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Qualitative Organic Acids

Centre: Spain

Final Report 2021

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 on page18 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, as scheme organiser (sub-contractor on behalf of ERNDIM), both appointed by and according to procedures laid down the ERNDIM Board. CSCQ dispatches the EQA samples to the scheme participants and provides a website for on-line submission of results and access to scheme reports.

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 2021 seventy three laboratories from many different countries participated in the QLOU *Barcelona* scheme. Two laboratories were educational participants in 2021 (1 in 2020, 2 in 2019). They 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

Country	*Number of laboratories*		*Country*	*Number of laboratories*
ARGENTINA	3		ITALY	15
BRAZIL	2		KINGDOM OF SAUDIA ARABIA	1
CHILE	1		LEBANON	1
CHINA	6		PHILIPPINES	1
COLOMBIA	1		PORTUGAL	2
CYPRUS	1		QATAR	1
FRANCE	21		REPUBLIC OF SINGAPORE	1
GERMANY	2		SPAIN	9
GREECE	1		UK	1
INDIA	3			

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, 4 from affected patients and 2 from healthy individuals.
In 2021 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 by some participants:

Patient A: Normal sample. –Inherited Metabolic Disease lab in Hospital Clínic, Barcelona
Patient B: AADC deficiency – Metabolic center Heidelberg. This sample has been sent to all labs participating to the QLOU of three centers Heidelberg, Sheffield and Barcelona.
Patient C: Isovaleric acidemia – Inherited Metabolic Disease lab in Hospital Clínic, Barcelona
Patient D: Phenylketonuria (PKU) – Inherited Metabolic Disease lab in Hospital Clínic, Barcelona
Patient E: Glutaric aciduria type I low excretor – Inherited Metabolic Disease lab in Hospital Clínic, Barcelona
Patient F: Normal sample – Inherited Metabolic Disease lab in Hospital Clínic, Barcelona

All samples selected by the Scientific Advisor have been heat-treated and were tested for suitability in the Scientific Advisor's laboratory.
Mailing is performed 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 9, 2021: shipment of samples of Survey 1 and Survey 2 and of the clinical data by e-mail
- May 11, 2021: analysis start, clinical data available and submission availability in the website (Survey 1)
- June 1, 2021: deadline for result submission (Survey 1)
- September 7, 2021: analysis start, clinical data available and submission availability in the website (Survey 2)

- September 27, 2021: deadline for result submission (Survey 2)
- November 24, 2021: interim report of Survey 1 available in the website
- November 24, 2021: interim report of Survey 2 available in the website
- October 21 and 22, 2021: ERNDIM Workshop on-line
- January, 2022: annual report available.

5. Results

64 of 73 labs returned results for both surveys, mainly by the deadline.

	Survey 1	**Survey 2**
Receipt of results	66	68
No answer	7	5

Submissions	Number of laboratories	%
2	64	88
1	6	8
0	3	4

6. Website 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 out by the scientific advisor. At present the concept of a second assessor as in the DPT schemes will be implemented in 2022. At the SAB meeting in November 12, 2021, 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 2021, the SAB decided that sample E has to be considered as a critical error for the labs who failed to identify an increase of 3-hydroxyglutaric acid and nor the diagnosis of glutaric aciduria type 1 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 2021. Any partial submitters will receive a letter from the ERNDIM Executive Administrator, Sara Gardner.

