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Qualitative Organic Acids

Centre: Spain

Final Report 2022

prepared by
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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 and the ERNDIM Privacy Policy on www.erndim.org.

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, a subcontractor of ERNDIM.

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 2022 seventy-four laboratories from many different countries participated in the QLOU *Barcelona* scheme, without any educational participants (2 in 2021, 1 in 2020, 2 in 2019). 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.

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.

[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.

1. Geographical distribution of participants

For the first survey and for the second survey 72 laboratories submitted results.

Country	Number of participants	Country	Number of participants
Argentina	3	Lebanon	1
Brazil	2	People's Republic of China	1
Chili	1	Philippines	1
Colombia	1	Portugal	2
Cyprus	1	Qatar	1
France	21	Saudi Arabia	1
Germany	1	Singapore	1
Greece	1	Spain	9
Hong Kong	5	United Kingdom	1
India	4	Uruguay	1
Italia	15		

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

Patient A: Multiple acyl-CoA dehydrogenases deficiency- Barcelona, Spain
Patient B: Alkaptonuria - Montevideo, Uruguay
Patient C: Normal sample - Barcelona, Spain
Patient D: Propionic acidemia – Barcelona, Spain
Patient E: 2-amino/2-ketoadipic aciduria – Barcelona, Spain
Patient F: Pyroglutamic aciduria –Barcelona, Spain

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.

3. Tests

Required method is the determination of organic acids.

4. Schedule of the scheme

- February 2, 2022: shipment of samples of Survey 1 and Survey 2
- May 9, 2022: analysis start, clinical data available and submission availability in the website (Survey 1)
- May 30, 2022: deadline for result submission (Survey 1)
- August 8, 2022: interim report of Survey 1 available in the website
- August 29, 2022: analysis start, clinical data available and submission availability in the website (Survey 2)
- September 19, 2022: deadline for result submission (Survey 2)
- November 1, 2022: interim report of Survey 2 available in the website
- January, 2023: annual report with scoring by e-mail

5. Results

72 of 74 labs returned results for both surveys, mainly by the deadline.

	Survey 1	**Survey 2**
Receipt of results	72	72
No answer	2	2

6. 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.

7. 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 24th & 25th 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 2022, the SAB decided that sample A has to be considered as a critical error for the labs who failed to identify an increase of ethylmalonate, 2-hydroxyglutarate and 2-hydroxyglutarate lactone, various acylglycins and dicarboxilic aciduria and nor the diagnosis of Multiple Acyl-CoA dehydrogenase deficiency, and not provide any further recommendations to rule out it. Also, SAB decided that sample F has to be considered as a critical error for the labs who failed to identify increase of pyroglutamic acid and nor diagnosis of Glutathione synthetase deficiency and, and not provide any 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. Two performance support letters will be sent by the Scheme Advisor for 2022. Any partial submitters will receive a letter from the ERNDIM Executive Administrator, Sara Gardner.

7.1. 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.

8. Results of samples and evaluation of reporting

8.1. Patient A

Multiple acyl-CoA dehydrogenases deficiency

Patient details provided to participants

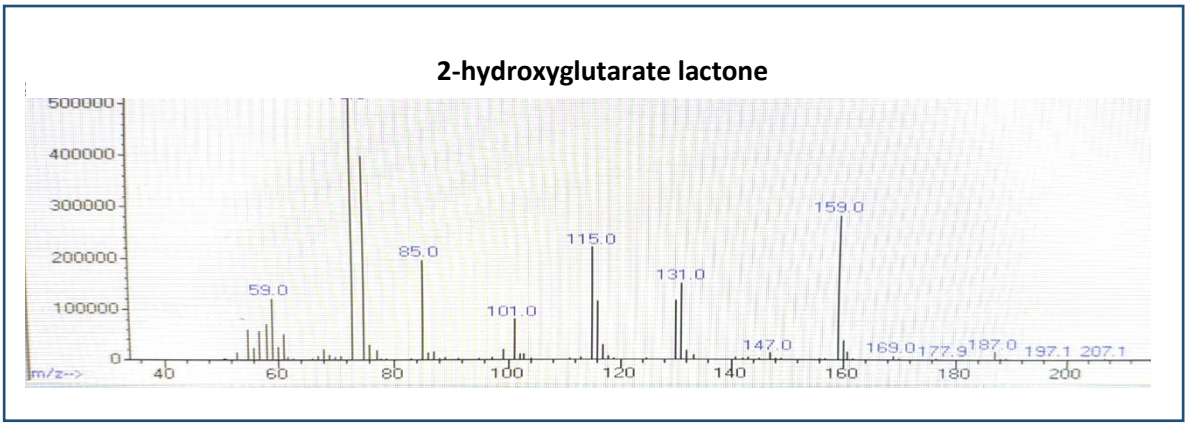
Female with mild cognitive retardation, decompensations for fasting and / or intercurrent infections. Currently under treatment.

Patient details

The urine sample is from a patient diagnosed of multiple acyl-CoA dehydrogenase deficiency at 1 year of age. The sample was collected at 18 years of age, under carnitine treatment. Currently she presents severe intellectual deficit and recurrent epilepsy.
She presents mutations in the *ETFB* gene with the following mutations: p.[Cys42Arg] ; [Lys202del] .
The organic acid profile shows the typical pattern of the disease in adults with elevated excretion of ethylmalonate, 2-hydroxyglutarate, 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.

