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Diagnostic Proficiency Testing

Centre: Switzerland

Final Report 2022

prepared by Déborah Mathis
reviewed by Brian Fowler

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 2022, 20 labs participated to the Proficiency Testing Switzerland Scheme.

1. Geographical distribution of participants

20 laboratories submitted results for both surveys.

Country	Number of participants
Australia	2
Austria	2
Canada	3
Czechia	1
Estonia	1
Germany	3
Hong Kong	1
Norway	1
Sweden	2
Switzerland	2
United States of America	2

[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.

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 (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: three urine samples have been provided by the scheme organizer, two were provided by one of the participant, and one was the common sample.

Patient A: MGA-Barth – Joanne Croft, Sheffield. This sample has been sent to all labs participating to the DPT scheme in Europe
Patient B: OTC def. – Dr med Sabine Scholl-Bürgi, Medizinische Universität Innsbruck
Patient C: MPS VI – Inselspital, Bern
Patient D: HMGL def – Inselspital, Bern
Patient E: Tyr 1 – Inselspital, Bern
Patient F: ATPS def. – Dr med Sabine Scholl-Bürgi, Medizinische Universität Innsbruck

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 mucopolysaccharides were required in 2022.

4. Schedule of the scheme

- Feb 02, 2022: shipment of samples of Survey 1 and 2
- March 14, 2022: analysis of samples of the first survey
- March 28, 2022: deadline for result submission (Survey 1)
- June 06, 2022: analysis of samples of the second survey
- June 21, 2022: deadline for result submission (Survey 2)
- August 30, 2022: annual meeting of participants, Freiburg, Germany

5. Results

20 of 20 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 2022 have been also scored by George Ruijter, from the DPT Netherland scheme. At the SAB meeting in November 2022, 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 a critical error has to be considered from sample C for the labs who missed MPS diseases in general and did not recommend to analyse GAGs.
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). One performance support letter has been 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%) are needed for satisfactory performance.

8. Results of samples and evaluation of reporting

8.1. Patient A

3-Methylglutaconic aciduria in association with Barth Syndrome (OMIM 302060).

Patient details provided to participants

Pre-natal growth concerns. Monitored throughout life for poor growth. Presented at 4 years of age due to lips going blue during exercise.

Diagnosis

3-Methylglutaconic aciduria in association with Barth Syndrome (OMIM 302060).

Analytical performance

Detecting increased concentration of 3-methyl-glutaconate was scored with 2 points (20/20 labs).

Figure 1: Organic acid analysis by GC-MS of sample A

Interpretative proficiency

Barth syndrome (as primary or alternate diagnosis) or secondary 3-methyl glutaconic aciduria (as main or alternative diagnosis) were scored with 2 points (19/20).

Primary 3-methylglutaconic aciduria (type 1) (either HMG-CoA-lyase or 3-methylglutaconyl-CoA-hydratase deficiency) or non-specified with no mention of Barth syndrome received one point only (1/20 lab).

Appropriate further investigations

Genetic analysis of TAZ gene, monolysocardiolipin/cardiolipin ratio in WBCs.

Overall impression

Overall proficiency was excellent at 100% for analytical and 98% for interpretation.

Multiple distributions of similar samples

	2013	2022
Overall performance	68%	99%

8.2. Patient B

Hyperammonemia due to ornithine transcarbamylase deficiency (OMIM 311250).

Patient details provided to participants

22 year old woman on specific treatment, admitted into the emergency department with vomiting, confusion and later seizures

Diagnosis

Hyperammonemia due to ornithine transcarbamylase (OTC) deficiency (OMIM 311250).

Analytical performance

Arginine increase was scored with one point (17/20 labs).
Increased uracil and/or hippuric/benzoic acid was scored one point (20/20 labs).

