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Diagnostic Proficiency Testing

Centre: France

Final Report 2023

prepared by
C. Vianey-Saban and C. Acquaviva-Bourdain

Note: This annual report is intended for participants of the ERNDIM DPT France 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 terms and conditions on page18 and the ERNDIM Privacy Policy on www.erndim.org.

1. Geographical distribution of participants

In 2023, 22 labs registered to DPT France. One lab withdrawn registration and 2 other ones did not submit results for one of the 2 surveys. Only 19 labs submitted results for the 2 surveys.

Country	Number of participants
France	8
Italia	5
Portugal	2
Spain	6
Switzerland	1

2. Design and logistics of the scheme including sample information

The scheme has been designed and planned by Christine Vianey-Saban and Cécile Acquaviva as Scientific Advisors and coordinated by Alessandro Salemma (alessandro.salemma@hcuge.ch) and

[1] If this report is not Version 1 for this scheme year, go to APPENDIX 2 for details of the changes made since the last version of this document.

Nicola Braik (nicola.braik@hcuge.ch) as scheme organizer (sub-contractor on behalf of CSCQ), 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 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: Urine samples have been provided by the Scientific Advisors, by Petr Chrastina (DPT CZ) and by George Ruijter (DPT NL).

Patient A: Argininosuccinic aciduria
Patient B: 2-methylbutyryl-CoA dehydrogenase deficiency
Patient C: Isovaleric acidemia
Patient D: Combined MCAD and OCTN2 deficiency
Patient E: Fucosidosis
Patient F: Phenylketonuria.

The samples have been heat-treated. They were pre-analysed in our institute after 2 weeks 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 are mandatory.

4. Schedule of the scheme

- February 8 — Shipment of samples of Survey 1 and Survey 2 by CSCQ
- March 13 — Clinical data available on CSCQ website and start analysis of samples A, B, C (Survey 1)
- March 27 — Reminder for website submission
- April 3 — Deadline for result submission (Survey 1)
- May 15 — Interim report of Survey 1 available on CSCQ website (sent to CSCQ by SA on May 10)
- June 5 — Clinical data available on the CSCQ website and start analysis of samples D, E, F (Survey 2)
- June 19 — Reminder for website submission
- June 26 — Deadline for result submission (Survey 2)
- July 25 — Interim report of Survey 2 available on CSCQ website (sent to CSCQ by SA on July 24)
- August 29 — Meeting of participants in Jerusalem during the SSIEM Symposium
- December 1 — SAB meeting: definition of critical errors
- December 2023 — Annual Report with definitive scoring

5. Results

One lab withdrawn registration and 2 others did not submit results for one of the 2 surveys.

	Survey 1	**Survey 2**
Receipt of results	20	20
No answer	2	2

6. Web site reporting

The website reporting system is compulsory for all centres. Please carefully read 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.

Unfortunately, several participants still don't follow these recommendations: the risk is an inadequate scoring of their results. Moreover, it enhances the work of the scientific advisors who are obliged to read all the reports in order to avoid wrong scoring.

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 France 2023 have been also scored by Dr George Ruijter from DPT Netherlands. At the SAB meeting in Prague on December 1st, 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 2023, no critical errors have been assigned.

A certificate of participation is issued for participation, and it is 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. No performance support letters will be sent by the Scheme Advisor for 2023. Partial- or non- submitters will receive a letter from the ERNDIM Executive Administrator, Sara Gardner.

7.1. Score for satisfactory performance

In November 2021, the SAB decided that **the score for satisfactory performance will be increased from 15 points to 17 points from the maximum of 24 (70%)**, in accordance with the other qualitative schemes.

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

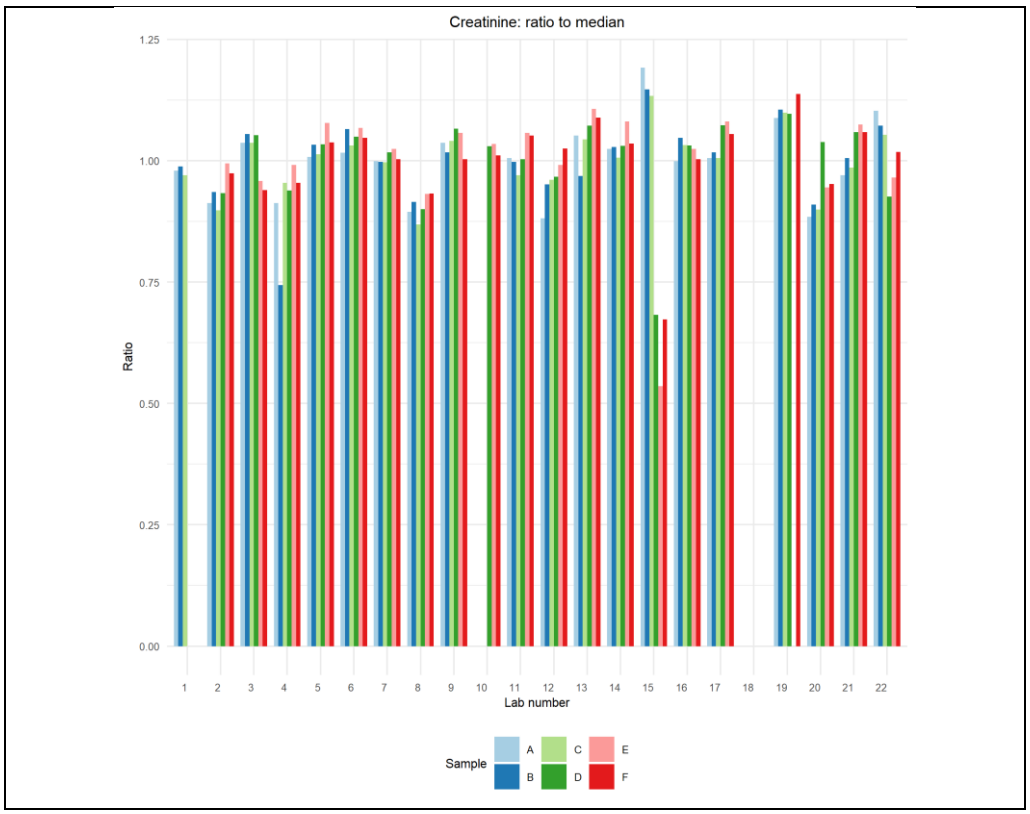
8.1. Creatinine measurement for all samples

After exclusion of some wrong values, the CV for creatinine determination ranged from 5.1 % (sample E and F) to 7.8 % (sample A), which is satisfying. It is comparable to the interlab CV 2022 for Special Assays in Urine (5.7 %, n = 136).

The median values for creatinine determination were:
- Sample A: 15.80 mmol/L
- Sample B: 10.40 mmol/L
- Sample C: 11.40 mmol/L
- Sample D: 14.70 mmol/L
- Sample E: 3.11 mmol/L
- Sample F: 4.16 mmol/L

In the figure below, creatinine values are expressed as the ratio of each measurement over the median for all labs.

Creatinine: ratio to median



8.2. Patient A

Argininosuccinic aciduria (argininosuccinate lyase deficiency)

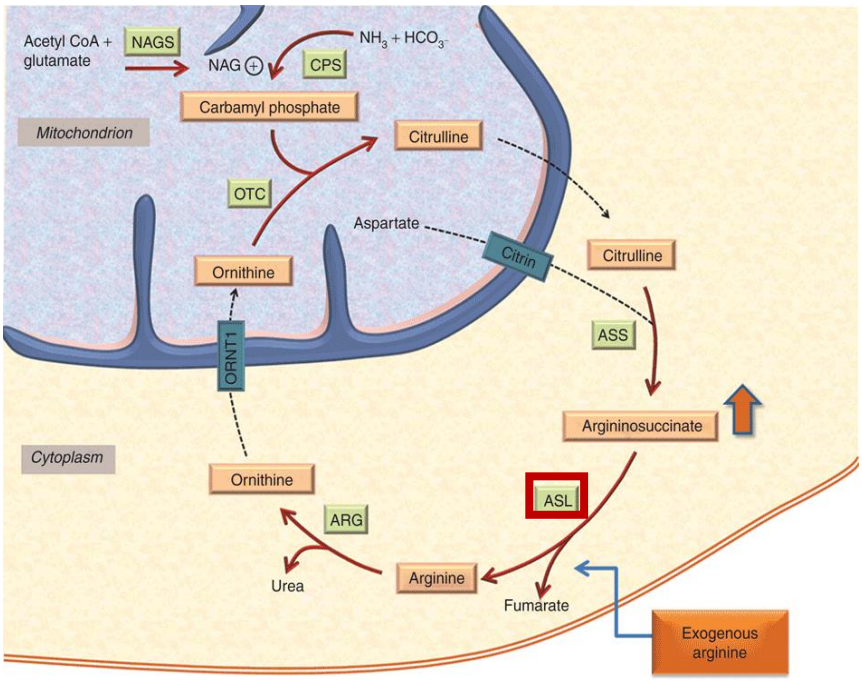
Patient details provided to participants

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 details

This patient is affected with a mild form of argininosuccinic aciduria due to argininosuccinate lyase deficiency. The patient is treated with a low protein diet, and the diagnosis has been confirmed genetically.