Analytical performance

-72 laboratories of 74 active participants submitted results for sample A.
- 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: 94% and 93% of the participants detected the increase of ethylmalonate and 2- hydroxyglutarate respectively. 74% of the laboratories reported increased isovalerylglycine and 71% the increase of hexanoylglycine. The increase of other acylglycines (isobutyrylglycine and suberylglycine), and other dicarboxylic acids were detected between the 50 and 55% of participants.
-The 2-hydroxyglutarate lactone, also a characteristic metabolite, was detected only in 17% of the labs. For this reason, the mass spectrum is provided:



Diagnosis / Interpretative proficiency

-The 65 laboratories (90%) of the participants reported multiple acyl-CoA dehydrogenases deficiency or glutaric aciduria type II as the correct diagnosis.
-4 participants give the diagnosis of 2-hydroxylutaric aciduria. 1 laboratory reported isovaleryl-CoA dehydrogenase deficiency and 2 labs reported as normal sample.

Recommendations

-78% of laboratories recommended performing acylcarnitine analysis
-The genetic study of *ETFA, ETFB* and *ETFDH* was recommended for 62% of the laboratories
-Only 21% of the laboratories considered studying genes involved in riboflavin metabolism and transport.
-Some laboratories didn't specify the genes to study and also recommended study of fatty acid oxidation in fibroblasts or lymphocytes and riboflavin test.

Scoring

- Analytical results: increased 2-hydroxyglutarate and ethylmalonate plus some dicarboxylic acid or acylglycines (score 2). If a key metabolite is missed (score 1).

- Interpretation of results: diagnosis of multiple acyl-CoA dehydrogenases deficiency or glutaric aciduria type II (score 2). If other diagnosis is reported but in the recommendations the study of acylcarnitines is specified (score 1).

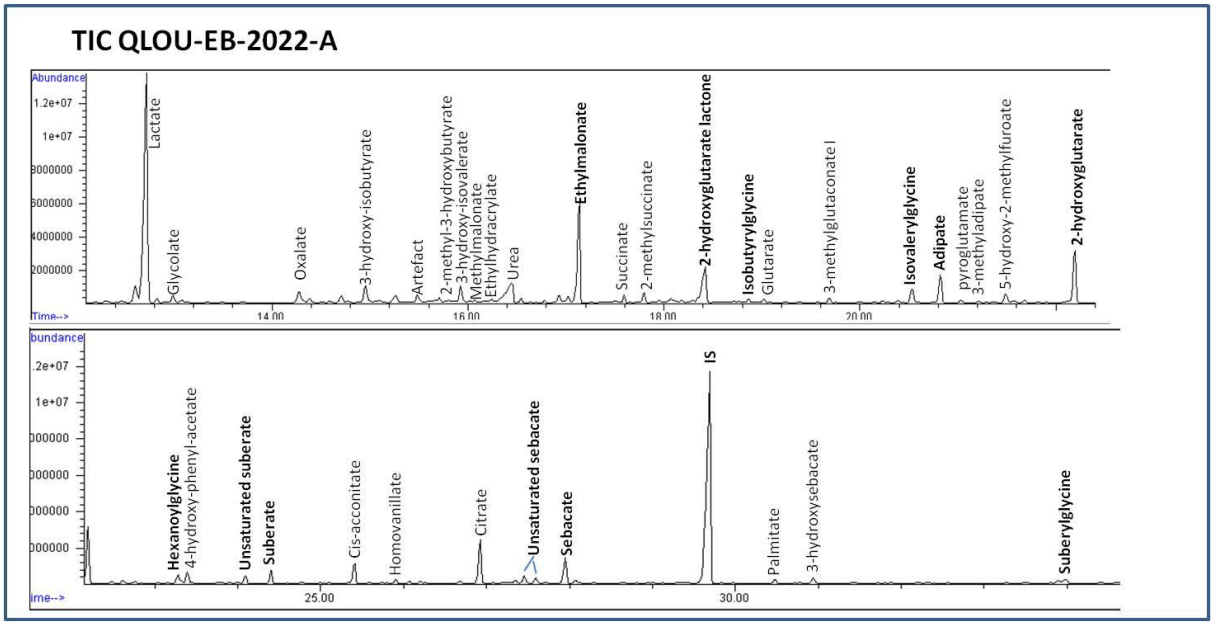
Overall impression
The overall performance was 91%.

Multiple distributions of similar samples
The same sample was circulated at 2018 and an improvement in th2 2022 circulation was observed:

Circulation	2018	2022
Overall performance	77%	91%

-In 2018 6 labs reported MCAD diagnosis, (no any MCAD reported in 2022)
-In 2028 5 labs reported 2-hydroxyglutaric aciduria (4 in 2022)
-In 2028 2 labs reported Ethylmalonic encephalopathy (ETHE1), any lab reported this diagnosis in 2022

Chromatogram sample A:



8.2. Patient B

Alkaptonuria

Patient details provided to participants

Sine one month of age the mother noticed diapers stained black in several opportunities. Currently under treatment.

Patient details

The sample was from a patient with Alkaptonuria at the age of 7 years-old and under treatment. Clinically, the mother noticed diapers stained black in several opportunities since he was 1 month of age. Several studies were performed on blood and urine, but it was not possible to confirm a causal diagnosis, during infancy. When he was 3 years of age, the analysis of homogentisic acid was performed and the diagnosis was established. He did not have development delay or cognitive impairment. He receives vitamin C and follows protein-limited diet.