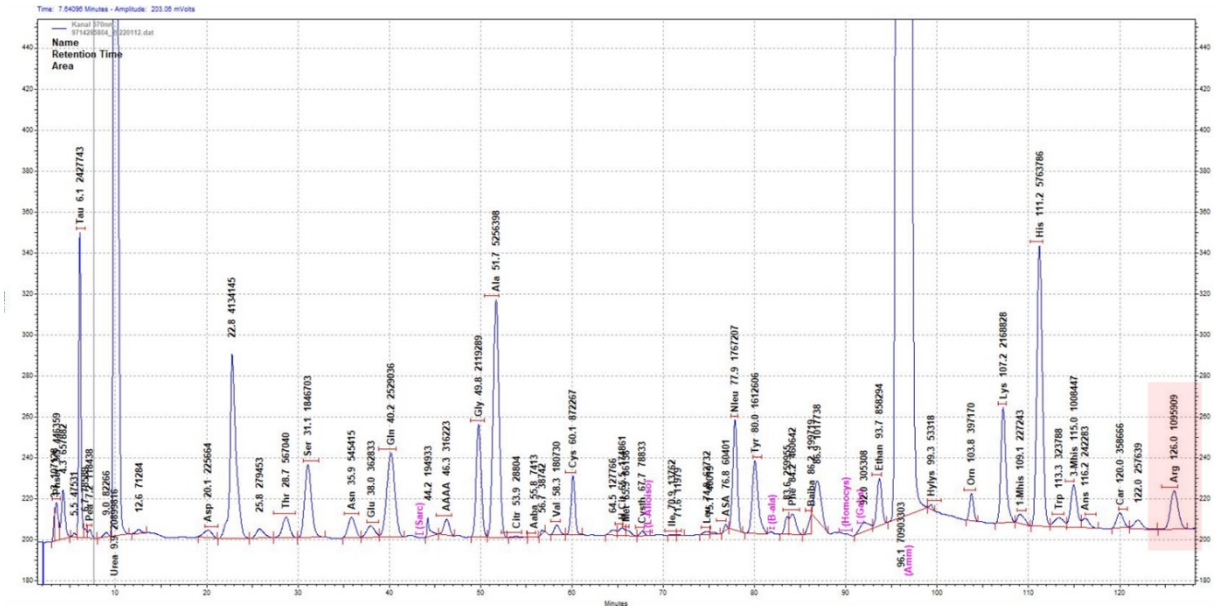

Figure 2: Amino acid analysis by ion-exchange chromatography of sample B

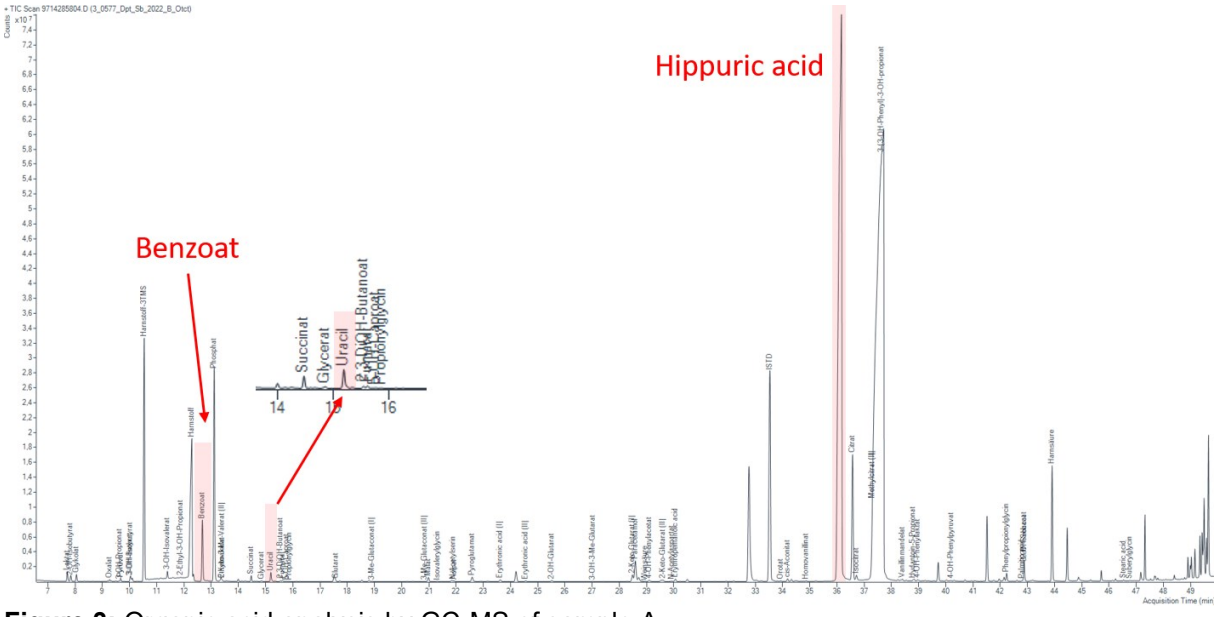

Figure 3: Organic acid analysis by GC-MS of sample A

Interpretative proficiency

Mention of OTC deficiency, arginase deficiency or urea cycle disorder as main diagnosis received two points (19/20 labs).
Mention of urea cycle disorder as alternate diagnosis was scored with one point (1/20 labs).

Appropriate further investigations

Determination of ammonia, determination of orotic acid, plasma amino acids (citrulline), genetic analysis of OTC gene.

Overall impression
Overall proficiency was good at 93% for analytical and 98% for interpretation. Overall proficiency was of 95%

Multiple distributions of similar samples

	2007	2022
Overall performance	77%	95%

8.3. Patient C
Mucopolysaccharidosis type VI, arylsulfatase B deficiency (OMIM 253200).

Patient details provided to participants
4 years old girl with developmental delay and macrocephaly

Diagnosis
Mucopolysaccharidosis type VI, arylsulfatase B deficiency (OMIM 253200).

Analytical performance
Differentiation of MPS was reported by 14 labs. All 14 labs reported increase dermatan sulphate, with or without other MPS, and this was scored two points
Unspecific MPS increase was scored 1 point (5/20 labs)

