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# Diagnostic Proficiency Testing

# Centre: France

# Final Report 2022

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 ERNDIM Privacy Policy on www.erndim.org.

In 2022, 21 labs participated to the Proficiency Testing Scheme France.

## 1. Geographical distribution of participants

For the first survey, 20 laboratories submitted results and 21 for the second survey.

| Country | Number of participants |
|---|---|
| France | 8 |
| Italia | 5 |
| Portugal | 2 |
| Spain | 5 |
| United Kingdom | 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 CSCQ as scheme organizer (sub-contractor on behalf of ERNDIM), both appointed by and according to procedures laid down the ERNDIM Board.

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

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 Joanne Croft (DPT UK) and Claus-Dieter Langhans (QLOU scheme - Heidelberg).

Patient A: Barth syndrome
Patient B: Propionic acidaemia due to propionyl-CoA carboxylase deficiency
Patient C: MPS IVA
Patient D: No IEM
Patient E: 3MCC deficiency
Patient F: AADC deficiency.

The samples have been heat-treated. They were pre-analyzed in our institute after 14 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. Problems occurred with Spanish customs.

## 3. Tests

Analyses of amino acids, organic acids, mucopolysaccharides, oligosaccharides and purines / pyrimidines are mandatory.

## 4. Schedule of the scheme

- February 2, 2022 Shipment of samples of Survey 1 and Survey 2 by CSCQ
- March 14, 2022 Clinical data available on CSCQ website and start analysis of samples A, B, C (Survey 1)
- March 28, 2022 Reminder for website submission
- April 4, 2022 Deadline for result submission (Survey 1)
- May 4, 2022 Interim report of Survey 1 available on CSCQ website (sent to CSCQ by SA on April 19)
- June 6, 2022 Clinical data available on the CSCQ website and start analysis of samples D, E, F (Survey 2)
- June 21, 2022 Reminder for website submission
- June 28, 2022 Deadline for result submission (Survey 2)
- July 20, 2022 Interim report of Survey 2 available on CSCQ website (sent to CSCQ by SA on July 19)
- August 30, 2022 Meeting of participants in Freiburg during the SSIEM Symposium
- November 25, 2022 SAB meeting: definition of critical errors
- January 20, 2023 Annual Report with definitive scoring

## 5. Results

Twenty of 21 participants returned results for the first survey by the deadline. All participants returned results for the second survey by the deadline.

Unfortunately, one participant swapped the DPT samples of the first survey with those of the QLOU scheme. They noticed this after the results were available on the website. So, it was too late to correct this error.

| | **Survey 1** | **Survey 2** |
|---|---|---|
| Receipt of results | 20 | 21 |
| No answer | 1 | 0 |

## 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 2022 have been also scored by Dr Déborah Mathis from DPT Switzerland. At the SAB meeting in Rome on November 25th, 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 the common sample A (alpha-mannosidosis) has to be considered as a critical error for the labs who did not perform oligosaccharides and did not recommend performing it. Nonidentification of an increase of proline in sample F (Hyperprolinemia type II) has also been advised by the SAB as a critical error, since seizures in this disorder are pyridoxine responsive.

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. Two performance support letters have been sent by the Scheme Advisor for 2021 for critical error and low score. Partial- or non- submitters have received 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 2022**, in accordance with the other qualitative schemes.

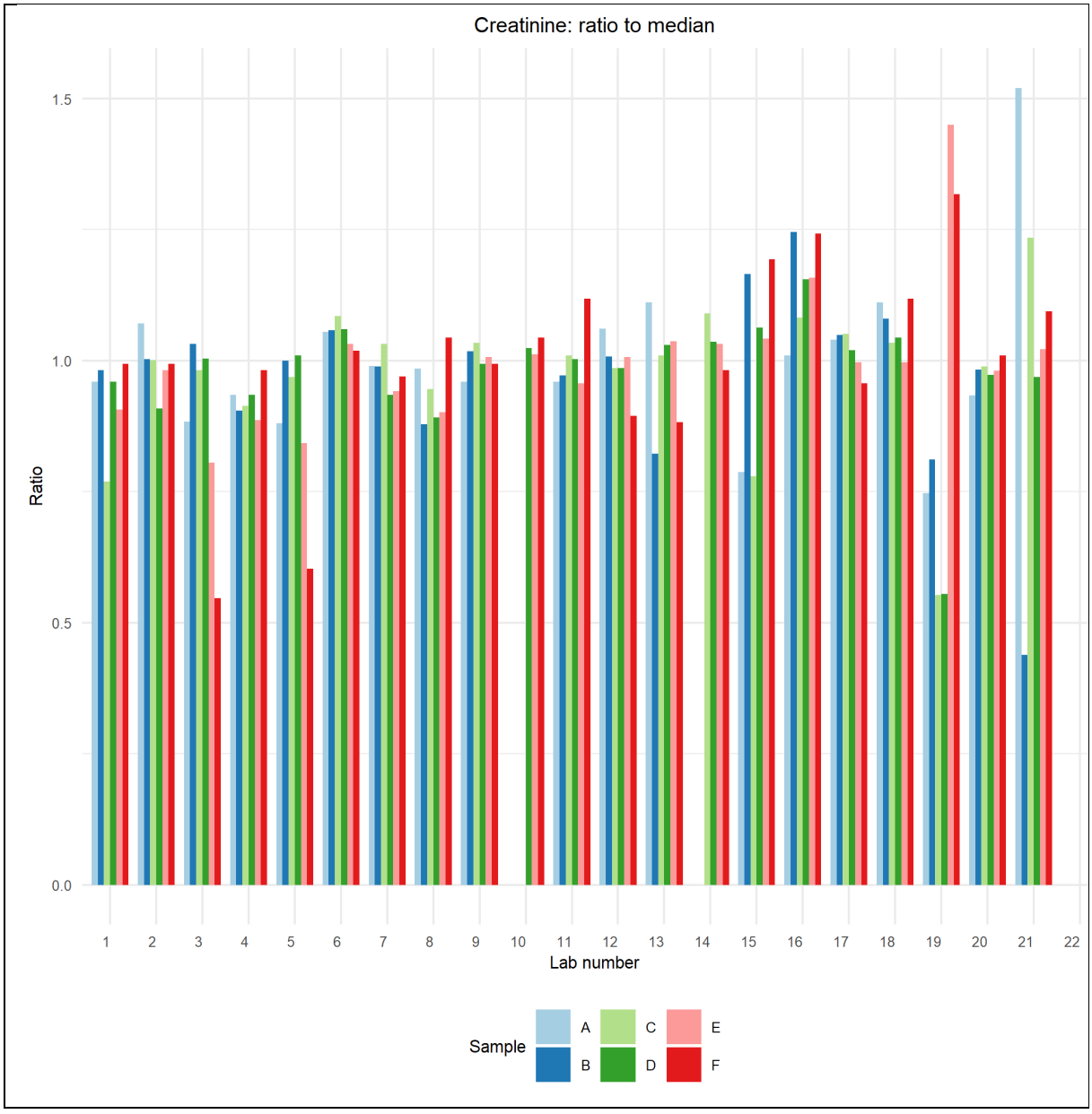
If your laboratory is assigned poor performance and you wish to appeal against this classification please email the ERNDIM Administration Office (admin@erndim.org), with full details of the reason for your appeal, within one month receiving your Performance Support Letter. Details of how to appeal poor 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 5.9 % (sample D) to 17.4 % (sample F); this is higher than the interlab CV 2021 for Special Assays in Urine (5.8 %, n = 130). But three samples (sample A, E and F) had low creatinine values.

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




The median values for creatinine determination were:

- Sample A: 1.95 mmol/L
- Sample B: 19.37 mmol/L
- Sample C: 4.20 mmol/L
- Sample D: 11.80 mmol/L
- Sample E: 1.98 mmol/L
- Sample F: 0.80 mmol/L

## 8.2. Patient A

Barth syndrome (tafazzin deficiency)

**Patient details provided to participants**

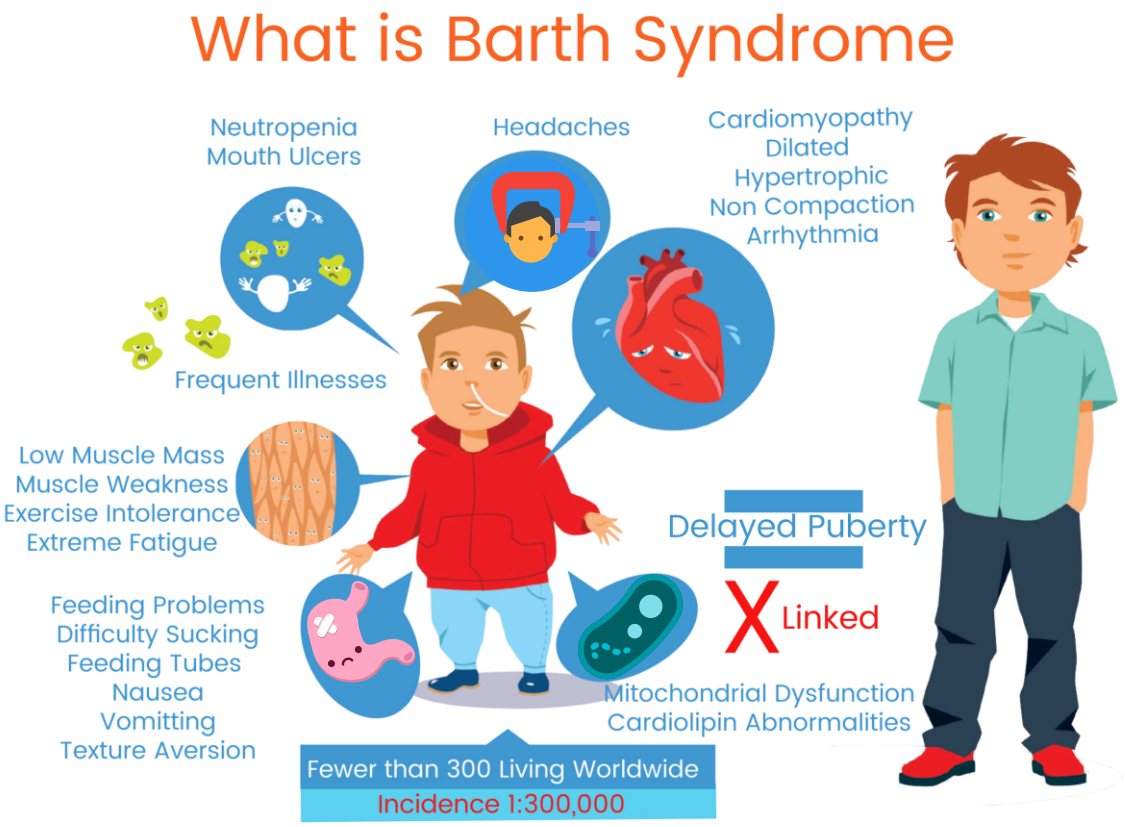
Pre-natal growth concerns. Monitored throughout life for poor growth. Presented at 4 years of age due to lips going blue during exercise.

