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Diagnostic Proficiency Testing

Centre: Switzerland

Final Report 2023

prepared by Déborah Mathis

Note: This annual report is intended for participants of the ERNDIM DPT Switzerland 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 ERNDIM Privacy Policy on www.erndim.org.

In 2023, 21 labs participated to the Proficiency Testing Switzerland Scheme.

1. Geographical distribution of participants

21 laboratories submitted results for both surveys.

Country	Number of participants
Australia	3
Austria	2
Canada	3
China	1
Estonia	1
Germany	4
Netherlands	1
Norway	1
Sweden	2
Switzerland	1
United States of America	2

2. Design and logistics of the scheme including sample information

The scheme has been designed and planned by Déborah Mathis as Scientific Advisor (SA) and by Brian Fowler as Deputy SA, and coordinated by Alessandro Salemma and Nicola Braik as scheme organiser

[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.

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

2 surveys	Round 1: patients A, B and C
	Round 2: patients D, E and F

Origin of patients Samples used in 2023 have been provided by 4 different centres: Inselspital Bern, Switzerland; Kinderspital Zürich, Switzerland; Medizinische Universität Innsbruck, Austria (donator: PD Dr. med. Sabine Scholl-Bürgi) and General University Hospital in Prague, Czech Republic.

Patient A: ASL deficiency
Patient B: Prolidase deficiency
Patient C: Alkaptonuria
Patient D: GM2-gangliosidosis
Patient E: Cystinuria
Patient F: MADD

The samples have been heat-treated. They were analysed in our institute after 3 days incubation at ambient temperature (to mimic possible changes that might arise during transport). In all five samples the typical metabolic profiles were preserved after this process. The common sample was checked by the provider.
Mailing: samples were sent by DHL; FedEx or the Swiss Post at room temperature.

3. Tests
Analyses of amino acids, organic acids and oligosaccharides were required in 2023.

4. Schedule of the scheme
- Feb 08, 2023: shipment of samples of Survey 1 and 2
- March 13, 2023: analysis of samples of the first survey
- March 27, 2023: deadline for result submission (Survey 1)
- June 05, 2023: analysis of samples of the second survey
- June 19, 2023: deadline for result submission (Survey 2)
- September 12, 2023: annual meeting of participants, online.

5. Results
21 of 21 labs returned results for both surveys by the deadline.

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 is 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 (correct diagnosis was indicated)	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 as well as by a second assessor who changes every year. The results of DPT Switzerland 2023 have been also scored by Joanne Croft, from the DPT UK scheme. At the SAB meeting in November 2023, the definitive scores have been finalized. Sample D was decided to be educational. 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 2023, the SAB decided that a critical error has to be considered from sample C for the labs who missed the diagnosis alkaptonuria.
A certificate of participation will be issued for participation and it will be additionally notified whether the participant has received a performance support letter. A performance support letter is sent out if the performance is evaluated as unsatisfactory (low score or critical error). Three performance support letters has been sent by the Scientific Advisor for 2023. Any partial submitters will receive a letter from the ERNDIM Executive Administrator, Sara Gardner.

7.1. Score for satisfactory performance

As sample D was decided by the SAB to be educational, at least 14 points from the maximum of 20 (70%) are needed for satisfactory performance.

8. Results of samples and evaluation of reporting

8.1. Patient A

Diagnosis
Argininosuccinic aciduria due to argininosuccinate lyase deficiency (OMIM #207900)

Patient details provided to participants
This boy was referred at the age of 7 years with attention deficit disorder. The sample was collected at the age of 25 years on the specific treatment.

Patient detailed information
Sample from a patient with mild form of argininosuccinic aciduria due to argininosuccinate lyase deficiency. The patient is treated with low protein diet. The diagnosis was confirmed genetically.

Analytical performance
Detection of increased concentration of argininosuccinic acid or its anhydrides was scored with 2 points (17/21 labs).