7.1. Score for satisfactory performance

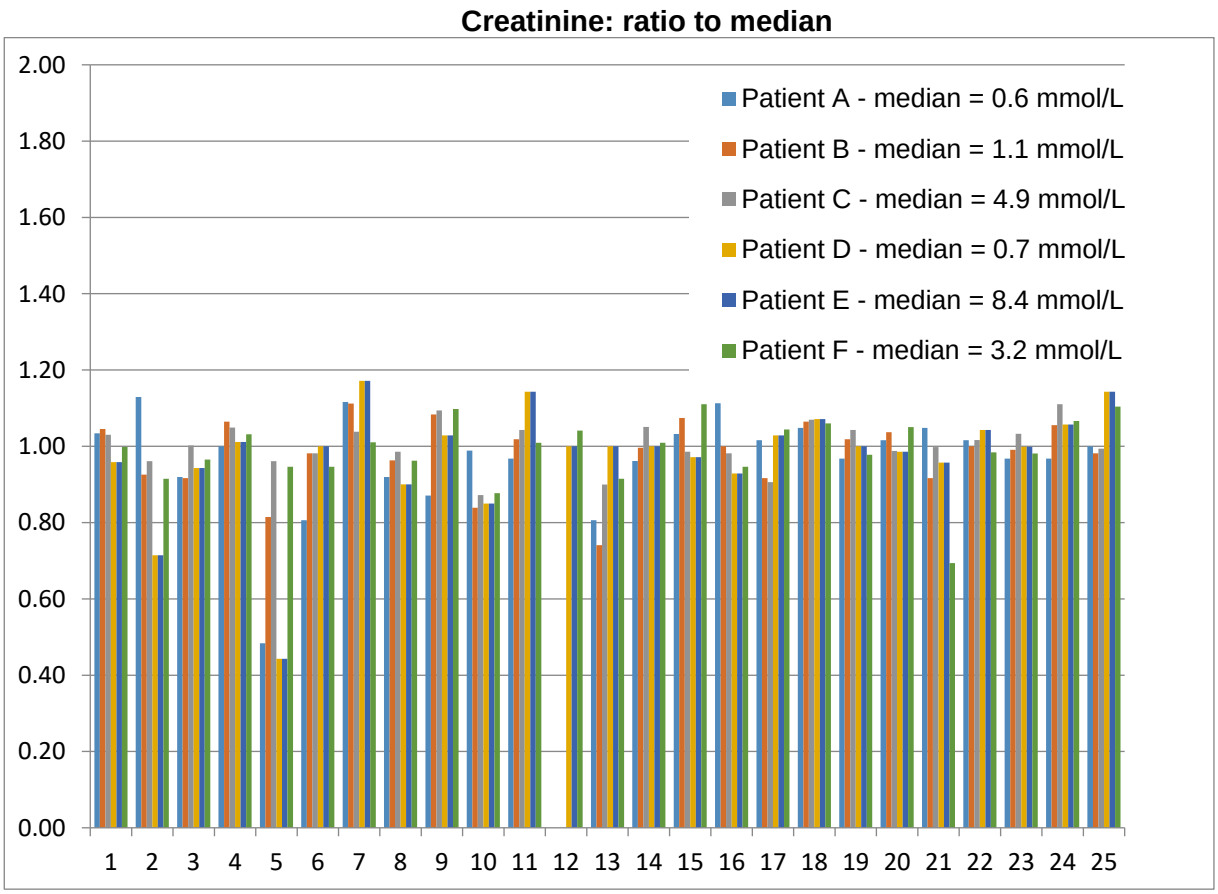
At least 17 points from the maximum of 24 (71%).

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.

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.

8. Results of samples and evaluation of reporting

8.1. Creatinine measurement for all samples



8.2. Patient A

Normal profile.

Patient details provided to participants

10 year-old female. Autistic spectrum disorder.

Patient details

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

Analytical performance

-66 laboratories of 73 active participants submitted results for sample A.

-All laboratories, 66 (100%), reported correctly the result as profile without significative alterations.

NOTE: only 23 laboratories put correctly normal profile in the key metabolite box, the majority put normal profile in the comment box or only give the interpretation as normal sample. It is important to know that if the normal profile is not put in the key metabolite box it couldn't be scored, as it is done automatically with a software. To be extracted from the database – input parameter and format to be defined.

Diagnosis / Interpretative proficiency

All laboratories, 66 (100%), reported correctly as normal sample.

Recommendations

-Many laboratories, due to the clinical presentation, have recommended: Plasma amino-acid, creatine and guanidinoacetate, SAICAR, purine and pyrimidine studies. -Other labs recommended plasma acylcarnitines, lactate and pyruvate and 7-dehydrocholesterol. Transferrin isoelectric focusing for glycosylation studies. Urinary analysis of mucopolysaccharides and oligosaccharides. Neurotransmitters and folic acid in CSF. CGHArray, rule out fragile X syndrome. Molecular analysis of Autism spectrum disorder or NGS study.

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 100%.

8.3. Patient B

Aromatic l-amino acid decarboxylase (AADC) deficiency

Patient details provided to participants

8 year old boy with severe, predominantly truncal hypotonia and intermittent dystonic posturing. On treatment during sample collection in ICU.

Patient details

This is a common sample distributed in the three QLOU schemes of this year. It is a sample from an 8 year old boy with severe, predominantly truncal hypotonia and intermittent dystonic posturing. On treatment in ICU during sample collection. He was diagnosed of aromatic l-amino acid decarboxylase (AADC) deficiency.
Pathological excretion of vanil-lactate was observed, also an increase of n-acetyltyrosine was detected due to parenteral nutrition, but small quantity of n-actyltyrosine can be observed in AADC deficient patient without parenteral nutrition

Analytical performance

-The key metabolite is the vanil-lactate, which is increased. Also an increase of n-acteyltyrosine is detected due to parenteral nutrition treatment in ICU.

-65 laboratories of 73 active participants submitted results for sample B.

-Only 33 participants (51%) reported the increase of vanil-lactate. 29 labs (45%) only indicated the presence of nacteyltyrosine, although this metabolite was detected by a total of 57 participants (88%). 3 laboratories did not report any key metabolite.