**Patient details**

Male patient, with pre-natal growth concerns. He was monitored throughout life for poor growth and presented at 4 years of age with lips going blue during exercise. He did not get a diagnosis until the age of 14 years, when exome sequencing was performed and concluded to Barth syndrome. The diagnosis has been confirmed by cardiolipin analysis in dried blood spot. The urine sample has been collected at 14 years of age.

This is the common sample distributed to all participants of the 5 DPT schemes. Results from all centers has been presented at the ERNDIM meeting on August 30th at the SSIEM meeting in Freiburg and are available on the ERNDIM website.

The clinical presentation of Barth syndrome, a X-linked disorder, is summarized in the figure below (from https://www.barthsyndrome.org/barthsyndrome/familyresources/toolsforschool/resources.html).




Barth syndrome is due to tafazzin deficiency. Tafazzin, coded by *TAZ* gene, is an enzyme involved in the remodelling of cardiolipin, an essential constituent of mitochondrial membranes, which plays a role in many mitochondrial processes (from Dudek, Front. Cell Dev. Biol. 2017;5:90).

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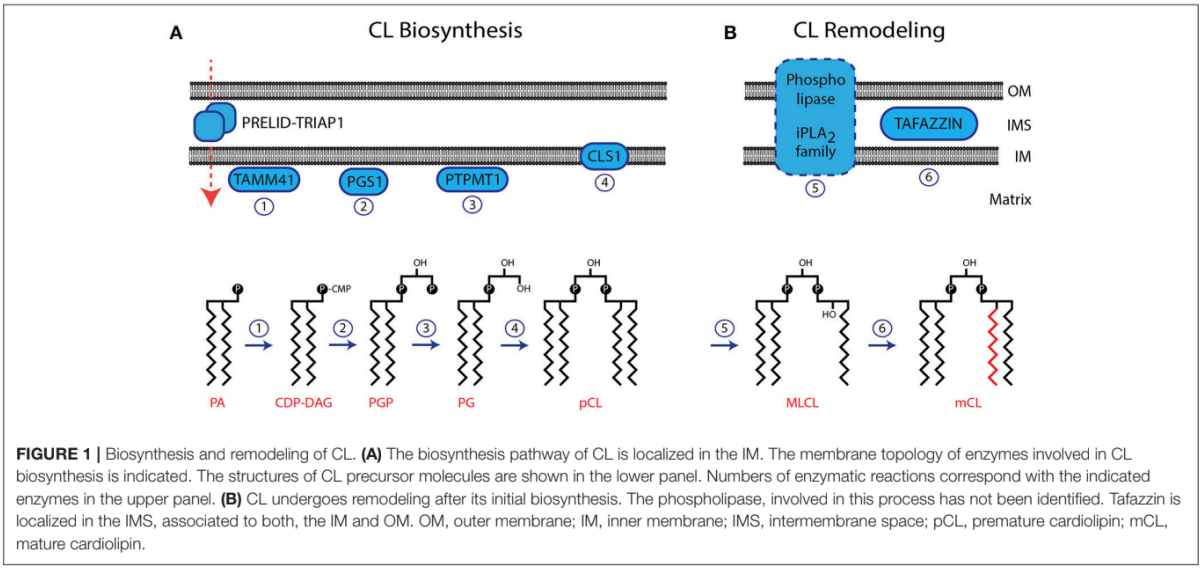
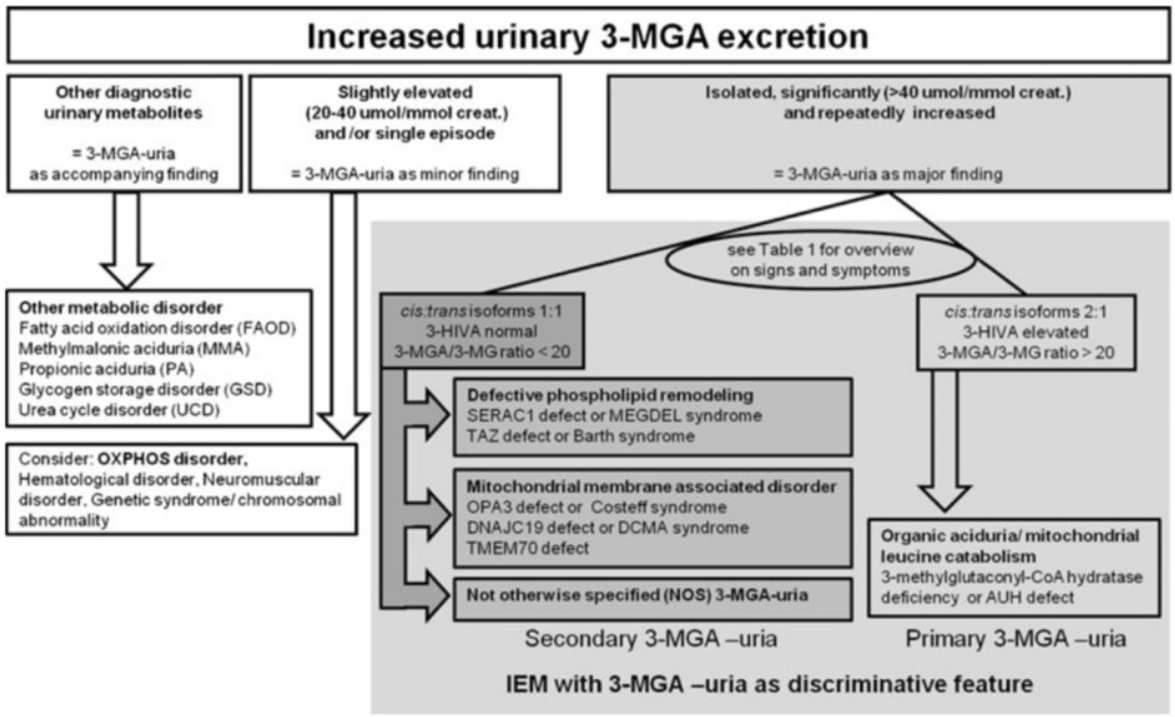


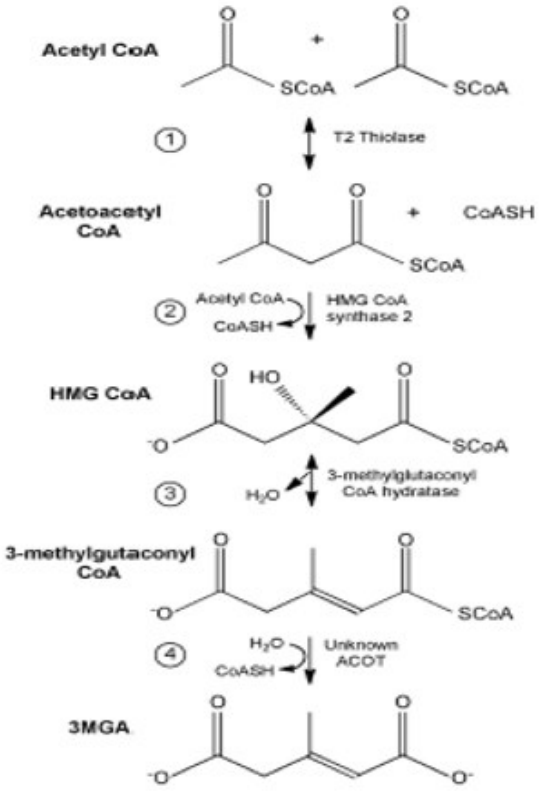

**FIGURE 1 |** Biosynthesis and remodeling of CL. **(A)** The biosynthesis pathway of CL is localized in the IM. The membrane topology of enzymes involved in CL biosynthesis is indicated. The structures of CL precursor molecules are shown in the lower panel. Numbers of enzymatic reactions correspond with the indicated enzymes in the upper panel. **(B)** CL undergoes remodeling after its initial biosynthesis. The phospholipase, involved in this process has not been identified. Tafazzin is localized in the IMS, associated to both, the IM and OM. OM, outer membrane; IM, inner membrane; IMS, intermembrane space; pCL, premature cardiolipin; mCL, mature cardiolipin.

PA: phosphatidic acid; PGP: phosphaditylglycerol phosphate; PG: phosphatidylglycerol; pCL: premature cardiolipin; MLCL: monolysocardiolipin; mCL: mature cardiolipin

Excretion of 3-methylglutaconic acid (3MGA) is increased in Barth syndrome. The following algorithm (from Wortmann et al, JIMD 2013;36:923) helps for the delineation of an increased excretion of 3-metylglutaconic.




The mechanism leading to 3-MGA excretion in secondary 3-MGA aciduria is not completely elucidated, and not directly related to Leu breakdown. Su and Ryan (J. Inherit Metab Dis 2014; 37(3):359-368) proposed the following pathway: under conditions where the Krebs cycle flux is impeded, some portion of acetyl-CoA is diverted towards an alternate non energy yielding metabolic fate that, in 4 steps, generates 3MGA.

