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Published: 26 April 2022[1]

Diagnostic Proficiency Testing

Centre: Switzerland

Final Report 2021

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 2021, 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	Country	Number of participants
Undefined country	1	Hong Kong	1
Australia	3	Norway	1
Austria	2	Sweden	2
Canada	3	Switzerland	2
Estonia	1	United States of America	3
Germany	3		

2. Design and logistics of the scheme including sample information

The scheme has been designed and planned by Déborah Mathis as Scientific Advisor and coordinated by CSCQ as scheme organiser (sub-contractor on behalf of ERNDIM), both appointed by and according to procedures laid down 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

[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.

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

Patient A: alfa-mann. – Dr Ruijter, Rotterdam. This sample has been sent to all labs participating to the DPT scheme in Europe
Patient B: Tyr 2 – Dr med Sabine Scholl-Bürgi, Medizinische Universität Innsbruck
Patient C: ASL def. – Inselspital, Bern
Patient D: MPS II – Inselspital, Bern
Patient E: Xp21 del syndrome – Inselspital, Bern
Patient F: APRT deficiency – Dr med Sabine Scholl-Bürgi, Medizinische Universität Innsbruck

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

3. Tests

Analyses of amino acids, organic acids, mucopolysaccharides, oligosaccharides and purines/ pyrimidines were required in 2021.

4. Schedule of the scheme

- Feb 09, 2021: shipment of samples of Survey 1 and 2
- March 08, 2021: analysis of samples of the first survey
- March 29, 2021: deadline for result submission (Survey 1)
- June 07, 2021: analysis of samples of the second survey
- June 28, 2021: deadline for result submission (Survey 2)
- September, 2021: annual meeting online

5. Results

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

	Survey 1	**Survey 2**
Receipt of results	21	21
No answer	1	1

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 by a second assessor who changes every year as well as by the scientific advisor. The results of DPT Switzerland 2021 have been also scored by Petr Chrastina, from DPT Czech Republic scheme. At the SAB meeting in 25-26.11.2021, 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 A has to be considered as a critical error for the labs who missed the correct diagnosis alpha-mannosidosis and did not recommend oligosaccharides analysis or point to a possible lysosomal storage disease.
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. Four 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

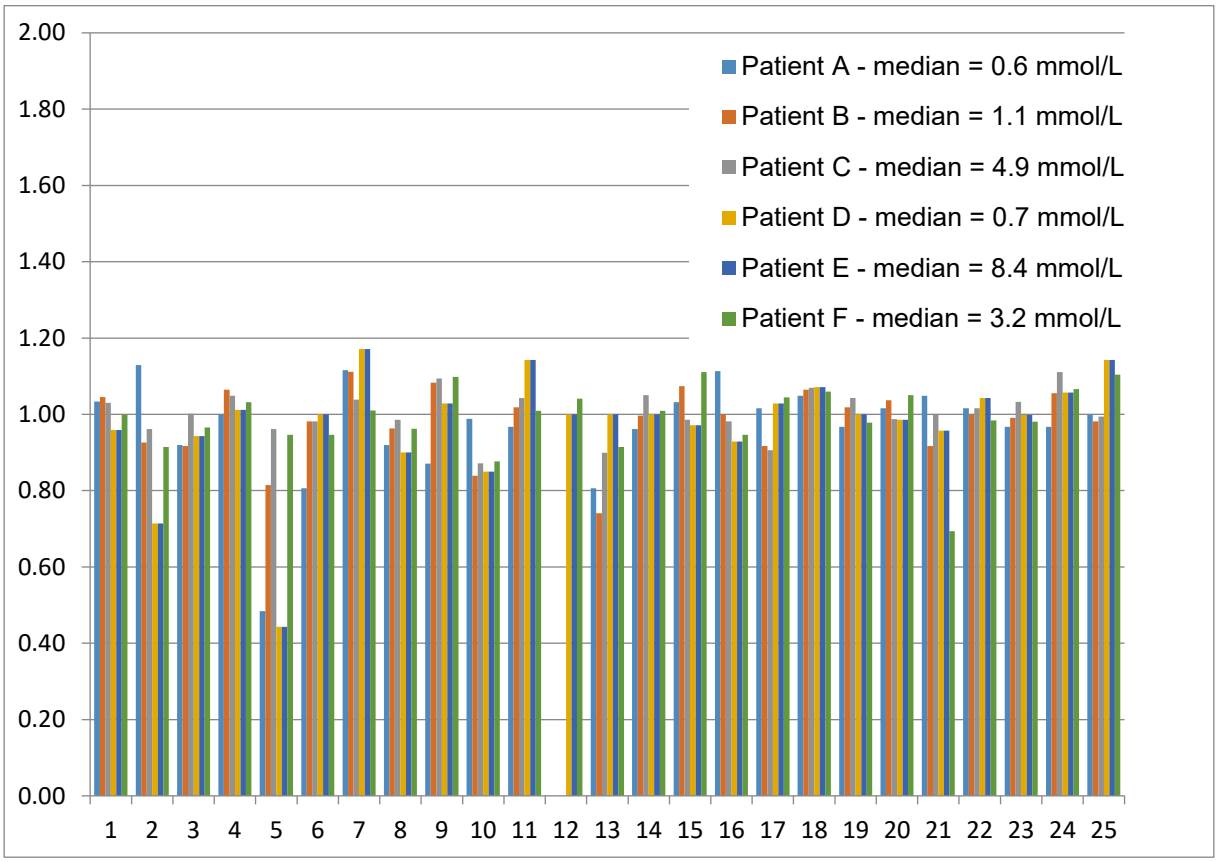
At least 15 points from the maximum of 24 (62%).

