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Qualitative Organic Acids

Centre: Spain

Final Report 2024

prepared by
Judit Garcia Villoria and Margarida Silva

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.

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 2024 seventy seven laboratories from many different countries participated in the QLOU Barcelona scheme, without any educational participants (0 in 2023, 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 participants
Argentina	1
Brazil	2
Chile	1
China	1
Colombia	1
Cyprus	1
France	22
Germany	1
Greece	1
Hong Kong	5
India	4
Italy	14
Lebanon	1
Philippines	1
Portugal	2
Qatar	1
Saudi Arabia	1
Singapore	1
Spain	13
Turkey	1
United Kingdom	1
Uruguay	1

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 2024 were authentic human urine samples, 5 from affected patients and 1 from healthy individuals. In 2024 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: all urine samples have been provided by the scheme organizers or specified participants.

Patient A: Phenylketonuria – Hospital Clínic de Barcelona, Spain
Patient B: L-2-hydroxyglutaric aciduria - Hospital Clínic de Barcelona, Spain
Patient C: Ornithine transcarbamylase deficiency – Hospital Clínic de Barcelona, Spain
Patient D: Multiple acyl-CoA dehydrogenase deficiency – Hospital Clínic de Barcelona, Spain

Patient E: Normal profile – Hospital Clínic de Barcelona, Spain
Patient F: Glutaric aciduria type I – Hospital Clínic de Barcelona, Spain

All samples selected by the Scientific Advisor have been heat-treated and were tested for suitability in the Scientific Advisor's laboratory before and after shipping process. 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

- February 7, 2024: shipment of samples of Survey 1 and Survey 2
- May 7, 2024: analysis start, clinical data available and submission availability in the website (Survey 1)
- May 28, 2024: deadline for result submission (Survey 1)
- August 12, 2024: interim report of Survey 1 available in the website
- August 26, 2024: analysis start, clinical data available and submission availability in the website (Survey 2)
- September 16, 2024: deadline for result submission (Survey 2)
- October 10, 2024: interim report of Survey 2 available in the website
- January - March 2025: annual report

6. Results

	Survey 1	**Survey 2**
Receipt of results	73	71
No answer	4	6

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 2024 have been also scored by Dr Joachim Janda, from QLOU Heidelberg. At the SAB meeting in 28th and 29th November, 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 2024, the SAB decided that sample B has to be considered as a critical error for the labs who failed to identify an increase of 2-hydroxyglutari acid and not give the diagnosis of 2-Hydroxyglutaric aciduria, and not provide any further recommendations to rule out it. SAB also decided that Sample D should be considered a critical error for laboratories that failed to identify the increase in ethylmalonic acid, 2-hydroxyglutarate, and acylglycines, without considering multiple acyl-CoA dehydrogenase deficiency, and did not provide any further recommendations to rule it out. Similarly, Sample F was considered a critical error if laboratories failed to identify the increase in 3-hydroxyglutaric acid and did not diagnose glutaric aciduria type I or provide any further recommendations to rule it out.

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 2024. Any partial submitters will receive a letter from the ERNDIM Executive Administrator, Sara Gardner.

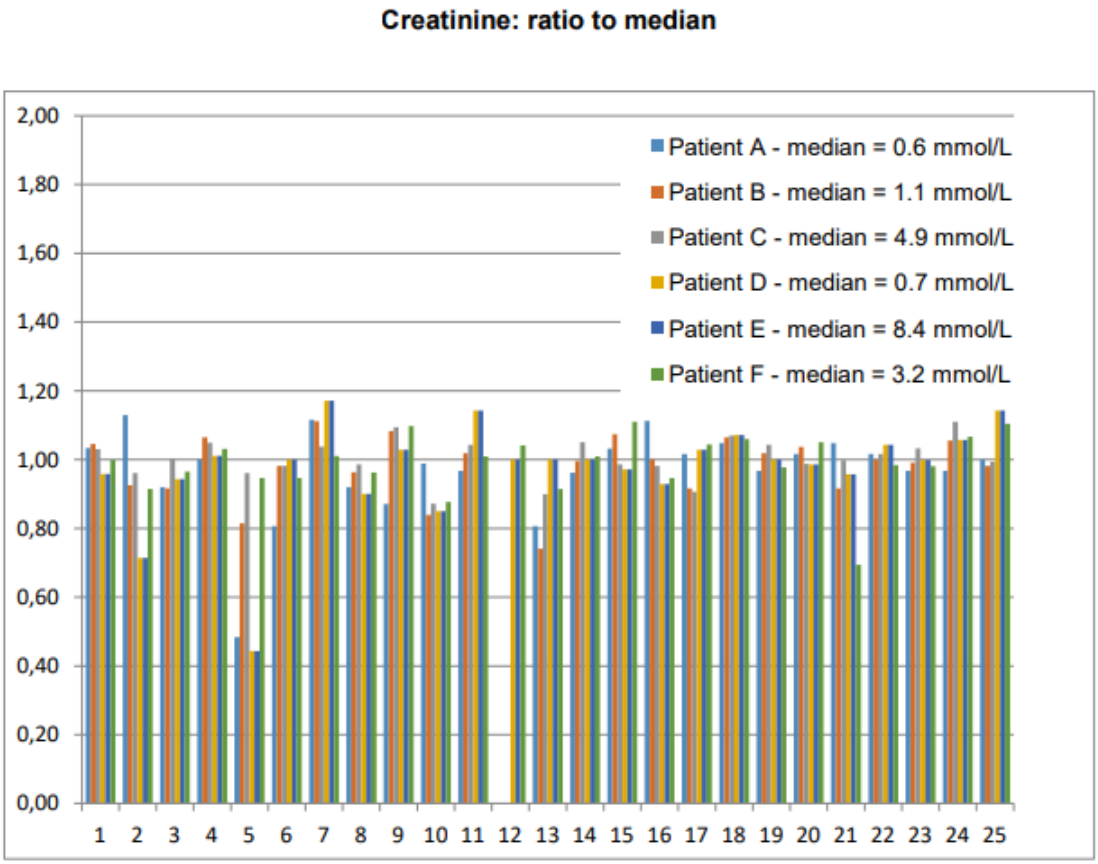
8.1. Score for satisfactory performance

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 (admin@erndim.org), 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. Creatinine measurement for all samplesScore for satisfactory performance



9.2. Patient A

Phenylketonuria or phenylalanine hydroxylase deficiency

Patient details provided to participants
Female with severe mental retardation and obesity, under treatment

Patient details
The urine sample is from a female patient diagnosed with phenylketonuria in the neonatal period. The present sample has been collected at the age of 53 years, and is under treatment, although the adherence to it is doubtful.
At present the patient presents low intelligence quotient, severe mental retardation and obesity

Analytical performance
-73 laboratories of 77 active participants submitted results for sample A.
-The majority of the laboratories reported the key metabolites. 66 laboratories (90%) detected increased phenyllactate; 56 participants (77%) reported the increase of phenylpyruvate; 64 laboratories (88%) detected increased phenylacetate; 53 participants (73%) reported the increase of 2-hydroxy-phenylacetate. In addition, high amounts of mandelic acid, 4-hydroxy-phenyllactate and 4-hydroxy-phenylpiruvate were detected by 39 laboratories (53 %), 36 laboratories (49 %, and 30 laboratories (41%) respectively.