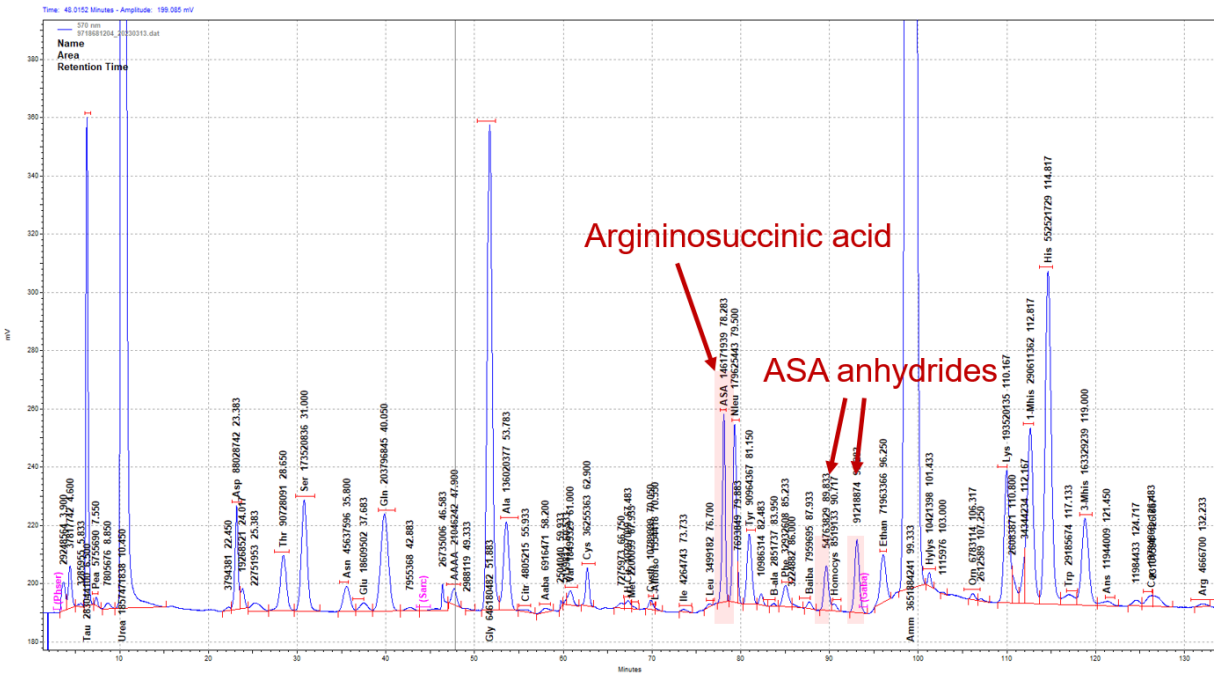

Figure 1: Amino acid analysis by ion-exchange chromatography of sample A

Interpretative proficiency
Argininosuccinic aciduria due to argininosuccinate lyase deficiency was scored with 2 points (17/21 labs). Other urea cycle disorders would have been scored one point (0/21 labs).

Appropriate further investigations
Analysis of ammonia and plasma amino acids; confirmation of diagnosis by molecular analysis of ASL gene.

Overall impression
4/21 labs failed to detect argininosuccinc acid and therefore failed to report the right diagnosis. The other 17 labs that detect ASA reported the right diagnosis. Overall proficiency was of 81%.

Multiple distributions of similar samples

	2006	2009	2012	2016	2021
Overall performance	75%	95%	87%	100%	100%

8.2. Patient B

Diagnosis
Prolidase deficiency (OMIM #170100)

Patient details provided to participants
17 years old boy with mental retardation, hepatosplenomegaly (chronic EBV infection), dysmorphism, dwarfism and skin ulcers.

Analytical performance
Detection of iminodipeptiduria was scored with 2 points (17/21 labs).
Methods that labs used and missed detection of iminodipeptides were: one reverse-phase HPLC, one IEC ninhydrin, one LC-MS/MS, one LC-MS/MS (kit).