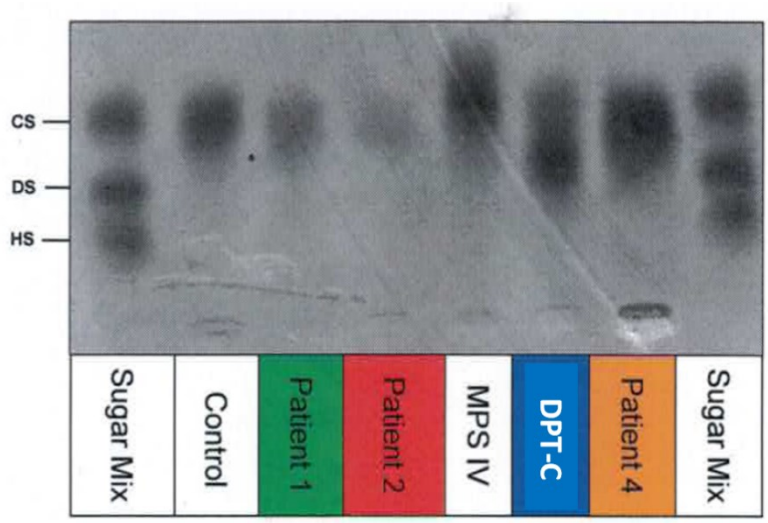

Figure 4: MPS differentiation by gel electrophoresis of sample C

Interpretative proficiency
MPS VI as main or alternative diagnosis or mentioned in the comments was scored with two points (13/20 labs).
Other or unspecified MPS as most likely diagnosis was scored 1 point (6/20 labs).
No MPS disorder with no recommendation to measure GAGs received zero point (1/20 labs)

Appropriate further investigations
Differentiation of MPS if not performed
Arylsulfatase B enzyme activity and/or genetic analysis of ARSB gene

Overall impression
Proficiency was very good for the labs that measured the differentiated GAGs (14/20).
Labs that only measured total MPS pointed to MPS diseases.
Overall proficiency was 81%
This sample was considered eligible for critical error if the diagnosis of MPS diseases was missed in general and if no recommendation to analyse MPS was mentioned.

Multiple distributions of similar samples

	2018	2022
Overall performance	72%	84%

8.4. Patient D

HMG-CoA lyase deficiency (OMIM # 246450)

Patient details provided to participants

12 years old boy with normal development, on treatment. The diagnosis was made in the neonatal period due to metabolic decompensation.

Diagnosis

HMG-CoA lyase deficiency (OMIM # 246450).