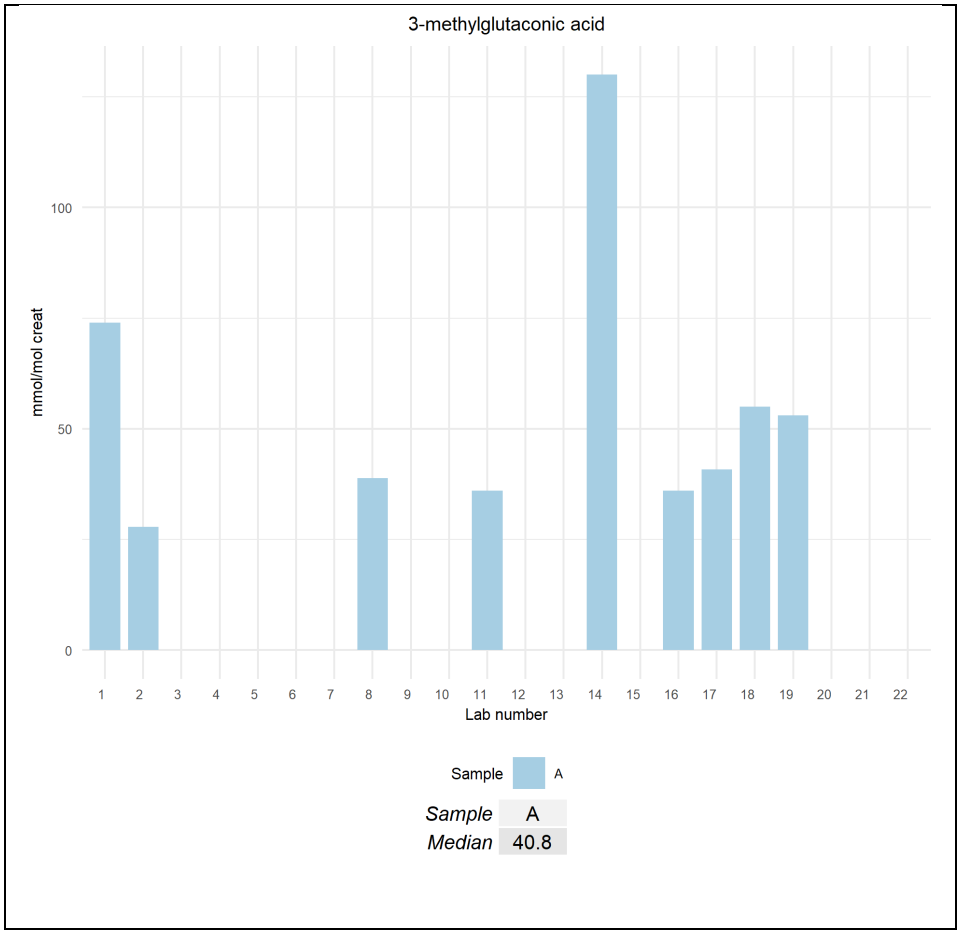


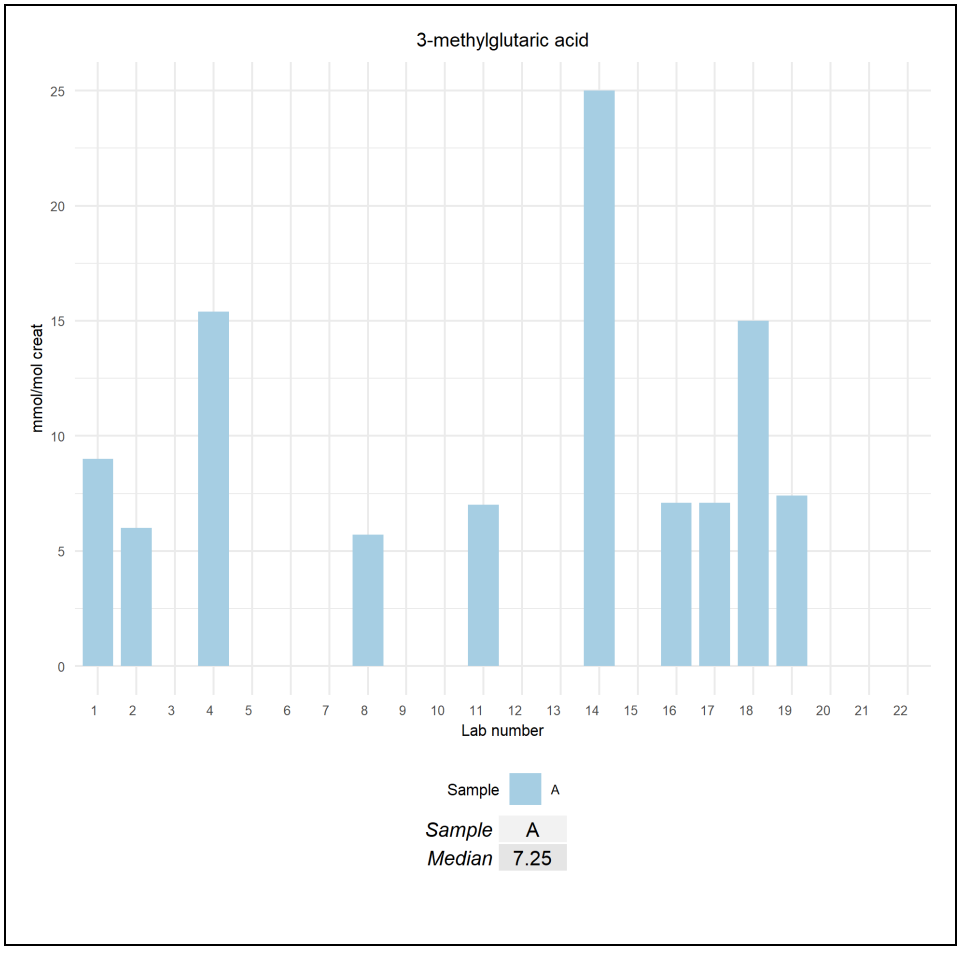

Thanks to Dr Cristiano Rizzo (Rome) who provided this information.

**Analytical performance**

All participants performed **organic acids** (20/20). They reported an increase of:

- **3-methyglutaconic acid** 18
- (median = 40.8 mmol/mol creatinine; range: 27.8 – 130 ; n = 9)
- **3-methylglutaric acid** 16
- (median = 7.25 mmol/mol creatinine; range: 7.7 – 25 ; n = 10)
- 2-ethylhydracrylic acid 3
- Orotic acid 1
- Lactic, 2-hydroxyglutaric, EMA, sebacic, isovaleryl-, isobutyrylglycine 1


3-methylglutaconic acid
mmol/mol creat
0
50
100
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 A
Sample A
Median 40.8


3-methylglutaric acid
mmol/mol creat
0
5
10
15
20
25
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 A
Sample A
Median 7.25

Thirteen out of the 14 participants who performed a**mino acids** (14/20), mentioned an increased excretion of glycine (median = 643 mmol/mol creatinine; range: 385 – 1418 ; n = 13).

### Diagnosis / Interpretative proficiency

| | |
|---|---|
| Most likely diagnosis | |
| Barth syndrome (3-methylglutaconic aciduria type II) | 6 |
| Secondary 3-methylglutaconic aciduria, possibly Barth | 4 |
| Secondary 3-methylglutaconic aciduria | 4 |
| 3-methylglutaconic aciduria type IV | 1 |
| 3-methylglutaconic aciduria type I (3-methylglutaconyl-CoA hydratase) | 1 |
| Lysinuric protein intolerance | 1 |
| Multiple acyl-CoA dehydrogenase deficiency | 1 |
| Alternative diagnosis | |
| Other causes of secondary 3-methylglutaconic aciduria | 5 |
| Barth syndrome (3-methylglutaconic aciduria type II) | 6 |
| Other 3-methylglutaconic acidurias | 2 |
| 3-methylglutaconic aciduria type I | 2 |
| 3-methylglutaconic aciduria type V, VIII or VII | 1 |
| 3-methylglutaconic aciduria type II, III, IV or V | 1 |
| Hyperlysinemia | 1 |

### Scoring

- Analytical performance
  - Increase of 3-methylglutaconic acid (score 2)
- Interpretation of results
  - Barth syndrome (3-methylglutaconic aciduria type II) or secondary 3-methylglutaconic aciduria as first or alternative diagnosis (score 2)
  - Primary 3-methylglutaconic aciduria or 3-methylglutaconic aciduria without any information if it is primary or secondary (score 1)

The overall performance of all DPT participants was excellent. Therefore, the SAB decided that the common sample A (Barth syndrome) has to be considered as a critical error for the two labs who did not identify 3-methylgutaconic acid.

### Overall impression

The overall performance was 89%.

## 8.3. Patient B

Propionic acidemia due to propionyl-CoA carboxylase deficiency

### Patient details provided to participants

16-year-old male patient, first child of non-consanguineous parents. He presented at 2 days of life with whining, feeding difficulties, and metabolic acidosis. On treatment in good clinical condition.