Diagnosis / Interpretative proficiency
All laboratories, 72 (99%), except for one that did not put anything in the diagnostic box, reported the correct diagnosis of phenylketonuria (PKU) or hyperphenylalaninemia.

Recommendations
The majority of the participants recommended plasma or DBS aminoacid analysis, urine and/or plasma and/or CSF pterin analysis, BH4 loading test, DHPR assay and mutation analysis of *PAH* gene, if not mutation is detected perform BH4 pathway genes analysis

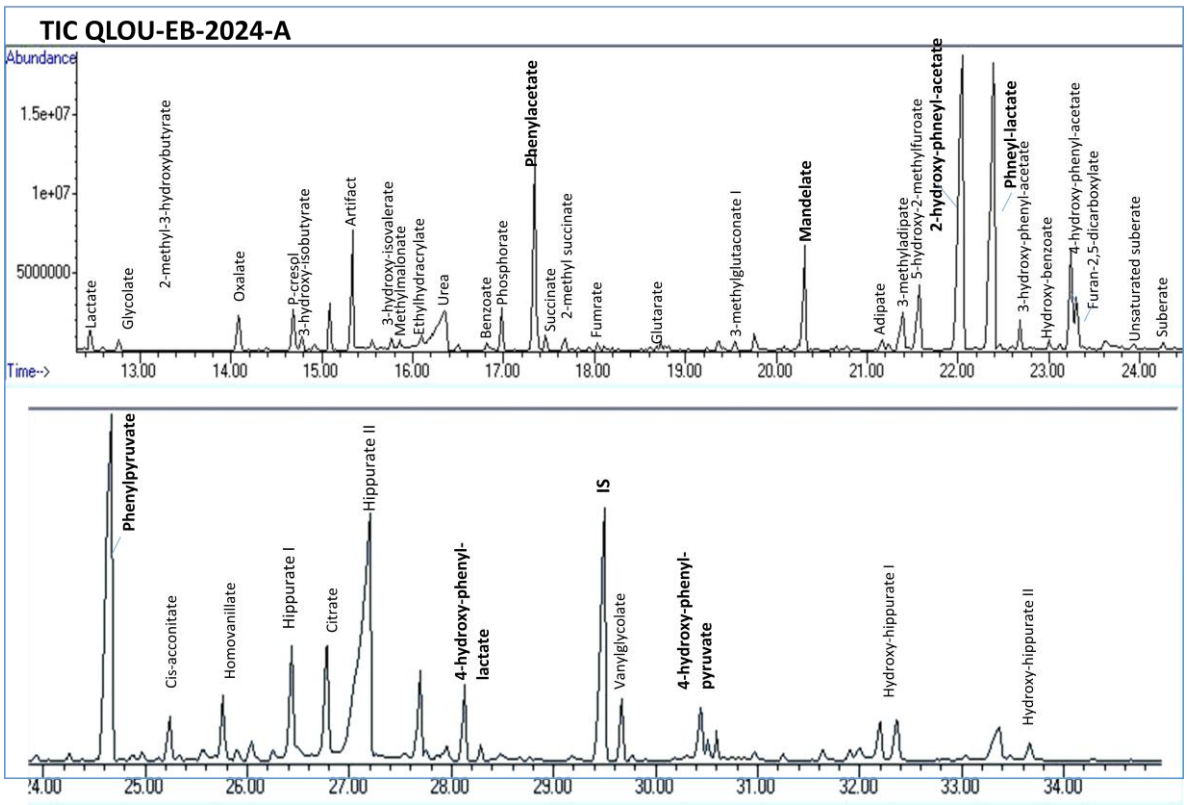
Scoring
- Analytical results: 2 points are given for the detection of a minimum two of these key metabolites.
- Interpretation of results: 2 points are given for the correct diagnosis.

Overall impression
The overall performance was 99%.

Multiple distributions of similar samples
The same proficiency was obtained in other circulation in 2021.

Circulation	2021
Overall performance	99%

Chromatogram sample A:



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 B

L-2-hydroxyglutaric aciduria

Patient details provided to participants

Patient diagnosed in childhood. Currently undergoing treatment and has mental retardation, dystonic tetraparesis, and microcephaly

Patient details
Female patient diagnosed in the childhood with the presence of 2-hydroxyglutaric acid in urine. She exhibited poor language skills, little eye contact, ataxia, and strabismus. The MRI showed a parasagittal frontal lesion and multiple lesions in the white matter. Additionally, she had microcephaly and has required special schooling. Despite treatment, she currently at 19 years-old, experiences tonic-clonic seizures, dystonic tetraparesis and has behavioral and social relationship problems. Sequencing of the *L2HGDH* gene was performed and mutations were found confirming the diagnosis of L-2-hydroxyglutaric aciduria.

Analytical performance
-74 laboratories of 77 active participants submitted results for sample B.
-71(96%), reported correctly the increase of 2-hydroxyglutarate. One of them put the increase of this metabolite in comment box, is very important to put the altered metabolite in the key metabolite box to be scored correctly. In this case it was able to do but maybe in the future the result could be unnoticed.
-41 laboratories (55%) also reported the increase of 2-hydroxyglutarate lactone, another key metabolite of the disease.

Diagnosis / Interpretative proficiency
-The majority of the laboratories, 62 (84%), reported the L-2-hydroxyglutaric aciduria as correct diagnosis.
-Two labs diagnosed as combined D- and L-2-hydroxyglutaric aciduria, without the correct further studies to rule out other types of 2-hydroxyglutaric acidurias.
-One lab reported as D-2-hydroxyglutaric aciduria due to the chiral study, but the diagnosis was L-2-hydroxuglutric aciduria, and another two labs put 2-hydroxyglutaric aciduria as alternative but without specific further recommendations.
-Three labs reported multyple acil-CoA dehydrogenase deficiency.
-Two labs reported as normal or other not related alternative disorders.