Diagnosis / Interpretative proficiency
-Only 30 laboratories (46%), reported aromatic l-amino acid decarboxylase (AADC) deficiency as correct diagnosis in the first diagnosis or as alternative diagnosis. -5 participants did not give the correct diagnosis, but recommend to perform neurotransmitter analysis in CSF, so they were scoring with 1 point. -9 labs gave the diagnosis of tyrosinemia, 3 tyrosine hydroxylase deficiency, 2 glutaric acidemia type II and 2 pyrimidine metabolism deficiency. Other individual diagnosis were: dystonia with L-DoPA response, glutathione synthase deficiency, propionic acidemia, mitochondrial disease with SLC30A10 mutations, beta-ketohyiolse, 3-hydroxyacyl-CoA dehydrogenase deficiency and combined malonic and methylmalonic aciduria.

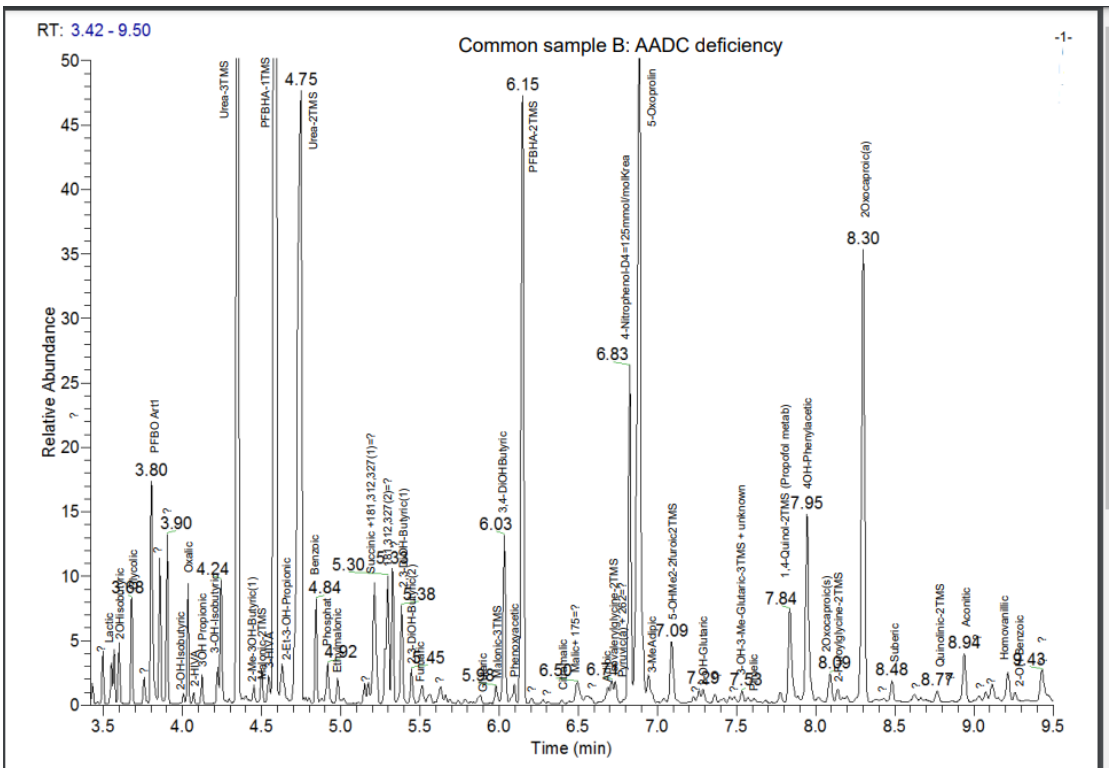
Recommendations
-The majority of the participants recommended analysis of CSF monoamine neurotransmitters and pyridoxal phosphate analyses, AADC activity in plasma and genetic testing (DDC and PNPO genes).
-Some laboratories also recommend measurement of plasma amino acids, acylcarnitines, VLCFA, pristanic and phytanic acids levels. Succinylacetone in plasma and urine and deltaaminolevulinic in urine. If CSF analysis is normal: NGS analysis (hypotonia and dystonia related genes).