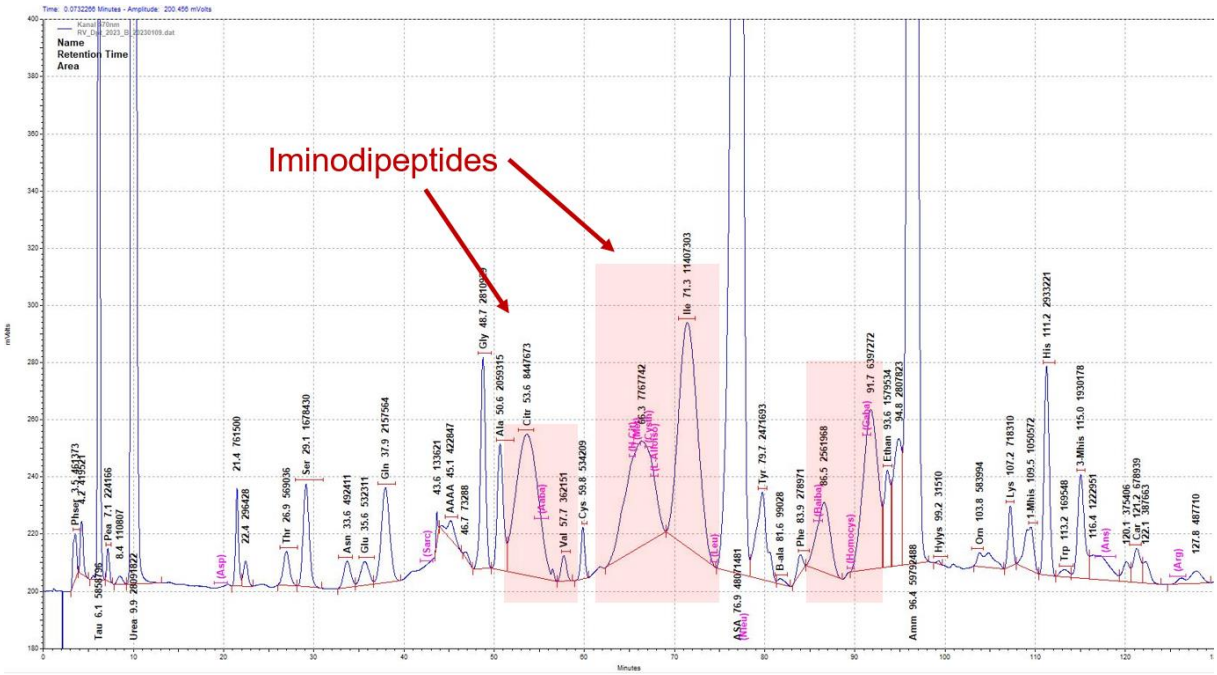

Figure 2: Amino acid analysis by ion-exchange chromatography of sample B

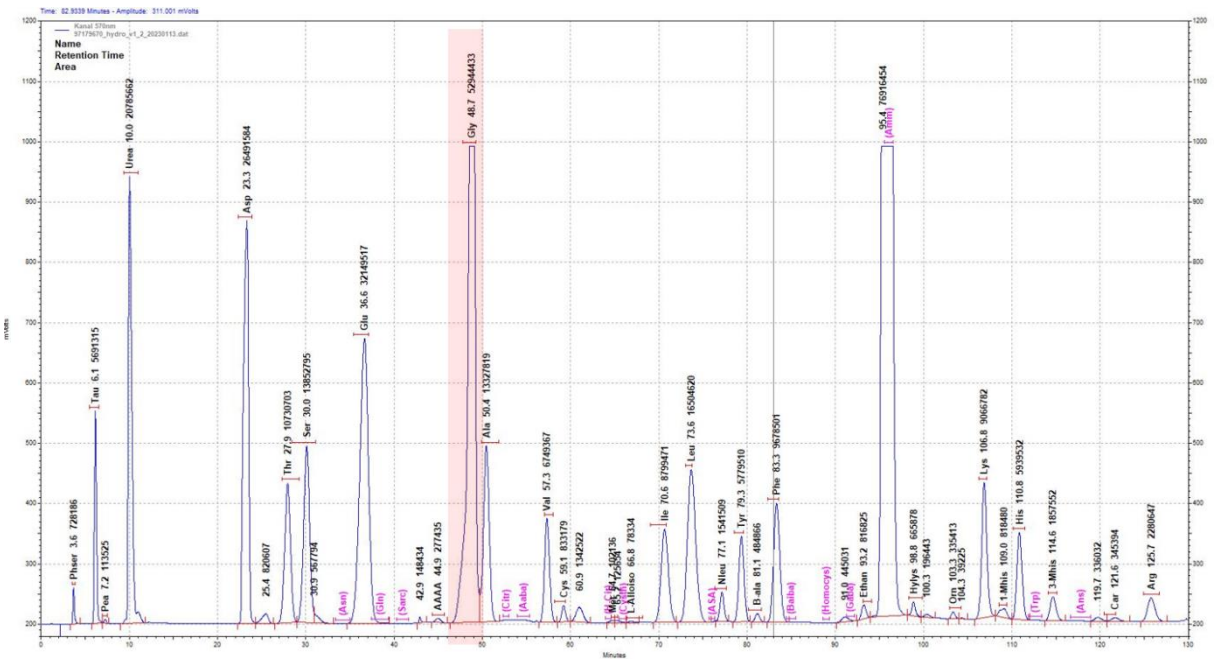

Figure 3: Amino acid analysis by ion-exchange chromatography of sample B after hydrolysis with HCl.

Interpretative proficiency
Prolidase deficiency was scored with two points (18/21 labs).

Appropriate further investigations
Confirmation of diagnosis with enzymatic activity or genetic analysis of PEPD gene.

Overall impression
4 labs failed to detect iminodipeptides with amino acid analysis leading to a analytical proficiency of 81%. One lab correctly pointed towards the right diagnosis based on the clinical information only. Overall proficiency was of 83%.