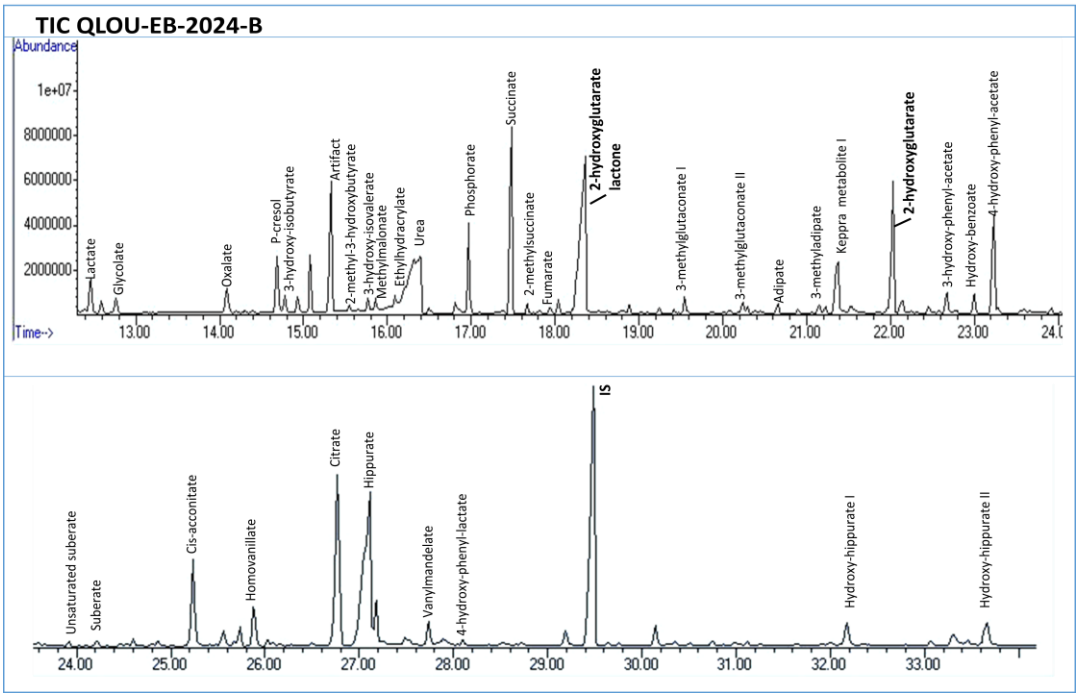
Recommendations
The majority of the participants recommend:
-Chiral metabolite analysis to distinguish L/D forms.
-Perform genetic analysis of *L2HGDH* gene and *D2HGDH*, less laboratories mentioned the analysis of *IDH2* and *SLC25A1* genes

Scoring

- Analytical results: 2 points are given for the detection of 2-hydroxyglutarate.
- Interpretation of results: 2 points are given for the diagnosis of L-2-hydroxiglutaric aciduria or 2-hydroxyglutaric aciduria with the recommendation to study chiral study or differential diagnosis by molecular studies to differentiate D- and L-2-Hydroxiglutarica aciduria.
  1 point is given for the diagnosis of D-2-hydroxyglutaric acid and 2-hydroxiglutaric aciduria without additional specific recommendations.
- CRITICAL ERRORS: 2 labs that reported as normal sample and one lab that gave the diagnosis of Maple syrup urine disease (MSUD).

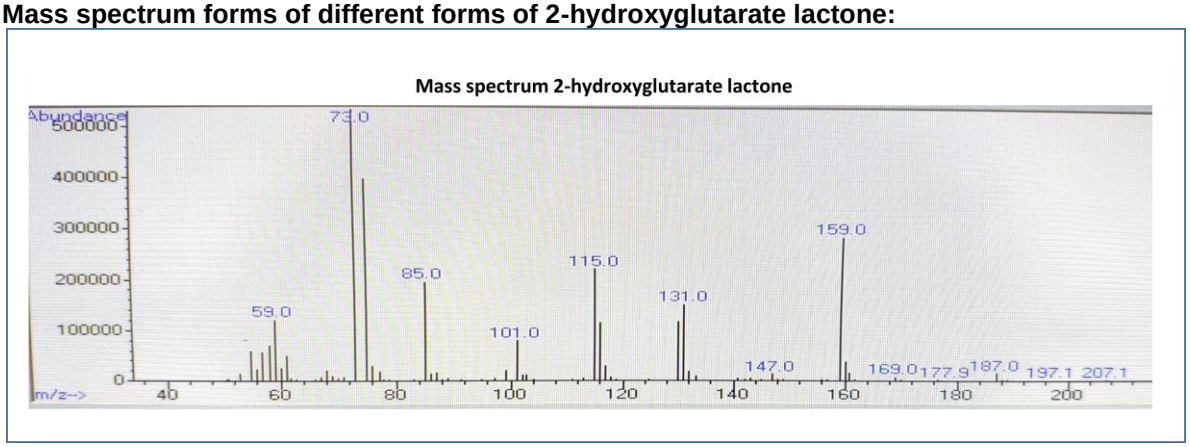
Overall impression
The overall performance was 92%

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.

Mass spectrum forms of different forms of 2-hydroxyglutarate lactone:



9.4. Patient C

Ornithine transcarbamylase deficiency

Patient details provided to participants

Female with development delay, diagnosed at 6 years old when she presented hiperamonemia after an episode of infection. At present she is under treatment.

Patient details

Female patient who at 6 years old presented ataxic gate, vomits, bradypsychia, disorientation and hyperammonemia after an episode of infection. The plasmatic aminoacid analysis showed increase of glutamine and decrease of citrulline, together with an increase of orotic acid in urine. The ornithine transcarbamylase deficiency was confirmed by enzymatic and molecular analysis. At present she is 31 years old, continues with the corresponding treatment and presents developmental delay.

Analytical performance

-73 laboratories of 77 active participants submitted results for sample C.
-39 laboratories (52%), reported correctly the increase of uracil, one of them put the increase of uracil in the comment box and not in the key metabolite box.
-29 laboratories (40%) reported the increase of orotic acid, six of them put the increase of orotic acid in the comment box and not in the key metabolite box.
-In addition, 15 participants (21%) reported increased hippurate.

Diagnosis / Interpretative proficiency
-58 laboratories (54%), reported correctly the diagnosis of ornithine transcarbamylase deficiency or urea cycle
disorder.
-11 participants reported as normal profile, and one lab not put anything in diagnosis box.

Recommendations
The majority of the laboratories recommend performing aminoacids in plasma and urine, orotic acid in urine and molecular diagnosis of urea cycle disorder.