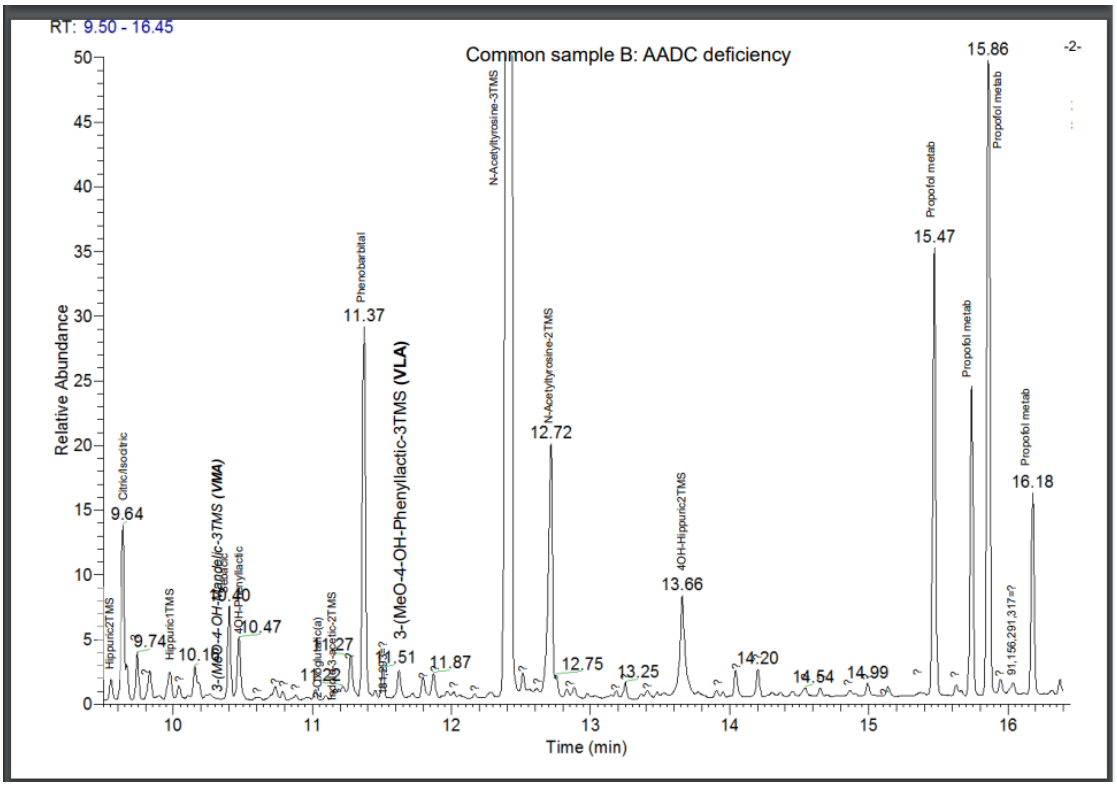
Scoring
This sample was considered by the SAB to be an **educational sample**. Scores are not to be taken into account in evaluating overall performance.

Please note that all scores given in the interim reports are always only provisional and have to be verified by the SAB.

Overall impression
Estimation of the amount of vanil-lactic acid in this sample seemed to be a problem.

Chromatogram sample B:





8.4. Patient C

Isovaleric acidemia or isovaleryl-CoA dehydrogenase deficiency

Patient details provided to participants

44 year-old male, diagnosed at 8 years when presenting with developmental delay, feeding refusal and lethargy. At present under treatment.

Patient details

Male patient diagnosed of isovaleric acidemia at 8 years old presenting feeding refusal, lethargy and developmental delay. Currently he is 44 years old and is under treatment with hypoporteic diet and carnitine supplementation.
Pathological excretion of isovalerylglycine and isovalerylglutamate were detected.

Analytical performance

-The key metabolites were isovalerylglycine and isovalerylglutamate, which are increased. The 3-hydroxy-isovaleric acid in this sample was not increased.

-66 laboratories of 73 active participants submitted results for sample C.

-All the laboratories, except one, 65 (98%), reported correctly the increase of isovalerylglycine. One lab did not put anything in the analytical results, but with correct diagnosis.

-Only 18 (27%) participants detected the increase of isovalerylglutamate. In the sample of isovaleric aciduria circulated in 2018 only the 19% detected high amounts of isovalerylglutamate.

Diagnosis / Interpretative proficiency

All laboratories, 66 (100%), reported the isovaleric acidemia as correct diagnosis.

Recommendations

- The majority of the participants recommend plasma or DBS acylcarnitine analysis and molecular analysis of IVD gene. -Some participants also recommended plasma amino acid analysis and determination of isovaleryl CoA dehydrogenase activity in white blood cells or fibroblasts.