Results from all labs participating to DPT is available on ERNDIM website.



From Erez, Genet Med 2013;15:251-257

Patients with argininosuccinic aciduria present with fewer hyperammonemic episodes than other urea cycle disorders such as OCT or CPSI deficiency, because excreted ASA is a nitrogen-rich compound. But there is a greater risk for poor neurocognitive outcome, seizures, hypertension and liver disease, despite early treatment.

The pathophysiology is mainly due to the deficiency of the endogenous synthesis of arginine, a substrate for the generation of multiple metabolites:

- Nitric oxide (NO), catalysed by nitric oxide synthase (NOS): NO is involved in cell signalling and survival. Decrease of NO production increases production of free radicals and this can explain hypertension,
- Polyamines, proline, creatine, glutamate, agmatine (cell signalling)

The decrease of endogenous synthesis of fumarate possibly affects the Krebs cycle.

Moreover argininosuccinate lyase is structurally required to maintain a complex that facilitates the channelling of exogenous arginine to NOS for NO synthesis.

Supplementation with high doses of Arg is harmful because it induces an increase of guanidinoacetate, known as a cellular and neuronal toxin. Conversely treatment with NO can be helpful.

From Erez, Genet Med 2013;15:251-257

Analytical performance

All participants performed **amino acid analysis** (20/20), they reported:

Increase in:

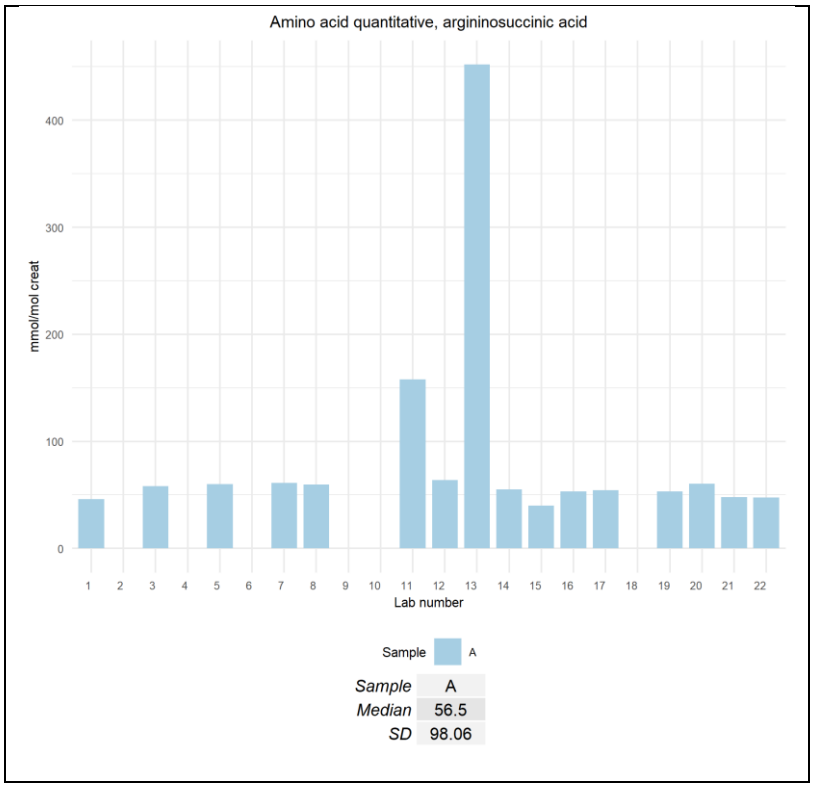
- **Argininosuccinic acid** 18

(median = 56.5 mmol/mol creatinine; range: 40 – 452 ; n = 16)

- **Anhydrides of argininosuccinic acid** 1

Normal excretion of:

- Citrulline 8
- Glutamine 7



The two participants who did not identify argininosuccinic acid are using UPLC and ion-exchange chromatography with ninhydrin detection.

Eleven participants performed organic acids (11/20), and reported either a profile without any significant abnormality (8) or a normal excretion of orotic acid (3). The fourteen labs who performed quantification of orotic acid (14/20), reported a normal excretion (median = 1.25 mmol/mol creatinine; range : 0.34 – 5.0 ; n = 13)

Diagnosis / Interpretative proficiency

Most likely diagnosis

Argininosuccinic aciduria (argininosuccinate lyase deficiency)	18
No diagnosis	2

Alternative diagnosis

No other possible diagnosis	2
Arginase deficiency (under arginase enzyme therapy?)	1

Scoring

- **Analytical performance**
  - Increase of argininosuccinic acid and/or its anhydrides (score 2)
- **Interpretation of results**
  - Argininosuccinic aciduria (score 2)
  - Other urea cycle (score 1)

Overall impression

The overall proficiency was 90 %

Multiple distributions of similar samples

A similar urine sample has been distributed in 2016: the overall performance is almost similar.

	2016	2023
Analytical performance	92 %	90 %
Interpretative performance	92 %	90 %
Overall performance	92 %	90 %

8.3. Patient B

2-methylbutyryl-CoA dehydrogenase deficiency (short/branched chain acyl-CoA dehydrogenase deficiency)

Patient details provided to participants

This male infant was referred for delayed motor milestones and hypotonia at age 1 y. Currently, at age 6 years, his intellectual development is normal. He is receiving specific treatment.