Multiple distributions of similar samples

	2017
Overall performance	65%

8.3. Patient C

Diagnosis
Alkaptonuria (OMIM #203500)

Patient details provided to participants
8 years old boy with pseudo-proteinuria on routine urinary analysis.

Patient further information
Patient on slightly restricted-protein intake, but not on Nitisinone.

Analytical performance
Increased homogentisic acid was scored with two points (19/21 labs).

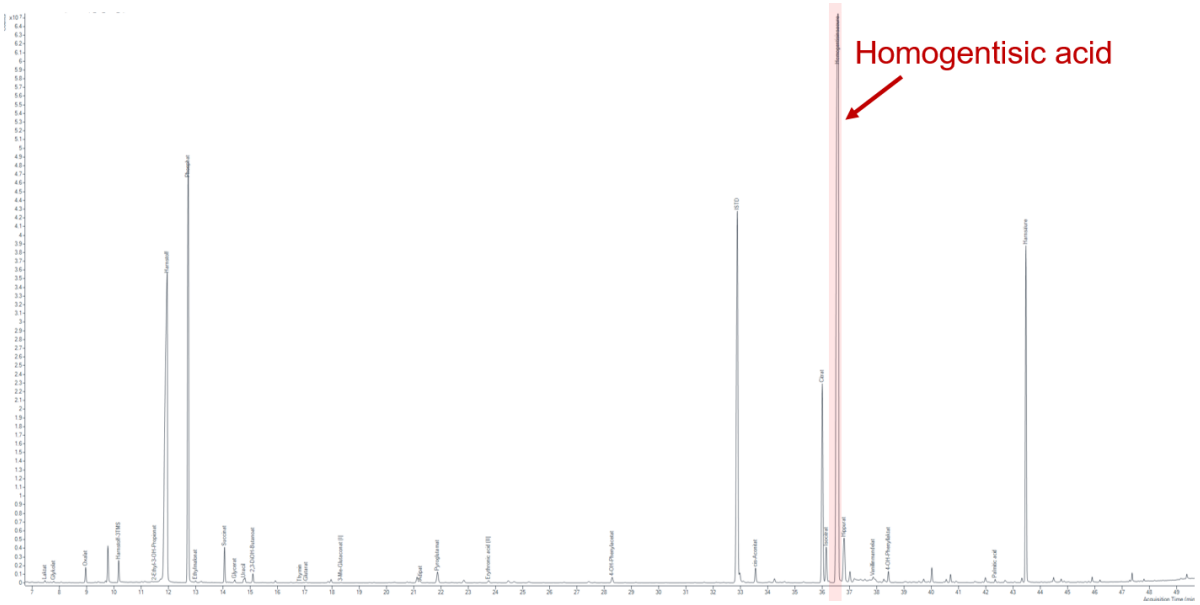

Figure 4: Organic acid analysis by GC-MS of sample D

Interpretative proficiency
Alkaptonuria as main diagnosis was scored with two points (20/21 labs).