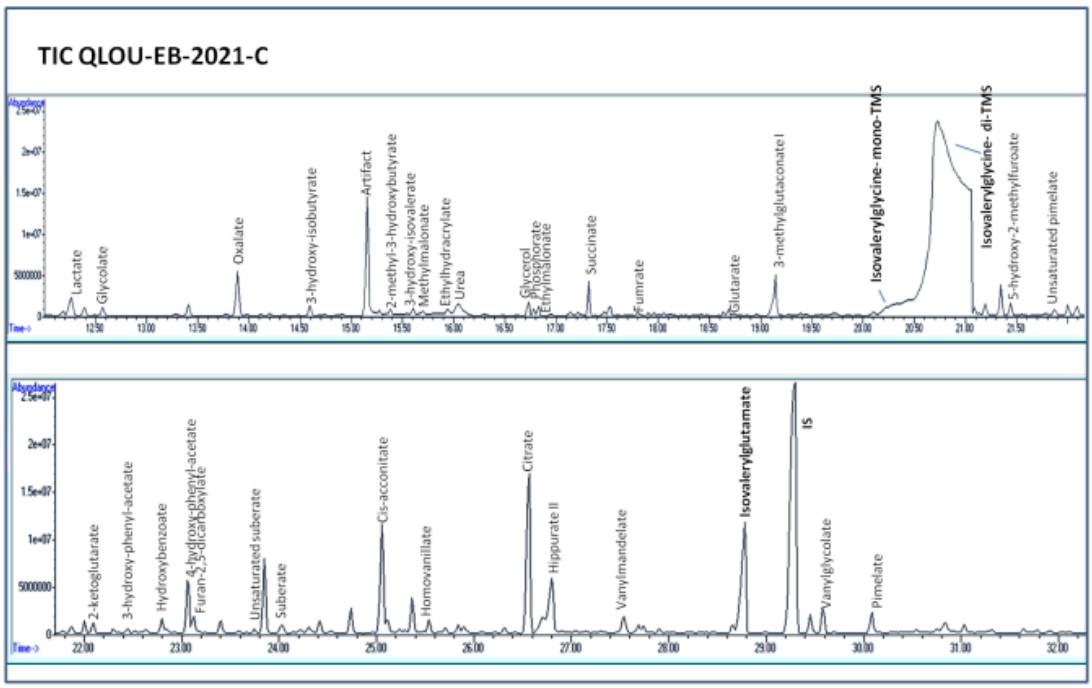
Scoring

- Analytical results: 2 points are given for the detection of isovalerylglycine.
- Interpretation of results: 2 points are given for the diagnosis of isovaleric acidemia or isovaleryl-CoA dehydrogenase deficiency.

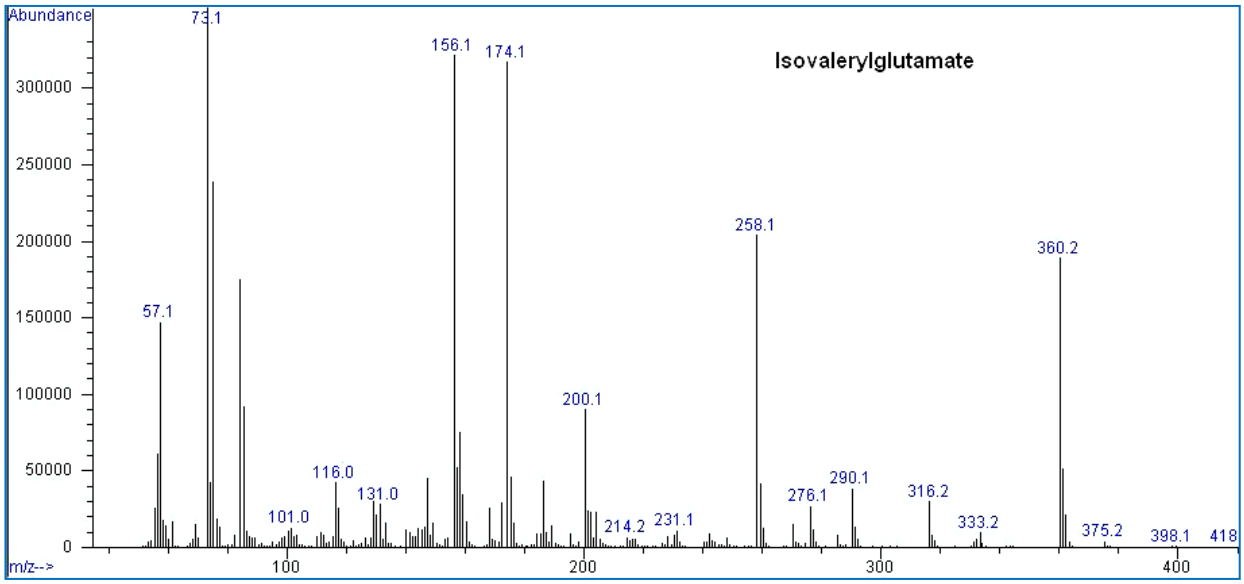
Overall impression

The overall performance was 99%.

Chromatogram sample C and isovalerylglutamate ion spectrum:



Total ion chromatogram sample QLOU-EB-2021-C



Multiple distributions of similar samples

A similar urine sample from a patient with isovaleric aciduria had been distributed in 2018: the overall performance was similar.

	2018	2021
Overall performance	97 %	99 %

8.5. Patient D

Phenylketonuria (PKU)

Patient details provided to participants

Female with low intelligence quotient, severe mental retardation and obesity. At present under treatment

Patient details

The urine sample is from a patient diagnosed with phenylketonuria in the neonatal period. The present sample has been collected at the age of 51 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.
Pathological excretion of

Analytical performance

-68 laboratories of 73 active participants submitted results for sample D.