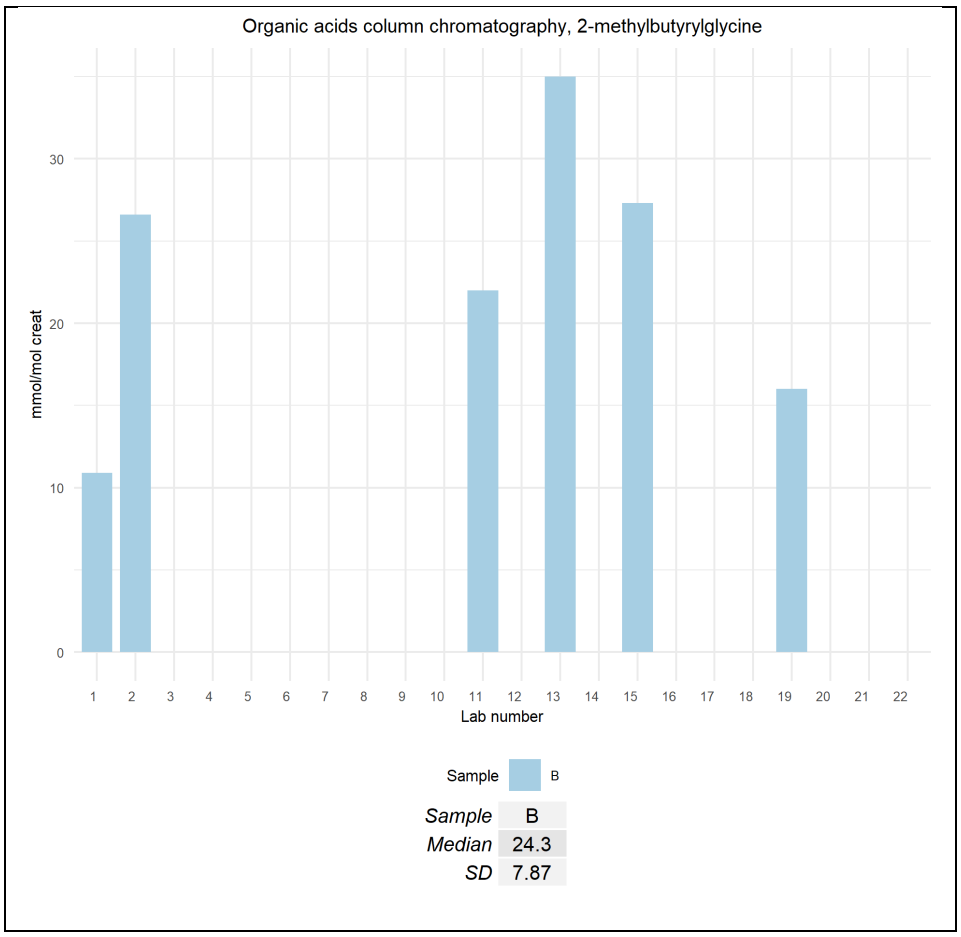
Patient details

While presently most MBD deficiencies are identified through newborn screening, the urine sample distributed in this survey was obtained from a patient that presented with clinical symptoms.
2-methylbutyryl-CoA dehydrogenase (MBD) activity: 0.11 nmol/mg/min (controls: 0.50 +/- 0.10).
The median for 2-methylbutyrylglycine excretion was 39 mmol/mol creat.

2-methylbutyryl-CoA dehydrogenase (MBD) deficiency also called short/branched-chain acyl-CoA dehydrogenase (SBCAD) deficiency is an inborn error of Isoleucine metabolism. The enzyme is coded by *ACADSB* gene. Few patients have been diagnosed a,d presented with hypotonia, mental retardation, autistic features, hypoglycemia, … Patients identified by newborn screening are all asymptomatic, and a founder mutation has been described in the Hmong Chinese population who are all asymptomatic. That is why the clinical relevance of this disorder remains in doubt.

Analytical performance

Only 17 labs performed **organic acids (17/20),** and they all reported an increase in **2-methylbutyrylglycine** (median = 24.3 mmol/mol creatinine; range: 10.9 – 35.0 ; n = 6). One participant additionally mentioned an increase in isovalerylglycine, and another one an unknown acylglycine.



Eight labs performed acylcarnitines (8/20), and they reported either an increase in C5-carnitine (FIA-MS/MS) or an increase in 2-methylbutyrylcarnitine (LC-MS/MS) (median = 23.5 mmol/mol creatinine; range: 13.0 – 32.4 ; n = 7)

The eight participants who performed amino acids (8/20) reported a profile without any significant abnormality.

Diagnosis / Interpretative proficiency

Most likely diagnosis

2-methylbutyryl-CoA dehydrogenase deficiency (short/branched-chain acyl-CoA dehydrogenase deficiency)	18
No diagnosis	2

Alternative diagnosis

Multiple acyl-CoA dehydrogenase deficiency	2
Pompe disease	2
Short-chain acyl-CoA dehydrogenase deficiency	1
Ethylmalonic aciduria	1

Scoring

- **Analytical performance**
  - Increase of 2-methylbutyrylglycine and/or 2-methylbutyrylcarnitine (score 2)

- **Interpretation of results**
  - MBD / SBCAD deficiency (score 2)

Overall impression

The overall proficiency was 89 %

Multiple distributions of similar samples
The same urine sample was distributed in DPT-NL scheme in 2015: the overall performance was lower.

	2015 DPT-NL	2023
Analytical performance	78 %	85 %
Interpretative performance	80 %	90 %
Overall performance	79 %	89 %

8.1. Patient C

Isovaleric acidemia (isovaleryl-CoA dehydrogenase deficiency)

Patient details provided to participants

This 14-year-old girl had feeding difficulties since birth, with progressive failure to thrive and psychomotor retardation. At 2.5 years of age, she presented vomiting, metabolic acidosis and hypoglycaemia. The urine sample has been collected under treatment.

Patient details

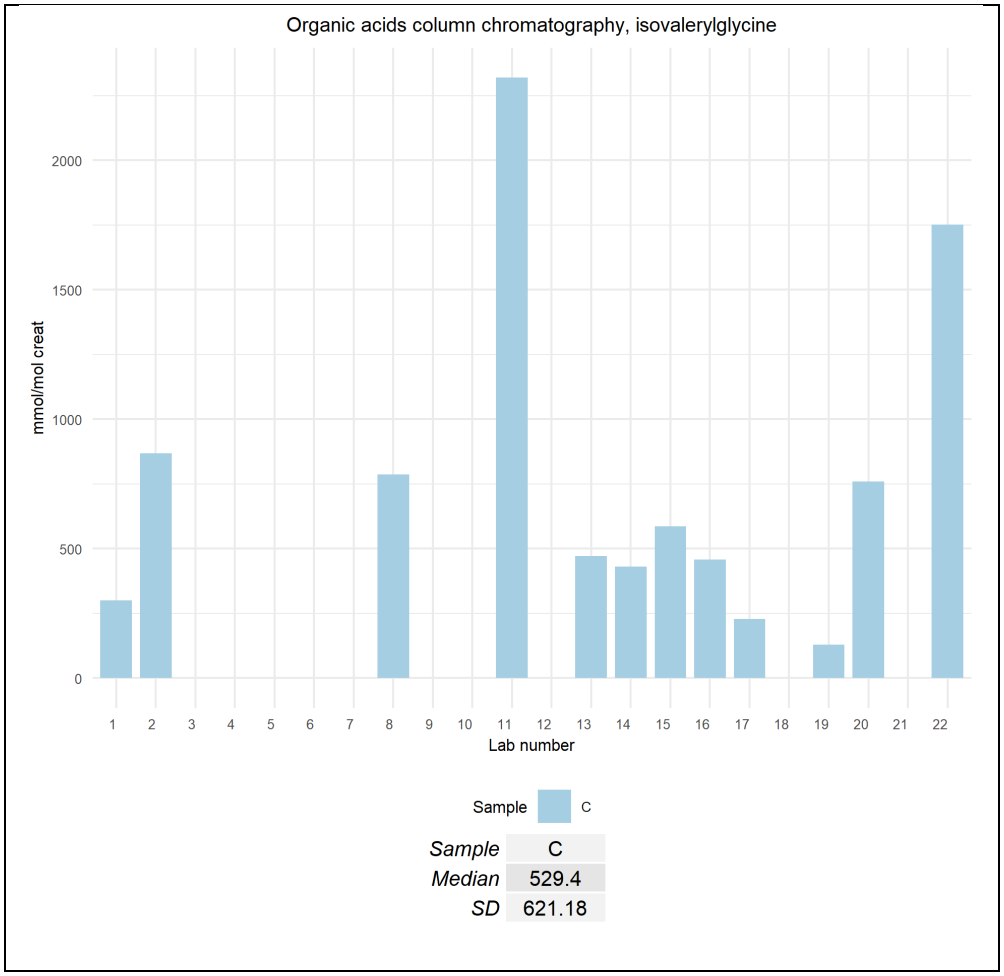
The diagnosis of isovaleric acidaemia has been confirmed by mutation analysis.

Analytical performance

All participants performed **organic acids** (20/20). They identified:
Increase in

- **Isovalerylglycine** **20**
  (median = 529.4 mmol/mol creatinine; range : 129.0 – 2319 ; n = 12)
- Isovalerylglutamic acid 7
- Isovalerylglutamine 1
- 3-hydroxyisovaleric acid 1

Conversely, ten labs mentioned a normal excretion in 3-hydroxyisovaleric acid.



Eight participants performed acylcarnitines (8/20) and reported an increase in:

- C5-carnitine 8
  (median = 65.5 mmol/mol creatinine; range: 39.14 - 231.3 ; n=7)
- free carnitine 4
  (median = 221 mmol/mol creatinine; range: 195 - 245 ; n=4)

Sixteen labs performed amino acids (16/20): 12 reported an increase in glycine (median = 592 mmol/mol creatinine; range: 286 – 695.9 ; n = 13), while 4 mentioned no significant abnormality.