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

Creatinine: ratio to median



8.2. Patient A

alfa-mannosidosis (OMIM #248500)

Patient details provided to participants

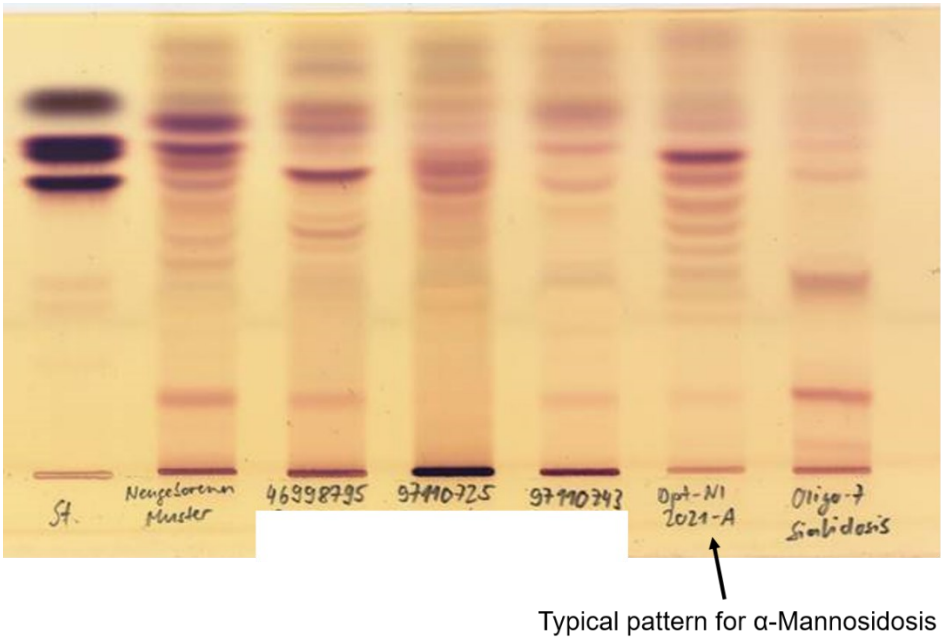
A 36 year old male with craniosynostosis, dysmorphic facial features, retardation and deafness.

Patient details

It is a 36-year old male with craniosyntosis, dysmorphic facial features, retardation and deafness. Activity of alpha-mannosidase was 0 mU/ml in plasma and 0 mU/mg in leucocytes. Activity in DBS 4.72 pmol/punch/h (5% residual activity).

Analytical performance

Abnormal oligosaccharide pattern (TLC or MS) was scored two points (14/21 labs).



Typical pattern for α-Mannosidosis

Diagnosis / Interpretative proficiency

Alfa-mannosidosis as a first diagnosis was scored two points (14/21 labs).
Oligosaccharidosis not specified or with a wrong type of oligosaccharidosis was scored one point (0 labs).
Recommendation to perform oligosaccharides analysis was scored one point (2/21 labs).

Recommendations

As recommendations for further tests, 12/21 labs mentioned enzymatic analysis and 14/21 labs mentioned MAN2B1 mutation testing or genetic analysis. Two labs that did not analyze oligosaccharides recommend doing so.