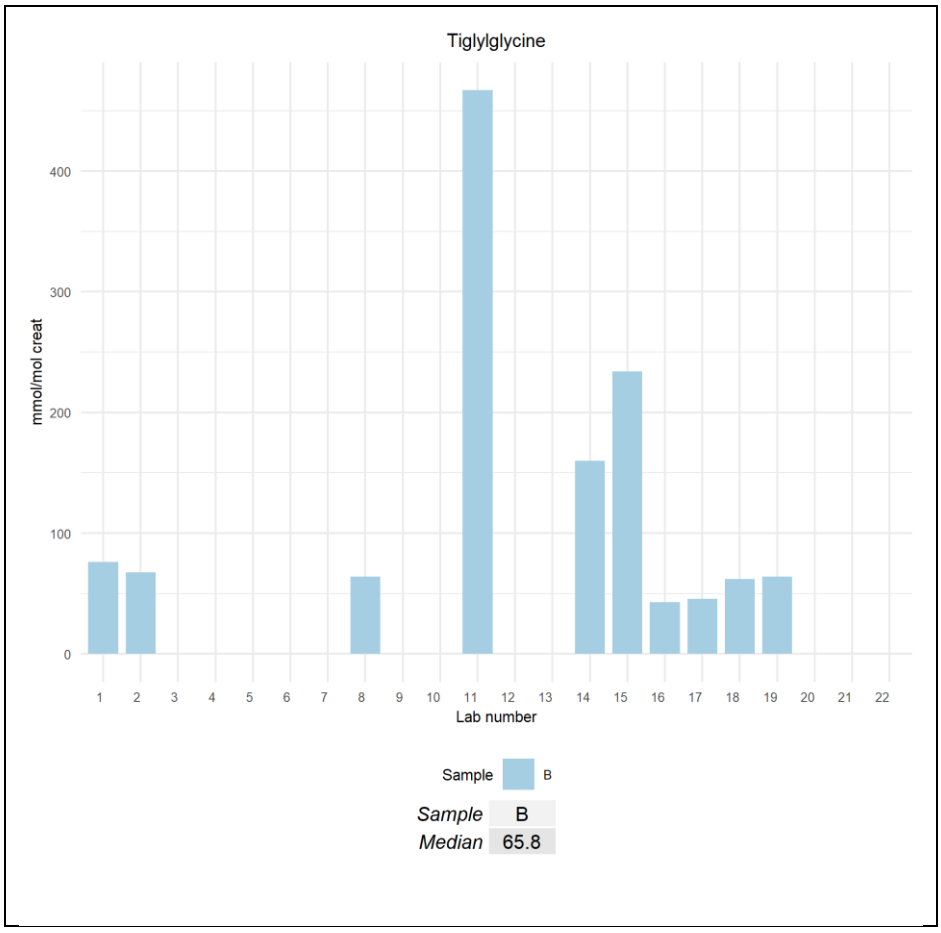
### Patient details

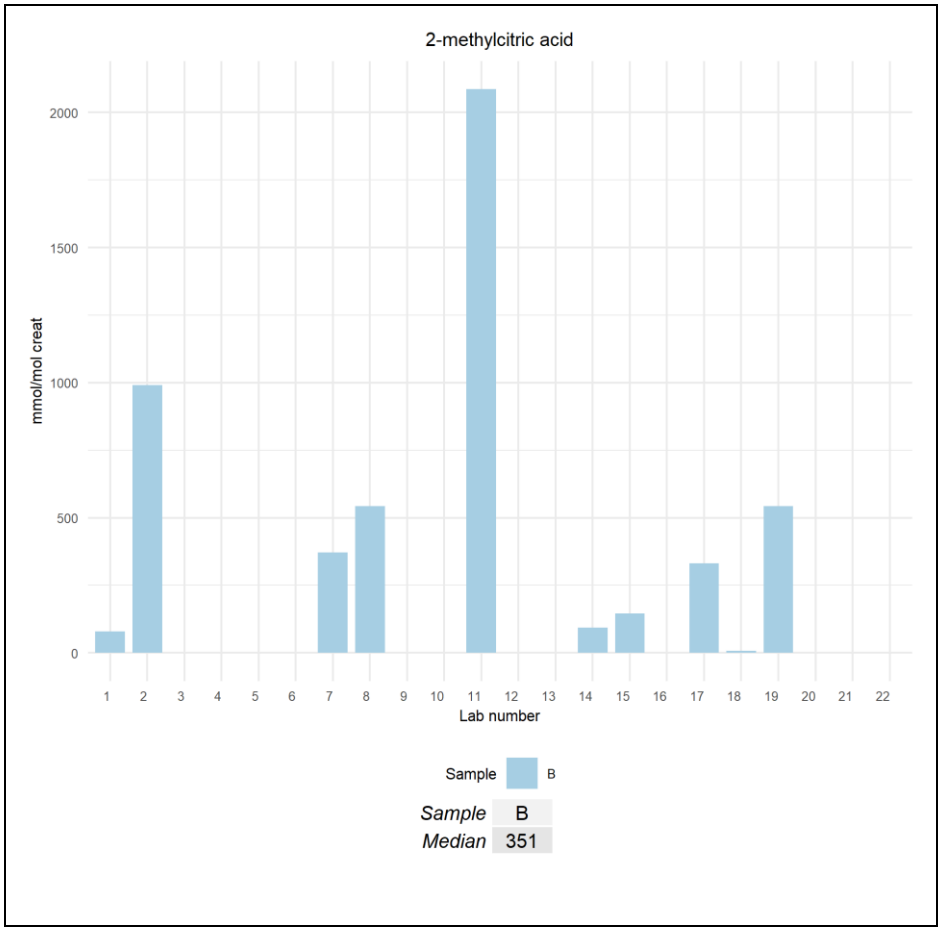
The diagnosis of propionic aciduria was confirmed by mutation analysis. The urine sample was collected when the patient was 16-year-old, and in good clinical condition.

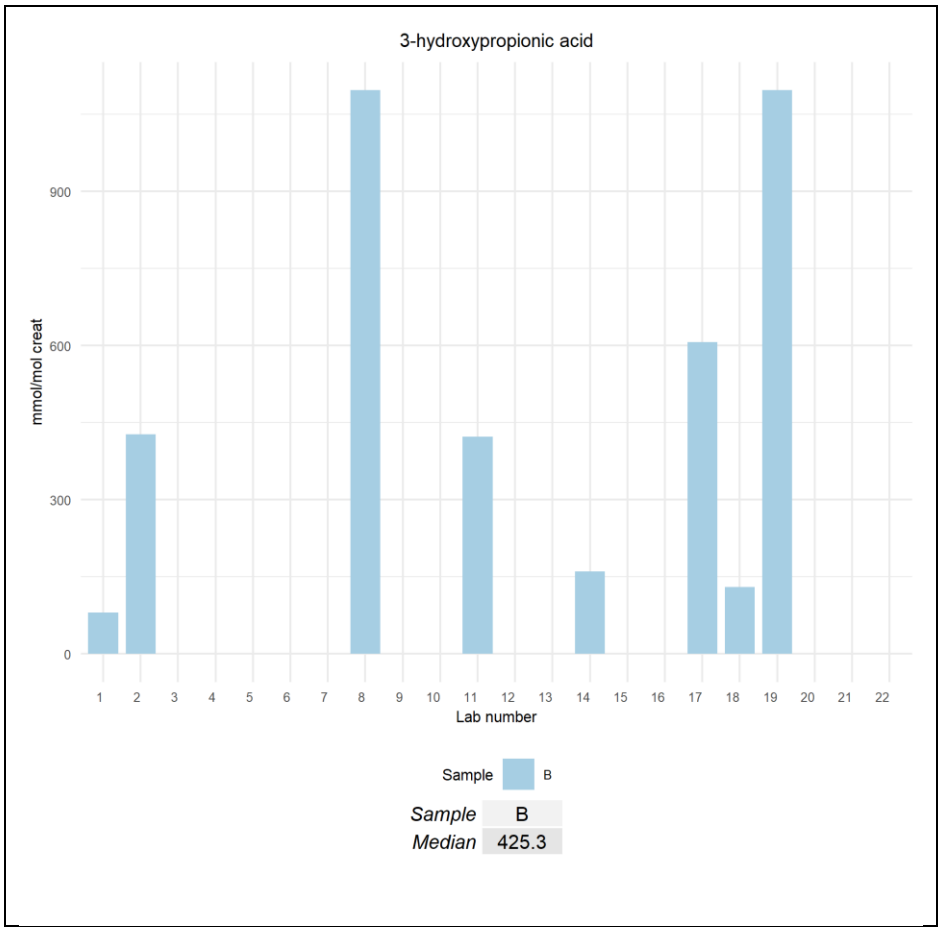
### Analytical performance

All participants performed **organic acids** (20/20), and reported an increase of:

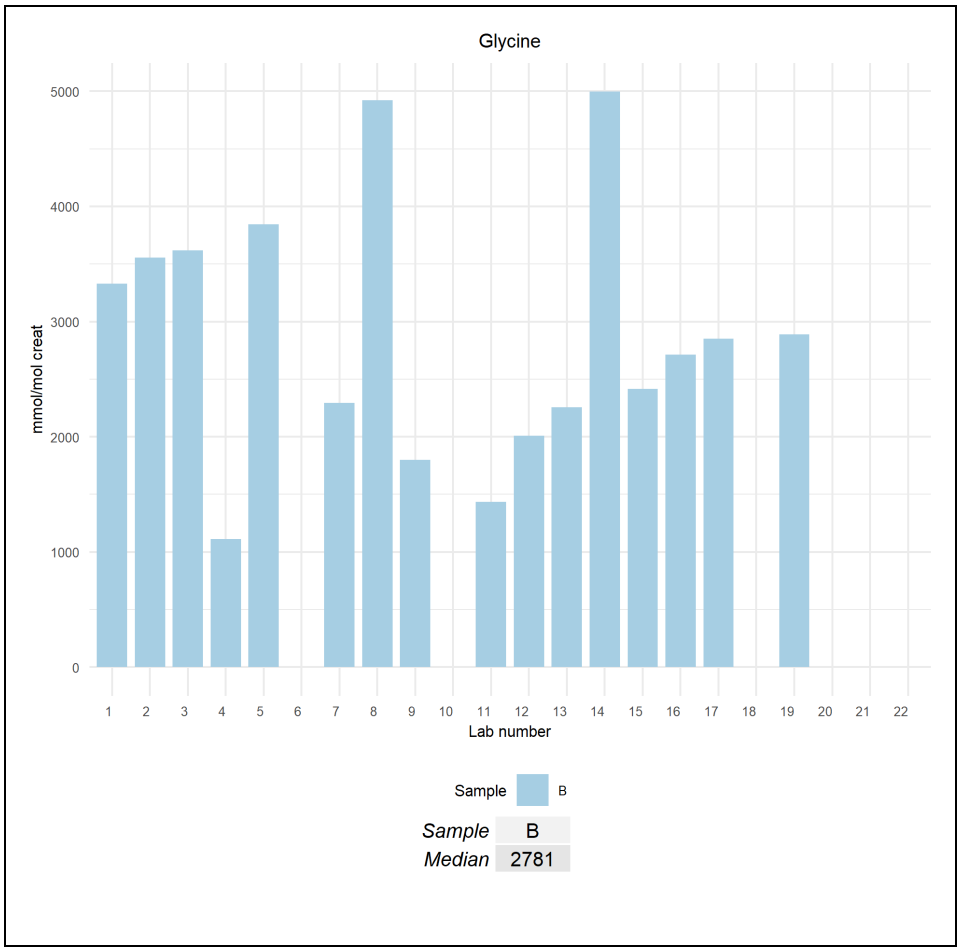
- **Tiglylglycine** 18
  (median = 65.8 mmol/mol creatinine; range: 43 – 467; n = 10)
- **2-methylcitric acid** 18
  (median = 351 mmol/mol creatinine; range: 7 – 2086; n = 10)
- **3-hydroxypropionic acid** 18
  (median = 425 mmol/mol creatinine; range: 80 – 1097; n = 8)
- **Propionylglycine** 17
  (median = 181 mmol/mol creatinine; range: 46 – 393; n = 6)
- Homogentisic acid 1




2-methylcitric acid
mmol/mol creat
2000
1500
1000
500
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 B
Sample B
Median 351


3-hydroxypropionic acid
mmol/mol creat
900
600
300
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 B
Sample B
Median 425.3

The 18 participants who performed **amino acids** reported an increase of glycine (median = 2781 mmol/mol creatinine; range: 1114 – 4997; n = 16).




Four participants performed **acylcarnitines (4/20)** and reported an increase of **propionylcarnitine** (median = 48.4 mmol/mol creatinine; range: 32 – 119.6 ; n = 4).

