ERNDIM
Qualitative Organic acids Urine
Sheffield ANNUAL REPORT 2019

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1. Introduction

The ERNDIM Qualitative Organic Acids in urine scheme offers urine samples obtained from confirmed patients with confirmed diagnoses to enable laboratories to gain or maintain experience to identify organic acid disorders. The scheme is organised by *Camilla Scott Sheffield 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.

2. Participants

In 2019 seventy three laboratories from many different countries participated in the QLOU *Sheffield* scheme. There were no educational participants in 2019 (1 in 2018). 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 be 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.

Table 1: Geographical distribution of participants

Country	*Number of laboratories*		*Country*	*Number of laboratories*
AUSTRALIA	6		PAKISTAN	1
BELGIUM	7		POLAND	2
CHINA	3		SOUTH AFRICA	2
FINLAND	2		SPAIN	1
HUNGARY	1		SWEDEN	2
IRELAND	1		UK	16
ISRAEL	2		USA	18
JAPAN	3			
MALAYSIA	3			
NEW ZEALAND	2			
NORWAY	1			

3. Design of the scheme and logistics

As usual, the samples used in 2019 were authentic human urine samples, 5 from affected patients and 4 from healthy individuals.
All samples selected by the Scientific Advisor have been heat-treated and were tested for suitability in the Scientific Advisor's laboratory.
In 2019 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.

4. Schedule of the scheme

Table 2: Time schedule in the 2019 ERNDIM QLOU *Sheffield* scheme.

	1st Submission Round	2nd Submission Round	3rd Submission Round
Sample ID's:	QLOU-US-2019-A QLOU-US-2019-B QLOU-US-2019-C	QLOU-US-2019-D QLOU-US-2019-E QLOU-US-2019-F	QLOU-US-2019-G QLOU-US-2019-H QLOU-US-2019-I
Shipment of samples	February 5th, 2019		
Start of analysis (clinical data available)	May 13th, 2019	July 8th, 2019	September 9th, 2019
Reminder for result submission	May 27th, 2019	July 22nd 2019	September 23rd, 2019
Results submission deadline:	June 3rd, 2019	July 29th, 2019	September 30th, 2019
	18th July 2019	*23rd September 2019*	*21st October 2019*

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.

Table 3: Samples included in the 2019 ERNDIM QLOU Sheffield scheme.

Survey	Sample no.	Diagnosis
03-06-OUS	QLOU-US-2019-A	Citrullinaemia
	QLOU-US-2018-B	Normal
	QLOU-US-2018-C	SCADD
29-07-OUS	QLOU-US-2018-D	Normal
	QLOU-US-2018-E	VLCADD
	QLOU-**US**-2018-F	Isovaleric Acidaemia
30-09-OUS	QLOU-US-2018-G	LCHADD/MCT
	QLOU-US-2018-H	Normal
	QLOU-US-2018-I	Normal

The scheme format was kept identical to those of previous years. Samples were shipped by regular mail. Details regarding stability of samples are provided in the sample package.

Evaluation of results was performed using Excel with the submitted results extracted from the database by the website manager.

5. Results

Table 4: Receipt of results in the 2019 ERNDIM QLOU *Sheffield* scheme.

Survey	In time	Late	Total
03-06-OUS	71	0	71
29-07-OUS	70	0	70
30-09-OUS	71	0	71

Table 5: Returned results in the 2019 ERNDIM QLOU *Sheffield* scheme.

Submissions	Number of laboratories	%
3	69	95
2	2	3
1	1	1
0	1	1

6. Website reporting

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

- 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.**
- ***Diagnosis***
  - **Don't enter the diagnosis 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 of results

A scoring system was developed in 2012 and approved by the ERNDIM Scientific Advisory Board. Similar to other qualitative (proficiency testing) ERNDIM schemes, the maximum score for a sample is 4 points.
Qualitative results and diagnostic proficiency of the 2019 samples were scored using the criteria given in Table 6. These criteria have been set by the Scientific Advisor, approved by the Scientific Advisory Board. The final decision about scoring of the scheme is made in the Scientific Advisory Board (SAB) during the Autumn meeting (November 21st, 2019).