Scoring

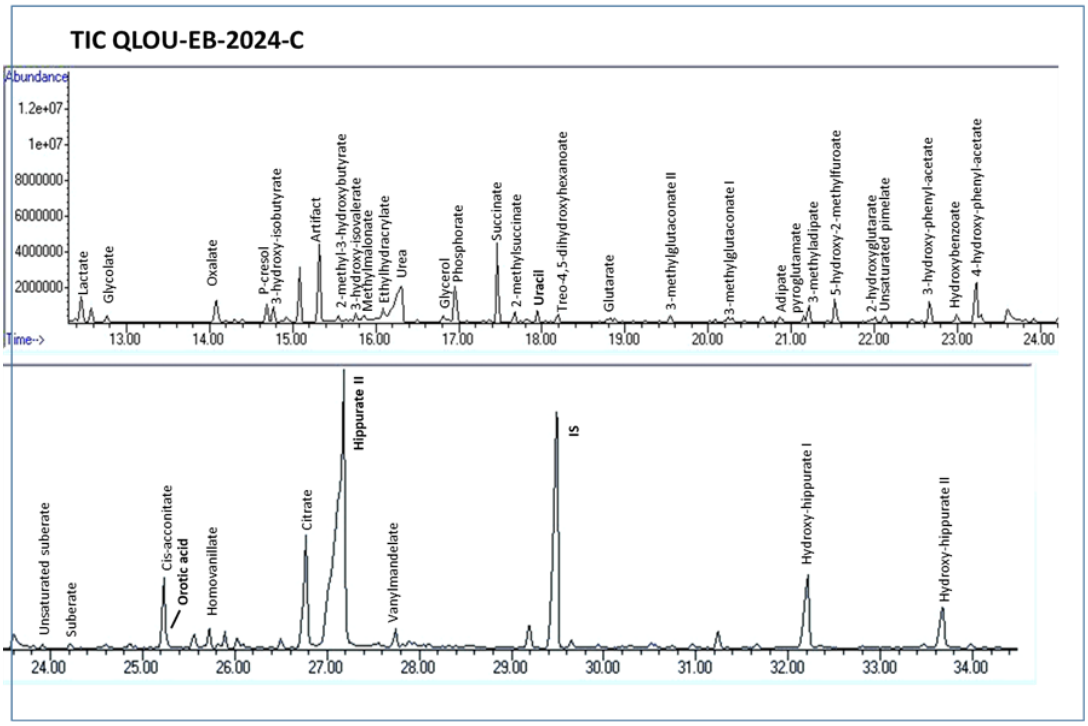
- Analytical results: 2 points are given for the detection of uracil and /or orotic acid.
  1 point is given for the detection of increased hippurate without any key metabolite.
- Interpretation of results: 2 points are given for the diagnosis or alternative diagnosis of ornithine transcarbamylase deficiency or urea cycle disorder.
  1 point is given for the recommendations to analyze amino acids, orotic acid o rule out urea cycle disorder.

Overall impression
The overall performance was 76%.

Multiple distributions of similar samples
A lower proficiency was observed in other circulation in 2020.

Circulation	2020
Overall performance	68%

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.

9.5. Patient D

Multiple acyl-CoA dehydrogenases deficiency

Patient details provided to participants
Female diagnosed at 4 years of age. She presented hypoglycemia and hiperamoniemia after pneumonia. At present she is under treatment.

Patient details
The urine sample is from a patient diagnosed of multiple acyl-CoA dehydrogenase deficien-cy at 4 years of age.
The sample was collected at 21 years of age, under carnitine and riboflavin treatment. Currently she presents mild cognitive impairment and myopathy. The diagnosis confirmation was done by identification of mutations in *ETFDH* gene.
The organic acid profile shows the typical pattern of the disease in adults with elevated excretion of ethylmalonate,2-hydroxyglutarate and acylglycines with slight dicarboxylic aciduria.

Analytical performance
- 71 laboratories of 77 active participants submitted results for sample D.
- Pathological excretion of ethylmalonate, 2-hydroxyglutarate and 2-hydroxyglutarate lactone, isobutyrylglycine, isovalerylglycine, hexanoylglycine, suberylglycine, adipate, suberate, unsaturated suberate, sebacate and unsaturated sebacate (considered as key metabolites). In addition, an increase of lactate was observed.
-Regarding key metabolites: 72% and 94% of the participants detected the increase of ethylmalonate and 2-hydroxyglutarate respectively. In addition, 38% of participants detected 2-hydroxyglutarate lactone, 55% of the laboratories reported increased isovalerylglycine and 46% the increase of hexanoylglycine. The increase of other acylglycines (isobutyrylglycine and suberylglycine), and other dicarboxylic acids were detected between the 20 and 14% of participants.
-The increase of lactate was observed by 52% of laboratories.

Diagnosis / Interpretative proficiency
-The 57 laboratories (80%) of the participants reported multiple acyl-CoA dehydrogenases deficiency or glutaric
aciduria type II as the correct diagnosis.
-9 participants give the diagnosis of 2-hydroxylutaric aciduria.
-1 laboratory reported propionic acidemia, other multyple mitochondrial syndrome 1, other isovaleric acidemia and other hyperinsulinism.
- 1 lab reported as normal sample apparently due to a swap with sample E.

Recommendations
The majority of laboratories recommended to perform acylcarnitine analysis and genetic analysis.

Scoring
- Analytical results: 2 points are given for the detection of 2-hydroxyglutarate and ethylmalonate or some acylglicines or dicarboxylic acids. 1 point is given is only the increase of one key metabolite is given.
- Interpretation of results: 2 points are given for the diagnosis of multiple acyl-CoA dehydrogenases deficiency or glutaric aciduria type II. 1 point is given if other diagnosis is reported but in the recommendations the study of acylcarnitines is specified
- CRITICAL ERRORS: 1 lab that reported as propionic academia, 1 lab that gave the diagnosis of hyperinsulinism, and 1 lab that reported as normal apparently due to a swap with sample E, and without additional specific recommendations.