Diagnosis / Interpretative proficiency

Most likely diagnosis

Isovaleric acidaemia (isovaleryl-CoA dehydrogenase deficiency, isovaleric aciduria)	20

Alternative diagnosis

No other possible diagnosis	2

Scoring

- **Analytical performance**
  - Increase of isovalerylglycine (score 2)

- **Interpretation of results**
  - Isovaleric acidaemia (score 2)

Overall impression

The overall proficiency was 100 %

8.1. Patient D

Combined MCAD and OCTN2 deficiency

Patient details provided to participants

12-year-old boy. Third child of 1st cousin parents. At 14 months of age, in the course of a viral illness, he had a malaise with pallor and hypotonia. The urine sample has been collected under treatment.

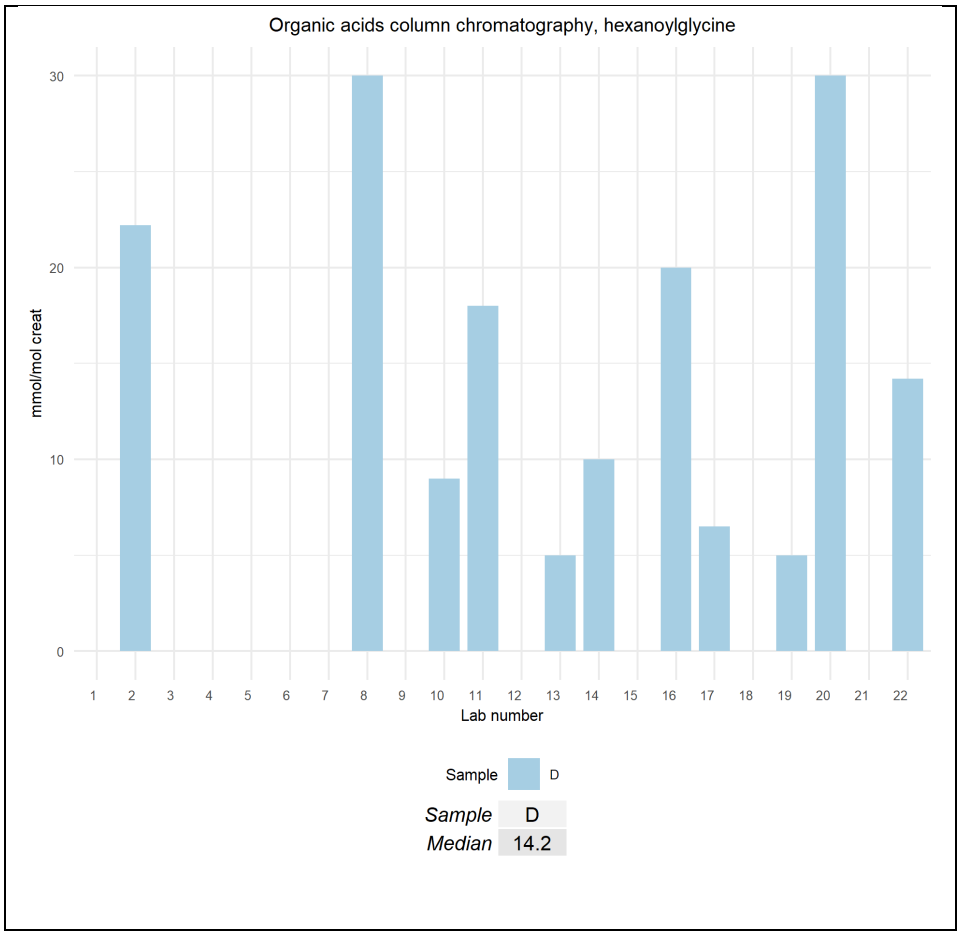
Patient details

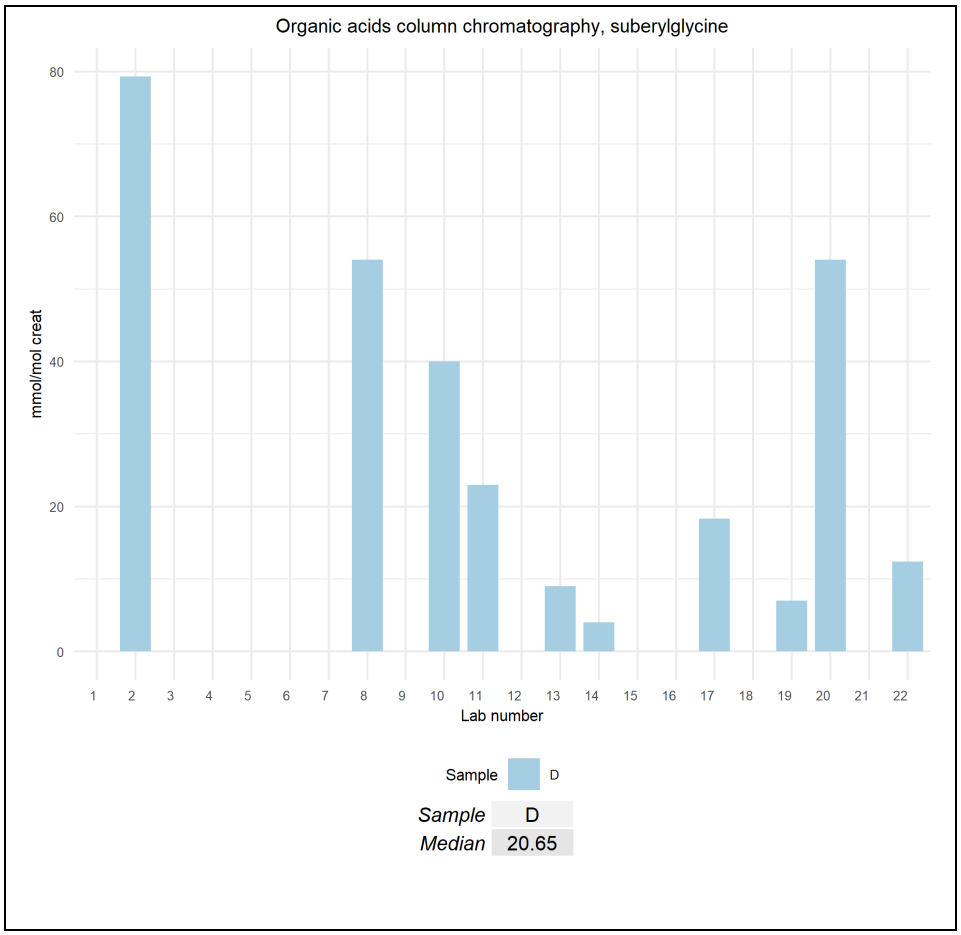
The patient had from birth a good psychomotor development but was asking for food every 3-4 hours. At 14 months of age, in the course of a viral illness, he had a malaise with pallor, hypotonia, drowsiness. Glycemia was severely decreased (0.26 g/L), and he presented a large hepatomegaly after correction of hypoglycemia. ASAT = 330 UI/L, ALAT = 299 UI/L, CK = 2245 UI/L. Plasma free and total carnitine were below 5 µmol/L, contrasting with a conserved urinary excretion. The plasma acylcarnitine profile was consistent with MCAD deficiency. Under treatment, he never presented other episodes.
The urine sample has been collected at 12 years of age under treatment.
Mutation analysis revealed a homozygous variant in *ACADM* gene (medium-chain acyl-CoA dehydrogenase deficiency) and in *SLC22A5* gene (primary carnitine deficiency). Parents are heterozygous for these 2 variants.