Analytical performance

Elevated 3-hydroxy-3-methylglutaric acid was scored one point (19/20 labs).
Other related metabolites, e.g. 3-methylglutarate/3-methylglutaconic acid were also scored with one point (20/20 labs).

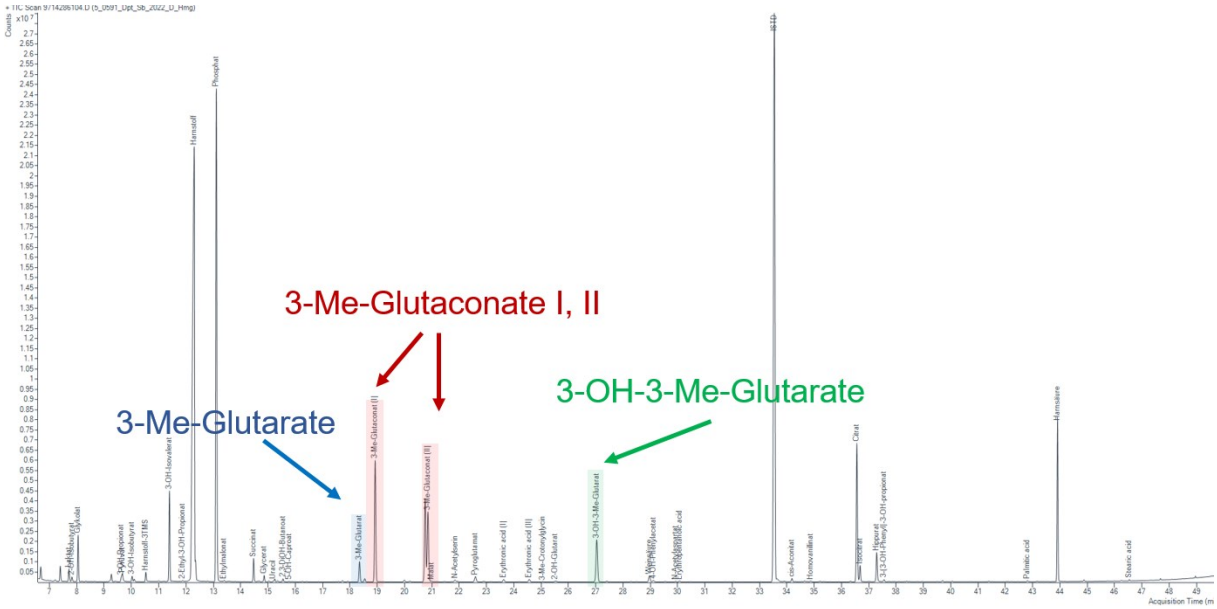

Figure 5: Organic acid analysis by GC-MS of sample D

Interpretative proficiency

HMG-CoA lyase deficiency was scored with two points (19/20 labs).
3-Methylglutaconic aciduria was scored with zero points (1 lab).

Appropriate further investigations

Determination of acylcarnitines in blood, enzyme activity assay of 3-hydroxy-3-methylglutaryl-CoA lyase in lymphocytes, genetic analysis of HMGCL gene.

Overall impression

All but one lab successfully diagnosed HMG-CoA lyase deficiency with overall proficiency of 96%. Analytical proficiency was 97%, interpretation 95%.

Multiple distributions of similar samples

	2016	2022
Overall performance	96%	96%

8.5. Patient E

Tyrosinaemia type 1 due to fumarylacetoacetatehydrolase deficiency (OMIM # 276700).

Patient details provided to participants

14 years old girl with persistent gingival bleeding, hepatomegaly and rickets

Diagnosis

Tyrosinaemia type 1 due to fumarylacetoacetate hydrolase deficiency (OMIM # 276700), on treatment with NTCB.

