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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 & Sharon Colyer, 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 2020 seventy-four laboratories from many different countries participated in the QLOU *Sheffield* scheme. There was one educational participant in 2020 (0 in 2019 and 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.

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

¹ If these scheme instructions are not Version 1 for this scheme year, go to APPENDIX 1 for details of the changes made since the last version of this document

3. Design of the scheme and logistics

As usual, the samples used in 2020 were authentic human urine samples, 6 from affected patients and 3 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 2020 ERNDIM QLOU *Sheffield* scheme.

	1 st Submission Round	2 nd Submission Round	3 rd Submission Round
Sample ID's:	QLOU-US-2020-A QLOU-US-2020-B QLOU-US-2020-C	QLOU-US-2020-D QLOU-US-2020-E QLOU-US-2020-F	QLOU-US-2020-G QLOU-US-2020-H QLOU-US-2020-I
Shipment of samples	February 5th, 2020		
Start of analysis (clinical data available)	May 13th, 2020	July 8th, 2020	September 9th, 2020
Reminder for result submission	May 27th, 2020	July 22nd 2020	September 23rd, 2020
Results submission deadline:	June 3rd, 2020	July 31st, 2020	September 30th, 2020

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 2020 ERNDIM QLOU *Sheffield* scheme.

Survey	Sample no.	Diagnosis
27-05-OUS	QLOU-US-2020-A	Maple Syrup Urine Disease (MSUD)
	QLOU-US-2020-B	Methyl Malonic Acidaemia (MMA)
	QLOU-US-2020-C	Normal
22-07-OUS	QLOU-US-2020-D	Normal
	QLOU-US-2020-E	Propionic Acidaemia (PA)
	QLOU-US-2020-F	Methyl Malonic Acidaemia (MMA) mild
23-09-OUS	QLOU-US-2020-G	Medium Chain Acyl CoA Dehydrogenase Deficiency (MCADD)
	QLOU-US-2020-H	Normal
	QLOU-US-2020-I	Fumarate Hydratase Deficiency (FH)

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 the CSCQ evaluation database by the website manager.

5. Results

Table 4: Receipt of results in the 2020 ERNDIM QLOU *Sheffield* scheme.

Survey	In time	Late	Total
27-05-OUS	73	1	74
22-07-OUS	72	2	74
23-09-OUS	72	0	72

Table 5: Returned results in the 2020 ERNDIM QLOU *Sheffield* scheme.

Submissions	Number of laboratories	%
3	72	97
2	2	3
1	0	0
0	0	0

6. Website reporting

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

- Results
 - Enter the key metabolites with the evaluation **in the tables**.
 - Quantitative data can be included if available or relevant, but is not a requirement
 - If the profile is normal: enter "Normal profile" in "Key metabolites".
 - **Please do not enter results in the "comments" window, otherwise your results will not be included in the evaluation program.**
- **Diagnosis**
 - **Please do not 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 is not scored.
 - **Please do not give advice for further investigation within the "Comments on diagnosis" field: 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 2020 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 19th, 2020).

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 13th, 2020.

Table 7: Samples eligible for critical errors in the 2020 ERNDIM QLOU *Sheffield* scheme.

Sample	Critical errors
QLOU-US-2020-G	1 for missing MCADD
QLOU-US-2020-I	1 for failing to identify fumarate as an abnormal metabolite

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.

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.

8. Proficiency of the 2020 surveys

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

In 2020, 72 participants submitted all three returns, including one educational participant. From the 71 ordinary (non-educational) participants, 69 (94%) achieved satisfactory performance (score $\geq 25/36$, no critical error). Two participants submitted two out of the three returns and achieved satisfactory performance ($>17/24$ points) for these.

Two participants did not accomplish satisfactory performance: one for critical error alone, and one for not meeting the set satisfactory performance by score and critical error.. Overall proficiencies of each sample are depicted in Table 8.

Table 8: Overall proficiencies of the 2020 surveys.