Analytical performance

-72 laboratories of 74 active participants submitted results for sample B.

-100 % of the laboratories identified the increased homogentisic acid.

Diagnosis / Interpretative proficiency

-100% of participants reported Alkaptonuria as correct diagnosis.

Recommendations

-92% of the laboratories recommended confirming the diagnosis with de *HGD* gene study.
-13% of the participants considered to analyse plasmatic aminoacids.
-The analysis of homogentisic acid in another urine sample was mentioned by 11% of the laboratories.
-7% of the participants recommended performing homogentisate 1,2-dioxygenase activity in the liver.

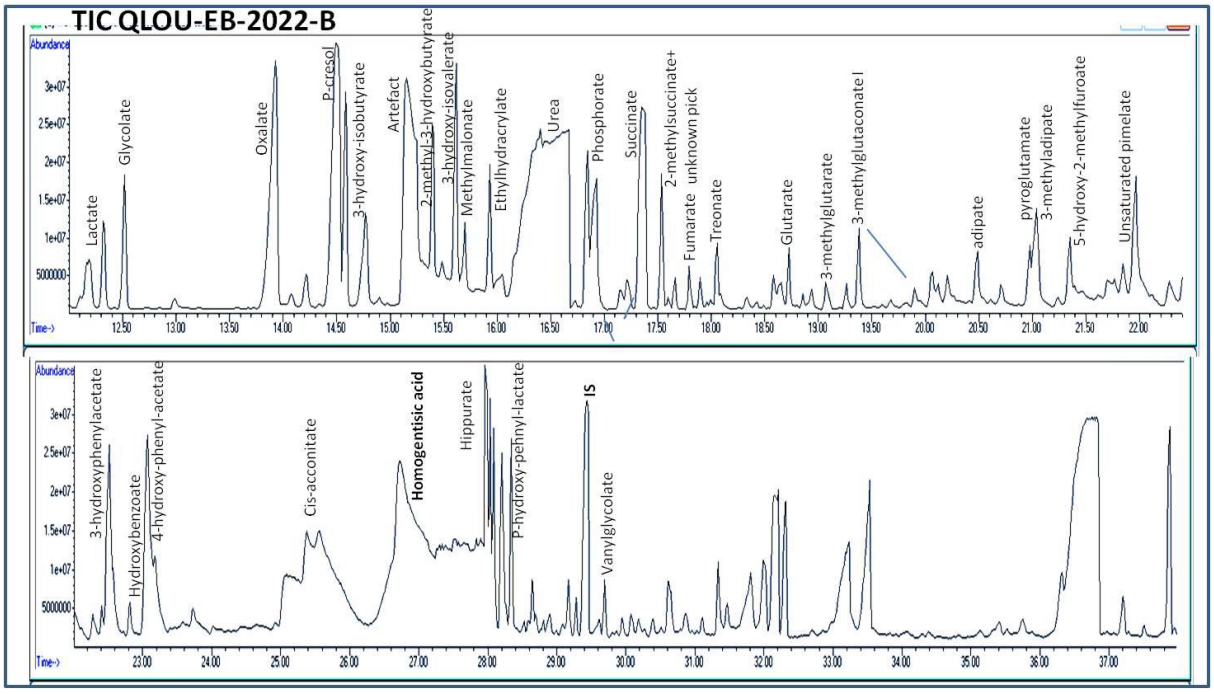
Scoring

- Analytical results: increase of homogentisic acid (score 2)
- Interpretation of results: diagnosis of Alkaptonuria and study (score 2)

Overall impression

The overall performance was 100%.

Chromatogram sample B:



8.3. Patient C

Normal profile

Patient details provided to participants

18 year-old female with Epilepsy

Patient details

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

Analytical performance

-72 laboratories of 74 active participants submitted results for sample C.
-96% of laboratories no abnormalities were detected in organic acid profile.

Diagnosis / Interpretative proficiency

-99% of participants reported as normal sample.
-1 laboratory give the diagnosis of folate deficiency.

Recommendations

-25% of the laboratories recommended analyzing aminoacids
-16% of the participants suggested performing NGS genetic test
-About 9% of the labs recommended purine and pyrimidines, folate and vitamins B6 and B12, pipecolic and Alphaaminoadipic
semialdehyde, acylcarnitines, and neurotransmitters.
-Less than 7% suggested performing oxysterols, creatine and guanidinoacetate, homocysteine, ammonia, lactate,
pyruvate and to rule out peroxisomal, lysosomal, and CDG defects.

Scoring

- Analytical results: normal profile (score 2)
- Interpretation of results: normal sample (score 2).

Overall impression

The overall performance was 97%.

8.4. Patient D

Propionic acidemia

Patient details provided to participants

32 year-old female with severe intellectual deficit and recurrent epilepsy. The diagnosis was performed in the first year of life. Currently under treatment

Patient details

The urine sample is from a patient diagnosed with propionic acidemia, which was collected at 32 years of age, under carnitine and dietary treatment. The patient was diagnosed at 1 year of age and currently, she presents severe intellectual deficit and recurrent epilepsy.
The organic acid profile shows the typical pattern of the disease with elevated excretion of 3-hydroxypropionate, 2-methylcitrate and propionylglycine.
The diagnosis of propionic acidemia was confirmed by detecting mutations in *PCCB* gene.