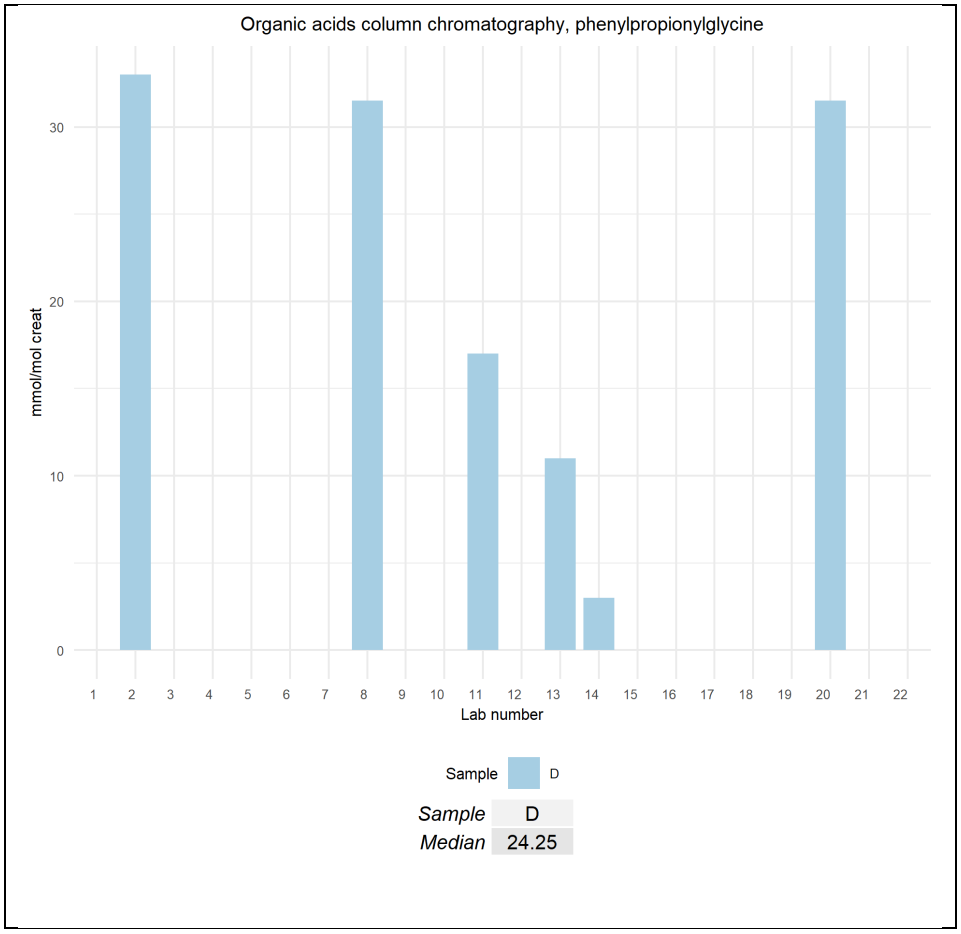
Analytical performance

All participants performed **organic acids** (20/20). They identified an increase in:

- **Hexanoylglycine** **20**
  (median = 14.2 mmol/mol creat, range: 5.0 – 30.0 ; n=11)
- **Suberylglycine** **16**
  (median = 20.65 mmol/mol creat, range: 4.0 – 79.3 ; n=10)
- **Phenylpropionylglycine** **16**
  (median = 24.25 mmol/mol creat, range: 3.0 – 33.0 ; n=6)
- **5-hydroxyhexanoic acid** **8**
- **7-hydroxyoctanoic acid** **8**




Organic acids column chromatography, suberylglycine
mmol/mol creat
80
60
40
20
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Lab number
Sample D
Sample D
Median 20.65



Six labs performed acylcarnitines (6/20). They identified an increase in:

- Octanoylcarnitine (C8) 6
  (median = 11.82 mmol/mol creat, range: 0.53 – 20.02 ; n=4)
- Free carnitine (C0) 4
  (median = 246.62 mmol/mol creat, range: 176 – 279 ; n=4)
- Hexanoylcarnitine (C6) 4
  (median = 5.38 mmol/mol creat, range: 2.08 – 16.4 ; n=4)
- Decenoylcarnitine (C10:1) 2
  (0.62 ; 3.21 mmol/mol creat)

Diagnosis / Interpretative proficiency

Most likely diagnosis

MCAD deficiency	20

Alternative diagnosis

Multiple acyl-CoA dehydrogenase deficiency (MADD)	3
No other possible diagnosis	1

Scoring

- **Analytical performance**
  - Increase in at least 2 organic acids increased in MCAD deficiency (suberylglycine, hexanoylglycine phenylpropionylglycine, hexanoic, 5-hydroxyhexanoic, or 7-hydroxyoctanoic acids) and/or medium-chain acylcarnitines (score 2)

- **Interpretation of results**
  - MCAD deficiency (score 2)

Overall impression

The overall proficiency was excellent: 100 %

Multiple distributions of similar samples

A similar urine sample has been distributed in 2006: the overall performance has improved.

	2006	2023
Analytical performance	87 %	100 %
Interpretative performance	95 %	100 %
Overall performance	93 %*	100 %

*Recommendations were scored separately

8.1. Patient E

Fucosidosis (alpha-L-fucosidase deficiency)

Patient details provided to participants

The patient is a 7-year-old boy. He presents with psychomotor retardation, ventilation and balance disorders, epilepsy, and a non-specific dysmorphia. At MRI, he has abnormalities of the white matter and the basal ganglia.

Patient details

No further details are available.
Diagnosis was suspected on urinary oligosaccharide profile and was confirmed by measurement of alpha-L-fucosidase activity in leukocytes:

(µKat/kg protein)	Patient	Control	Reference values
Alpha-L-fucosidase	0.0	21.5	11.0 – 26.0
Total hexosaminidase	572	478	240 - 780

Fucosidosis is a rare oligosaccharidosis, inherited as an autosomal recessive trait. There is no typical facial dysmorphism, but patient often have coarse facies. They present:

- Variable neurodegenerative disorder
- Seizures
- Dysostosis
- Often prominent and widespread angiokeratomas, which frequently progress with age

Analytical performance

Among the 18 participants who performed oligosaccharides (18/20):

- 17 reported an abnormal profile consistent with fucosidosis, using:
  - LC-MS/MS 9
  - one dimension TLC with orcinol staining 6
  - MS/MS without separation 1
  - non-specified method 1
- one reported a borderline profile, using one dimension TLC with orcinol staining.

An educational kit containing 9 common oligosaccharidosis samples is available to purchase on a not-for-profit basis from MCA Laboratories in the Netherlands. The samples included in the educational kit are: GM1 gangliosidosis, GM2 gangliosidosis, M. Pompe (infantile), aspartylglucosaminuria, alpha-mannosidosis, alpha-NAGA deficiency, sialidosis, fucosidosis, beta-mannosidosis. Further details of the Educational Panels / Oligosaccharide kit are available from MCA Laboratories:
https://erndimqa.nl/Information.aspx

Only one participant among the fourteen ones who also performed mucopolysaccharides quantification (14/20) mentioned a grossly elevated result.

Four participants performed mucopolysaccharides fractionation (4/20): three of them reported a normal profile, and one an elevation of keratan sulphate (there is no information on the method used).

Diagnosis / Interpretative proficiency

Most likely diagnosis

Fucosidosis (alpha-L-fucosidase deficiency) 17

Mucopolysaccharidosis type IVA	1
No diagnosis	2

Alternative diagnosis

Other oligosaccharidosis (GM1 gangliosidosis)	1
Other lysosomal storage disorder	1
Other mucopolysaccharidosis (type I, II, III, VI, VII)	1

Scoring

- **Analytical performance**
  - Oligosaccharide profile in agreement with fucosidosis (score 2)
  - Abnormal oligosaccharide profile (score 1)

- **Interpretation of results**
  - Fucosidosis as first or alternative diagnosis (score 2)

Overall impression

The overall proficiency was quite satisfying for this difficult sample: 89 %

Multiple distributions of similar samples

Two similar urine samples have been distributed in 2004 and 2014: the overall performance has significantly improved.

	2004	2014	2023
Analytical performance	66 %	59 %	88 %
Interpretative performance	66 %	65 %	90 %
Overall performance	69 %*	62 %	89 %

*Recommendations were scored separately

8.1. Patient F

Phenylketonuria (phenylalanine hydroxylase deficiency)

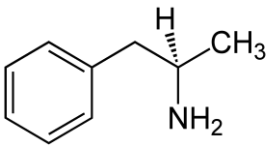
Patient details provided to participants

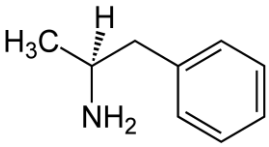
Young adult (26 years) with a nearly normal psychomotor development, under treatment for many years. When he applied for a job in police force, a urinary test was found positive for amphetamines, but he assured that he never used drugs.

Patient details

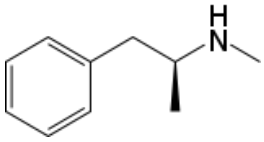
This 26-year old young man was diagnosed through the neonatal screening. He is under treatment from the first week of life. His psychomotor development is almost normal but his compliance to treatment is not strict.