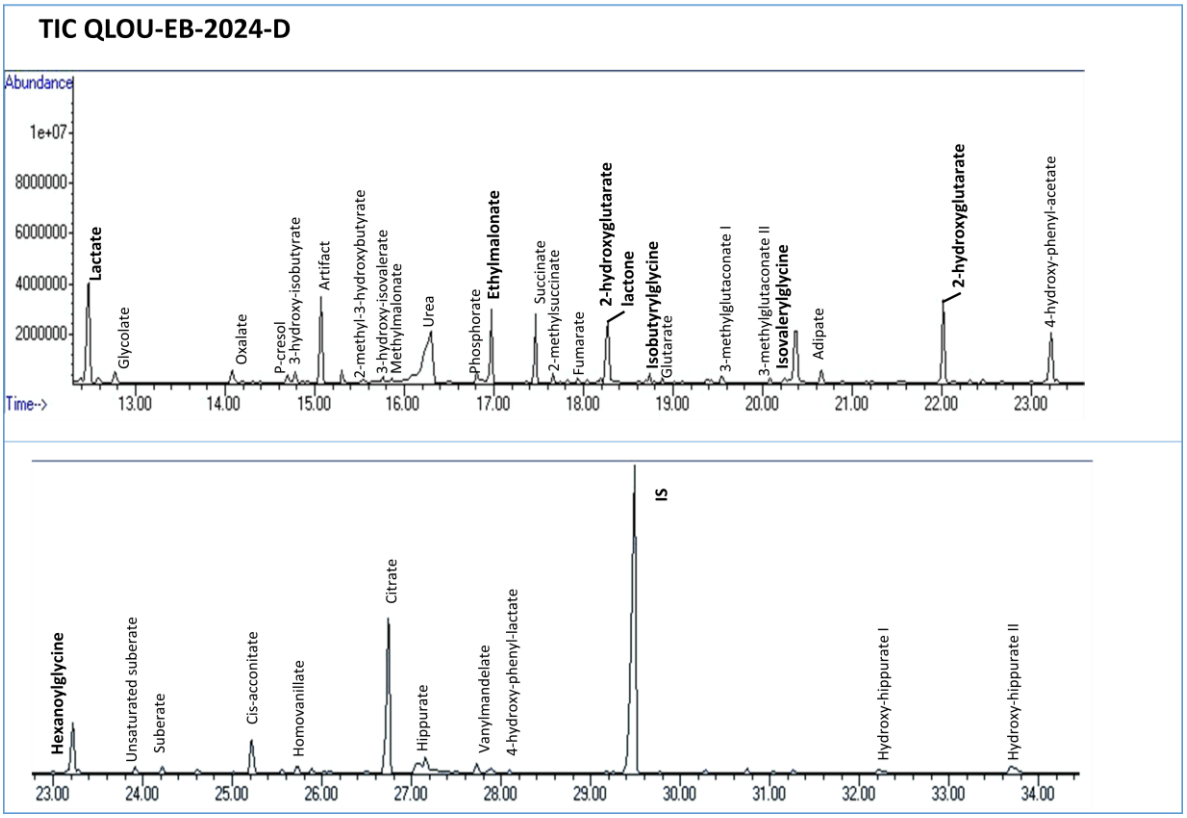
Overall impression

The overall performance was 85%.

Multiple distributions of similar samples
A higher proficiency was obtained in other circulation in 2020.

Circulation	2020
Overall performance	91%

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.

8.5. Patient E

Normal profile

Patient details provided to participants
Autistic features and neurodegeneration.

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

Analytical performance
-71 laboratories of 77 active participants submitted results for sample E.
-The majority of laboratories, 67 (94%), reported correctly the result as profile without significative alterations.
-One laboratory detected an increase of 2-hydroxyglutaric acid, other methilmalonic acid, other 3-methylglutaconic acid, and other 3-hydroxyacids.

Diagnosis / Interpretative proficiency

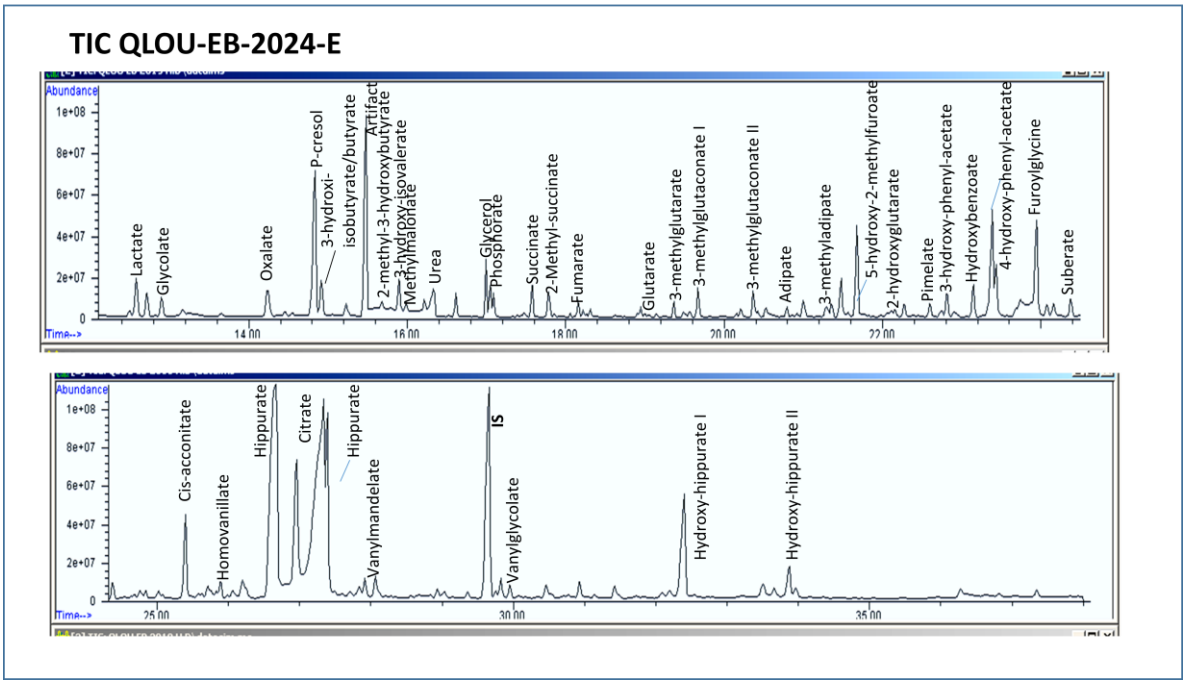
-67 laboratories (94%), reported correctly as normal sample.
-One participant gave de diagnosis of 2-hydroxyglutaric aciduria apparently due to a swap with sample D. Other laboratory gave the diagnosis of vitamin B12 deficiency, other of LCHAD and other of 3-methylglutaconic aciduria.

Recommendations
Some participants recommended to analyze plasma aminoacids, acylcarnitine profile, VLCFA, purines and pyrimidines, delta-aminolevulinic acid (ALA), alpha aminoadipic and pipecolic acids in urine, plasma and CSF, plasma and CSF B6 analysis, creatine metabolism, thiamine concentration, cholestanol, oxysterols, lactate, pyruvate and ammoniemia. In addition, NGS genetic screening.