Analytical performance

-72 laboratories of 74 active participants submitted results for sample D.
- In addition to the pathological excretion of key metabolites: 3-hydroxypropionate, 2-methylcitrate and propionylglycine, the increase of other organic acids from isoleucine catabolic pathway such a tiglylglycine and 2-methyl-3-hydroxybutyrate, were detected, as well as other compounds such a 3-hydroxisovaleric. High excretion of lactate and fumarate were present too. The presence of drug metabolites such as ethosuximide and carbamazepine can also be detected.
-The 97 % of participants detected the increase of 2-methylcitrate and propionylglycine. 96% of laboratories reported increased 3-hydroxypropionate levels. In total, 90% of participants remarked on the pathological excretion of the three metabolites.
-In addition, 28% and 25 % of the labs reported an increase of fumarate and lactate respectively. Less than 20% reported increased levels of 2.methyl-3-hydroxybutyrate, 3-hydroxyisovalerate and ethosuxmide and carbamazepine metabolites.

Diagnosis / Interpretative proficiency

- 71 laboratories (99%) reported propionic aciduria as the correct diagnosis.
- Two laboratories established the diagnosis of multiple carboxylase deficiency or biotinidase deficiency, but one of
them put an alternative diagnosis of propionic acidemia.

Recommendations

The majority of the laboratories recommend performing both blood aminoacids and acylcarnitines, and mutation analysis in *PCCA* and *PCCB* genes. If mutations are not found, the propionyl-CoA carboxylase activity can be measured in fibroblasts.

Scoring

- Analytical results: 3-hydroxypropionate, 2-methylcitrate and propionylglycine (score 2). 3-hydroxypropionate, 2-methylcitrate and propionylglycine. If a key metabolite is missed (score 1).
- Interpretation of results: diagnosis of propionic acidemia as the most likely diagnostic or alternative (score 2).

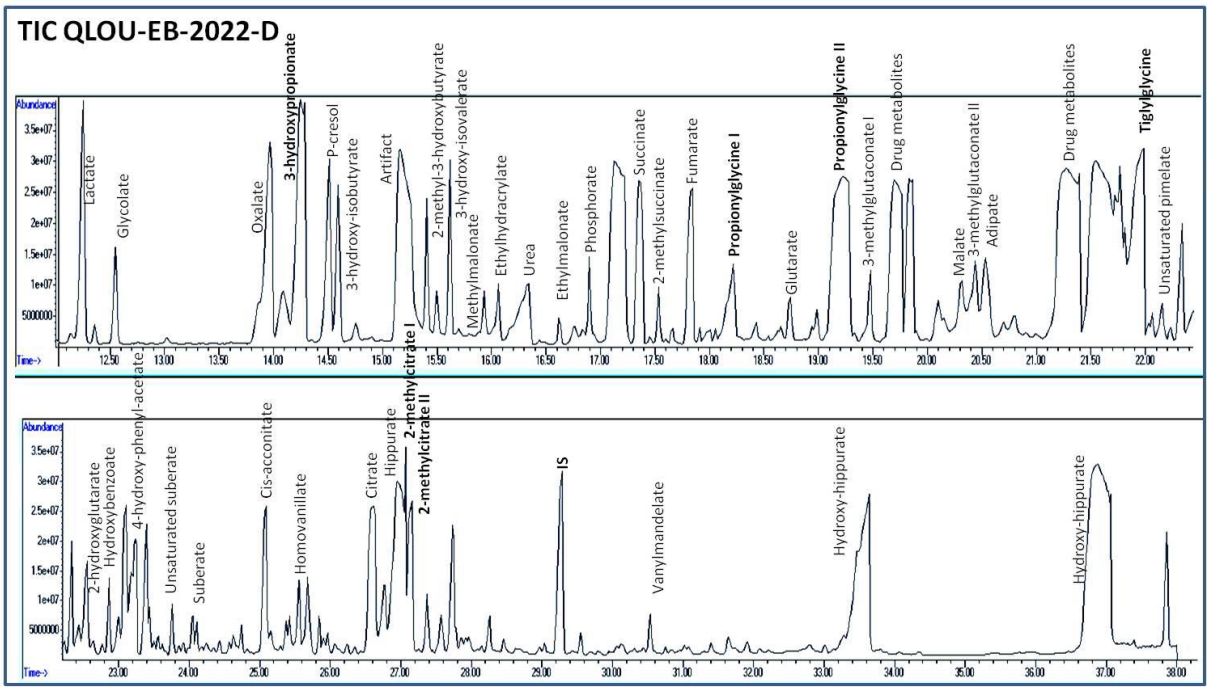
Overall impression

The overall performance was 97%.

Multiple distributions of similar samples

Similar proficiency was obtained in other circulation in 2018.

Circulation	2018	2022
Overall performance	99%	97%


TIC QLOU-EB-2022-D
Lactate
Glycolate
Oxalate
3-hydroxypropionate
P-cresol
3-hydroxy-isobutyrate
Artifact
2-methyl-3-hydroxybutyrate
3-hydroxy-isovalerate
Methylmalonate
Ethylhydracrylate
Urea
Ethylmalonate
Phosphorate
Succinate
2-methylsuccinate
Fumarate
Propionylglycine I
Glutarate
Propionylglycine II
3-methylglutaconate I
Drug metabolites
Malate
3-methylglutaconate II
Adipate
Drug metabolites
Tiglylglycine
Unsaturated pimelate
2-hydroxyglutarate
Hydroxybenzoate
4-hydroxy-phenyl-acetate
Unsaturated suberate
Suberate
Cis-aconitate
Homovanillate
Citrate
Hippurate
2-methylcitrate I
2-methylcitrate II
IS
Vanylmandelate
Hydroxy-hippurate
Hydroxy-hippurate

8.5. Patient E

2-amino/2-ketoadipic aciduria

Patient details provided to participants

Asymptomatic mother of a child who was asked for a second sample of a neonatal screening due to elevation of methylmalonic acid. After different studies a maternal B12 deficiency was ruled out.