Table 6: General criteria used to score results

Satisfactory	4	Helpful but incomplete	3
Not helpful	2	Slightly misleading	1
Misleading	0		

Starting with the 2014 schemes the concept of 'critical error' is introduced to the assessment of the qualitative schemes. Labs failing to make a correct diagnosis of a sample considered eligible for this category will be deemed not to have reached a satisfactory performance even if their total points for the year is sufficient according to the requirement set by the SAB. The classification of samples to be judged for critical error was undertaken at the SAB meeting held on November 21st, 2019.

Table 7: Samples eligible for critical errors in the 2019 ERNDIM QLOU *Sheffield* scheme.

Sample	Critical errors
QLOU-US-2019-A	10 for missing orotic acid
QLOU-US-2019-F	2 for failing to identify IVA

Details are given under item 9 'Results of individual samples and evaluation of reporting'.

We are required to define "Participation" for the purpose of the ERNDIM Annual Certificate which covers all ERNDIM schemes. For this urinary organic acid scheme we have defined "**Participation**" as requiring **at least two returns during the year**. Failure to meet this requirement will result in the certificate of participation showing 'non-submitter' rather than 'satisfactory' or 'unsatisfactory'.

Satisfactory performance is defined as **70% of maximum score** which equates **25/36** points for three returns and **17/24** points for two returns.

8. Proficiency of the 2019 surveys

ERNDIM provides a single certificate for all its schemes with details of participation and performance.

In 2019, 69 participants submitted 3 reports including no educational participants. From the 73 ordinary (non-educational) participants 61 (84%) achieved satisfactory performance (score ≥ *25 / 17*, no critical error). 12 participants did not accomplish satisfactory performance, including 2 due to incomplete submission of results (i.e. no report or 1 survey report submitted instead of 2 reports). Overall proficiencies of each sample are depicted in Table 8.

Table 8: Overall proficiencies of the 2019 surveys.

Sample ID	Sample type	Proficiency (%)
QLOU-US-2019-A	Citrullinaemia	87
QLOU-US-2019-B	Normal	100
QLOU-US-2019-C	SCADD	80
QLOU-US-2019-D	Normal	97
QLOU-US-2019-E	VLCADD	37
QLOU-US-2019-F	IVA	97
QLOU-US-2019-G	LCHADD/MCT	86
QLOU-US-2019-H	Normal	93
QLOU-US-2019-I	Normal	92

Eleven Performance Support letters will be sent for the 2019 surveys. Five of these participants have also received a performance support letter in 2018 or 2017. Unsatisfactory performance (either due to overall score or due to critical error) within an EQA scheme for at least 2 out of 3 years that the participant has subscribed for will result in a notification letter of unsatisfactory performance to the quality manager or head of department.
For the 2018 scheme 5 Performance Support letters were sent.

9. Results of individual samples and evaluation of reporting

The samples sent out in 2019 achieved mixed proficiency across the board. It is reassuring to see the majority of laboratories were successful in identifying the key metabolites and advising on the correct diagnosis in the majority of cases. Three samples however were discussed in depth at the recents Scientific Advisory Board.

The sample **QLOU-US-2019-E VLCADD** had the lowest proficiency. This was partly due to the presence of a small peak of hexanoyl glycine resulting in a number of participants opting for MCADD as the most likely diagnosis and partly due to difficulty of assigning the specific diagnosis of VLCADD based on the organic acid profile alone. Subsequently it was agreed at the autumn SAB that this sample would be rescored to give full marks to any participant that recognised the key metabolites and suggested any fatty acid oxidation defect as the likely diagnosis.

The detection of orotic acid in sample **QLOU-US-2019-A Citrullinaemia** was also challenging for some participants. Orotic acid detection been proved difficult in past distributions with critical error previously also awarded to laboratories that struggled to detect it. We urge participants to put in steps using regular positive controls and selected ion profiles to ensure this key metabolite is not missed.

Ten participants failed to identify increased orotic acid excretion (see Figure 2 below for ion spectra). This is of concern as this will potentially result in a missed opportunity to diagnose a urea cycle disorder in the context of a hyperammonaemic patient and subsequently expedite further investigations such as amino acids to confirm. Referral to a specialist metabolic clinician to instigate appropriate treatment could be delayed, which may have long term neurological consequences for the patient. Subsequently it was decided at the recent SAB that failing to identify orotic acid would be classified as a critical error.