-The majority of the laboratories reported the key metabolites. 62 laboratories (91%) detected increased phenyllactate; 53 participants (78%) reported the increase of phenylpyruvate; 55 laboratories (81%) detected increased phenylacetate; 57 participants (84%) reported the increase of 2-hydroxy-phenylacetate. In addition, high amounts of 4-hydroxy-phenyllactate and 4-hydroxy-phenylpiruvate were detected by 31 laboratories (46 %) and 27 laboratories (40%) respectively.

Diagnosis / Interpretative proficiency

All laboratories, 68(100%), reported the correct diagnosis of phenylketonuria (PKU) or hyperphenylalaninemia.

Recommendations

The majority of the participants recommended plasma or DBS amino acid 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 the four key metabolites.0 points if no key metabolites were detected.
- Interpretation of results: 2 points are given for the correct diagnosis.

Overall impression

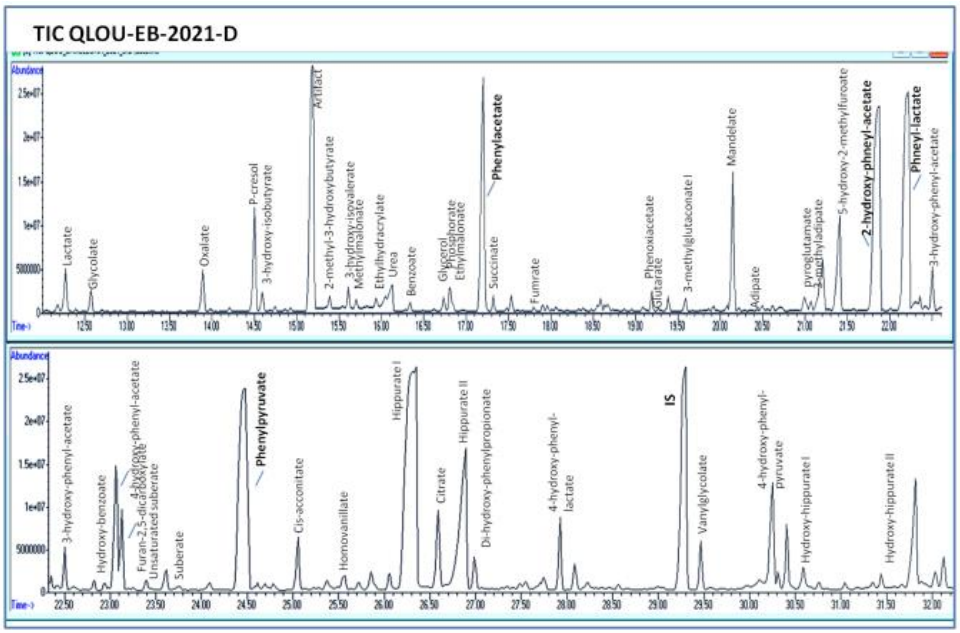
The overall performance was 99%

Multiple distributions of similar samples

A similar urine sample from a patient with phenylketonuria had been distributed in 2018: the overall performance was the same.

	2018	2021
Overall performance	99 %	99 %

Chromatogram sample D:



Total ion chromatogram sample QLOU-EB-2021-D

8.6. Patient E

Glutaric aciduria type I low excretor

Patient details provided to participants

32 year-old male with spastic-dystonic tetraparesis and macrocephaly. At present under treatment.

Patient details

The urine sample is from a patient diagnosed of glutaric aciduria type I. The organic acid profile was the characteristic of low excretor patient showing only a slight increase of 3-hydroxyglutarate. The patient was compound heterozygous for the following mutations [c.680G>C]; [c.463T>C] ([p.Arg227Pro]; [p.Tyr155His]). The c. 680G>C (p.Arg227Pro) mutation has been associated to low excretors (C. Busquets, et al. 2000. Pediatr. Res 48: 315-322), which is the biochemical phenotype presented by this patient. The sample was collected at 31 years of age, under carnitine treatment. Currently, the patient presents spastic dystonic tetraparesia with severe disability and wheelchair depend-ency.

Analytical performance

-68 laboratories of 73 active participants submitted results for sample E.

-62 participants (91%) detected the increase of 3-hydroxyglutarate, which is the key metabolite in this sample. The excretion of glutarate in this sample was not increased. 10 participants also reported the increase of 3-methylglutaconate, which presented a slightly increase together with increased lactate.

Diagnosis / Interpretative proficiency

-The majority of the laboratories, 64 (94%), reported glutaric aciduria type 1 or glutaryl-CoA dehydrogenase deficiency as correct diagnosis.
-Other individual reported diagnosis were: exposition aromatic polycyclic hydrocarbon, mitochondrial complex I deficiency, 2-hydroxyglutaric aciduria and normal.