Overall impression

The participants did very well if they analyzed oligosaccharides (overall proficiency of 100%) but many labs did not perform oligosaccharides, thus the overall proficiency lowered to 69%.

Multiple distributions of similar samples

A similar urine sample has been distributed in 2020 (alpha-mannosidosis): the overall performance is the lower this year.

	2020	2021
Overall performance	78 %	69 %

8.3. Patient B

Tyrosineamia type 2 (OMIM #276600)

Patient details provided to participants

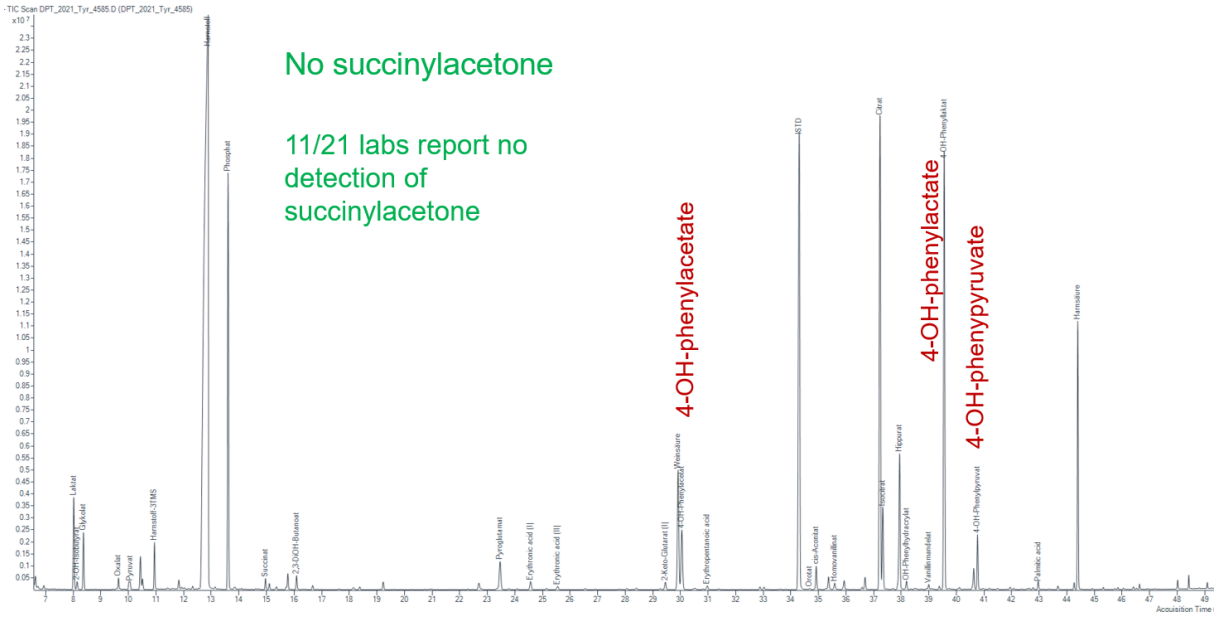
6 years old boy with photophobia

Patient details

6 years old boy with photophobia, eye pain but otherwise normal (especially the skin). Parent consanguineous.

Analytical performance

Increase amount of tyrosine was scored one point (all labs, mean Tyr 232 mmol/mol creatinine, SD 53).
Increase amount of at least one of the 4-hydroxyphenylderivate was score one point (all labs).



Diagnosis / Interpretative proficiency

20/21 labs reported tyrosinemia type 2 as most likely diagnosis and was scored two points. One lab reported tyrosineamia type 1 as most likely diagnosis and was scored one point.
15/21 labs reported other tyrosinemias as alternative diagnosis. 1/21 lab reported liver disease as alternative diagnosis.

Recommendations

Recommendations for further tests included plasma amino acids (16/21 labs) and molecular testing of TAT gene (20/21 labs). 3/21 labs recommended liver function tests and 2/21 labs succinylacetone in blood.
8/21 labs recommended Phe/Tyr-restricted or protein-restricted diet. 4/21 labs recommended ophthalmologic consultation.

Overall impression

Very good overall proficiency of 99%.