Scoring
- Analytical results: 2 points are given for the result of normal profile.
- Interpretation of results: 2 points are given for normal sample.

Overall impression
The overall performance was 94%.

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.

9.6. Patient F

Glutaric aciduria type I low excretor

Patient details provided to participants
Patient diagnosed at 15 months of age with movement disorders and psychomotor retardation. Currently he is under treatment and presents with a tetraparesia.

Patient details
The urine sample is from a patient diagnosed of glutaric aciduria type I in childhood, confirmig the diagnosis by molecular studies. The patient currently presents with macrocephaly and spasticdystonic tetraparesia with severe disability.
The organic acid profile was the characteristic of low excretor biochemical phenotype showing only a

slight increase of glutarate and 3-hydroxyglutarate.
The sample was collected at 25 years of age, under carnitine treatment.

Analytical performance
-71 laboratories of 77 active participants submitted results for sample F.
-65 participants (92%) detected the increase of glutarate and 3-hydroxyglutarate.
-5 laboratories only detected one of the two metabolites.
-One laboratory only reported the increase of 3-methylglutaconic acid and 3-methylglutaric acid and other detected increase of 2-hydroxyglutarate.

Diagnosis / Interpretative proficiency
-The majority of the laboratories, 68 (96%), reported glutaric aciduria type 1 or glutaryl-CoA dehydrogenase deficiency as correct diagnosis.
-Other individual reported diagnosis were: 2-hydroxyglutaric aciduria, lipoic deficiency and 3-methylglutconic aciduria.

Recommendations
The majority of the participants recommended analysis of acylcarnitines in plasma or DBS or urine, plasma aminoacid measurement and molecular studies of *GCDH* gene.

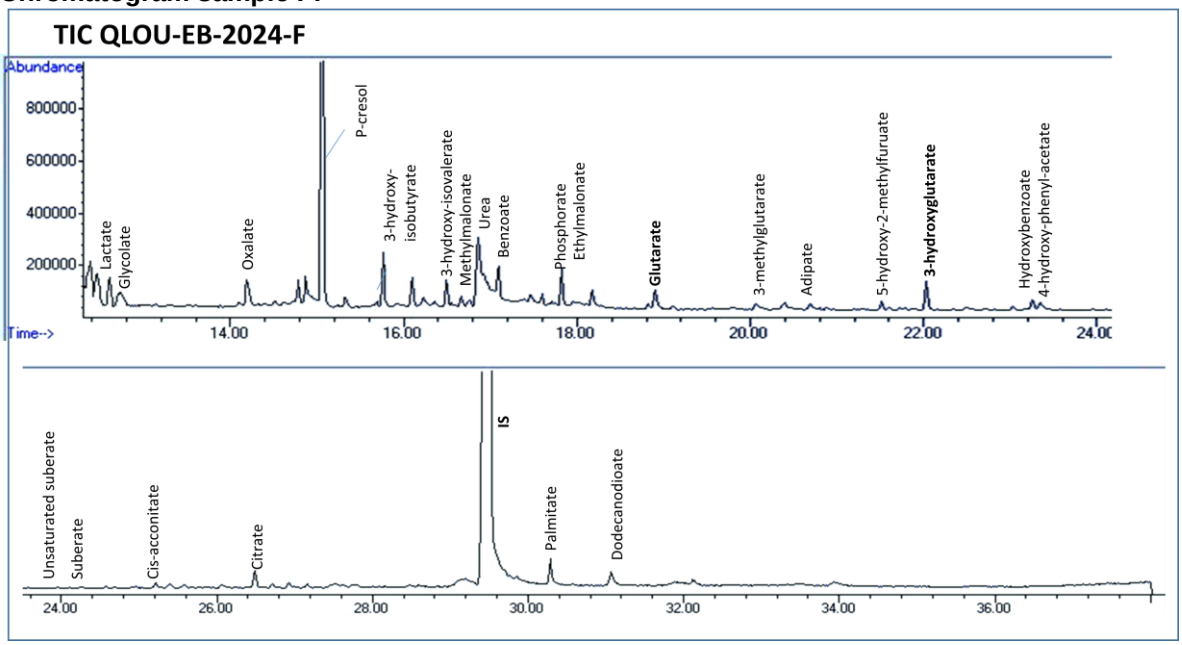
Scoring
- Analytical results: 2 points are given for the detection of the glutarate and 3-hydroxyglutarate. 1 point is given if only one of the two metabolites is detected.
- Interpretation of results: 2 points are given for the correct diagnosis of glutaric aciduria type I.
- CRITICAL ERRORS: 1 lab that reported as 2-hydroxyglutaric aciduria, 1 lab that gave the diagnosis of lipoic acid defects and 1 lab that reported the diagnosis of 3-methylglutaconic aciduria.

Overall impression
The overall performance was 95%.

Multiple distributions of similar samples
The same proficiency was obtained in last circulation in 2021.

Circulation	2021	2018
Overall performance	95 %	49 %

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.

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 Phenylketonuria			Patient B L-2-hydroxyglutaric aciduria			Patient C Ornithine transcarbamylase deficiency			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**	-	-	-	**8**
3	2	2	**4**	2	2	**4**	0	0	**0**	**8**
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	1	**3**	**11**
7	2	2	**4**	2	2	**4**	0	1	**1**	**9**
8	2	2	**4**	2	2	**4**	2	2	**4**	**12**
9	2	2	**4**	2	1	**3**	2	2	**4**	**11**
10	2	2	**4**	2	2	**4**	2	2	**4**	**12**
11	0	2	**2**	2	0	**2**	0	2	**2**	**6**
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**	1	2	**3**	**11**
19	2	2	**4**	2	2	**4**	2	2	**4**	**12**
20	2	2	**4**	2	2	**4**	0	2	**2**	**10**
21	2	2	**4**	2	2	**4**	0	2	**2**	**10**
22	2	2	**4**	2	1	**3**	2	2	**4**	**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**