Recommendations

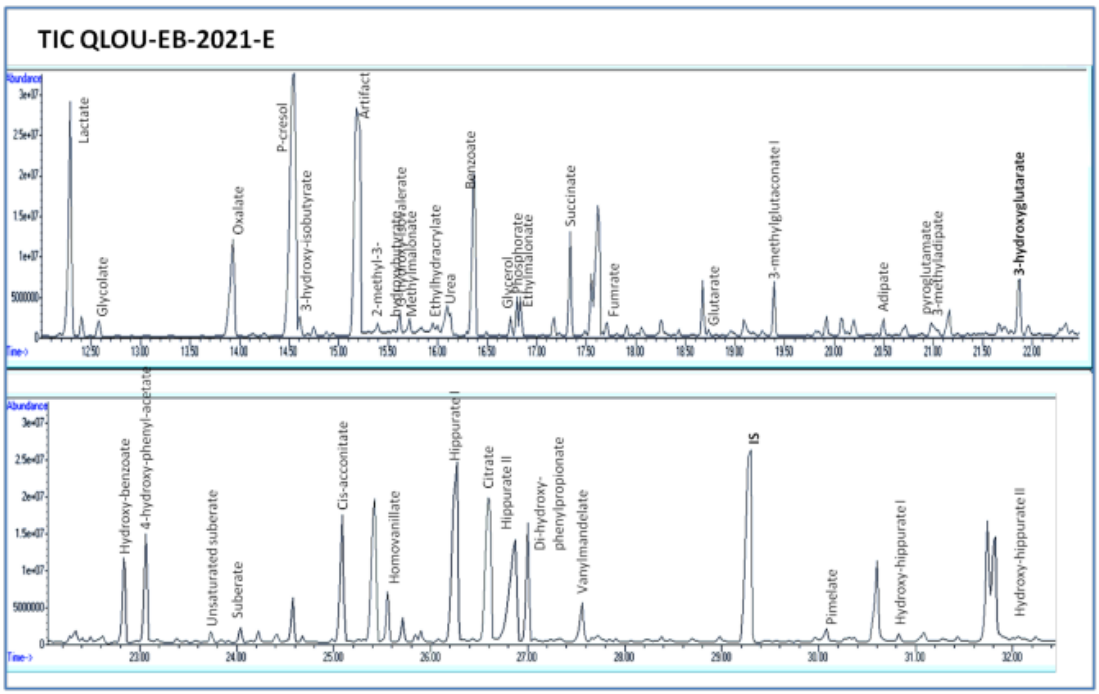
The majority of the participants recommended analysis of acylcarnitines in plasma or DBS or urine, plasma amino acid measurement and molecular studies of GCDH gene.

Scoring

- Analytical results: 2 points are given for the detection of the 3-hydroxyglutarate.
- Interpretation of results: 2 points are given for the correct diagnosis of glutaric aciduria type I.

Overall impression
-The overall performance was 95%.

Chromatogram sample E:



Total ion chromatogram sample QLOU-EB-2021-E

Multiple distributions of similar samples
A similar urine sample from a patient with glutaric aciduria type I low excretor had been distributed in 2018: the overall performance was lower in 2018.

	2018	2021
Overall performance	49 %	95 %

8.7. Patient F

Normal profile

Patient details provided to participants
25 year-old male with epilepsy.

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

Analytical performance
-68 laboratories of 73 active participants submitted results for sample A. -The majority of laboratories, 66 (97%), reported correctly the result as profile without significative alterations. -One laboratory detected an increase of 2-hydroxyglutaric acid and other increased pyrroline-5-carboxylate.

NOTE: only 19 laboratories put correctly normal profile in the key metabolite box, the majority put normal profile in the comment box or only gives the interpretation as normal sample. It is important to know that if the normal profile is not put in the key metabolite box it couldn't be scored, as it is done automatically with software.

Diagnosis / Interpretative proficiency
-All laboratories except two, 66 (97%), reported correctly as normal sample.
-One participant gave de diagnosis of hyperprolinemia type II and the other of 2-hydroxyglutaric aciduria.

Recommendations
Some participants recommended to analyze: organic acids in catabolic or acute situation, plasma amino acids, 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 ammonaemia. In addition, genetic screening (epilepsy gene panel) studies.

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 97%.

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).

Detailed scores

Lab no	A	B*)	C	Sum	D	E	F	Sum	Total score	% of total	Performance
1	4		4	8	4	4	4	12	20	100	
2	4		4	8	4	4	4	12	20	100	Educational Participant
3	4		4	8	4	4	4	12	20	100	
4	4		4	8	4	4	4	12	20	100	
5				0				0	0	0	NO RETURN
6	4		4	8	4	4	4	12	20	100	
7	4		4	8	4	4	4	12	20	100	
8	4		4	8	4	4	4	12	20	100	
9	4		4	8	4	4	4	12	20	100	
10	4		4	8	4	4	4	12	20	100	
11	4		4	8	4	4	4	12	20	100	
12	4		4	8				0	8	100	1 RETURN (partial submitter)
13	4		4	8	4	1	4	9	17	85	
14	4		4	8	4	4	4	12	20	100	
15	4		4	8	4	4	4	12	20	100	
16				0	4	4	0	8	8	67	1 RETURN (partial submitter)
17	4		4	8	4	4	4	12	20	100	
18	4		4	8	2	4	4	10	18	90	
19	4		4	8	4	4	4	12	20	100	
20	4		4	8	4	4	4	12	20	100	
21				0	4	2	4	10	10	83	1 RETURN (partial submitter)
22	4		4	8	4	4	4	12	20	100	
23	4		4	8	4	4	4	12	20	100	
24	4		4	8	4	4	4	12	20	100	
25	4		4	8	4	0	4	8	16	80	CE