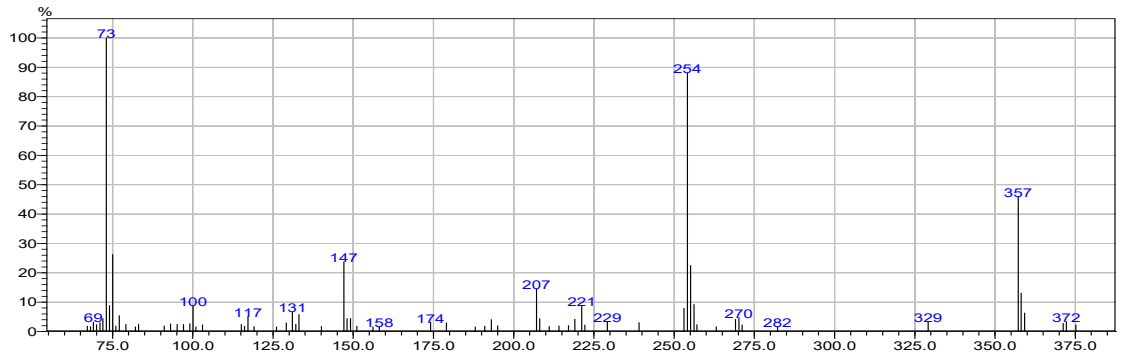

Figure 2: Ion spectra for orotic acid (TMS derivative)

It was also decided at the November SAB critical error meeting that the failure to identify isovaleric acid in sample **OLOU-US-2019 F** would also be classed as a critical error**.** Two participants failed to identify isovaleric and subsequently were awarded critical error.

10. Scores of participants

Table 9 presents detailed scores and performance data for all participants.

Scores and performance data were confirmed by the Scientific Advisory Board meeting in November 2019.

The anonymous data are accessible to all participants. Individual data are only visible to your laboratory

Lab no	A	B*)	C	sum	D	E	F	sum	G	H	I	sum	Total score	Performance
1	3	4	4	11	4	4	4	12	4	4	4	12	35	
2	0	4	4	8	4	4	4	12	4	4	4	12	32	CE
3	4	4	4	12	4	4	4	12	4	4	4	12	36	
4	4	4	4	12	4	4	4	12	4	4	4	12	36	

Lab no	A	B*)	C	sum	D	E	F	sum	G	H	I	sum	Total score	Performance
5	3	4	4	11	4	4	4	12	2	4	4	10	33	
6	1	4	2	7	4	4	4	12	4	4	4	12	31	CE
7	4	4	4	12	4	4	4	12	4	4	4	12	36	
8	4	4	4	11	4	4	4	12	4	4	4	12	35	
9	4	4	4	12	4	4	4	12	4	4	4	12	36	
10	4	4	4	12	4	4	4	12	4	4	4	12	36	
11	4	4	3	11	4	4	4	12	4	4	4	12	35	
12	4	4	4	12				12	4	4	4	12	24	2 returns
13	4	4	4	12	4	4	4	12	4	4	4	12	36	
14	4	4	4	12	4	4	4	12	4	4	4	12	36	
15	4	4	2	10	4	4	4	12	4	4	4	12	34	
16	3	4	4	11	4	4	4	12	4	4	0	8	31	
17	4	4	4	12	4	4	4	12	4	4	4	12	36	
18	4	4	4	12	4	4	4	12	4	4	4	12	36	
19	3	4	4	11	4	4	4	12	4	4	4	12	35	
20	1	4	4	9	4	4	4	12	4	4	3	11	32	CE
21	4	4	2	10	0	4	0	4	4	4	4	12	26	CE
22	0	4	4	8	4	4	4	12	4	4	4	12	32	CE
3	3	4	2	9	4	4	4	12	4	4	4	12	33	
24	4	4	4	12	4	4	4	12	4	4	4	12	36	
25	4	4	4	12	4	4	4	12	4	4	0	8	32	
26	3	4	2	9	4	4	4	12	4	4	4	12	33	
27	4	4	4	12	4	4	4	7	4	4	4	12	36	
28	3	4	4	11	4	4	4	12	4	4	4	12	35	