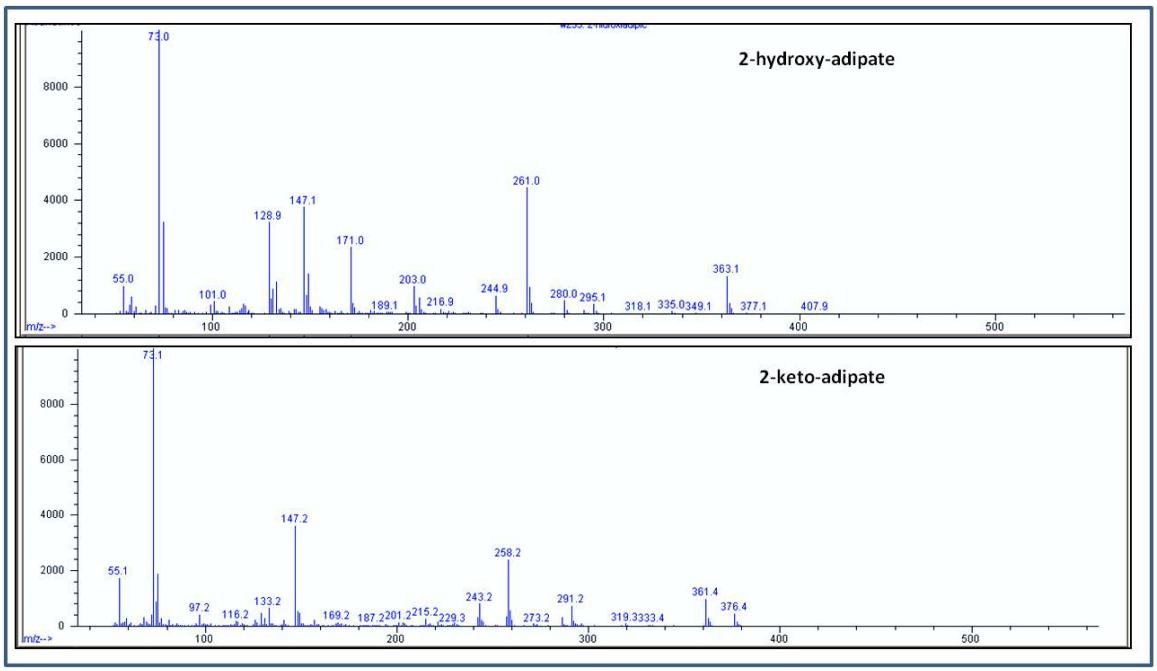
Patient details

The urine sample was from an asymptomatic vegetarian mother. Her child was breastfeeding and presented an increase of propionylcarnitine in the neonatal screening. For that reason, both the child and the mother were studied to rule out maternal vitamin B12 deficiency. The maternal organic acid profile showed an increase of 2- hydorxyadipate, 2-ketoadipate, and glutarate. This incidental finding let to the diagnosis of 2-amino/2-ketoadipic aciduria. In addition, she was taking ibuprofen.

Analytical performance

-72 laboratories of 74 active participants submitted results for sample E.
-49 laboratories (68%) reported elevated excretion of 2-hydroxyadipate and 47 laboratories (65%) detected an elevation of 2-ketoadipate. In addition, 39% and 25 % of participants detected an increase of glutarate and ibuprofen metabolites respectively.

The mass spectrum of both key metabolites is provided:



Diagnosis / Interpretative proficiency

-The correct diagnosis of 2-amino/2-ketoadipic aciduria was performed by 49 laboratories (68%).
-21 laboratories (29%) reported as a normal sample. One laboratory established the diagnosis of glutaric aciduria type III and another participant reported a multiple acyl-CoA dehydrogenase deficiency.

Recommendations

The majority of the laboratories recommend performing urinary amino acids looking for increased aminoadipic acid and *DHTKD1* gene analysis.

Scoring

- Analytical results: increase of 2-ketoadipate (score 1), increased 2-hydroxyadipate (score 1).
- Interpretation of results: 2-amino/2-ketoadipic aciduria as the most likely diagnostic or alternative (score 2).