Lab no	A	B*)	C	Sum	D	E	F	Sum	Total score	% of total	Performance
26	4		4	8	4	4	4	12	20	100	
27	4		4	8	4	4	4	12	20	100	
28	4		4	8	4	4	4	12	20	100	
29	4		4	8	4	4	4	12	20	100	
30	4		4	8	4	4	0	8	16	80	
31	4		4	8	4	4	4	12	20	100	
32	4		4	8	4	4	4	12	20	100	
33	4		4	8	4	4	4	12	20	100	
34	4		4	8	4	4	4	12	20	100	
35	4		4	8	4	4	4	12	20	100	
36	4		4	8	4	4	4	12	20	100	
37	4		4	8	4	4	4	12	20	100	
38	4		4	8	4	4	4	12	20	100	
39	4		4	8	4	4	4	12	20	100	
40	4		4	8	4	4	4	12	20	100	
41	4		4	8	4	4	4	12	20	100	
42	4		4	8	4	4	4	12	20	100	
43	4		4	8	4	4	4	12	20	100	
44	4		4	8	4	4	4	12	20	100	
45	4		4	8	4	4	4	12	20	100	
46	4		4	8	4	4	4	12	20	100	
47	4		4	8	4	4	4	12	20	100	
48	4		4	8	4	4	4	12	20	100	
49	4		4	8	4	4	4	12	20	100	
50	4		4	8	4	4	4	12	20	100	
51	4		4	8	4	4	4	12	20	100	
52	4		4	8	4	4	4	12	20	100	
53				0				0	0	0	NO RETURN
54	4		4	8	4	0	4	8	16	80	CE
55	4		4	8	4	4	4	12	20	100	
56	4		4	8				0	8	100	1 RETURN (partial submitter)
57	4		4	8	4	4	4	12	20	100	
58	4		4	8	4	4	4	12	20	100	
59				0				0	0	0	NO RETURN
60	4		4	8	4	4	4	12	20	100	
61				0	4	4	4	12	12	100	1 RETURN (partial submitter)
62	4		4	8	4	4	4	12	20	100	
63	4		4	8	4	4	4	12	20	100	
64	4		4	8	4	4	4	12	20	100	
65	4		4	8	4	4	4	12	20	100	

Lab no	A	B*)	C	Sum	D	E	F	Sum	Total score	% of total	Performance
66	4		4	8	4	4	4	12	20	100	
67	4		4	8	4	4	4	12	20	100	
68	4		4	8	4	4	4	12	20	100	
69	4		4	8	4	4	4	12	20	100	
70	4		4	8	4	4	4	12	20	100	
71	4		2	6	4	4	4	12	18	90	
72	4		4	8	4	4	4	12	20	100	
73				0	4	4	4	12	12	100	1 RETURN, Educational

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

Performance

	Number of labs	% total labs
Satisfactory performers (≥ 60 % of adequate responses)	62	85
Unsatisfactory performers (< 60 % adequate responses and/or critical error)	2	1,4
Partial and non-submitters	9	12

Overall Proficiency

Sample ID	Diagnosis	Proficiency (%)
QLOU-EB-2021-A	Normal profile	100%
QLOU-EB-2021-B	Aromatic l-amino acid decarboxylase (AADC) deficiency (QLOU common sample) - **Educational sample**	62%
QLOU-EB-2021-C	Isovaleric aciduria	99%
QLOU-EB-2021-D	Phenylketonuria	99%
QLOU-EB-2021-E	Glutaric aciduria type 1 low excretor	95%
QLOU-EB-2021-F	Normal profile	97%

10. 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:

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!).

11. 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 it 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.

12. Tentative schedule and fee in 2022

CSCQ Sample dispatch date:	02 February 2022	
	1st Submission Round	**2nd Submission Round**
Sample ID's:	QLOU-EB-2022-**A** QLOU-EB-2022-**B** QLOU-EB-2022-**C**	QLOU-EB-2022-**D** QLOU-EB-2022-**E** QLOU-EB-2022-**F**
Analysis start & Website submission availability:	09 May 2022	29 August 2022
Reminder for result submission:	23 May 2022	12 September 2022
Results submission deadline:	30 May 2022	19 September 2022

13. 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, 2022-04-27

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APPENDIX 1. **Change log (changes since the last version)**

Version Number	Published	Amendments
1	29 April 2022	2021 annual report published

END