Recommendations: Surprisingly, only 10 labs discussed the positiveness of amphetamines, although this problem compromises the patient's professional future. Screening for amphetamines is a one step immunoassay. Molecular structure for amphetamines and its derivative, metamphetamine, is very close to phenylalanine and its metabolites phenylethylamine and phenolic acids.

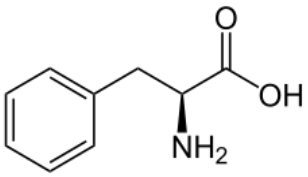




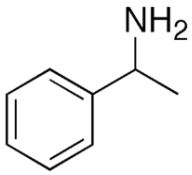
L- et D-amphetamine



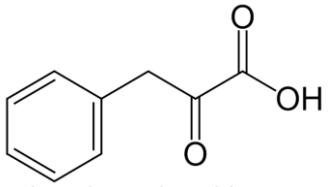
Metamphetamine



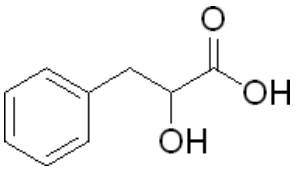
Phenylalanine



Phenylethylamine



Phenylpyruvic acid

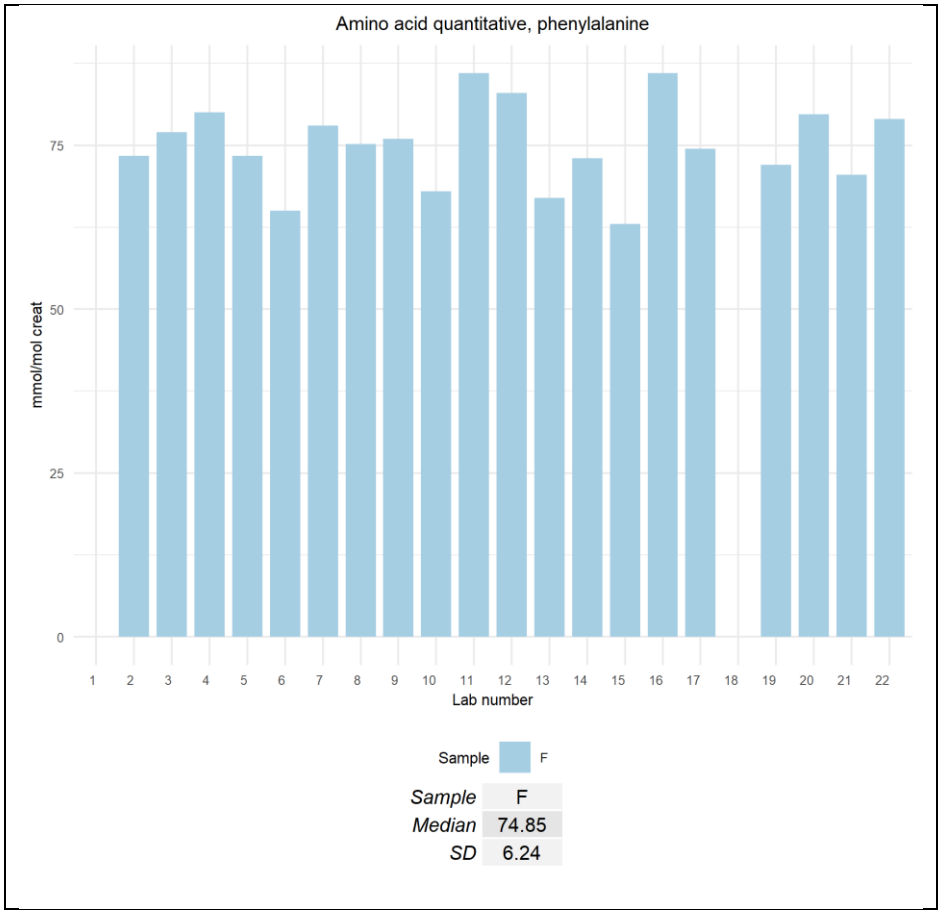


Phenyllactic acid

Screening for amphetamines can also be falsely positive test with drugs such as Largactil®, Tercian®, Survector®, Nivaquine®. In this patient, another test for amphetamines by GC/MS was performed and found negative, confirming the false positiveness of the screening test. Otherwise, recommendations for the confirmation of phenylketonuria were appropriate.

Analytical performance

All labs performed **amino acids (20/20)** and reported an **increase in phenylalanine** (median = 74.85 mmol/mol creatinine; range: 63 – 86 ; n=20).



All labs also performed **organic acids (20/20),** and reported an increase in:

- **Phenyllactic acid** **18**

(median = 550 mmol/mol creatinine; range : 365 – 1431 ; n=5)

- **Phenylpyruvic acid** **16**

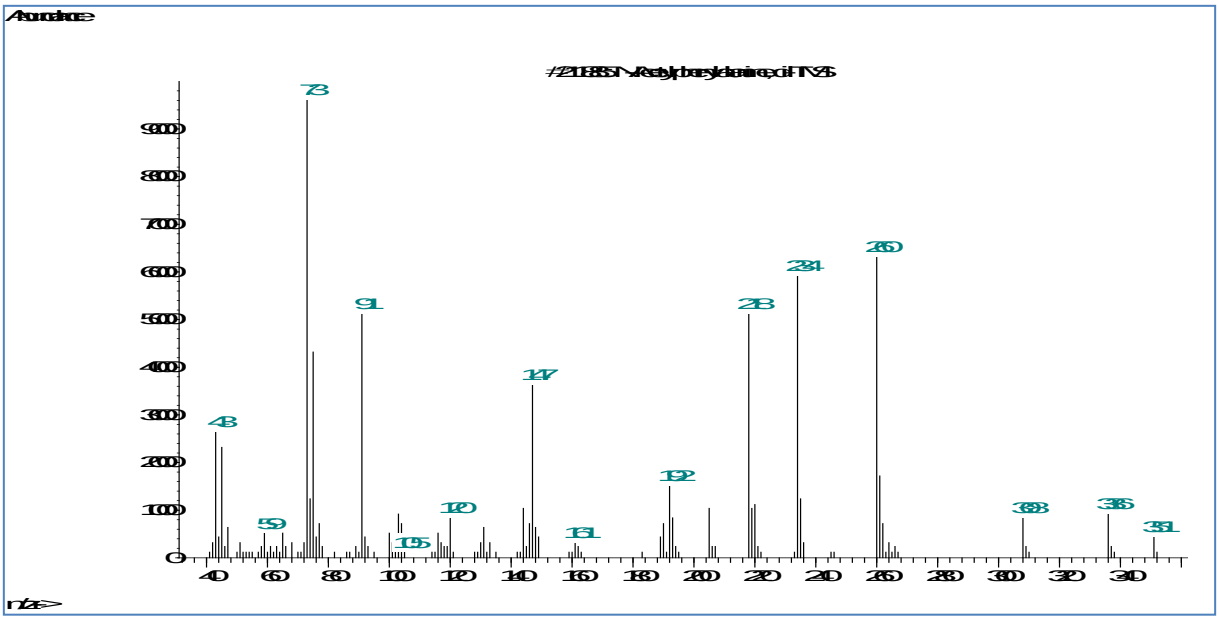
(median = 204.5 mmol/mol creatinine; range : 108 – 1764 ; n=4)

- **2-hydroxyphenylacetic acid** **15**
- **Phenylacetic acid** **12**

(median = 61 mmol/mol creatinine; range : 39 – 157 ; n=4)

- **Mandelic acid** **12**
- **N-acetylphenylalanine** **7**

The figure below shows the mass spectrum of N-acetylphenylalanine.



Diagnosis / Interpretative proficiency

Most likely diagnosis

Phenylketonuria (PKU, phenylalanine hydroxylase deficiency)	20

Alternative diagnosis

Disorders of BH4 cofactor metabolism	4
Biopterin deficiency	1
No other possible diagnosis	1

Scoring

- **Analytical performance**
  - Increase in phenylalanine (score 1)
  - Increase in at least two organic acids present in phenylketonuria (phenylpyruvic, mandelic, phenyllactic, N-acetylphenylalanine, phenylacetic, 2-hydroxyphenylacetic) (score 1)

- **Interpretation of results**
  - Phenylketonuria (score 2)

Overall impression

The overall proficiency was 99 %

Multiple distributions of similar samples

Two similar urine samples have been distributed in 2004 and 2014: the overall performance has improved.