Lab n°	Patient A Phenylketonuria			Patient B L-2-hydroxyglutaric aciduria			Patient C Ornithine transcarbamylase deficiency			TOTAL
	A	I	TOTAL	A	I	TOTAL	A	I	TOTAL	
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**	0	0	**0**	0	2	**2**	**6**
30	2	2	**4**	2	2	**4**	2	2	**4**	**12**
31	2	2	**4**	2	2	**4**	2	2	**4**	**12**
32	2	2	**4**	2	2	**4**	2	2	**4**	**12**
33	2	2	**4**	2	2	**4**	2	2	**4**	**12**
34	2	2	**4**	2	1	**3**	2	2	**4**	**11**
35	2	2	**4**	2	2	**4**	0	0	**0**	**8**
36	2	2	**4**	2	2	**4**	2	2	**4**	**12**
37	-	-	**-**	-	-	**-**	-	-	**-**	**-**
38	2	2	**4**	2	2	**4**	2	2	**4**	**12**
39	2	2	**4**	2	0	**2**	0	0	**0**	**6**
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	2	2	**4**	2	2	**4**	2	2	**4**	**12**
44	2	2	**4**	2	2	**4**	0	0	**0**	**8**
45	2	2	**4**	2	2	**4**	2	2	**4**	**12**
46	2	2	**4**	0	0	**0**	2	2	**4**	**8**
47	2	2	**4**	2	2	**4**	0	2	**2**	**10**
48	2	2	**4**	2	2	**4**	2	2	**4**	**12**
49	2	2	**4**	2	2	**4**	1	1	**2**	**10**
50	2	0	**2**	2	0	**2**	2	0	**2**	**6**
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**	0	1	**1**	**5**
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**	0	0	**0**	**8**
57	2	2	**4**	2	2	**4**	0	2	**2**	**10**
58	2	2	**4**	2	2	**4**	0	0	**0**	**8**

Lab n°	Patient A Phenylketonuria			Patient B L-2-hydroxyglutaric aciduria			Patient C Ornithine transcarbamylase deficiency			TOTAL
	A	I	TOTAL	A	I	TOTAL	A	I	TOTAL	
59	-	-	**-**	-	-	**-**	-	-	**-**	**-**
60	2	2	**4**	2	2	**4**	2	2	**4**	**12**
61	2	2	**4**	2	2	**4**	0	0	**0**	**8**
62	-	-	**-**	-	-	**-**	-	-	**-**	**-**
63	2	2	**4**	2	2	**4**	0	2	**2**	**10**
64	2	2	**4**	2	1	**3**	0	2	**2**	**9**
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	2	2	**4**	2	2	**4**	0	0	**0**	**8**
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	1	**3**	2	2	**4**	**11**
72	2	2	**4**	0	0	**0**	2	2	**4**	**8**
73	2	2	**4**	2	2	**4**	2	2	**4**	**12**
74	2	2	**4**	2	2	**4**	0	2	**2**	**10**
75	2	2	**4**	2	0	**2**	0	0	**0**	**6**
76	2	2	**4**	2	2	**4**	0	2	**2**	**10**
77	2	2	**4**	2	2	**4**	2	2	**4**	**12**

Detailed scores –Round 2

Lab n°	Patient D Multiple acyl-CoA dehydrogenase deficiency			Patient E Normal sample			Patient F Glutaric aciduria type I			TOTAL
	A	I	TOTAL	A	I	TOTAL	A	I	TOTAL	
1	2	2	**4**	2	2	**4**	2	2	**4**	**12**
2	-	-	**-**	-	-	**-**	-	-	**-**	**-**
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**

Lab n°	Patient D Multiple acyl-CoA dehydrogenase deficiency			Patient E Normal sample			Patient F Glutaric aciduria type I			TOTAL
	A	I	TOTAL	A	I	TOTAL	A	I	TOTAL	
8	1	0	**1**	2	2	**4**	2	2	**4**	**9**
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**	0	0	**0**	1	2	**3**	**6**
12	2	2	**4**	2	2	**4**	1	0	**1**	**9**
13	2	2	**4**	2	2	**4**	2	2	**4**	**12**
14	2	2	**4**	2	2	**4**	2	2	**4**	**12**
15	1	0	**1**	2	2	**4**	2	2	**4**	**9**
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**	1	2	**3**	**11**
21	2	2	**4**	2	2	**4**	2	2	**4**	**12**
22	1	0	**1**	2	2	**4**	2	2	**4**	**9**
23	2	2	**4**	2	2	**4**	2	2	**4**	**12**
24	1	2	**3**	2	2	**4**	2	2	**4**	**11**
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	1	0	**1**	2	2	**4**	2	2	**4**	**9**
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	0	0	**0**	0	0	**0**	2	2	**4**	**4**
36	2	2	**4**	2	2	**4**	2	2	**4**	**12**
37	1	0	**1**	2	2	**4**	2	2	**4**	**9**
38	2	2	**4**	2	2	**4**	2	2	**4**	**12**
39	1	2	**3**	2	2	**4**	2	2	**4**	**11**

Lab n°	Patient D Multiple acyl-CoA dehydrogenase deficiency			Patient E Normal sample			Patient F Glutaric aciduria type I			TOTAL
	A	I	TOTAL	A	I	TOTAL	A	I	TOTAL	
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	0	**1**	2	2	**4**	2	2	**4**	**9**
44	2	2	**4**	2	2	**4**	2	2	**4**	**12**
45	2	2	**4**	2	2	**4**	2	2	**4**	**12**
46	1	0	**1**	0	0	**0**	2	2	**4**	**5**
47	2	2	**4**	2	2	**4**	1	0	**1**	**9**
48	-	-	**-**	-	-	**-**	-	-	**-**	**-**
49	2	2	**4**	0	0	**0**	2	2	**4**	**8**
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	2	**4**	2	2	**4**	2	2	**4**	**12**
54	2	2	**4**	2	2	**4**	2	2	**4**	**12**
55	1	0	**1**	2	2	**4**	2	2	**4**	**9**
56	-	-	**-**	-	-	**-**	-	-	**-**	**-**
57	2	2	**4**	2	2	**4**	0	2	**2**	**10**
58	2	2	**4**	2	2	**4**	2	2	**4**	**12**
59	1	0	**1**	2	2	**4**	2	2	**4**	**9**
60	2	2	**4**	2	2	**4**	2	2	**4**	**12**
61	2	2	**4**	2	2	**4**	2	2	**4**	**12**
62	-	-	**-**	-	-	**-**	-	-	**-**	**-**
63	2	2	**4**	2	2	**4**	0	0	**0**	**8**
64	1	0	**1**	2	2	**4**	2	2	**4**	**9**
65	1	1	**2**	2	2	**4**	2	2	**4**	**10**
66	-	-	**-**	-	-	**-**	-	-	**-**	**-**
67	1	2	**3**	2	2	**4**	2	2	**4**	**11**
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**	2	2	**4**	**12**
71	2	2	**4**	2	2	**4**	2	2	**4**	**12**