8.4. Patient C

Argininosuccinate lyase deficiency (OMIM #207900)

Patient details provided to participants

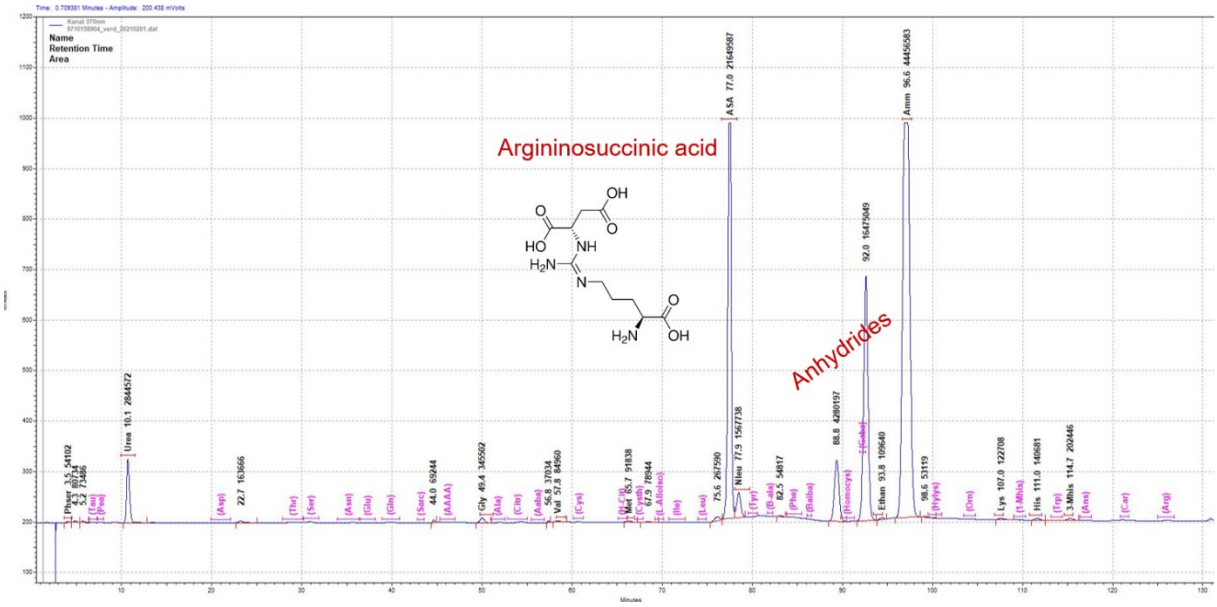
34 years old man admitted comatose in the emergency unit

Patient details

34 years old man admitted comatose in the emergency unit.

Analytical performance

Increased amount of argnininosuccinate was scored two points (all labs, mean 11000 mmol/mol creatinine, SD 14000).



Diagnosis / Interpretative proficiency

ASL deficiency as most likely diagnosis was scored two points (all labs).

Recommendations

17/21 labs recommended to analyse ammonia and 19/21 labs amino acids in plasma. 5/21 labs recommended liver function tests and 2/21 labs orotic acid in urine. 16/21 labs propose to confirm the diagnosis with ASL mutation testing and 5/21 labs with enzyme activity tests.

Overall impression

Excellent overall proficiency of 100%.

Multiple distributions of similar samples

Similar urine samples have been distributed in 2009 and 2012 (Argininosuccinate lyase deficiency).

	2009	2012	2021
Overall performance	95%	87%	100%

8.5. Patient D

Mucopolysaccharidosis type II (OMIM #309900)