During the participants' meeting, the usefulness of urinary acylcarnitine profiling was discussed. Of course, as part of DPT scheme, it is often performed, since plasma/DBS samples are not available. In "real life", it was agreed that urinary acylcarnitines are useless because less informative than plasma/DBS, except in two conditions: 1) patients with glutaric aciduria type I, low excretors: increased excretion of glutarylcarnitine (C5DC), 2) symptomatic female carriers of 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency who do not excrete 2-methyl-3-hydroxybutyric acid: increased excretion of tiglylcarnitine (C5:1) and to a lesser extent of 2-methyl-3-hydroxybutyrylcarnitine (C5OH).

**Diagnosis / Interpretative proficiency**

| | |
|---|---|
| Most likely diagnosis | |
| Propionic acidaemia | 19 |
| 3-hydroxypropionic acidaemia | 1 |
| Alkaptonuria | 1 |
| Alternative diagnosis | |
| Disorders of biotin metabolism | 2 |
| Carbonic anhydrase 5A deficiency | 1 |

**Scoring**

- **Analytical performance**
  - Increase of at least two metabolites of propionyl-CoA metabolism (tiglylglycine, 2-methylcitric acid, 3-hydroxypropionic acid, propionylglycine, propionylcarnitine) (score 2)

- **Interpretation of results**
  - Propionic acidaemia (score 2)
  - 3-hydroxypropionic acidaemia (score 1)

Propionic acidaemia is a treatable disorder, so the SAB decided that missing this diagnosis was a critical error.

### Overall impression

The overall proficiency was 94 %

### Multiple distributions of similar samples

A similar urine sample has been distributed in 2004: the overall performance is similar.

| | 2004 | 2022 |
|---|---|---|
| **Analytical performance** | 92 % | 95 % |
| **Interpretative performance** | 100 % | 92 % |
| **Overall performance** | 97 % | 94 % |

## 8.4. Patient C

Mucopolysaccharidosis type IVA (Morquio A disease)

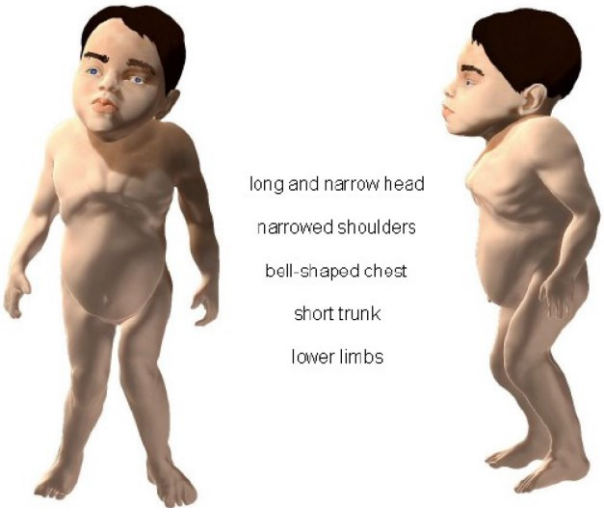
**Patient details provided to participants**

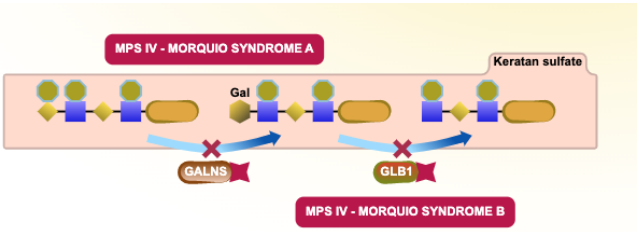
13-year-old boy, presenting with multiple epiphyseal abnormalities and vertebral platyspondyly.

**Patient details**

The patient, a boy, is born from non-consanguineous parents. From the age of 1 month, he presented with a slight hypotonia, He could walk at 1 year but with abnormal tiptoes walk. He had several otitis, and pain with ambulation from the age of 5 years. At 8 years, he had short trunk, dorsal kyphosis, and a limited walking range. X ray revealed epiphyseal dysplasia, and platyspondyly. He had hip surgery at 11 years. At 13 years, he is measuring 1.66 m, his weight is 41kg, and he presents with carinate breast, school difficulties because of frequent absences.
He was investigated at 13 years of age. Mucopolysaccharides analysis showed an increase of keratan sulphate. Galactose-6-sulfate sulfatase activity was decreased in leukocytes as well as the ratio Gal6sulf / total hexosaminidase.
The urine sample has been collected at 13 years of age.

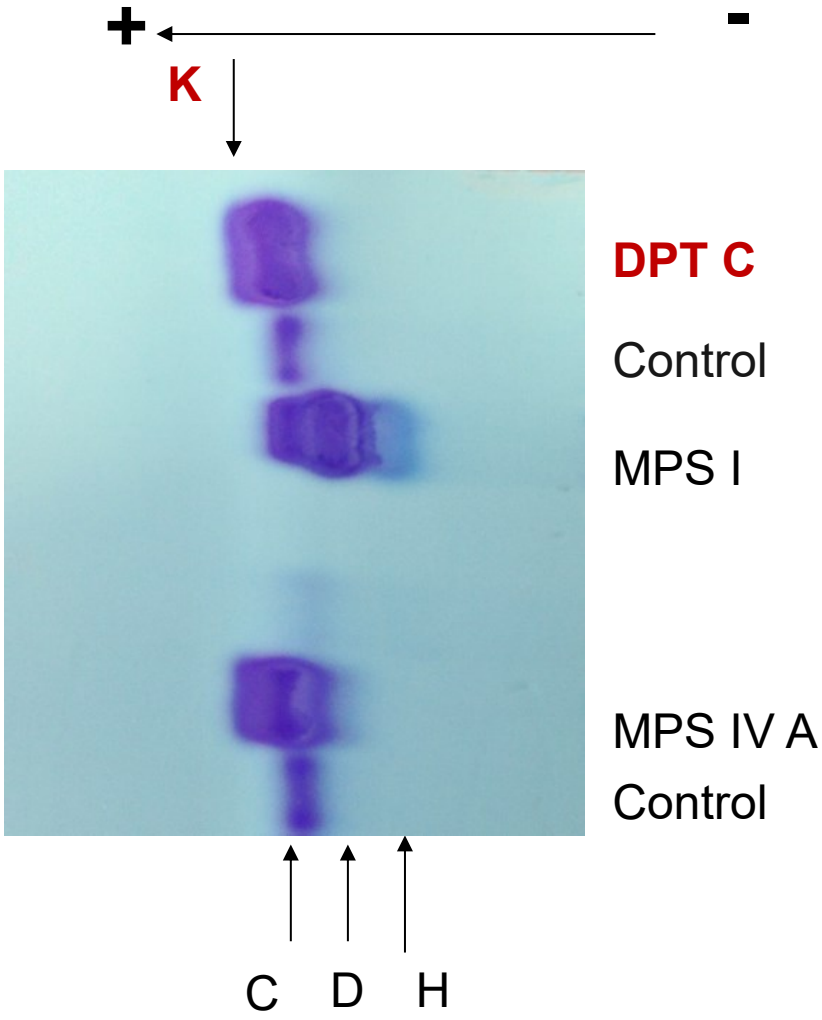
The figures below summarize the clinical presentation of Morquio A disease (from Rózdzynska-Swiatkowska et al, Diagnostics 2020;10:116) and the metabolic pathway: deficiency of galactose-6-sulfate sulfatase activity in the lysosomal degradation pathway of keratan sulphate (from https://reactome.org/PathwayBrowser/#/R-HSA-2206281)




**Analytical performance**

Seventeen out of 20 participants performed the **quantification of glycosaminoglycans**, and 13 of them reported an increased concentration. Sixteen participants performed **GAGs fractionation**: 14 reported an increase of keratan sulphate, 8 an increase of chondroitin sulphate, whereas one participant reported a normal profile. The figure below illustrates the electrophoretic pattern of GAGs fractionation of patient C.




K: keratan sulphate, C: chondroitin sulphate, D: dermatan sulphate, H: heparan sulphate

Some participants expressed their concern about the shortage of cellulose acetate plates for GAGs electrophoresis that are no longer manufactured. So far, nobody found an alternative except the development of tandem MS methods.

Ten participants performed oligosaccharides and all but one reported a normal profile.

**Diagnosis / Interpretative proficiency**

Most likely diagnosis

| | |
|---|---|
| Mucopolysaccharidosis type IV A | 9 |
| Mucopolysaccharidosis type IV | 5 |
| Mucopolysaccharidosis | 6 |

(on an increase of GAGs quantification, or clinical presentation, or another MPS)

Alternative diagnosis

| | |
|---|---|
| MPS IVB | 6 |
| MPS VII | 1 |
| Other MPS | 1 |

**Scoring**

- Analytical performance
  - Increase of keratan sulphate (score 2)
  - Increase of glycosaminoglycans quantification without fractionation (score 1)
- Interpretation of results

- Mucopolysaccharidosis type IV on analytical analysis (score 2)
- Mucopolysaccharidosis type IV on increase of GAGs and/or clinical presentation or another mucopolysaccharidosis (score 1)

**Overall impression**

The overall proficiency was excellent for a lysosomal disorder: 85 %.

**Multiple distributions of similar samples**

Two similar urine samples have been distributed in 2013 and 2016: the overall performance has improved.

| | 2013 | 2016 | 2022 |
|---|---|---|---|
| **Analytical performance** | 80 % | 79 % | 85 % |
| **Interpretative performance** | 83 % | 88 % | 85 % |
| **Overall performance** | 82 % | 83 % | 85 % |

## 8.5. Patient D

No inborn error of metabolism.

### Patient details provided to participants

70-year-old male patient presenting with muscle pain after prolonged exercise.

### Patient details

The urine sample was from the Scientific Advisor's husband after a 6 km walk in Parc de la Tête d'Or in Lyon and paracetamol intake because of back pain! But he did not take energy drinks.

### Analytical performance

All participants performed **organic acids** (21/21) and all reported that there was **no significant abnormality**, or at least metabolites of paracetamol (n=6).

All but one also performed **amino acids** (20/21) and likewise reported that there was **no significant abnormality**, or at least an increase of taurine (median = 246 mmol/mol creat, range: 122 – 414; n=8) or of glycine (median = 200 mmol/mol creat, range: 143.5 – 843; n=5).

Among the 4 labs who performed acylcarnitines, 2 reported a normal profile and 2 an increase of C4DC.