	2011	2020	2023
Analytical performance	95 %	91 %	98 %
Interpretative performance	100 %	100 %	100 %
Overall performance	87 %*	95 %	99 %

*Recommendations were scored separately

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 your laboratory is 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 Argininosuccinic aciduria (argininosuccinate lyase deficiency)			Patient B 2-methylbutyryl-CoA dehydrogenase deficiency (short/branched chain acyl-CoA dehydrogenase deficiency)			Patient C Isovaleric acidemia (isovaleryl-CoA dehydrogenase deficiency)			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	2	4	2	2	4	2	2	4	12
2	0	0	0	2	2	4	2	2	4	8
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	0	0	0	2	2	4	2	2	4	8
7	2	2	4	2	2	4	2	2	4	12
8	2	2	4	0	0	0	2	2	4	8
9	2	2	4	2	2	4	2	2	4	12
10	--	--	--	--	--	--	--	--	--	0
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	0	2	2	2	2	4	10
15	2	2	4	2	2	4	2	2	4	12
16	2	2	4	2	2	4	2	2	4	12
17	2	2	4	2	2	4	2	2	4	12
18	--	--	--	--	--	--	--	--	--	0
19	2	2	4	2	2	4	2	2	4	12
20	2	2	4	0	0	0	2	2	4	8
21	2	2	4	2	2	4	2	2	4	12
22	2	2	4	2	2	4	2	2	4	12

Detailed scores – Round 2

Lab n°	Patient D Combined MCAD and OCTN2 deficiency			Patient E Fucosidosis (alpha-L-fucosidase deficiency)			Patient F Phenylketonuria (phenylalanine hydroxylase deficiency)			
	A	I	Total	A	I	Total	A	I	Total	Total
1	--	--	--	--	--	--	--	--	--	0
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	0	1	1	2	2	4	9
5	2	2	4	2	2	4	1	2	3	11
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	2	4	12
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	1	0	1	2	2	4	9
15	2	2	4	0	1	1	2	2	4	9
16	2	2	4	2	2	4	2	2	4	12
17	2	2	4	2	2	4	2	2	4	12
18	--	--	--	--	--	--	--	--	--	0
19	2	2	4	2	2	4	2	2	4	12
20	2	2	4	2	2	4	2	2	4	12
21	2	2	4	2	2	4	2	2	4	12
22	2	2	4	2	2	4	2	2	4	12

Total scores

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Critical error
1	4	4	4	--	--	--	12	50	
2	0	4	4	4	4	4	20	83	
3	4	4	4	4	4	4	24	100	
4	4	4	4	4	1	4	21	88	
5	4	4	4	4	4	3	23	96	
6	0	4	4	4	4	4	20	83	
7	4	4	4	4	4	4	24	100	
8	4	0	4	4	4	4	20	83	
9	4	4	4	4	4	4	24	100	
10	--	--	--	4	4	4	12	50	
11	4	4	4	4	4	4	24	100	
12	4	4	4	4	4	4	24	100	
13	4	4	4	4	4	4	24	100	
14	4	2	4	4	1	4	19	79	
15	4	4	4	4	1	4	21	88	
16	4	4	4	4	4	4	24	100	
17	4	4	4	4	4	4	24	100	
18	--	--	--	--	--	--	0	0	
19	4	4	4	4	4	4	24	100	
20	4	0	4	4	4	4	20	83	
21	4	4	4	4	4	4	24	100	
22	4	4	4	4	4	4	24	100	

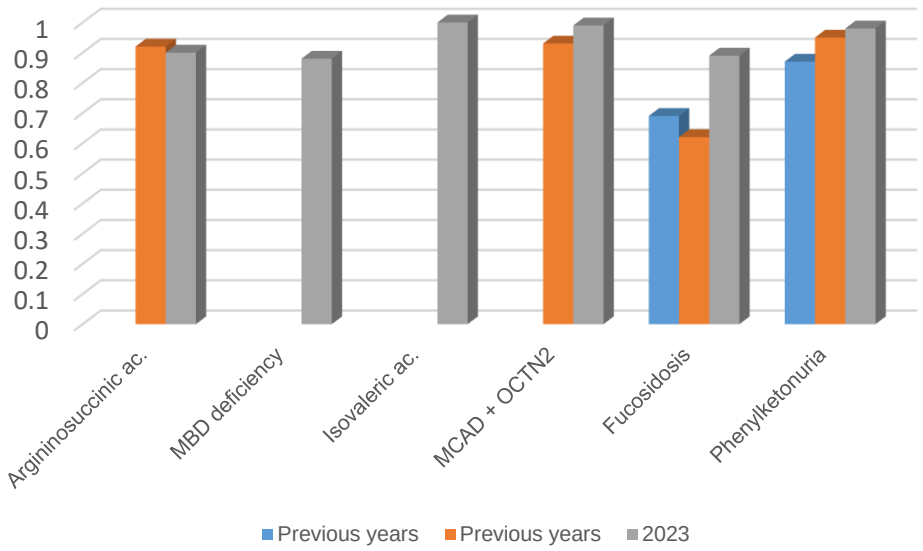
Performance

	Number of labs	% total labs
Satisfactory performers (≥ 70 % of adequate responses)	19	86
Unsatisfactory performers (< 70 % adequate responses and/or critical error)	2	9
Partial and non-submitters	3	14

Overall Proficiency

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Total (%)
DPT-FL-2023-A	Argininosuccinic aciduria (argininosuccinate lyase deficiency)	90	90	90
DPT-FL-2023-B	2-methylbutyryl-CoA dehydrogenase deficiency (short/branched chain acyl-CoA dehydrogenase deficiency)	85	90	88
DPT-FL-2023-C	Isovaleric acidemia (isovaleryl-CoA dehydrogenase deficiency)	100	100	100
DPT-FL-2023-D	Combined MCAD and OCTN2 deficiency	100	100	100
DPT-FL-2023-E	Fucosidosis (alpha-L-fucosidase deficiency)	88	90	89
DPT-FL-2023-F	Phenylketonuria (phenylalanine hydroxylase deficiency)	98	100	99

Improvement DPT France



10. Annual meeting of participants

It took place in Jerusalem on August 29th 2023 from 9.00 to 10.30, before the SSIEM Meeting.

Participants

Participants: 7 people from 6 labs
Silvia Funghini, Sabrina Malvaglia (Florence), Marguerite Gastaldi (Marseille), Apolline Imbard (Paris), Dulce Quelhas (Porto), Cristiano Rizzo (Roma), Cristobal Colon (Santiago de Compostella).
Hila Sameach from Seba Hospital, Israel also participated.

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

- **Scoring policy for DPT scheme in 2024**: the score for satisfactory performance is **at least 17 points from the maximum of 24 (70%)**, in accordance with the other qualitative schemes.
- **Reference materials** are provided by MCA Laboratories: they are not related to EQA samples. There are two concentration levels for each group of analytes. The most suitable low and high concentration levels have been defined by the respective scientific advisors. Analytes and their concentrations will be approximately the same in consecutive batches of control material. These reference materials can be ordered through the ERNDIM website (www.erndimqa.nl). Participants are encouraged to use them as internal control, but they cannot be used as calibrants. On the website a new section for data management completes the ERNDIM internal Quality Control System. Laboratories have the option to submit results and request reports showing their result in the last run in comparison to defined acceptance limits, their own historical data and the mean of all laboratories using the same batch control material.
- A set of **organic acid standards** has been developed by Amsterdam UMC (University Medical Center), following request and advice from ERNDIM. The product is currently available at: organic.synthesis.lab@amsterdamumc.nl
- **Training**: SSIEM Academy training courses.
  - A 2-day course will be organized on Monday and Tuesday 22nd and 23rd April 2024 in Amsterdam. The topics will be:
    - Lysosomal storage disorders

- Peroxisomal disorders
- Purines & pyrimidines disorders
- Trace elements and metal disorders

- Registrations are now closed. The lectures will be available on the SSIEM website

- **Urine samples**: we remind you that every year, each participant must provide to the scheme organizer at least 250 ml of urine from a patient affected with an established inborn error of metabolism or a "normal" urine, together with a short clinical report. If possible, please collect at least 1200 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. For "normal" urine, the sample must be collected from a symptomatic patient. Appendix 1 gives the list of the urine samples we already sent.