Overall impression

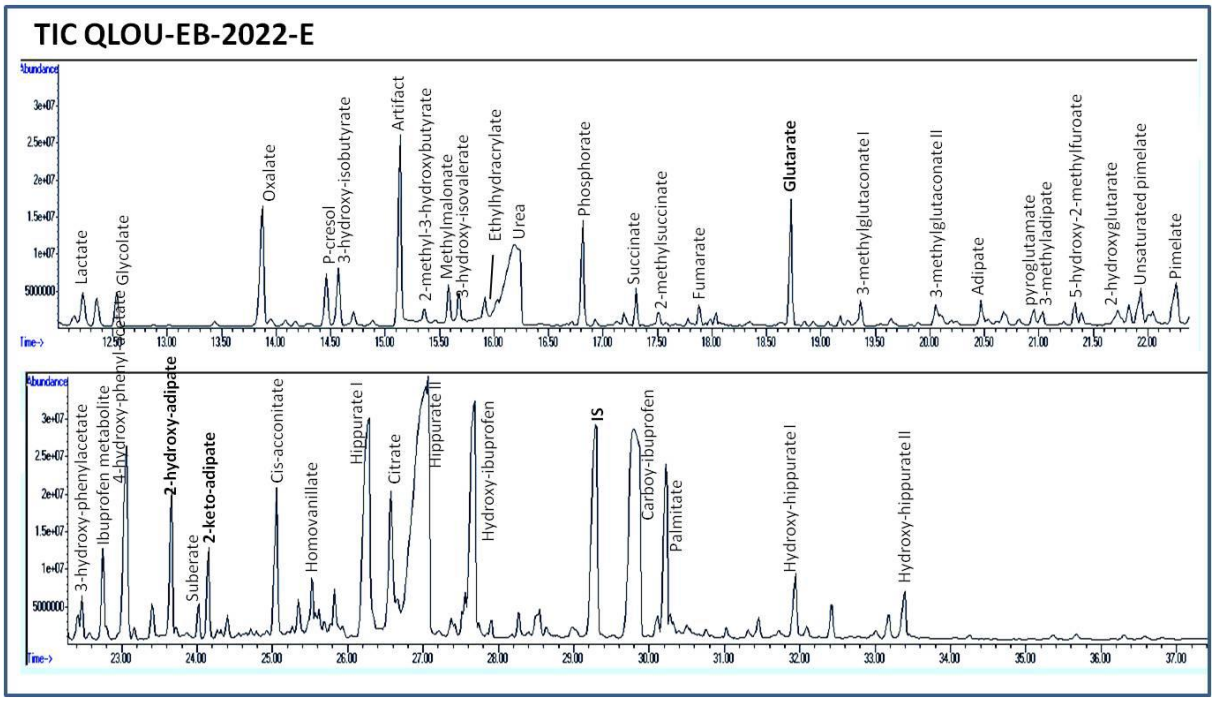
The overall performance was 67%.

Multiple distributions of similar samples

Circulation	2019	2022
Overall performance	67%	67%

9 participants reported as normal samples in both circulations. 9 participants established the correct diagnosis in 2019 but in this circulation reported as normal. 10 laboratories improve their proficiency

Chromatogram sample E:



8.6. Patient F

Glutathione synthetase deficiency

Patient details provided to participants

At first year of life haemolytic anemia. The diagnosis was performed at 1 year of life. Currently she has dysplasia and osteoporosis, and is under treatment.

Patient details

The urine samples was from a patient who onset with hemolytic anemia at the first year of life which lead to the diagnosis of piroglutamic aciduria. The sample was collected at 30 years of life under treatment. The current symptoms are the crisis of hemolytic anemia, metabolic acidosis, neuropathy, psychomotor retardation, stroke,ataxia, spasticity, tremor, frequent bacterial infections, retinal dystrophy, dysplasia, and osteoporosis. The organic acid profile shows the typical pattern of the disease with elevated excretion of pyroglutamic acid.

Analytical performance

-72 laboratories of 74 active participants submitted results for sample F.
-69 of the participants (96%) detected an increase of pyroglutamic acid. In addition, ketosis and lactic acidosis could be detected. Increase of 3-hydroxybutyrate was reported by 39% of labs and increased acetoacetate by 21% of labs. The increase of lactic acid was detected by 19% of participants.

Diagnosis / Interpretative proficiency

-69 of the participants (96%) reported pyroglutamic aciduria as the correct diagnosis.
-Three laboratories established the diagnosis of oxoprolinase deficiency but two of them put an alternative diagnosis pyroglutamic acidemia. Two laboratories reported as a normal sample.

Recommendations

The majority of participants recommend measuring Glutathione synthetase activity in red blood cells, lymphocytes, or in fibroblasts and quantifying Glutathione in red blood cells, leukocytes, or fibroblasts. In addition, perform the mutational analysis of the GSS gene. Some laboratories recommended exploring mutation analysis (OPLAH gene) if necessary. However, the clinical presentation was suggestive of GSS deficiency.