### Diagnosis / Interpretative proficiency

Most likely diagnosis

| | |
|---|---|
| No IEM | 19 |
| (no significant abnormality, rhabdomyolysis, taurine supplementation for muscle pain) | |
| SUCLA1 deficiency | 1 |
| No interpretation | 1 |

Alternative diagnosis

| | |
|---|---|
| Mitochondrial fatty acid oxidation defect | 4 |
| Myoadenylate-deaminase deficiency | 2 |
| No defect | 1 |
| Consumption of large doses of energetic drinks | 1 |

### Recommendations

The recommendation of performing CK and/or plasma / DBS acylcarnitines, or of asking for more detailed clinical information or to refer to a specialized centre was scored 1 point.

### Scoring

- Analytical performance
  - Normal metabolic investigation with at least non-significant organic acid profile and amino acid profile (or increased taurine excretion) (score 2)
- Interpretation of results
  - No indication for an inborn error of metabolism as first or alternative diagnosis (score 1)
  - Recommendation of performing CK, plasma / DBS acylcarnitines, or asking for more detailed clinical information or to refer to a specialized centre (score 1)

### Overall impression

The overall proficiency was quite satisfying: 92 %.

### Multiple distributions of similar samples

A similar urine sample has been distributed in 2017: the overall performance has improved.

| | 2017 | 2022 |
|---|---|---|
| **Analytical performance** | 84 % | 98 % |
| **Interpretative performance** | 84 % | 86 % |
| **Overall performance** | 84 % | 92 % |

## 8.6. Patient E

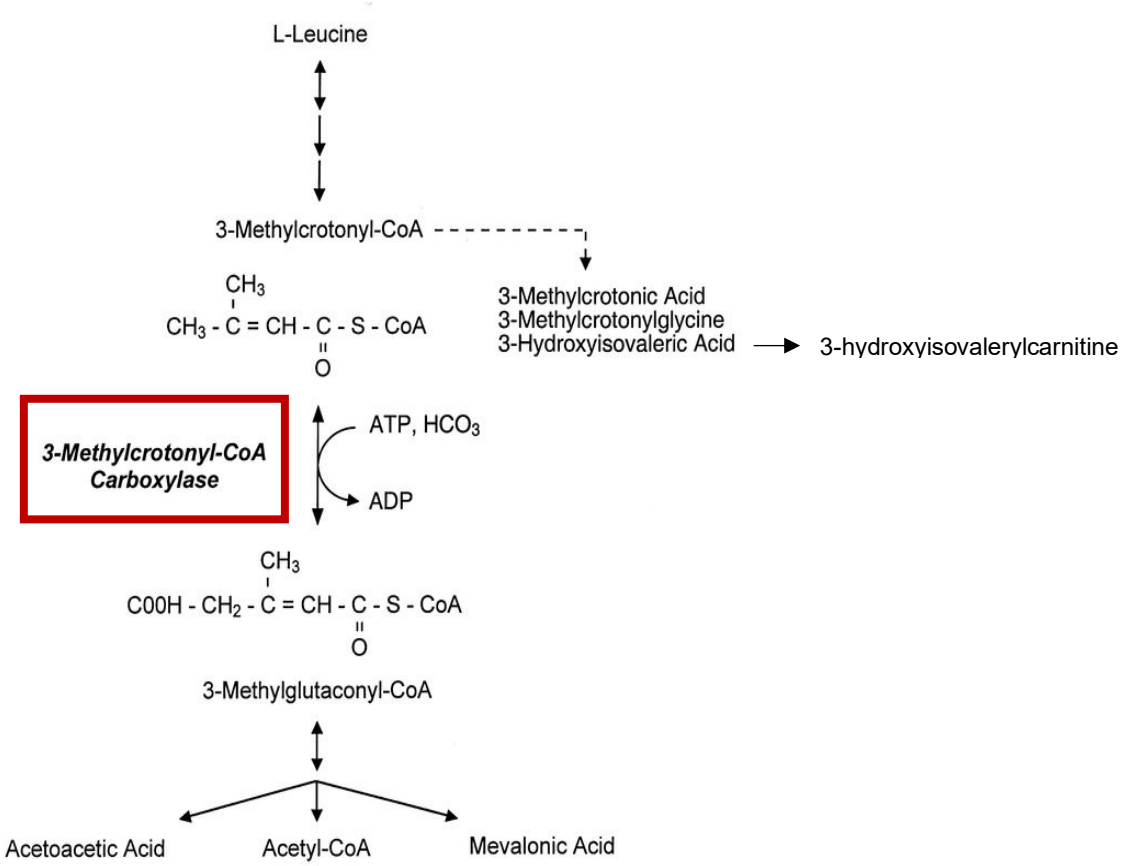
3-methylcrotonyl-CoA carboxylase deficiency (3-methylcrotonylglycinuria).

**Patient details provided to participants**

33-year-old woman. She presented at 14 and 16 months of age two episodes of hypoglycaemia with ketoacidosis in the context of febrile illness.

**Patient details**

This 33-year-old woman is born from consanguineous parents (first cousins). She presented at 14 and 16 months of age two episodes of hypoglycaemia with ketoacidosis in the context of a febrile illness. Organic acid profile exhibited ketosis and huge peaks of 3-hydroxyisovaleric acid and 3-methylcrotonylgycine. Diagnosis has been confirmed by measurement of 3-methylcrotonyl-CoA carboxylase (3MCC) activity in cultured skin fibroblasts.
She is currently receiving L-carnitine, glycine and has an almost normal protein diet (42 g/day). Her psychomotor development is normal.



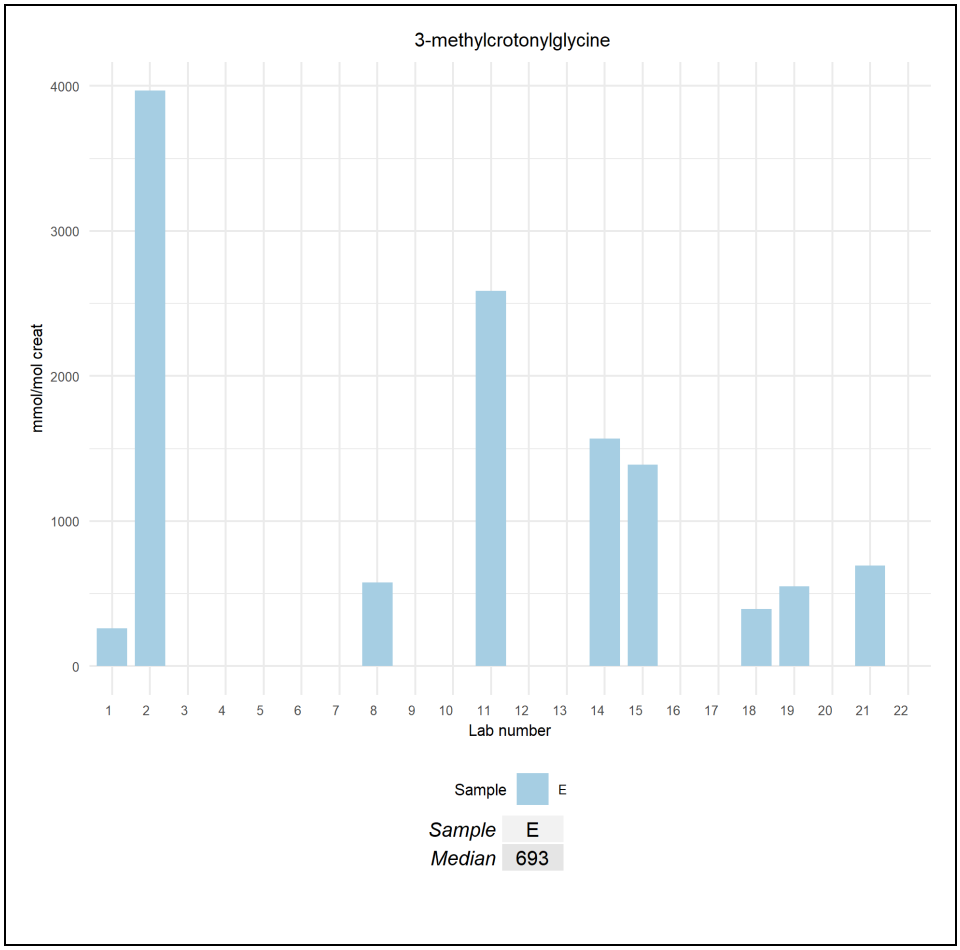

Modified from Baumgartner et al *J Clin Invest 2001;107:495*

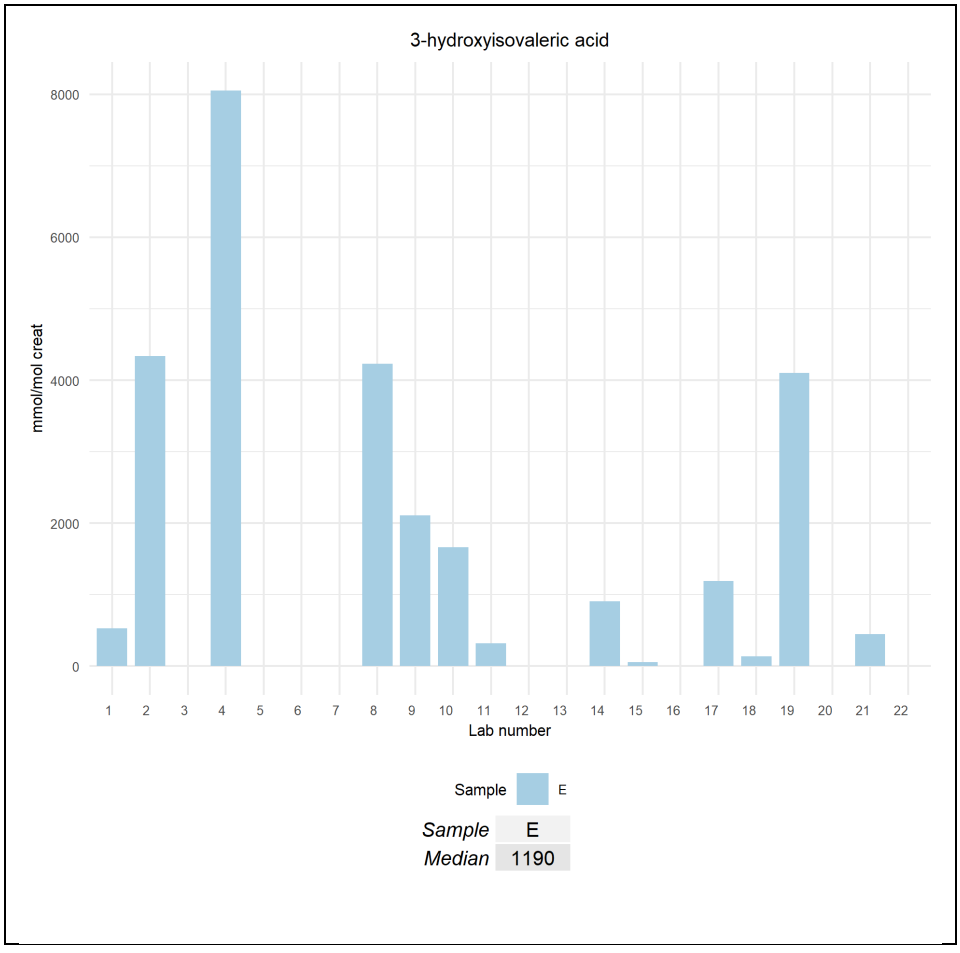
**Analytical performance**

All labs performed **organic acids** (21/21). They reported an increase of:

- **3-methylcrotonylglycine** **20**
  (median = 693 mmol/mol creatinine; range: 261 – 3968 ; n=9)
- **3-hydroxyisovaleric acid** **20**
  (median = 1190 mmol/mol creatinine; range: 55 – 8052 ; n=13)
- Isovalerylglycine 6
- Tiglylglycine 2
- Abnormal profile 1

The slight increase of isovalerylglycine and tiglylglycine can be secondary to glycine supplementation.