Analytical performance

Elevated tyrosine was scored one point (20/20 labs).
Phenolic acids AND mention of normal succinylacetone, one point (20/20 labs)

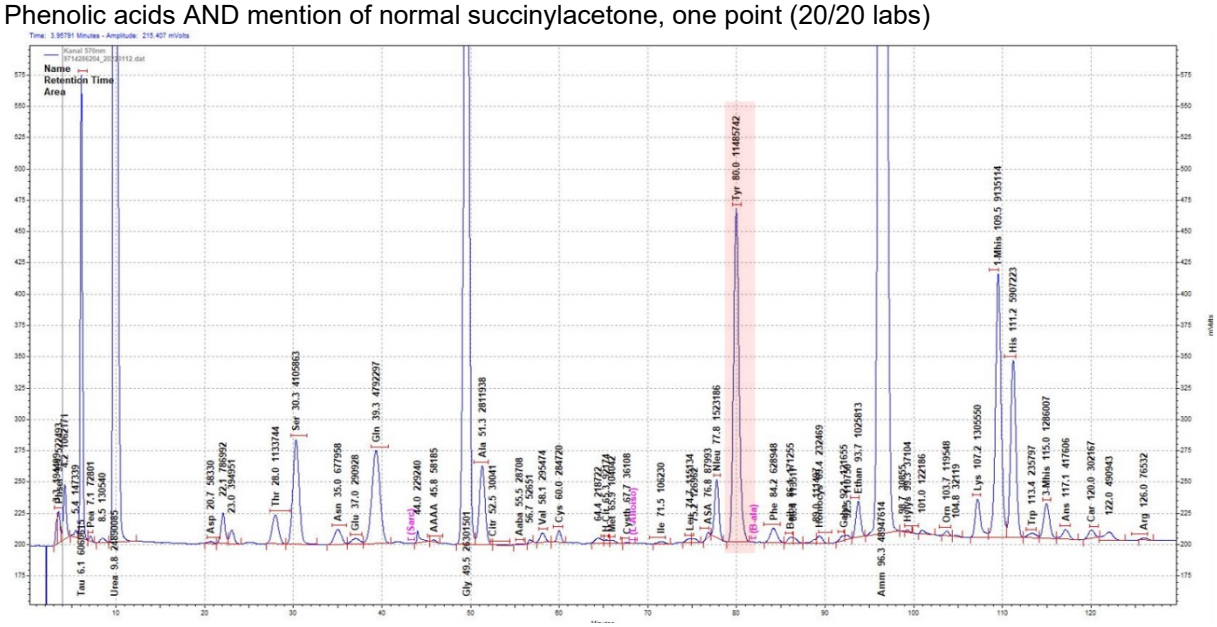

Figure 6: Amino acid analysis by ion-exchange chromatography of sample E

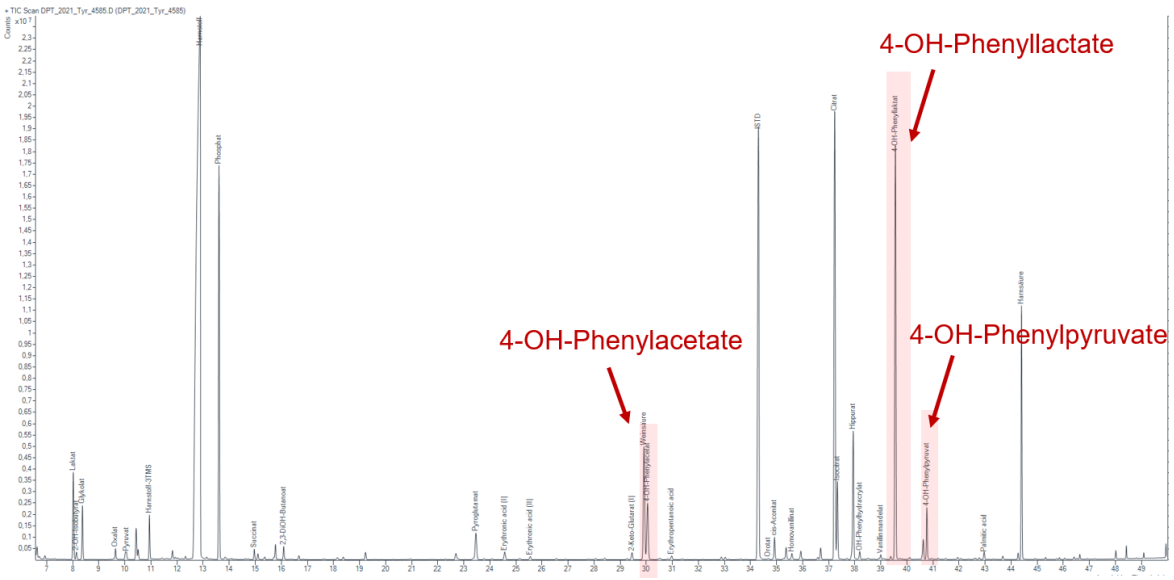

Figure 7: Organic acid analysis by GC-MS of sample E

Interpretative proficiency

Mention of tyrosinaemia type I (on treatment) was scored with two points (19/20 labs). Combined liver and kidney disorders, without mention of tyrosinaemia type 1 ended to zero points (1/20 labs)

Appropriate further investigations

Amino acids in plasma, succinylacetone in plasma, enzymatic activity of fumarylacetoacetase in lymphocytes, genetic testing of *FAH* gene

Overall impression
Overall proficiency of 98% was very good with all but one lab that correctly identified tyrosinaemia type I. Analytical proficiency was 100% and interpretation 95%.