Patient details provided to participants

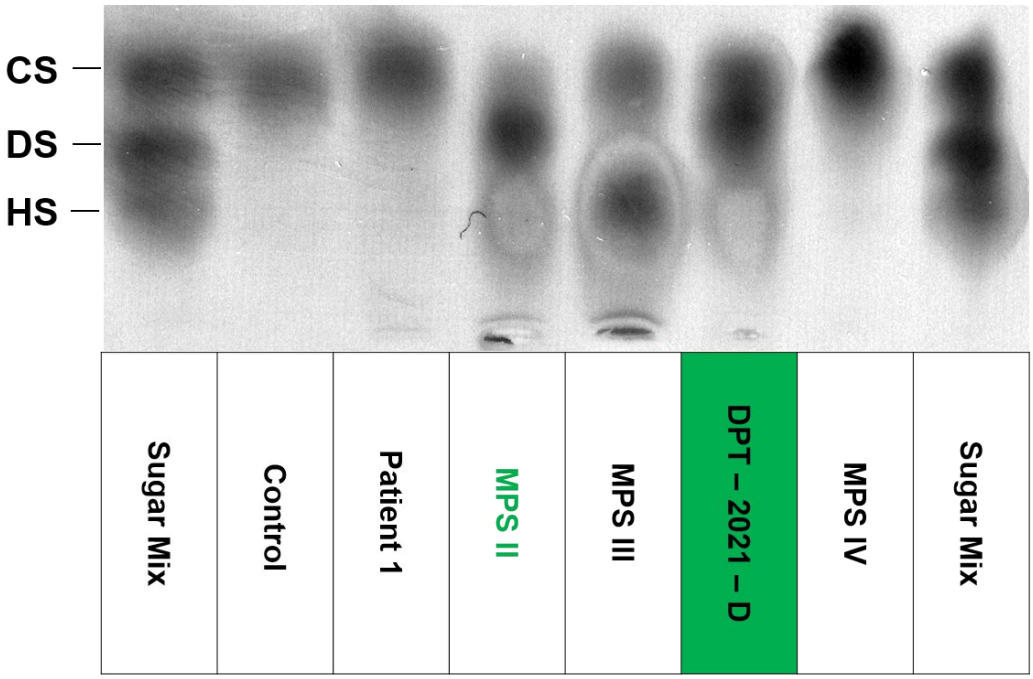
4 years old boy, assigned with macrocephaly, recurrent infections of the upper respiratory tract and motor deficit

Patient details

4 years old boy, assigned with macrocephaly, recurrent infections of the upper respiratory tract and motor deficit.

Analytical performance

Increase of dermatan and heparan sulfate or statement of a MPS II pattern by GAGs measurement was scored 2 points (10/20 labs). Unspecific MPS increase was scored 1 point (7/20 labs).



CS Chondroitin Sulfate
DS Dermatan Sulfate
HS Heparan Sulfate

Diagnosis / Interpretative proficiency

MPS II as most likely diagnosis was scored 2 points (10/20 labs). Other MPS as most likely diagnosis was scored 1 point (7/20 labs).

Recommendations

All labs that pointed towards the right diagnosis recommended confirming the diagnosis by enzyme activity testing and/or genetic analysis.

Overall impression

Proficiency was excellent for the labs that analyzed the differentiated GAGs. Most labs that only measured total MPS pointed to MPS diseases. 3/20 labs did not measure GAGs. 1 lab did not report any result. Overall proficiency was 73%.

Multiple distributions of similar samples

Similar urine samples have been distributed in 2010 and 2013 (MPSII): the overall performance lowers.

	2010	2013	2021
Overall performance	83%	92%	73%

8.6. Patient E

Chromosome Xp21 deletion syndrome – complex glycerol kinase deficiency (OMIM #300679)

Patient details provided to participants

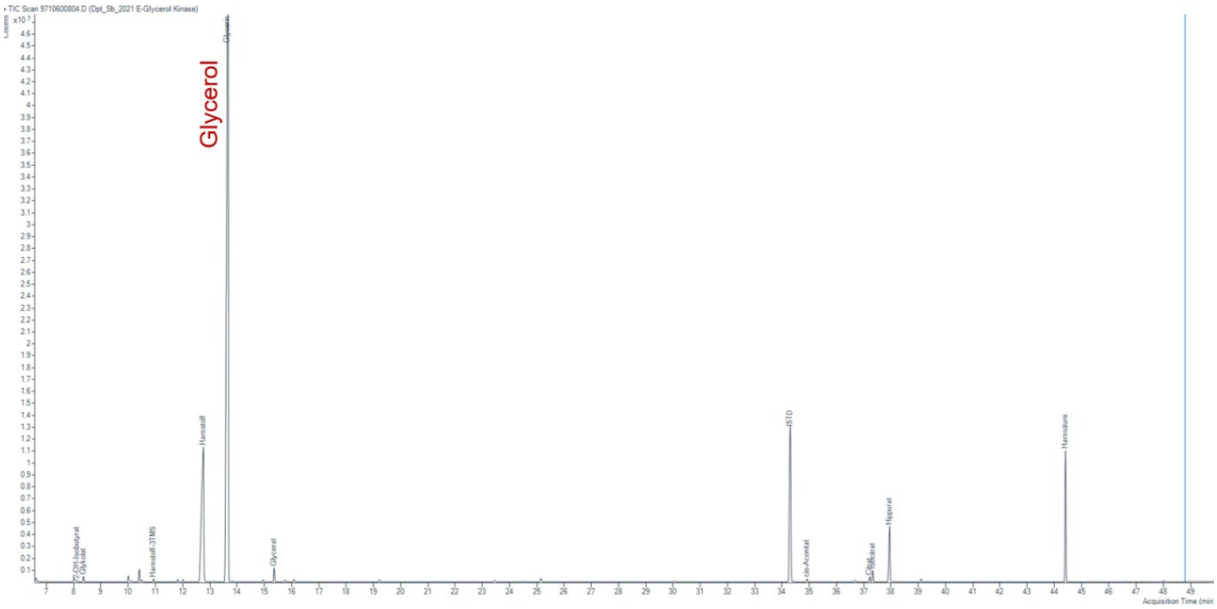
2 years old boy, admitted in hospital with metabolic crisis during a catabolic condition. Urine while in hospital during infection