Appropriate further investigations
Confirmation of diagnosis with genetic testing of the HGD gene.

Overall impression
Overall proficiency was of 93%. Two labs did not detect homogentisic acid. One of those labs suggest alkaptonuria as main diagnosis, based on darkening of urine but couldn't detect homogentisic acid in the organic acid analysis. This sample was considered eligible for critical error for lab that did not find

the right diagnosis.

Multiple distributions of similar samples

	2012
Overall performance	87%

8.4. Patient D

Diagnosis
GM2-gangliosidosis, Sandhoff disease with juvenile onset (OMIM 268800).

Patient details provided to participants
16 years old girl with learning difficulties and progressing ataxia since 3 years ago. No therapy.

Analytical performance
Abnormal oligosaccharide pattern compatible with GM2-gangliosidosis was scored 2 points (4/21 labs). Borderline results in oligosaccharide analysis was scored 1 point (1/21 lab). 10/21 labs reported normal oligosaccharides or too faint bands to be interpreted and 6/21 labs did not perform oligosaccharide analysis.

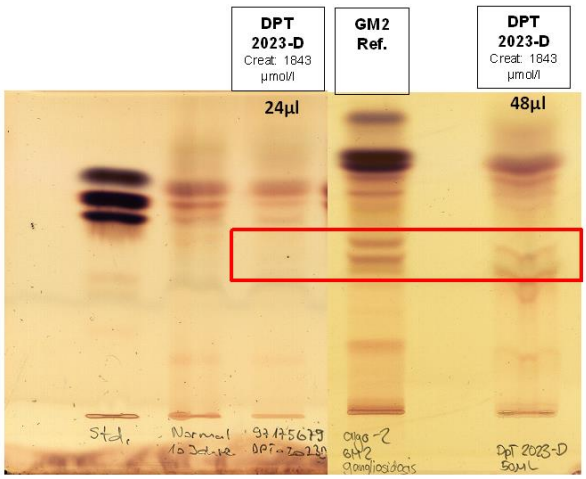

Figure 5: Qualitative TLC oligosaccharides of sample D

Interpretative proficiency
GM2-gangliosidosis (Tay-Sachs or Sandhoff disease) was scored 2 points (4/21 labs).
As the urine sample was quite diluted, recommendations to perform further tests on a fresh sample was scored one point (17/24 labs).

Overall impression
Only 4/21 labs could detect an abnormal oligosaccharide pattern and thus pointed to the right diagnosis. 1 lab reported borderline results and 10 labs reported normal or too low bands to be interpreted (6 labs did not perform oligosaccharide analysis). Analytical performance was of only 21%. This sample was classed as educational by the scientific advisory board (SAB) during the Meeting in November 2023.

8.5. Patient E

Diagnosis
Cystinuria (OMIM 220100)

Patient details provided to participants
14 years old girl currently without symptoms under therapy, but with a history of severe back pain during a febrile illness at 4 years of age.

Analytical performance
Increased cystine, lysine, arginine and ornithine was scored 2 points (21/21 labs)