8.6. Patient F

Mitochondrial complex V (ATP synthase) deficiency.

Patient details provided to participants
Newborn with respiratory distress, cardiomyopathy with cardiocirculatory failure, dysmorphia

Diagnosis
Mitochondrial complex V (ATP synthase) deficiency with homozygote mutation c.317-2A>G in TMEM70 gene

Analytical performance
Increased alanine/lactate was scored with one point (20 labs)
Increased 3-Me-glutaconic aciduria was scored with one point (15 labs).
No point was scored for elevated 3-Hydroxy-isobutyric acid.

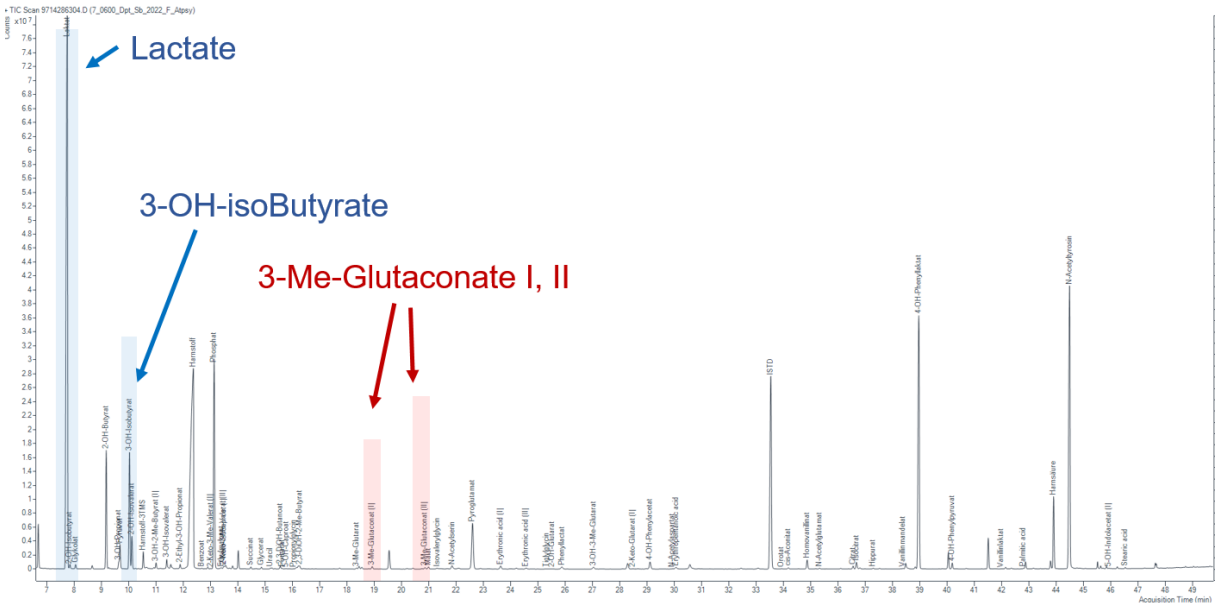

Figure 8: Organic acid analysis by GC-MS of sample F

Interpretative proficiency
Mention of a mitochondrial disorder or 3-methylglutaconic aciduria as main or alternative diagnosis was scored with two points (16/20 labs).
Barth Syndrome (without mention of mitochondrial disorder) was scored with one point (2/20 labs).

