample			Patient C Mevalonic aciduria			TOTAL
	A	I	TOTAL	A	I	TOTAL	A	I	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**	2	2	**4**	2	2	**4**	**12**
4	2	2	**4**	2	2	**4**	2	2	**4**	**12**
5	1	2	**3**	2	2	**4**	2	2	**4**	**11**
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	1	**3**	2	2	**4**	2	2	**4**	**11**
12	0	0	**0**	2	2	**4**	2	2	**4**	**8**
13	2	2	**4**	2	2	**4**	2	2	**4**	**12**
14	2	2	**4**	2	2	**4**	2	2	**4**	**12**
15	1	2	**3**	2	2	**4**	2	2	**4**	**11**
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	1	0	**1**	2	2	**4**	2	2	**4**	**9**
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**	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**
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**	0	0	**0**	2	2	**4**	**4**
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**	2	2	**4**	2	2	**4**	**12**
42	2	2	**4**	2	2	**4**	2	2	**4**	**12**
43	1	1	**2**	2	2	**4**	2	2	**4**	**10**
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	2	**4**	2	2	**4**	**12**
47	1	2	**3**	2	2	**4**	2	2	**4**	**11**
48	2	2	**4**	2	2	**4**	2	2	**4**	**12**
49	2	2	**4**	2	2	**4**	2	2	**4**	**12**
50	2	2	**4**	2	2	**4**	2	2	**4**	**12**
51	2	2	**4**	2	2	**4**	2	2	**4**	**12**
52	2	2	**4**	2	2	**4**	2	2	**4**	**12**
53	2	0	**2**	2	2	**4**	2	2	**4**	**10**
54	2	2	**4**	2	2	**4**	2	2	**4**	**12**
55	0	0	**0**	2	2	**4**	2	2	**4**	**8**
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**
60	0	0	**0**	2	2	**4**	2	2	**4**	**8**
61	2	2	**4**	2	2	**4**	2	2	**4**	**12**
62	2	2	**4**	2	2	**4**	2	2	**4**	**12**
63	0	0	**0**	0	0	**0**	2	2	**4**	**4**
64	1	2	**3**	2	2	**4**	2	2	**4**	**11**
65	2	2	**4**	2	2	**4**	2	2	**4**	**12**
66	2	2	**4**	2	2	**4**	2	2	**4**	**12**

67	2	2	**4**	2	2	**4**	2	2	**4**	**12**
68	1	2	**3**	2	2	**4**	2	2	**4**	**11**
69	2	2	**4**	2	2	**4**	2	2	**4**	**12**
70	1	2	**3**	2	2	**4**	2	2	**4**	**11**
71	1	2	**3**	2	2	**4**	2	2	**4**	**11**
72	2	2	**4**	2	2	**4**	2	2	**4**	**12**
73	2	2	**4**	0	0	**0**	2	2	**4**	**8**
74	0	0	**0**	2	2	**4**	2	2	**4**	**8**
75	0	2	**2**	2	2	**4**	2	2	**4**	**10**
76										**No submission**
77	2	2	**4**	2	2	**4**	2	2	**4**	**12**

Detailed scores – Round 2

Lab n°	**Patient D** 3-hydroxy-3-methylglutaryl-CoA lyase deficiency			**Patient E** L-2-hydroxyglutaric aciduria			**Patient F** Citrullinemia type I			**TOTAL**
	A	**I**	**TOTAL**	**A**	**I**	**TOTAL**	**A**	**I**	**TOTAL**	
1	2	2	**4**	2	2	**4**	2	2	**4**	12
2	2	2	**4**	2	2	**4**	0	0	**0**	8
3	2	2	**4**	2	2	**4**	0	0	**0**	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										**No submission**
12	2	2	**4**	1	1	**2**	0	0	**0**	6
13	2	2	**4**	2	2	**4**	1	2	**3**	11
14	2	2	**4**	2	2	**4**	2	2	**4**	12
15										**No submission**
16	1	0	**1**	2	2	**4**	2	2	**4**	9
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**	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	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
28	2	2	**4**	2	2	**4**	0	0	**0**	8
29										**No submission**
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	2	2	**4**	2	0	**2**	0	0	**0**	6
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**	2	2	**4**	1	2	**3**	11
42	2	2	**4**	2	2	**4**	0	0	**0**	8
43	2	2	**4**	2	2	**4**	2	2	**4**	12
44	2	2	**4**	2	2	**4**	2	2	**4**	12
45	1	0	**1**	2	2	**4**	1	1	**2**	7
46	2	2	**4**	2	2	**4**	0	1	**1**	9
47	2	2	**4**	2	2	**4**	0	0	**0**	8
48	2	2	**4**	2	2	**4**	2	2	**4**	12
49	2	2	**4**	2	2	**4**	2	2	**4**	12
50	2	2	**4**	2	2	**4**	2	2	**4**	12
51	2	2	**4**	2	2	**4**	2	2	**4**	12
52	2	2	**4**	2	2	**4**	0	1	**1**	9
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**	0	0	**0**	8
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**	1	2	**3**	11
59	2	2	**4**	2	2	**4**	0	0	**0**	8
60	2	2	**4**	2	2	**4**	0	0	**0**	8
61	2	2	**4**	2	2	**4**	1	2	**3**	11
62	2	2	**4**	2	2	**4**	0	2	**2**	10