3-methylcrotonylglycine
mmol/mol creat
4000
3000
2000
1000
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 E
Sample E
Median 693


3-hydroxyisovaleric acid
mmol/mol creat
8000
6000
4000
2000
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 E
Sample E
Median 1190

All the 17 participants who performed amino acids (17/21) reported an increase of glycine (median = 806 mmol/mol creatinine; range: 202 – 1509 ; n=15).

**Diagnosis / Interpretative proficiency**

| | |
|---|---|
| Most likely diagnosis | |
| 3-methylcrotonyl-CoA carboxylase deficiency (3-methylcrotonylglycinuria) | 19 |
| Holocarboxylase synthetase deficiency | 1 |
| Beta-ketothiolase deficiency | 1 |
| Alternative diagnosis | |
| 3-methylcrotonyl-CoA carboxylase deficiency | 1 |
| Multiple carboxylase deficiency (Holocarboxylase synthetase and/or biotinidase) | 8 |
| Isovaleric acidaemia | 1 |

**Scoring**

- **Analytical performance**
  - Increase of 3-methylcrotonylgycine (score 1)
  - Increase of 3-hydroxyisovaleric acid (score 1)
- **Interpretation of results**
  - 3-methylcrotonyl-CoA carboxylase deficiency as first diagnosis (score 2)
  - Holocarboxylase synthetase deficiency as first diagnosis, with 3MCC deficiency as alternative diagnosis (score 1)

The SAB decided to ascribe a critical error to the lab who did not identify an increase of 3-hydroxyisovaleric acid, and misdiagnosed 3-methylcrotonylglycine as tiglylglycine.

**Overall impression**

The overall proficiency was 94%.

**Multiple distributions of similar samples**

A similar urine sample has been distributed in 2008: the overall performance was better at that time.

| | 2008 | 2022 |
|---|---|---|
| **Analytical performance** | 98 % | 95 % |
| **Interpretative performance** | 100 % | 93 % |
| **Overall performance** | 99 % | 94 % |

## 8.7. Patient F

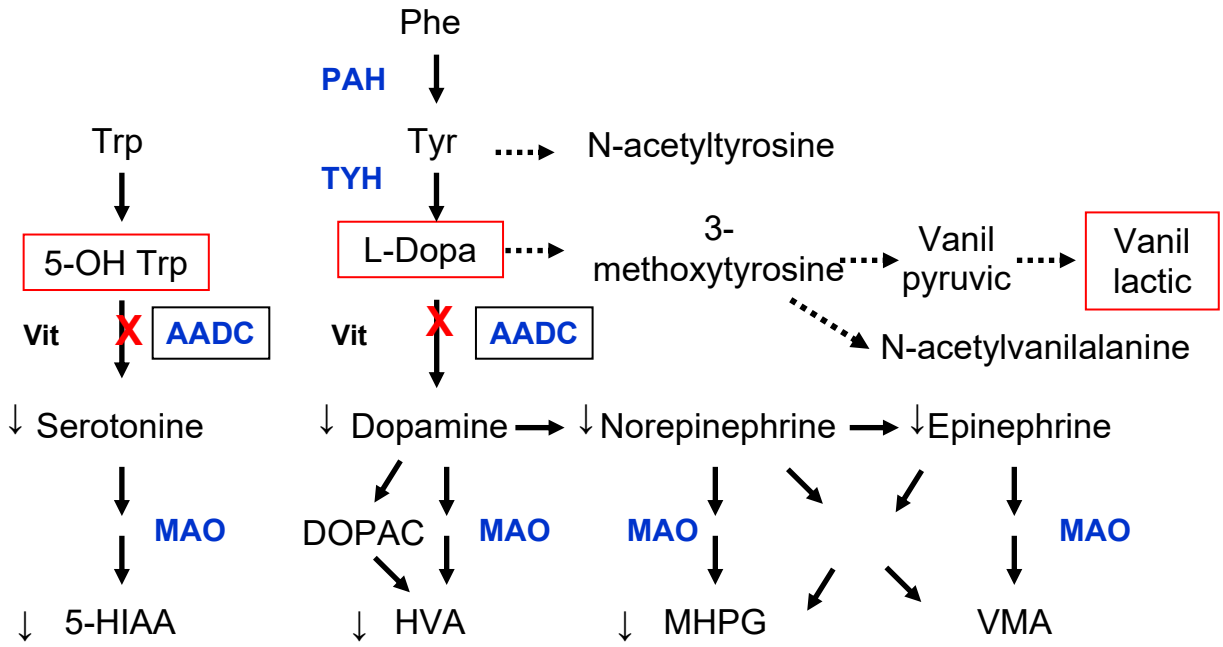
Aromatic L-aminoacid decarboxylase (AADC) deficiency

**Patient details provided to participants**

8-year-old boy with severe predominantly truncal hypotonia, intermittent dystonic posturing and oculogyric crises. On treatment during sample collection in ICU.

**Patient details**

This urine sample had been previously distributed in the QLOU scheme with a poor proficiency (59%), and considered as an educational sample. The patient is a term newborn. He presented with developmental delay noted at 2 months of age, global muscular hypotonia with dystonic movements and oculogyric crises. At the age of six months, neurotransmitter analysis in CSF showed significantly increased concentrations of 3-methoxytyrosine (3-*O*-methyldopa), L-DOPA and 5-hydroxytryptophane, contrasting with reduced concentrations of homovanillic acid and 5-hydroxyindoleacetic acid. Pterins were normal. Diagnosis was confirmed by enzyme analysis of aromatic L-amino acid decarboxylase (AADC) activity. The urine sample was collected at the age of eight years while the patient was in intensive care unit.



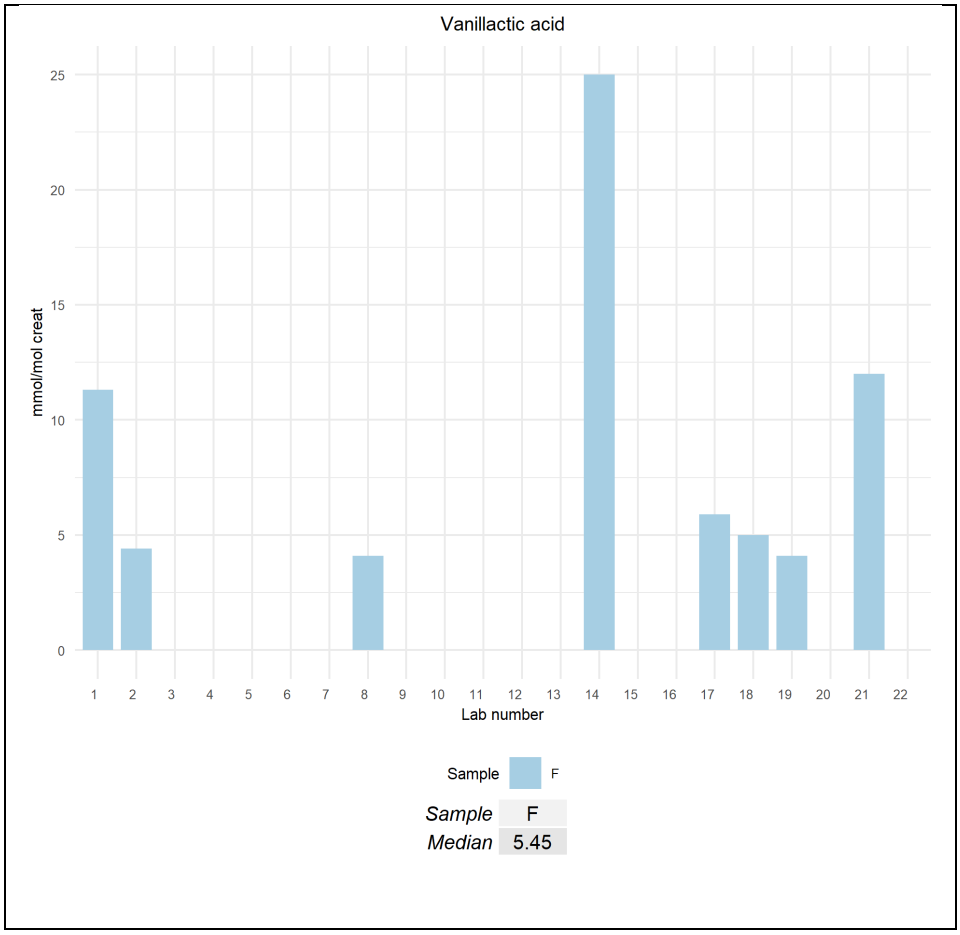

Aromatic L-amino acid decarboxylase is implicated in the synthesis of catecholamines. It requires pyridoxal phosphate as a cofactor. Affected patients usually develop, from the age of 4 months to adulthood, truncal hypotonia associated with limb rigidity, oculogyric crises, developmental delay, dystonia, autonomic dysfunction (temperature instability, paroxysmal sweating, …). These clinical signs are due to the deficiency of catecholamines and serotonine. The biochemical diagnostic is assessed by measurement of CSF neurotransmitters which shows: ↑5-OH Trp, L-DOPA, ↓ HVA, 5HIAA. Urinary organic acids can orientate towards the diagnosis by the identification of increased vanillactic acid, vanilpyruvic acid, N-acetyltyrosine, and N-acetylvanilalanine (Abdenur et al, Mol Genet Metab 2006; 87:48). However, an increase of vanillactic acid can also be observed in PNPO (pyridoxamine 5'-phosphate oxidase) deficiency, in patients receiving L-DOPA treatment or can be slightly increased in urines from newborn. In urine, 5-hydroxytryptophane and L-DOPA are increased (possibly measured in the amino acid profile using tandem MS). Plasma prolactin levels can be elevated in AADC deficiency, but it is non nonspecific since it is also present in tyrosine hydroxylase deficiency.