Lab no	A	B*)	C	sum	D	E	F	sum	G	H	I	sum	Total score	Performance
29	3	4	4	11	4	4	4	12	4	4	4	12	35	
30	3	4	4	11	4	4	4	12	4	4	4	12	35	
31	4	4	4	12	4	4	4	12	4	4	4	12	36	
32	4	4	4	12	4	4	4	12	4	4	4	12	36	
33	4	4	4	12	4	4	4	12	4	4	4	12	36	
34	3	4	4	11	4	4	4	12	4	4	4	12	35	
35	3	4	2	9	4	4	4	12	4	4	4	12	33	
36	4	4	4	12	4	4	4	10	4	4	4	12	36	
37	3	4	2	9	4	4	4	12	4	4	4	12	33	
38	3	4	4	11	4	4	4	12	4	4	4	12	35	
39	3	4	3	10									10	ONE RETURN
40	4	4	4	12	4	4	4	12	4	4	4	8	36	
41	0	4	4	8	4	4	4	12	4	4	0	8	28	CE
42	3	4	4	11	4	4	4	12	2	4	4	10	33	
43	4	4	2	10	4	4	4	12	4	4	4	12	34	
44	0	4	4	8	4	0	0	4	3	4	4	11	23	CE PP
45	4	4	4	12	4	4	4	12	4	4	4	12	36	
46	3	4	2	9	4	4	4	12	4	4	4	12	33	
47	3	4	4	11	4	4	4	12	4	4	3	11	34	
48	3	4	1	8	4	4	4	12	4	4	4	12	32	
49	3	4	4	11	4	1	4	9	0	4	4	8	28	
50	3	4	4	11	4	4	4	12	4	4	4	12	35	
51	0	4	2	6	4	4	4	12	4	4	4	12	30	CE
52	4	4	3	11	4	4	4	12	4	4	4	12	35	

Lab no	A	B*)	C	sum	D	E	F	sum	G	H	I	sum	Total score	Performance
53	3	4	4	11	4	4	4	12	2	4	4	10	33	
54	3	4	4 2	11	4	4	4	12	4	4	4	12	35	
55	4	4	4	12	4	4	4	12	4	4	4	12	36	
56	4	4	4	12	4	4	4	12	4	4	4	12	36	
57	3	4	4	12	4	4	4	12	4	4	4	12	35	
58					4	4	4	12	4	4	4	12	24	2 RETURN
59	3	4	4	11	4	0	4	8	0	4	4	8	27	
60	3	4	2	9	4	4	4	12	4	4	4	12	33	
61	2	4	4	10	4	4	4	12	2	4	0	6	28	
62	4	4	4	12	4	4	4	12	4	4	4	12	36	
63	4	4	4	12	4	4	4	11	4	4	0	8	32	
64	3	4	2	9	4	4	4	12	2	4	4	10	31	
65	4	4	4	12	4	4	4	12	4	4	4	12	36	
66	0	4	2	6	4	4	4	12	4	4	0	7	26	CE
67														NO RETURN
68	0	4	4	8	4	4	4	12	0	0	4	4	24	CE PP
69	3	4	2	9	4	4	4	12	1	4	4	9	30	
70	4	4	4	12	0	4	4	8	4	4	4	12	32	
71	4	4	4	12	4	4	4	12	4	4	4	12	36	
72	3	4	4	11	4	4	4	12	4	4	4	12	35	
73	0	4	3	7	4	4	4	12	4	4	4	12	31	CE

*) Educational sample
CE: Critical error
PP: Poor performance (on score)

11. Preview of the scheme in 2020

The format of the QLOU 2020 scheme will be similar to that of previous years.

Changes planned for 2020:
Interim reports are intended to be produced automatically by a software developed by CSCQ. This is already working in the proficiency testing schemes and has to be adopted to the QLOU requirements.

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January 2020

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Please note:
This annual report is intended for participants of the ERNDIM QLOU scheme. The contents should not be used for any publication without permission of the scheme advisor