63	2	2	**4**	2	2	**4**	0	0	**0**	8
64	2	2	**4**	2	2	**4**	1	2	**3**	11
65	2	2	**4**	2	2	**4**	2	2	**4**	12
66	2	2	**4**	2	2	**4**	2	2	**4**	12
67	2	2	**4**	2	2	**4**	0	0	**0**	8
68	2	2	**4**	2	2	**4**	2	2	**4**	12
69	2	2	**4**	2	2	**4**	2	2	**4**	12
70	2	2	**4**	2	2	**4**	0	0	**0**	8
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**	0	0	**0**	8
74	2	2	**4**	2	2	**4**	0	0	**0**	8
75	2	2	**4**	2	2	**4**	0	0	**0**	8
76	1	0	**1**	0	0	**0**			**No submission**	1
77	2	2	**4**	2	2	**4**	2	2	**4**	12

Total scores

LAB nº	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Performance
1	4	4	4	4	4	4	**24**	**100**	
2	4	4	4	4	4	0	**20**	**83**	
3	4	4	4	4	4	0	**20**	**83**	
4	4	4	4	4	4	3	**23**	**96**	
5	3	4	4	4	4	4	**23**	**96**	
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	4	4	4	**24**	**100**	
10	4	4	4	4	4	4	**24**	**100**	
11	3	4	4				**11**	**92**	ONE RETURN
12	0	4	4	4	2	0	**14**	**58**	PP
13	4	4	4	4	4	3	**23**	**96**	
14	4	4	4	4	4	4	**24**	**100**	
15	3	4	4				**11**	**92**	ONE RETURN
16	4	4	4	1	4	4	**21**	**88**	CE
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	1	4	4	4	4	0	**17**	**71**	
21	4	4	4	4	4	4	**24**	**100**	
22	4	4	4	4	4	4	**24**	**100**	
23	4	4	4	4	4	4	**24**	**100**	

24	4	4	4	4	4	4	**24**	**100**	
25	4	4	4	4	4	4	**24**	**100**	
26	4	4	4	4	4	4	**24**	**100**	
27	4	4	4	4	4	4	**24**	**100**	
28	4	4	4	4	4	0	**20**	**83**	
29	4	4	4				**12**	**100**	ONE RETURN
30	4	4	4	4	4	4	**24**	**100**	
31	4	4	4	4	4	4	**24**	**100**	
32	4	4	4	4	4	4	**24**	**100**	
33	4	4	4	4	4	4	**24**	**100**	
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	0	4	4	2	0	**10**	**42**	PP ,CE
39	4	4	4	4	4	4	**24**	**100**	
40	4	4	4	4	4	4	**24**	**100**	
41	4	4	4	4	4	3	**23**	**96**	
42	4	4	4	4	4	0	**20**	**83**	
43	2	4	4	4	4	4	**22**	**92**	
44	4	4	4	4	4	4	**24**	**100**	
45	4	4	4	1	4	2	**19**	**79**	CE
46	4	4	4	4	4	1	**21**	**88**	
47	3	4	4	4	4	0	**19**	**79**	
48	4	4	4	4	4	4	**24**	**100**	
49	4	4	4	4	4	4	**24**	**100**	
50	4	4	4	4	4	4	**24**	**100**	
51	4	4	4	4	4	4	**24**	**100**	
52	4	4	4	4	4	1	**21**	**88**	
53	2	4	4	4	4	4	**22**	**92**	
54	4	4	4	4	4	4	**24**	**100**	
55	0	4	4	4	4	0	**16**	**67**	PP, CE
56	4	4	4	4	4	4	**24**	**100**	
57	4	4	4	4	4	4	**24**	**100**	
58	4	4	4	4	4	3	**23**	**96**	
59	4	4	4	4	4	0	**20**	**83**	
60	0	4	4	4	4	0	**16**	**67**	PP, CE
61	4	4	4	4	4	3	**23**	**96**	
62	4	4	4	4	4	2	**22**	**92**	
63			4	4	4	0	**12**	**75**	
64	3	4	4	4	4	3	**22**	**92**	
65	4	4	4	4	4	4	**24**	**100**	
66	4	4	4	4	4	4	**24**	**100**	
67	4	4	4	4	4	0	**20**	**83**	
68	3	4	4	4	4	4	**23**	**96**	
69	4	4	4	4	4	4	**24**	**100**	