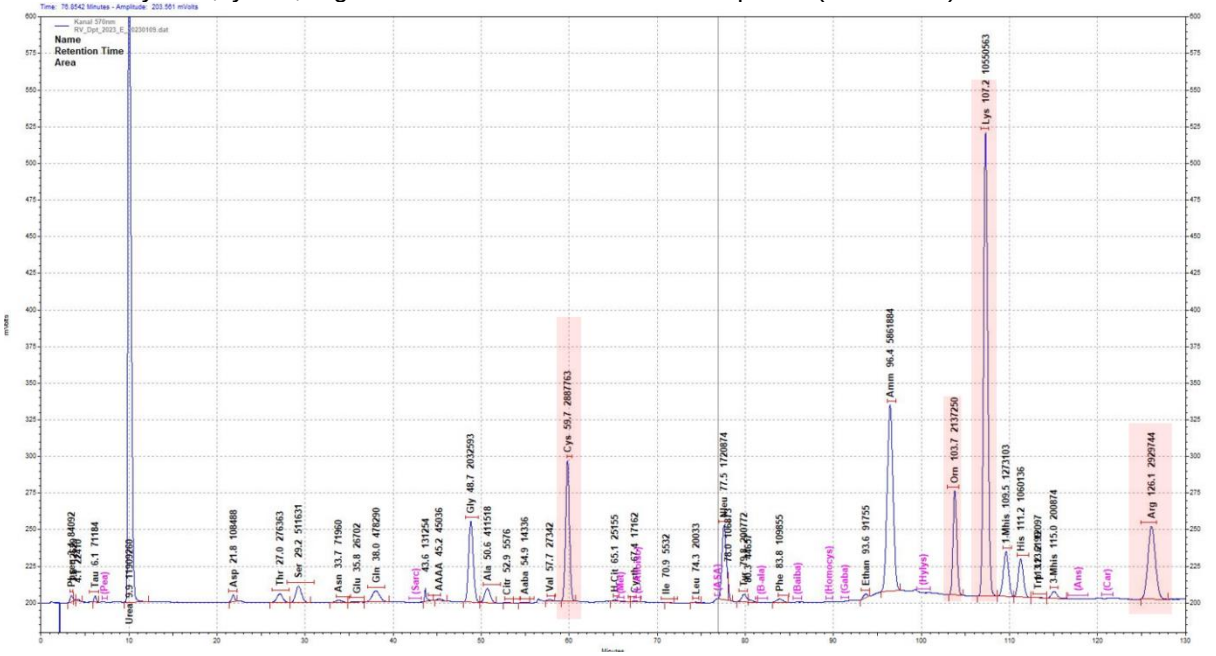

Figure 6: Amino acid analysis by ion-exchange chromatography of sample E

Interpretative proficiency
Cystinuria was scored two points (21/21 labs)

Overall impression
Excellent performance in this sample with 100% proficiency

Multiple distributions of similar samples

	2016
Overall performance	89%

8.6. Patient F

Diagnosis
Multiple acyl-CoA dehydrogenase deficiency (MADD) (OMIM #231680)

Patient details provided to participants
Muscular hypotonia and retardation in infancy; diagnosis at severe metabolic decompensation in the context of a viral infection at 2 years of age. Urine collected under treatment (sodium 3-hydroxybutyrate) at 16 years.

Analytical performance
Increase of at least two metabolites either specific of MADD (2-OH-glutarate, hexanoylglycine, 3-OH-glutarate, etc.) or 3-OH-butyrate was scored two points (13/21 labs). Increase of one metabolite either specific of MADD (2-OH-glutarate, hexanoylglycine, 3-OH-glutarate, etc.) or 3-OH-butyrate was scored one point (4/21 labs).