Patient details

2 years old boy, admitted in hospital with metabolic crisis during a catabolic condition. Urine while in hospital during infection. Diagnosis as infant, chromosome Xp21 deletion syndrome, on therapy for adrenal insufficiency.

Analytical performance

Elevation of glycerol was scored two points (18/21 labs, median 32'500 mmol/mol crea, range 474 – 277'000). 5 labs reported elevation of glyceric acid (median 209 mmol/mol crea, range 6-539). 3/6 labs that measured orotic acid reported elevation of orotic acid.



Diagnosis / Interpretative proficiency

Chromosome Xp21 deletion syndrome or glycerol kinase deficiency was scored 2 points (17/21 labs). One lab interpreted glycerol elevation not high enough for glycerol kinase deficiency and pointed towards contamination of the sample. Alternative diagnosis were as follows: 5 labs reported fructose-1,6-biphosphatase deficiency, 3 labs exogenous source of glycerol and 3 labs glycerate kinase deficiency. Interpretation proficiency was 81%.

Recommendations

10/17 labs that pointed toward the right diagnosis recommended repeating organic acids in a fresh urine sample. Some labs also recommended determining glycerol in plasma.

To clarify the diagnosis (differential diagnosis: GKD, chromosome Xp21 gene deletion syndrome, fructose-1,6-biphosphatase deficiency), labs recommended to determine blood glucose, lactate, blood gases, electrolytes, ammonia, CK, hormones of the adrenal gland, and triglycerides (pseudo hypertriglyceridemia).

To confirm the diagnosis, 5 labs recommended performing enzyme activity testing and 15 labs recommended performing molecular genetic testing. To differentiate between glycerol kinase deficiency and chromosome Xp21 gene deletion syndrome, some labs recommended expended molecular testing and cytogenetic testing. Some labs also recommended sequencing of the FBP1 gene.

Overall impression

3 out of 21 labs missed glycerol elevation, even though they analyzed organic acids and thus missed the right diagnosis. 1 lab misinterpreted glycerol elevation as contamination. Overall proficiency of 83%.

Multiple distributions of similar samples
A similar urine sample has been distributed in 2011 (glycerol kinase deficiency): the overall performance lowered this year.

	2011	2021
Overall performance	96%	83%

8.7. Patient F

Adenine phosphoribosyltansferase deficiency (OMIM # 614723)

Patient details provided to participants
28 years old woman on therapy. Diagnosis at 8 years with abdominal and back pain.

Patient details
28 years old woman on allopurinol therapy. Diagnosis at 8 years with abdominal and back pain.

Analytical performance
Increase of 2,8-dihydroxyadenine was scored 2 points (8/21 labs). Increase of adenine was scored 1 point (5 labs).

Diagnosis / Interpretative proficiency
13/21 labs reported APRT deficiency as the most likely diagnosis and this was scored 2 points. Statement that APRT deficiency cannot be excluded and recommendation to measure purines and pyrimidines was scored 1 point (1 lab). All labs that missed the diagnosis did not measure purines and pyrimidines (8/21 labs).

Recommendations
12 labs recommended molecular analysis of the APRT gene. Enzymatic studies was also pointed out by a few labs. 1 lab that did not measure purines and pyrimidines recommended doing so.

Overall impression
Analytical proficiency (50%) was low. The correct diagnosis was also reported with elevation of adenine only. Overall proficiency was of 57%.