Appropriate further investigations
Plasma lactate/pyruvate ratio, plasma amino acids and acylcarnitines, repeat organic acids, appropriate targeted genetic testing.

Overall impression
Overall proficiency was quite good (86%) for this fairly tricky sample.
Analytical proficiency was 88% and interpretation 85%.

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.

Detailed scores – Round 1

Lab n°	Patient A MGA-Barth			Patient B OTC def.			Patient C MPS VI			
	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	1	1	2	10
4	2	2	4	1	2	3	0	0	0	7
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	1	1	2	2	2	4	10
9	2	2	4	2	2	4	1	1	2	10
10	2	2	4	2	2	4	2	2	4	12
11	2	2	4	2	2	4	1	1	2	10
12	2	2	4	2	2	4	1	1	2	10
13	2	2	4	2	2	4	2	2	4	12
14	2	2	4	1	2	3	2	2	4	11
15	2	1	3	2	2	4	2	2	4	11
16	2	2	4	2	2	4	2	2	4	12
17	2	2	4	2	2	4	1	1	2	10
18	2	2	4	2	2	4	2	1	3	11
19	2	2	4	2	2	4	2	2	4	12
20	2	2	4	2	2	4	2	2	4	12
21	--	--	--	--	--	--	--	--	--	0

Detailed scores – Round 2

Lab n°	Patient D HMGL def			Patient E Tyr 1			Patient F ATPS def.			
	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	1	1	2	10
3	1	0	1	2	2	4	1	0	1	6
4	2	2	4	2	2	4	1	2	3	11
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	2	2	4	2	1	3	11
11	2	2	4	2	2	4	2	2	4	12
12	2	2	4	2	2	4	2	2	4	12
13	2	2	4	2	2	4	2	2	4	12
14	2	2	4	2	2	4	1	2	3	11
15	2	2	4	2	2	4	1	2	3	11
16	2	2	4	2	2	4	2	2	4	12
17	2	2	4	2	0	2	2	2	4	10
18	2	2	4	2	2	4	2	2	4	12
19	2	2	4	2	2	4	2	0	2	10
20	2	2	4	2	2	4	2	2	4	12
21	--	--	--	--	--	--	--	--	--	0

Total scores

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Critical error
1	4	4	4	4	4	4	24	100	
2	4	4	4	4	4	2	22	92	
3	4	4	2	1	4	1	16	67	
4	4	3	0	4	4	3	18	75	CE
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	2	4	4	4	4	22	92	
9	4	4	2	4	4	4	22	92	
10	4	4	4	4	4	3	23	96	
11	4	4	2	4	4	4	22	92	
12	4	4	2	4	4	4	22	92	
13	4	4	4	4	4	4	24	100	
14	4	3	4	4	4	3	22	92	
15	3	4	4	4	4	3	22	92	
16	4	4	4	4	4	4	24	100	
17	4	4	2	4	2	4	20	83	
18	4	4	3	4	4	4	23	96	
19	4	4	4	4	4	2	22	92	
20	4	4	4	4	4	4	24	100	
21	--	--	--	--	--	--	0	0	

Performance

	Number of labs	% total labs
Satisfactory performers (≥ 71 % of adequate responses)	18	90
Unsatisfactory performers (< 71 % adequate responses and/or critical error)	2	10
Partial and non-submitters	0	0

Overall Proficiency

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Total (%)
DPT-SB-2022-A	MGA-Barth	100	98	99
DPT-SB-2022-B	OTC def.	93	98	95
DPT-SB-2022-C	MPS VI	83	80	81
DPT-SB-2022-D	HMGL def	98	95	96
DPT-SB-2022-E	Tyr 1	100	95	98
DPT-SB-2022-F	ATPS def.	88	85	86

10. Annual meeting of participants

This took place on August 30th in Freiburg, Germany.

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. 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.

Date of report, 2023-02-06
Name and signature of Scientific Advisor

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

Version Number	Published	Amendments
1	13 February 2023	2022 annual report published

END