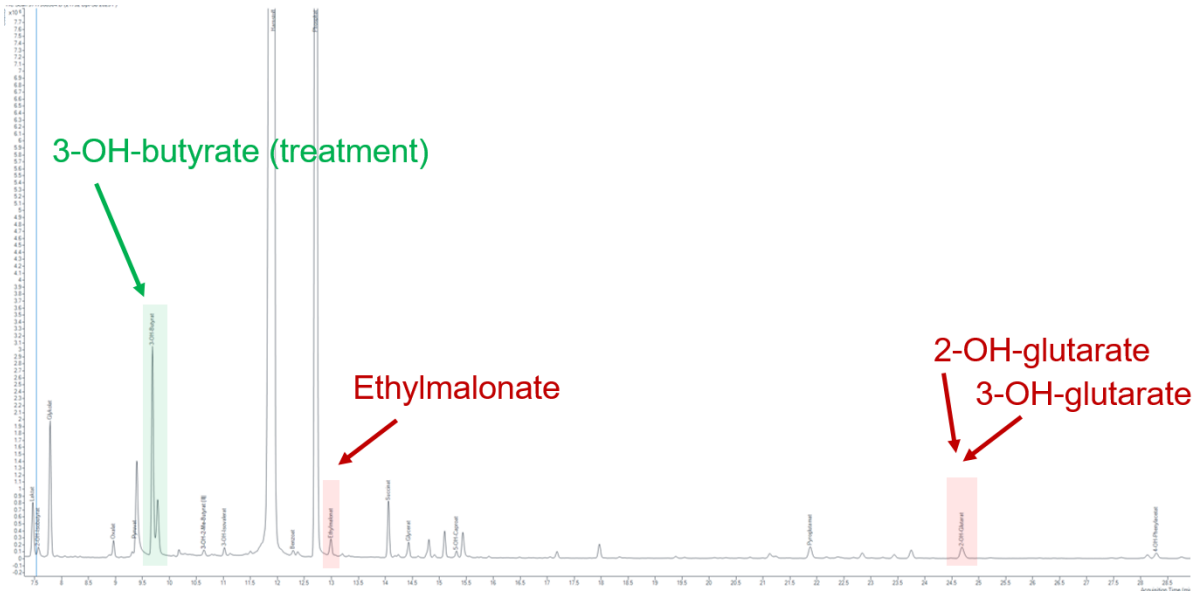

Figure 7: Organic acid analysis by GC-MS of sample F

Interpretative proficiency

Multiple acyl-CoA dehydrogenase deficiency (MADD) as main or alternative diagnosis was scored two points (11/21 labs).

Other organic acidurias as 2-OH-glutaric aciduria or glutaric aciduria type 1 or recommendation to perform acylcarnitine analysis was scored 1 point (8/21 labs).

Overall impression

This was a tricky sample with very low concentrations of key metabolites affording an overall proficiency of 71%.

9. Scores of participants

All data transfer, the submission of data as well as the request and viewing of reports proceed via the DPT-CSCQ results website. The results of your laboratory are confidential and only accessible to you (with your username and password).The anonymous scores of all laboratories are accessible to all participants and only in your version is your laboratory highlighted in the leftmost column.

If your laboratory is assigned poor performance and you wish to appeal against this classification please email the ERNDIM Administration Office (admin@erndim.org), with full details of the reason for your appeal, within one month receiving your Performance Support Letter. Details of how to appeal poor performance are included in the Performance Support Letter sent to poor performing laboratories.

Detailed scores – **Round 1**

Lab n°	Patient A ASL deficiency			Patient B Prolidase def.			Patient C Alkaptonuria			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	2	4	2	2	4	0	0	0	8
2	2	2	4	2	2	4	2	2	4	12
3	2	2	4	0	2	2	2	2	4	10
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
10	2	2	4	0	0	0	2	2	4	8
11	2	2	4	2	2	4	2	2	4	12
12	2	2	4	2	2	4	2	2	4	12
13	0	0	0	2	2	4	2	2	4	8
14	2	2	4	2	2	4	2	2	4	12
15	2	2	4	2	2	4	2	2	4	12
16	2	2	4	2	2	4	2	2	4	12
17	0	0	0	0	0	0	2	2	4	4
18	0	0	0	2	2	4	2	2	4	8
19	2	2	4	2	2	4	0	2	2	10
20	2	2	4	2	2	4	2	2	4	12
21	0	0	0	0	0	0	2	2	4	4

Detailed scores – Round 2

Lab n°	Patient D GM2-gangliosidosis			Patient E Cystinuria			Patient F MADD			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	2	4	2	2	4	2	1	3	11
2	0	1	1	2	2	4	2	1	3	8
3	1	1	2	2	2	4	1	1	2	8
4	0	1	1	2	2	4	0	0	0	5
5	0	1	1	2	2	4	0	1	1	6
6	2	2	4	2	2	4	2	1	3	11
7	0	1	1	2	2	4	2	2	4	9
8	0	1	1	2	2	4	1	2	3	8
9	0	1	1	2	2	4	2	2	4	9
10	2	2	4	2	2	4	0	0	0	8
11	0	1	1	2	2	4	1	1	2	7
12	1	1	2	2	2	4	2	1	3	9
13	0	1	1	2	2	4	2	2	4	9
14	0	1	1	2	2	4	2	2	4	9
15	2	2	4	2	2	4	2	2	4	12
16	0	1	1	2	2	4	1	2	3	8
17	0	1	1	2	2	4	2	2	4	9
18	0	1	1	2	2	4	2	2	4	9
19	0	1	1	2	2	4	2	2	4	9
20	0	1	1	2	2	4	2	2	4	9
21	0	1	1	2	2	4	0	0	0	5