Lab n°	Patient D Multiple acyl-CoA dehydrogenase deficiency			Patient E Normal sample			Patient F Glutaric aciduria type I			TOTAL
	A	I	TOTAL	A	I	TOTAL	A	I	TOTAL	
72	-	-	**-**	-	-	**-**	-	-	**-**	**-**
73	2	2	**4**	2	2	**4**	2	2	**4**	**12**
74	1	1	**2**	2	2	**4**	2	2	**4**	**10**
75	1	2	**3**	2	2	**4**	2	2	**4**	**11**
76	2	2	**4**	2	2	**4**	2	2	**4**	**12**
77	2	2	**4**	2	2	**4**	2	2	**4**	**12**

Total scores

Key:
CE: Critical error
PP: Poor performance (on score)
Blank in performance: Satisfactory

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Performance
1	**4**	**4**	**4**	**4**	**4**	**4**	**24**	**100**	
2	**4**	**4**					**8**	**33**	ONE RETURN
3	**4**	**4**	**0**	**4**	**4**	**4**	**20**	**83**	
4	**4**	**4**	**4**	**4**	**4**	**4**	**24**	**100**	
5	**4**	**4**	**4**	**4**	**4**	**4**	**24**	**100**	
6	**4**	**4**	**3**	**4**	**4**	**4**	**23**	**96**	
7	**4**	**4**	**1**	**4**	**4**	**4**	**21**	**88**	
8	**4**	**4**	**4**	**1**	**4**	**4**	**21**	**88**	CE
9	**4**	**3**	**4**	**4**	**4**	**4**	**23**	**96**	
10	**4**	**4**	**4**	**4**	**4**	**4**	**24**	**100**	
11	**2**	**2**	**2**	**3**	**0**	**3**	**12**	**50**	PP
12	**4**	**4**	**4**	**4**	**4**	**1**	**21**	**88**	CE
13	**4**	**4**	**4**	**4**	**4**	**4**	**24**	**100**	
14	**4**	**4**	**4**	**4**	**4**	**4**	**24**	**100**	
15	**4**	**4**	**4**	**1**	**4**	**4**	**21**	**88**	
16	**4**	**4**	**4**	**4**	**4**	**4**	**24**	**100**	
17	**4**	**4**	**4**	**4**	**4**	**4**	**24**	**100**	
18	**4**	**4**	**3**	**4**	**4**	**4**	**23**	**96**	
19	**4**	**4**	**4**	**4**	**4**	**4**	**24**	**100**	
20	**4**	**4**	**2**	**4**	**4**	**3**	**21**	**88**	

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Performance
21	4	4	2	4	4	4	22	92	
22	4	3	4	1	4	4	20	83	
23	4	4	4	4	4	4	24	100	
24	4	4	4	3	4	4	23	96	
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	4	24	100	
29	4	0	2	1	4	4	15	63	PP,CE
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	3	4	4	4	4	23	96	
35	4	4	0	0	0	4	12	50	PP,CE
36	4	4	4	4	4	4	24	100	
37				1	4	4	9	38	ONE RETURN
38	4	4	4	4	4	4	24	100	
39	4	2	0	3	4	4	17	71	
40	4	4	4	4	4	4	24	100	
41	4	4	4	4	4	4	24	100	
42	4	4	4	4	4	4	24	100	
43	4	4	4	1	4	4	21	88	
44	4	4	0	4	4	4	20	83	
45	4	4	4	4	4	4	24	100	
46	4	0	4	1	0	4	13	54	PP,CE
47	4	4	2	4	4	1	19	79	CE
48	4	4	4				12	50	ONE RETURN
49	4	4	2	4	0	4	18	75	
50	2	2	2	4	4	4	18	75	
51	4	4	4	4	4	4	24	100	
52	4	4	4	4	4	4	24	100	
53		4	1	4	4	4	17	71	
54	4	4	4	4	4	4	24	100	
55	4	4	3	1	4	4	20	83	
56	4	4	0				8	33	ONE RETURN
57	4	4	2	4	4	2	20	83	
58	4	4	0	4	4	4	20	83	
59				1	4	4	9	38	ONE RETURN
60	4	4	4	4	4	4	24	100	
61	4	4	0	4	4	4	20	83	

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Performance
62								0	NON-SUBMITTER
63	4	4	2	4	4	0	18	75	CE
64	4	3	2	1	4	4	18	75	
65	4	4	4	2	4	4	22	92	
66	4	4	4				12	50	ONE RETURN
67	4	4	4	3	4	4	23	96	
68	4	4	0	4	4	4	20	83	
69	4	4	4	4	4	4	24	100	
70	4	4	4	4	4	4	24	100	
71	4	3	4	4	4	4	23	96	
72	4	0	4				8	33	ONE RETURN,CE
73	4	4	4	4	4	4	24	100	
74	4	4	2	2	4	4	20	83	
75	4	2	0	3	4	4	17	71	
76	4	4	2	4	4	4	22	92	
77	4	4	4	4	4	4	24	100	

Performance

	Number of labs	% total labs
Satisfactory performers (≥ 71 % of adequate responses)	61	79
Unsatisfactory performers (< 71 % adequate responses and/or critical error)	9	11.6
Partial and non-submitters	8	10.3

Overall Proficiency

Sample ID	Diagnosis	Proficiency (%)
QLOU-EB-2024-A	Phenylketonuria	99
QLOU-EB-2024-B	L-2-hydroxyglutaric aciduria	92
QLOU-EB-2024-C	Ornithine transcarbamylase deficiency	76
QLOU-EB-2024-D	Multiple acyl-CoA dehydrogenase deficiency	85
QLOU-EB-2024-E	Normal sample	94
QLOU-EB-2024-F	Glutaric aciduria type I	95

11. Annual meeting of participants

In 2025, a 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 SKML: 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 ERNDIM website. 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 2025

Sample distribution	5 February
Start of analysis of Survey 2025/1 Website open	May 6
Survey 2025/1 - Results submission	May 27
Survey 2025/1 - Reports	July
Start of analysis of Survey 2025/2	August 18
Survey 2025/2 – Results submission	September 8
Survey 2025/2 - Reports	October
Annual Report 2025	January-March 2026

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.

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

Dr. Judit García Villoria
Hospital Clínic de Barcelona
Division of Inborn Errors of Metabolism
c/Mejía Lequerica s/n Edificio Helios III, pb
08028 Barcelona, Spain
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APPENDIX 1. **Change log (changes since the last version)**

Version Number	Published	Amendments
1	15 April 2025	2024 annual report published
2	24 April 2025	Fixed an error in the 'Total Scores' table in Section 9, where the percentage cumulative score was incorrect for some labs

END