Sample ID	Sample type	Proficiency (%)
QLOU-US-2020-A	MSUD	91
QLOU-US-2020-B	MMA	100
QLOU-US-2020-C	Normal	100
QLOU-US-2020-D	Normal	98
QLOU-US-2020-E	Propionic Acidaemia	91
QLOU-US-2020-F	MMA (mild)	100
QLOU-US-2020-G	MCADD	97
QLOU-US-2020-H	Normal	96
QLOU-US-2020-I	Fumarate Hydratase	96

Two performance Support letters will be sent for the 2020 surveys. One of these participants also received a performance support letter in 2019. Unsatisfactory performance (either due to overall score or due to critical error) within an EQA scheme for at least 2 out of 3 years to which the participant has subscribed, will result in a notification letter of unsatisfactory performance to the Laboratory's Quality Manager or Head of Department.

(For the 2019 scheme 11 Performance Support letters were sent).

9. Results of individual samples and evaluation of reporting

The samples sent out in 2020 achieved good 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 most cases.

The sample **QLOU-US-2020-E Propionic Acidaemia** had the lowest proficiency. This was partly due to the presence of a large peak of lactate resulting in a number of participants opting for mitochondrial, respiratory chain, or holocarboxylase synthase deficiency as the most likely diagnoses, and partly due to difficulty of assigning the specific diagnosis of Propionic Acidaemia based on the organic acid profile alone. It is acknowledged that in the majority of laboratories a metabolic diagnosis of Propionic Acidaemia will also be made in conjunction with the plasma acylcarnitine profile.

The presence of ketones in sample **QLOU-US-2020-G MCADD** caused some confusion for a few laboratories. The majority acknowledged that many MCADD patients will present with ketotic hypoglycaemia. Text book description of purely hypoketotic hypoglycaemia is rarely seen in clinical practice, and often a disproportionate lipolytic and ketotic response is the strong clinical clue for a diagnosis of a suspected fatty acid oxidation defect. The presence of hexanoyl and suberyl glycine with or without ketones is diagnostic for MCADD and this was identified as the most likely diagnosis for this profile in all but two of the participants. The failure to identify MCADD from this profile was discussed at the SAB meeting in November and it was decided that one participant would be awarded critical error for not discussing the possibility of this profile being from an MCADD patient. Missing MCADD could have potentially fatal consequences without appropriate treatment and subsequently it is critical that this profile is recognised by laboratories offering an organic acid diagnostic service. The presence of a moderate peak of malate in sample **QLOU-US-2020-I Fumarate Hydratase** was also confusing for some participants. This resulted in some participants opting for mitochondrial disease as a likely diagnosis. Participants were not marked down if fumarate hydratase was either second or first choice as a diagnosis. The source of malate is not clear in this sample but this has been observed in a fumarate hydratase patient in previous distributions. It was decided at the SAB in the autumn that the failure to identify the large peak of fumarate as abnormal would be classified as a critical error. One participant was awarded critical error for this sample.

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 2020.

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

Lab No.	A	B	C	Sum A-C	D	E	F	Sum D-F	G	H	I	Sum G-I	TOTAL
1	4	4	4	12	2	4	4	10	4	0	4	8	30
2	4	4	4	12	4	4	4	12	2	4	3	9	33
3	4	4	4	12	4	4	4	12	4	4	4	12	36
4	2	4	4	10	4	4	4	12	4	4	4	12	34
5	4	4	4	12	4	4	4	12	4	4	4	12	36
6	4	4	4	12	4	4	4	12	4	4	4	12	36
7	4	4	4	12	4	4	4	12	4	4	4	12	36
8	4	4	4	12	4	4	4	12	4	4	4	12	36
9	2	4	4	10	4	4	4	12	4	4	4	12	34
10	4	4	4	12	4	4	4	12	4	4	4	12	36