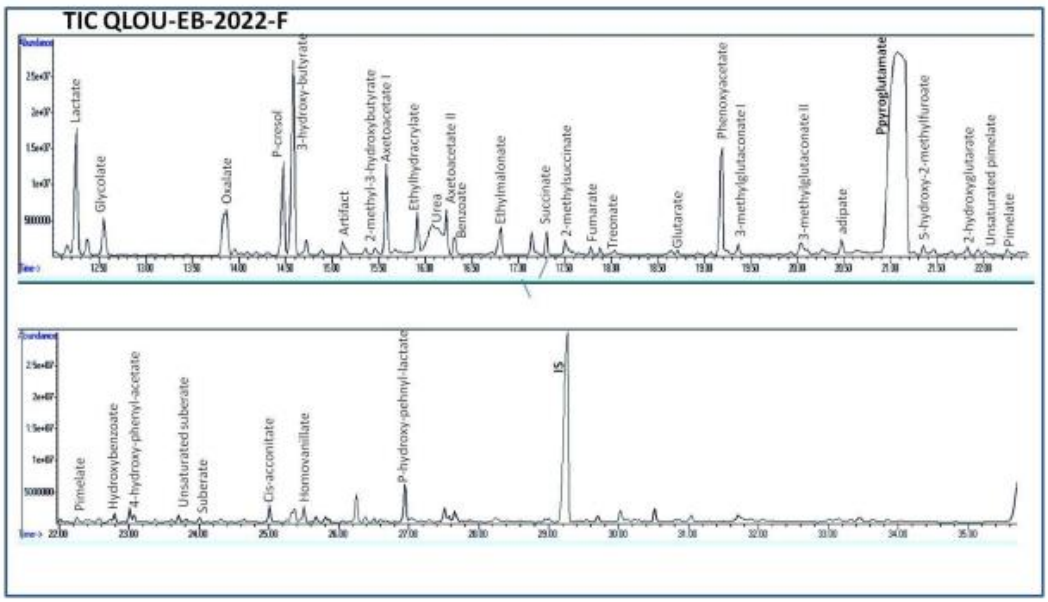
Scoring

- Analytical results: increased pyroglutamic acid (score 2).
- Interpretation of results: pyroglutamic aciduria or Glutathione synthetase deficiency (score 2).

Overall impression

The overall performance was 96%.

Chromatogram 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.

Detailed scores – **Round 1**

Lab n°	Patient A Multiple acyl-CoA dehydrogenases deficiency			Patient B Alkaptonuria			Patient C Normal sample			
	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	2	2	4	2	2	4	12
4	2	2	4	2	2	4	2	2	4	12
5	2	2	4	2	2	4	2	2	4	12
6	2	2	4	2	2	4	2	2	4	12
7	2	2	4	2	2	4	2	2	4	12
8	2	2	4	2	2	4	2	2	4	12
9	2	2	4	2	2	4	2	2	4	12
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13	2	2	4	2	2	4	2	2	4	12
14	1	2	3	2	2	4	2	2	4	11
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	1	1	2	2	2	4	2	2	4	10
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24	2	2	4	2	2	4	2	2	4	12
25	0	0	0	0	0	0	0	0	0	0
26	2	2	4	2	2	4	2	2	4	12
27	2	0	2	2	2	4	2	2	4	10

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	0	0	0	8
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	2	4	2	2	4	12
39	2	2	4	2	2	4	2	2	4	12
40	2	2	4	2	2	4	2	2	4	12
41	2	2	4	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	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	0	0	0	0	0	0	0	0	0	0
54	1	0	1	2	2	4	2	2	4	9
55	2	2	4	2	2	4	2	2	4	12
56	0	0	0	2	2	4	2	2	4	8
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	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	2	4	2	2	4	12
63	2	2	4	2	2	4	2	2	4	12
64	1	2	3	2	2	4	2	2	4	11

65	1	0	1	2	2	4	2	2	4	9
66	2	2	4	2	2	4	2	2	4	12
67	2	2	4	2	2	4	2	2	4	12
68	1	0	1	2	2	4	2	2	4	9
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	1	2	3	2	2	4	2	2	4	11
73	2	2	4	2	2	4	2	2	4	12
74	2	2	4	2	2	4	2	2	4	12

Detailed scores – Round 2

Lab n°	Patient D Propionic acidemia			Patient E 2-amino/2-ketoadipic aciduria			Patient F Pyroglutamic aciduria			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	2	4	1	2	3	2	2	4	11
2	2	2	4	2	2	4	2	2	4	12
3	2	2	4	2	2	4	2	2	4	12
4	2	2	4	2	2	4	2	2	4	12
5	2	2	4	2	2	4	2	2	4	12
6	2	2	4	2	2	4	2	2	4	12
7	2	2	4	2	2	4	2	2	4	12
8	2	2	4	2	2	4	2	2	4	12
9	2	2	4	1	0	1	2	2	4	9
10	2	2	4	2	2	4	0	2	2	10
11	2	2	4	2	2	4	2	2	4	12
12	2	2	4	0	0	0	0	2	2	6
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	0	0	0	2	2	4	8
16	2	2	4	0	0	0	2	2	4	8
17	1	2	3	2	2	4	2	2	4	11
18	2	2	4	2	2	4	2	2	4	12
19	2	2	4	0	0	0	2	2	4	8
20	2	2	4	1	0	1	2	2	4	9
21	2	2	4	2	2	4	2	2	4	12
22	2	2	4	0	0	0	2	2	4	8
23	2	2	4	1	0	1	2	2	4	9
24	2	2	4	2	2	4	2	2	4	12
25	2	2	4	1	2	3	2	2	4	11
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	2	2	4	8
30	2	0	2	2	2	4	2	2	4	10
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	0	2	2	2	2	4	10
36	2	2	4	0	0	0	2	2	4	8
37	2	2	4	0	0	0	2	2	4	8
38	2	2	4	2	2	4	2	2	4	12
39	2	2	4	2	2	4	2	2	4	12
40	2	2	4	2	2	4	2	2	4	12
41	2	2	4	0	0	0	2	2	4	8
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	2	2	4	12
45	2	2	4	1	2	3	2	2	4	11
46	2	2	4	1	0	1	2	2	4	9
47	2	2	4	1	2	3	2	2	4	11
48	2	2	4	0	0	0	2	2	4	8
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	0	0	0	0	0	0	0	0	0	0
54	2	2	4	0	0	0	2	2	4	8
55	2	2	4	2	2	4	2	2	4	12
56	1	2	3	1	2	3	2	0	2	8
57	2	2	4	2	2	4	2	2	4	12
58	2	2	4	0	0	0	2	2	4	8
59	1	2	3	1	0	1	2	0	2	6
60	2	2	4	2	2	4	2	2	4	12
61	1	2	3	0	0	0	2	2	4	7
62	2	2	4	0	0	0	2	2	4	8
63	2	2	4	0	0	0	2	2	4	8
64	2	2	4	2	2	4	2	2	4	12
65	2	2	4	0	0	0	2	2	4	8
66	2	2	4	2	2	4	2	2	4	12
67	2	2	4	1	2	3	2	2	4	11
68	1	0	1	1	2	3	0	0	0	4