  As soon as possible after collection, the urine sample must be heated at 50°C for 20 minutes. Make sure that this temperature is achieved in the entire urine sample, not only in the water bath. Separate 4 aliquots in 10 ml plastic tubes, add stoppers, and freeze these aliquots and the rest of the urine sample in a bulk. Send the bulk and the aliquots on dry ice by rapid mail or express transport to:

  C. VIANEY-SABAN, C. ACQUAVIVA-BOURDAIN
  Service Maladies Héréditaires du Métabolisme
  Centre de Biologie et de Pathologie Est
  59, Boulevard Pinel
  69677 Bron cedex
  France
  Tel +33 4 72 12 96 914
  e-mail
  christine.vianeysaban@gmail.com
  cecile.acquaviva-bourdain@chu-lyon.fr

  Please send us an e-mail on the day you send the samples.

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. Tentative schedule for 2024

Sample distribution	7 February 2024
Start of analysis of Survey 2024/1 Website open	March 12
Survey 2024/1 - Results submission	April 2
Survey 2024/1 – Interim Reports	May
Start of analysis of Survey 2024/2	June 3
Survey 2024/2 – Results submission	June 24
Survey 2024/2 – Interim Reports	July
Annual meeting of participants	September 5 Porto SSIEM
Annual Report 2024	December

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, Christine Vianey-Saban (christine.vianeysaban@gmail.com) and/or to the ERNDIM Administration Office (admin@erndim.org)

Date of report, 2023-12-16
Name and signature of Scientific Advisor

Christine Vianey-Saban Cécile Acquaviva

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e-mail
christine.vianeysaban@gmail.com
cecile.acquaviva-bourdain@chu-lyon.fr

APPENDIX 1.

DIAGNOSTIC PROFICIENCY TESTING (DPT) FRANCE

URINE SAMPLES ALREADY SENT

• 1998 : 1	A	OCT
	B	Propionic acidemia
• 1999 : 1	C	MPS I or II
	E	Cystinuria (common sample)
• 1999 : 2	D	CblC
	F	HMG-CoA lyase deficiency
• 2000 : 1	G	Iminodipeptiduria (common sample)
	H	Glutathion synthetase
• 2001 : 1	P1	Mevalonate kinase deficiency
	P2	L-2-OH glutaric
• 2001 : 2	P3	Methylmalonic (common sample)
	P4	MPS IIIA San Fillippo
• 2002 : 1	P1	LCHAD deficiency
	P2	Sulphite oxidase deficiency
• 2002 : 2	P3	Biotinidase deficiency (common sample)
	P4	MPS I
• 2003:1	P1	Tyrosinemia type I
	P2	SC-BCAD deficiency
	P3	Argininosuccinic aciduria
• 2003:2	P4	3-methylcrotonyl-CoA carboxylase deficiency
	P5	Sialidosis (common sample)
	P6	MSUD
• 2004:1	P1	Tyrosinemia type I, treated patient
	P2	Propionic acidemia
	P3	Non metabolic disease, septic shock
• 2004:2	P4	Mevalonic aciduria (common sample)
	P5	Fucosidosis
	P6	Alkaptonuria
• 2005:1	P1	Isovaleric acidemia
	P2	Tyrosinemia type II (common sample)
	P3	Disorder of peroxysome biogenesis
• 2005:2	P4	Multiple acyl-CoA dehydrogenase deficiency
	P5	Alpha-mannosidosis
	P6	4-hydroxybutyric aciduria
• 2006:1	P1	Aromatic amino acid decarboxylase deficiency
	P2	Hyperoxaluria type I
	P3	Mucopolysaccharidosis type VI
• 2006:2	P4	Hypophosphatasia (common sample)
	P5	Lysinuric protein intolerance
	P6	MCAD deficiency

• 2007:1	P1	Mitochondrial acetoacetyl-CoA thiolase
	P2	Homocystinuria due to CBS deficiency
	P3	Hyperlysinemia (common sample)
• 2007:2	P4	Aspartylglucosaminuria
	P5	Phenylketonuria
	P6	SCAD deficiency
• 2008:1	P1	Cbl C/D
	P2	Mucopolysaccharidosis type III (common sample)
	P3	2-hydroxyglutaric aciduria
• 2008:2	P4	Glycerol kinase deficiency
	P5	□-mannosidosis
	P6	3-methylcrotonyglycinuria
• 2009:1	P1	Mucopolysaccharidosis type III
	P2	Salla disease (common sample)
	P3	No metabolic disorder
• 2009:2	P4	Glutaric aciduria type I
	P5	Iminodipetiduria
	P6	Multiple acyl-CoA dehydrogenase deficiency
• 2010:1	P1	Mevalonic aciduria
	P2	Aminoacylase I deficiency
	P3	No metabolic disorder
• 2010:2	P4	Sialidosis type I (common sample)
	P5	Glutaric aciduria type I
	P6	Aspartylglucosaminuria
• 2011:1	A	Molybdenum cofactor deficiency
	B	GAMT deficiency (common sample)
	C	Methylmalonic semialdehyde dehydrogenase def.
• 2011:2	D	Mucopolysaccharidosis type IVA (Morquio)
	E	Phenylketonuria
	F	Citrullinemia type I
• 2012:1	A	Intermittent MSUD (common sample)
	B	HHH syndrome
	C	Mucopolysaccharidosis type I
• 2012:2	D	“RedBulluria”
	E	CblC
	F	SCAD deficiency
• 2013:1	A	NFU1 deficiency
	B	MNGIE syndrome (educational)
	C	Lysinuric protein intolerance (common sample)
• 2013:2	D	Mitochondrial acetoacetyl-CoA thiolase deficiency
	E	Morquio disease (MPS IV)
	F	Glycerol kinase deficiency
• 2014:1	A	Iminodipeptiduria
	B	HHH syndrome (common sample)
	C	4-hydroxybutyric aciduria

• 2014:2	D	Fucosidosis
	E	L-2-hydroxyglutaric aciduria
	F	SCHAD deficiency
• 2015:1	A	Combined malonic & methylmalonic aciduria
	B	Homocystinuria-CBS deficiency (common sample)
	C	Mucopolysaccharidosis type VI
• 2015:2	D	N-acetylaspartic aciduria
	E	D-2-hydroxyglutaric aciduria type II
	F	GM1 gangliosidosis
• 2016:1	A	Primary hyperoxaluria type II (common sample)
	B	Methionine S-adenosyltransférase (MAT) def.
	C	Glycerol kinase deficiency
• 2016:2	D	Ethylmalonic encephalopathy (*ETHE1* gene)
	E	Mucopolysaccharidosis type IVA
	F	Argininosuccinic aciduria
• 2017:1	A	Citrullinaemia type I (common sample)
	B	MNGIE
	C	Formiminoglutamic aciduria
• 2017:2	D	GM1 gangliosidosis
	E	No IEM
	F	Imerslund-Gräsbeck
• 2018:1	A	DPD deficiency (common sample)
	B	MPS VII
	C	SCHAD deficiency
• 2018:2	D	Glutaric aciduria type I (low excretor)
	E	OAT deficiency
	F	Dihydropyrimidine dehydrogenase (DPD) deficiency
• 2019:1	A	APRT deficiency (common sample)
	B	Beta-mannosidosis
	C	Hyperprolinaemia type II
• 2019:2	D	Multiple acyl-CoA dehydrogenase deficiency (MADD)
	E	MPS II
	F	Argininaemia
• 2020:1	A	PKU (common sample)
	B	Alkaptonuria
	C	MPS IVA
• 2020:2	D	Citrullinaemia type I
	E	Iminodipeptiduria
	F	GAMT deficiency
• 2021:1	A	Alpha-mannosidosis (common sample)
	B	Alpha-mannosidosis
	C	MAT deficiency (beta-ketothiolase)
• 2021:2	D	CBS deficiency
	E	4-hydroxybutyric aciduria
	F	Hyperprolinaemia type II

• 2022:1	A	Barth syndrome (common sample)
	B	Propionic acidaemia
	C	MPS IVA
• 2022:2	D	No IEM
	E	3-methylcrotonyl-CoA carboxylase deficiency
	F	Aromatic amino acid decarboxylase deficiency

APPENDIX 2. Change log (changes since the last version)

Version Number	Published	Amendments
1	09 January 2024	2023 annual report published

END