Multiple distributions of similar samples
Similar urine samples have been distributed in 2017 and 2019 (APRT deficiency): the overall performance is similar than in 2017, but lower than in 2019.

	2017	2019	2021
Overall performance	55%	70%	57%

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 alfa-mann.			Patient B Tyr 2			Patient C ASL 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	2	2	4	12
3	2	2	4	2	2	4	2	2	4	12
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	0	0	0	2	2	4	2	2	4	8
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	2	4	12
11	0	0	0	2	2	4	2	2	4	8
12	2	2	4	2	2	4	2	2	4	12
13	0	1	1	2	2	4	2	2	4	9
14	0	0	0	2	2	4	2	2	4	8
15	2	2	4	2	2	4	2	2	4	12
16	2	2	4	2	2	4	2	2	4	12
17	0	1	1	2	1	3	2	2	4	8
18	0	0	0	2	2	4	2	2	4	8
19	0	0	0	2	2	4	2	2	4	8
20	2	2	4	2	2	4	2	2	4	12
21	2	2	4	2	2	4	2	2	4	12
22	--	--	--	--	--	--	--	--	--	0

Detailed scores – Round 2

Lab n°	Patient D MPS II			Patient E Xp21 del syndrome			Patient F APRT deficiency			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	2	4	2	0	2	2	2	4	10
2	1	1	2	2	2	4	2	2	4	10
3	1	1	2	2	2	4	0	0	0	6
4	2	2	4	2	2	4	2	2	4	12
5	2	2	4	2	2	4	0	0	0	8
6	2	2	4	2	2	4	0	1	1	9
7	2	2	4	2	2	4	2	2	4	12
8	2	2	4	2	2	4	2	2	4	12
9	1	1	2	0	0	0	1	2	3	5
10	2	1	3	2	2	4	0	0	0	7
11	0	0	0	2	2	4	2	2	4	8
12	2	1	3	2	2	4	1	2	3	10
13	2	2	4	2	2	4	0	0	0	8
14	2	2	4	2	2	4	0	0	0	8
15	--	--	--	0	0	0	1	2	3	3
16	1	2	3	2	2	4	1	2	3	10
17	1	1	2	2	2	4	1	2	3	9
18	0	0	0	2	2	4	0	0	0	4
19	0	1	1	2	2	4	0	0	0	5
20	2	2	4	0	0	0	2	2	4	8
21	2	2	4	2	2	4	2	2	4	12
22	--	--	--	--	--	--	--	--	--	0

Total scores

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Critical error
1	4	4	4	4	2	4	22	92	
2	4	4	4	2	4	4	22	92	
3	4	4	4	2	4	0	18	75	
4	4	4	4	4	4	4	24	100	
5	4	4	4	4	4	0	20	83	
6	4	4	4	4	4	1	21	88	
7	0	4	4	4	4	4	20	83	
8	4	4	4	4	4	4	24	100	
9	4	4	4	2	0	3	17	71	
10	4	4	4	3	4	0	19	79	
11	0	4	4	0	4	4	16	67	
12	4	4	4	3	4	3	22	92	
13	1	4	4	4	4	0	17	71	
14	0	4	4	4	4	0	16	67	
15	4	4	4	--	0	3	15	62	
16	4	4	4	3	4	3	22	92	
17	1	3	4	2	4	3	17	71	
18	0	4	4	0	4	0	12	50	
19	0	4	4	1	4	0	13	54	
20	4	4	4	4	0	4	20	83	
21	4	4	4	4	4	4	24	100	
22	--	--	--	--	--	--	0	0	

Performance

	Number of labs	% total labs
Satisfactory performers (≥ 60 % of adequate responses)	19	86
Unsatisfactory performers (< 60 % adequate responses and/or critical error)	2	9
Partial and non-submitters	2	9

Overall Proficiency

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Total (%)
DPT-SB-2021-A	alfa-mann.	67	71	69
DPT-SB-2021-B	Tyr 2	100	98	99
DPT-SB-2021-C	ASL def.	100	100	100

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Total (%)
DPT-SB-2021-D	MPS II	73	73	73
DPT-SB-2021-E	Xp21 del syndrome	86	81	83
DPT-SB-2021-F	APRT deficiency	50	64	57

10. Annual meeting of participants

This took place on September 3th 2021 online.

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 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 on 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

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, 2022-03-04
Name and signature of Scientific Advisor

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

Version Number	Published	Amendments
1	26 April 2022	2021 annual report published

END