11	4	4	4	12	4	4	3	11	4	4	4	12	35
12	4	4	4	12	3	4	4	12	4	4	4	12	35
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	4	12	3	4	4	11	4	4	4	12	35
16	4	4	4	12	4	4	4	12	4	4	2	10	34
17	4	4	4	12	4	4	4	12	4	4	4	12	36
18	4	4	4	12	4	4	4	12	4	3	4	11	35
19	4	4	4	12	4	4	4	12	4	4	4	12	36
20	4	0	4	8	4	4	4	12	0	0	4	4	24
21	4	4	4	12	4	4	4	12	4	4	4	12	36
22	2	4	4	10	4	4	4	12	4	4	4	12	34
23	3	4	4	11	4	4	4	12	4	4	4	12	35
24	4	4	4	12	3	4	4	11	4	0	4	8	31
25	4	4	4	12	4	4	4	12	4	4	4	12	36
26	4	4	4	12	4	4	4	12	4	4	4	12	36
27	4	4	4	12	4	4	4	12	4	4	4	12	36
28	4	4	4	12	4	4	4	12	4	4	4	12	36
29	4	4	4	12	4	4	4	12	4	4	4	12	36
30	2	4	0	6	3	4	4	11	4	4	4	12	29
31	4	4	4	12	4	4	4	12	4	4	4	12	36
32	4	4	4	12	3	4	4	11	4	4	4	12	35
33	4	4	4	12	4	4	4	12	4	4	4	12	36
34	4	4	4	12	4	4	4	12	4	4	3	11	35
35	4	4	4	12	3	4	4	11	4	4	4	12	35
36	4	4	4	12	4	4	4	12	4	4	4	12	36
37	4	4	4	12	4	4	4	12	4	4	4	12	36
38	4	4	4	12	3	4	4	11	4	4	4	12	35
39	3	4	4	11	2	4	4	10	4	3	4	11	32
40	4	4	4	12	4	2	4	10	2	4	4	10	32
41	4	4	4	12	4	4	2	10	4	4	4	12	34
42	0	4	4	8	4	4	4	12	4	4	4	12	32
43	4	4	4	12	4	4	4	12	4	4	4	12	36
44	4	4	4	12	4	0	4	8	4	4	4	12	32
45	4	4	4	12	4	4	4	12	4	4	4	12	36
46	4	4	4	12	2	4	4	10	4	4	4	12	34

47	4	4	4	12	4	4	4	12	4	4	4	12	36
48	4	4	4	12	2	4	4	10	4	4	4	12	34
49	4	4	4	12	2	4	4	10	4	4	4	12	34
50	4	4	4	12	4	4	4	12	4	4	2	10	34
51	4	4	4	12	4	4	4	12	4	4	4	12	36
52	4	4	4	12	4	4	4	12	4	4	4	12	36
53	4	4	4	12	4	4	4	12	4	4	4	12	36
54	4	4	4	12	3	4	4	11	4	4	4	12	35
55	4	4	4	12	4	4	4	12	4	4	4	12	36
56	4	4	4	12	2	3	4	9	4	4	0	8	29
57	4	4	4	12	4	4	3	11	4	4	4	12	35
58	0	4	4	8	3	4	4	11	4	4	2	10	29
59	4	4	4	12	3	4	4	11	4	4	4	12	35
60	4	4	4	12	4	4	4	12	4	4	4	12	36
61	4	4	4	12	4	4	4	12	4	4	4	12	36
62	4	4	4	12	4	4	4	12	4	4	4	12	36
63	0	4	4	8	4	4	4	12	4	4	4	12	32
64	4	4	4	12	4	4	4	12	4	4	4	12	36
65	4	4	4	12	0	4	4	8	4	4	4	12	32
66	4	4	4	12	4	4	4	12	0	0	0	0	24
67	4	4	4	12	4	4	4	12	4	4	4	12	36
68	4	4	4	12	3	0	4	7	4	4	4	12	31
69	4	4	4	12	3	4	4	11	4	4	4	12	35
70	4	4	4	12	4	2	4	10	4	4	4	12	34
71	4	4	4	12	3	4	4	11	4	4	4	12	35
72	4	4	4	12	4	4	4	12	0	0	0	0	24
73	3	4	4	11	4	4	4	12	4	4	4	12	35
74	0	4	4	8	4	4	4	12	4	0	4	8	28

11. Preview of the scheme in 2021

The format of the QLOU 2020 scheme will be similar to that of previous years except **only six samples** will be sent out to harmonise with other ERNDIM schemes. Satisfactory scores will remain at 70% of the maximum achievable score with an absence of critical error. This equates to 17/24. The annual report for 2021 will be derived from the on-line reporting and will subsequently be more detailed and better aligned to the DPT annual report.

Camilla Scott & Sharon Colyer

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Camilla Scott
Scientific Advisor

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

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

Version Number	Published	Amendments
1	18 January 2021	2020 annual report published
2	8th February 2021	Page 5, Poor Performance Policy, information for appeal of poor performance added.

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