Total scores

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Critical error
1	4	4	0	4	4	3	19	79	
2	4	4	4	1	4	3	20	83	
3	4	2	4	2	4	2	18	75	
4	4	4	4	1	4	0	17	71	
5	4	4	4	1	4	1	18	75	
6	4	4	4	4	4	3	23	96	
7	4	4	4	1	4	4	21	88	
8	4	4	4	1	4	3	20	83	
9	4	4	4	1	4	4	21	88	
10	4	0	4	4	4	0	16	67	
11	4	4	4	1	4	2	19	79	
12	4	4	4	2	4	3	21	88	
13	0	4	4	1	4	4	17	71	
14	4	4	4	1	4	4	21	88	
15	4	4	4	4	4	4	24	100	
16	4	4	4	1	4	3	20	83	
17	0	0	4	1	4	4	13	54	
18	0	4	4	1	4	4	17	71	
19	4	4	2	1	4	4	19	79	
20	4	4	4	1	4	4	21	88	
21	0	0	4	1	4	0	9	38	

Performance

	Number of labs	% total labs
Satisfactory performers (≥ 70% of adequate responses)	17	81
Unsatisfactory performers (< 70% adequate responses and/or critical error)	4	19
Partial and non-submitters	0	0

Overall Proficiency

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Total (%)
DPT-SB-2023-A	ASL deficiency	**81**	**81**	**81**
DPT-SB-2023-B	Prolidase deficiency	**81**	**86**	**83**
DPT-SB-2023-C	Alkaptonuria	**90**	**95**	**93**
DPT-SB-2023-D	GM2-gangliosidosis	**21**	**60**	**40**
DPT-SB-2023-E	Cystinuria	**100**	**100**	**100**
DPT-SB-2023-F	MADD	**71**	**71**	**71**

10. Annual meeting of participants

This took place online on September 12.

Participants: We remind you that attending the annual meeting is an important part of the proficiency testing. The goal of the program is to **improve** the competence of the participating laboratories, which includes the critical review of all results with a discussion about improvements.

11. Information from the Executive Board and the Scientific Advisory Board

Urine samples: we remind you that each participant should endeavour to provide to the scheme organizer at least 300 ml of urine from a patient affected with an established inborn error of metabolism together with a short clinical report. If possible, please collect 1500 ml of urine: this sample can be sent to all labs participating to one of the DPT 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 over a short period of time from the same patient. Please don't send "normal" urine. Please send us an e-mail if you have such a sample and we will arrange the shipment.

12. Reminders

We remind you that to participate to the DPT-scheme, you must perform at least:

- Amino acids
- Organic acids
- Oligosaccharides
- Mucopolysaccharides
- Purine/pyrimidines

If you are not performing one of these assays, you can send the samples to another lab (cluster lab) but you are responsible for the results. Please send quantitative data for amino acids and, as much as possible, for organic acids.

13. Tentative schedule in 2024

Sample distribution	February 7, 2024
Start of analysis of Survey 2024/1 (website open)	March 4, 2024
Survey 2024/1 - Results submission deadline	April 2, 2024
Survey 2024/1 – Interim report available	April/May 2024
Start of analysis of Survey 2024/2 (website open)	June 3, 2024
Survey 2024/2 – Results submission deadline	June 24, 2024
Survey 2024/2 – Interim report available	July/August 2024
Annual meeting of participants	September 3, 2024 (Porto)
Annual Report 2024	January 2025

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 DPT scheme this certificate will indicate if results were submitted and whether satisfactory performance was achieved in the scheme.

15. Questions, Comments and Suggestions

If you have any questions, comments or suggestions please address to the Scientific Advisor of the scheme, Déborah Mathis (deborah.mathis@insel.ch) and/or to the ERNDIM Administration Office (admin@erndim.org)

Date of report, 2024-02-13
Name and signature of Scientific Advisor

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

Version Number	Published	Amendments
1	13th February 2024	2023 annual report published

END