69	2	2	4	1	0	1	2	2	4	9
70	2	2	4	2	2	4	2	2	4	12
71	1	2	3	2	2	4	2	2	4	11
72	0	0	0	0	0	0	0	0	0	0
73	2	2	4	2	2	4	2	2	4	12
74	1	2	3	0	0	0	2	2	4	7

Total scores

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Critical error
1	4	4	4	4	3	4	23	96	
2	4	4	4	4	4	4	24	100	
3	4	4	4	4	4	4	24	100	
4	4	4	4	4	4	4	24	100	
5	4	4	4	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	4	1	4	21	88	
10	4	4	4	4	4	2	22	92	
11	4	4	4	4	4	4	24	100	
12	4	4	4	4	0	2	18	75	
13	4	4	4	4	4	4	24	100	
14	3	4	4	4	4	4	23	96	
15	4	4	4	4	0	4	20	83	
16	4	4	4	4	0	4	20	83	
17	4	4	4	3	4	4	23	96	
18	4	4	4	4	4	4	24	100	
19	2	4	4	4	0	4	18	75	
20	4	4	4	4	1	4	21	88	
21	4	4	4	4	4	4	24	100	
22	4	4	4	4	0	4	20	83	
23	4	4	4	4	1	4	21	88	
24	4	4	4	4	4	4	24	100	
25	0	0	0	4	3	4	11	46	
26	4	4	4	4	4	4	24	100	
27	2	4	4	4	4	4	22	92	
28	4	4	4	4	4	4	24	100	
29	4	4	4	4	0	4	20	83	
30	4	4	0	2	4	4	18	75	
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	2	4	22	92	
36	4	4	4	4	0	4	20	83	
37	4	4	4	4	0	4	20	83	
38	4	4	4	4	4	4	24	100	
39	4	4	4	4	4	4	24	100	
40	4	4	4	4	4	4	24	100	
41	4	4	4	4	0	4	20	83	
42	4	4	4	4	4	4	24	100	
43	1	4	4	4	4	4	21	88	
44	4	4	4	4	4	4	24	100	
45	4	4	4	4	3	4	23	96	
46	4	4	4	4	1	4	21	88	
47	3	4	4	4	3	4	22	92	
48	4	4	4	4	0	4	20	83	
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	4	24	100	
53	0	0	0	0	0	0	0	0	
54	1	4	4	4	0	4	17	71	
55	4	4	4	4	4	4	24	100	
56	0	4	4	3	3	2	16	67	
57	4	4	4	4	4	4	24	100	
58	4	4	4	4	0	4	20	83	
59	4	4	4	3	1	2	18	75	
60	4	4	4	4	4	4	24	100	
61	4	4	4	3	0	4	19	79	
62	4	4	4	4	0	4	20	83	
63	4	4	4	4	0	4	20	83	
64	3	4	4	4	4	4	23	96	
65	1	4	4	4	0	4	17	71	
66	4	4	4	4	4	4	24	100	
67	4	4	4	4	3	4	23	96	
68	1	4	4	1	3	0	13	54	
69	4	4	4	4	1	4	21	88	
70	4	4	4	4	4	4	24	100	

71	4	4	4	3	4	4	23	96	
72	3	4	4	0	0	0	11	46	
73	4	4	4	4	4	4	24	100	
74	4	4	4	3	0	4	19	79	

Performance

	Number of labs	**% total labs**
Satisfactory performers (≥ 71 % of adequate responses)	69	93
Unsatisfactory performers (< 71 % adequate responses and/or critical error)	2	2.7
Partial and non-submitters	3	4

Overall Proficiency

Sample ID	**Diagnosis**	**Proficiency (%)**
QLOU-EB-2022-A	Multiple Acyl-CoA dehydrogenase deficiency	91.7%
QLOU-EB-2022-B	Alkaptonuria	100%
QLOU-EB-2022-C	Normal	98.6%
QLOU-EB-2022-D	Propionic acidemia	96.2%
QLOU-EB-2022-E	2-hydroxyadipic aciduria	67%
QLOU-EB-2022-F	Glutathione synthetase deficiency	95.8%

10. Annual meeting of participants

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

11. 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: The product is currently available at: https://www.vumc.com/departments/clinical-chemistry/metabolic-laboratory/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.

12. 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.

- Recommendation= 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.

13. Tentative schedule and fee in 2023

Sample distribution	8 February 2023
Start of analysis of Survey 2023/1 Website open	May 9
Survey 2023/1 - Results submission	May 30
Survey 2023/1 - Reports	July
Start of analysis of Survey 2023/2	August 29
Survey 2023/2 – Results submission	September 19
Survey 2023/2 - Reports	November
Annual Report 2023	January 2024

14. 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, 2023-08-15
Name and signature of Scientific Advisor

Dr. Judit García Villoria and Dr. Antònia Ribes Rubiò
Hospital Clínic de Barcelona
Division of Inborn Errors of Metabolism
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08028 Barcelona, Spain
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APPENDIX 1. **Change log (changes since the last version)**

Version Number	Published	Amendments
1	18 August 2023	2022 annual report published

END