70	3	4	4	4	4	0	**19**	**79**	
71	3	4	4	4	4	4	**23**	**96**	
72	4	4	4	4	4	4	**24**	**100**	
73	4	0	4	4	4	0	**16**	**67**	PP
74	0	4	4	4	4	0	**16**	**67**	PP, CE
75	2	4	4	4	4	0	**18**	**75**	
76				1	0		**1**	**13**	ONE RETURN, CE
77	4	4	4	4	4	4	**24**	**100**	

CE: Critical error
PP: Poor performance (on score)
Blank in performance=satisfactory

Performance

	Number of labs	**% total labs**
Satisfactory performers (≥ 71 % of adequate responses)	68	87
Unsatisfactory performers (< 71 % adequate responses and/or critical error)	9	11.5
Partial and non-submitters	3	3.8

Overall Proficiency

Sample ID	Diagnosis	Proficiency (%)
QLOU-EB-2023-A	Medium chain acyl-CoA dehydrogenase deficiency (MCADD)	87.7
QLOU-EB-2023-B	Normal sample	97.7
QLOU-EB-2023-C	Mevalonic aciduria	99.7
QLOU-EB-2023-D	3-hydroxy-3-methylglutaryl-CoA lyase deficiency	97
QLOU-EB-2023-E	L-2-hydroxyglutaric aciduria	97.3
QLOU-EB-2023-F	Citrullinemia type I	72.3

11. Annual meeting of participants

Probably the next year an on-line meeting to discuss QLOU samples will be organized.

12. Information from the Executive Board and the Scientific Advisory Board

- New **reference materials** are now provided by MCA: they are not related to EQA samples anymore. There are two concentration levels for each group of analytes. The most suitable low and high concentration levels are defined by the respective scientific advisors. Analytes and their concentrations will be approximately the same in consecutive batches of control material. These reference materials can be ordered through the MCA website (https://www.erndimqa.nl/). Participants are encouraged to use them as internal control, but they cannot be used as calibrants.

On the website a new section for data management completes the ERNDIM internal Quality Control System. Laboratories have the option to submit results and request reports showing their result in the last run in comparison to defined acceptance limits, their own historical data and the mean of all laboratories using the same batch control material.

- A set of **organic acid mixtures** has been developed by Dr Herman ten Brink in Amsterdam, following request and advice from ERNDIM. The product is currently available at: at: https://www.vumc.com/departments/clinical-chemistry/metaboliclaboratory/organic-synthesis-laboratory/organic-acids-mixture.htm
- **Urine samples**: we remind you that every year, each participant must provide to the scheme organizer at least 200 ml of urine from a patient affected with an established inborn error of metabolism or "normal" urine, together with a short clinical report. If possible, please collect 700 ml of urine: this sample can be sent to all labs participating from the three QLOU schemes. Each urine sample must be collected from a single patient (don't send urine spiked with pathological compounds). Please don't send a pool of urines, except if urine has been collected on a short period of time from the same patient. For "normal" urine, the sample must be collected from a symptomatic patient (don't send urine from your kids!). Send the aliquots on dry ice by rapid mail or express transport to:

  Dr. Judit García Villoria and Dr. Antònia Ribes Rubiò
  Hospital Clínic de Barcelona
  Division of Inborn Errors of Metabolism
  c/Mejía Lequerica s/n Edificio Helios III, pb
  08028 Barcelona, Spain
  Telephone (+)34 93 2275672
  Fax (+)34 93 2275668
  E-mail: jugarcia@clinic.cat

  Please send us an e-mail on the day you send the samples.

13. Reminders

-We remind you that the diagnosis of the sample should be done with the organic acid profile.

-For the normal samples for scoring adequately is very important to enter "Normal profile" in "Key metabolites" as well as, enter "Normal profile" in diagnosis box.

-Reccomendation= advice for further investigation is scored together with the interpretative score. Advice for treatment is not scored. Don't give advice for further investigation in "Comments on diagnosis": it will not be included in the evaluation program.

14. Tentative schedule and fee in 2024

Sample distribution	7 February
Start of analysis of Survey 2024/1 Website open	May 7
Survey 2024/1 - Results submission	May 28
Survey 2024/1 - Reports	July
Start of analysis of Survey 2024/2	August 26
Survey 2024/2 – Results submission	September 16
Survey 2024/2 - Reports	November
Annual Report 2024	January 2025

15. 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.

16. Questions, Comments and Suggestions

If you have any questions, comments or suggestions please address to the Scientific Advisor of the scheme, Dr. Judit García Villoria (jugarcia@clinic.cat) and/or to the ERNDIM Administration Office (admin@erndim.org).

Date of report, 2024-02-14
Name and signature of Scientific Advisor

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Hospital Clínic de Barcelona
Division of Inborn Errors of Metabolism
c/Mejía Lequerica s/n Edificio Helios III, pb
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APPENDIX 1. Change log (changes since the last version)

Version Number	Published	Amendments
1	04 Apr 2024	2023 annual report published

END