**Analytical performance**

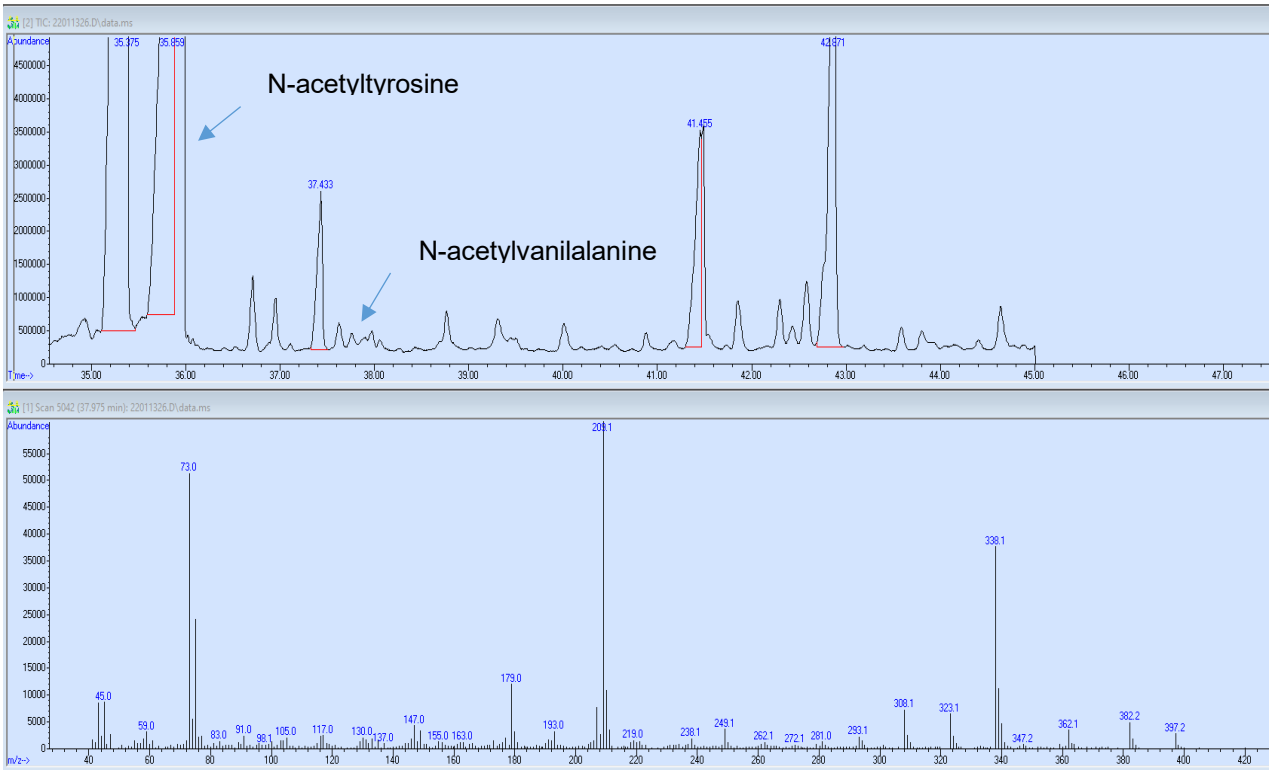
All labs performed **organic acids** (21/21), and identified an increase of:

- Vanillactic acid 20
  (median = 5.45 mmol/mol creatinine; range: 4.1 – 25.0 ; n=8)
- N-acetyltyrosine 12
  (556 ; 1000 mmol/mol creatinine ; n=2)

- N-acetylvanilalanine 3
- Vanilpyruvic 0
- Normal profile 1




N-acetylvanilalanine is eluted approximately 2 minutes later than N-acetyltyrosine. Its spectrum is given in the figure below.



Seventeen participants performed **amino acids** (17/21), and reported an increase of glycine (median = 1096 mmol/mol creatinine; range: 415 – 2624 ; n=11), serine (median = 652 mmol/mol creatinine; range: 278 – 757 ; n=9), and tyrosine (median = 135 mmol/mol creatinine; range: 97 – 155 ; n=8). One participant reported a significant increase of tryptophane.

### Diagnosis / Interpretative proficiency

| | |
|---|---|
| Most likely diagnosis | |
| **AADC deficiency** | **19** |
| Not sure diagnosis, analyse CSF neurotransmitters | 1 |
| Pyruvate dehydrogenase deficiency (E3) | 1 |
| Alternative diagnosis | |
| PNPO deficiency | 7 |
| Tyrosine hydroxylase deficiency treated with L-DOPA and L-DOPA decarboxylase inhibitor | 1 |
| Other defect in biopterin metabolism | 1 |
| Intermediate or intermittent MSUD | 1 |

### Recommendations

The recommendation to perform neurotransmitters analysis in CSF was scored one point.

### Scoring

- **Analytical performance**
  - Increase of vanillactic (score 1)
  - Increase of N-acetyltyrosine, or N-acetylvanilalanine or vanilpyruvic acid (score 1)

- **Interpretation of results**
  - Aromatic L-amino acid decarboxylase deficiency as first or alternative diagnosis (score 2)
  - Recommendation to perform neurotransmitters analysis in CSF (score 1)

All participants but one identified vanillactic in the urine sample. Therefore, the SAB considered that to miss the identification of this compound was a critical error.

### Overall impression

The overall proficiency was 88%.

### Multiple distributions of similar samples

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

| | 2006 | 2022 |
|---|---|---|
| **Analytical performance** | 58 % | 81 % |
| **Interpretative performance** | 68 % | 93 % |
| **Overall performance** | 65 % | 87 % |

## 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<br>Barth syndrome | | | Patient B<br>Propionic acidaemia due to propionyl-CoA carboxylase deficiency | | | Patient C<br>MPS IVA | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 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 | 1 | 3 | 2 | 2 | 4 | 1 | 1 | 2 | 9 |
| **5** | 0 | 0 | 0 | 2 | 2 | 4 | 2 | 2 | 4 | 8 |
| **6** | 2 | 2 | 4 | 2 | 2 | 4 | 2 | 2 | 4 | 12 |
| **7** | 2 | 2 | 4 | 2 | 2 | 4 | 1 | 1 | 2 | 10 |
| **8** | 2 | 2 | 4 | 2 | 2 | 4 | 2 | 2 | 4 | 12 |
| **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 | 1 | 1 | 2 | 10 |
| **13** | 2 | 2 | 4 | 2 | 2 | 4 | 2 | 2 | 4 | 12 |
| **14** | 2 | 2 | 4 | 2 | 2 | 4 | 1 | 1 | 2 | 10 |
| **15** | 2 | 2 | 4 | 2 | 2 | 4 | 1 | 1 | 2 | 10 |
| **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 | 2 | 4 | 12 |
| **19** | 2 | 2 | 4 | 2 | 2 | 4 | 2 | 2 | 4 | 12 |
| **20** | 2 | 2 | 4 | 2 | 1 | 3 | 2 | 2 | 4 | 11 |
| **21** | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 4 | 4 |

## Detailed scores – Round 2

| Lab n° | Patient D<br>No IEM | | | Patient E<br>3MCC deficiency | | | Patient F<br>AADC deficiency. | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 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 | 2 | 3 | 11 |
| **3** | 2 | 1 | 3 | 2 | 1 | 3 | 1 | 2 | 3 | 9 |
| **4** | 2 | 2 | 4 | 2 | 2 | 4 | 2 | 2 | 4 | 12 |
| **5** | 2 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| **6** | 1 | 2 | 3 | 2 | 2 | 4 | 2 | 2 | 4 | 11 |
| **7** | 2 | 2 | 4 | 2 | 2 | 4 | 1 | 2 | 3 | 11 |
| **8** | 2 | 2 | 4 | 2 | 2 | 4 | 1 | 2 | 3 | 11 |
| **9** | 2 | 2 | 4 | 2 | 2 | 4 | 2 | 2 | 4 | 12 |
| **10** | 2 | 1 | 3 | 2 | 2 | 4 | 2 | 2 | 4 | 11 |
| **11** | 2 | 1 | 3 | 2 | 2 | 4 | 2 | 2 | 4 | 11 |
| **12** | 2 | 2 | 4 | 2 | 2 | 4 | 2 | 2 | 4 | 12 |
| **13** | 2 | 2 | 4 | 2 | 2 | 4 | 2 | 2 | 4 | 12 |
| **14** | 2 | 0 | 2 | 2 | 2 | 4 | 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** | 2 | 2 | 4 | 2 | 2 | 4 | 2 | 2 | 4 | 12 |
| **19** | 2 | 2 | 4 | 2 | 2 | 4 | 1 | 2 | 3 | 11 |
| **20** | 2 | 2 | 4 | 2 | 2 | 4 | 2 | 1 | 3 | 11 |
| **21** | 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 | 4 | 4 | 4 | 24 | 100 | |
| **2** | 4 | 4 | 4 | 4 | 4 | 3 | 23 | 96 | |
| **3** | 4 | 4 | 4 | 3 | 3 | 3 | 21 | 88 | |
| **4** | 3 | 4 | 2 | 4 | 4 | 4 | 21 | 88 | |
| **5** | 0 | 4 | 4 | 3 | 0 | 0 | 11 | 46 | CE |
| **6** | 4 | 4 | 4 | 3 | 4 | 4 | 23 | 96 | |
| **7** | 4 | 4 | 2 | 4 | 4 | 3 | 21 | 88 | |
| **8** | 4 | 4 | 4 | 4 | 4 | 3 | 23 | 96 | |
| **9** | 4 | 4 | 4 | 4 | 4 | 4 | 24 | 100 | |
| **10** | -- | -- | -- | 3 | 4 | 4 | 11 | 46 | |
| **11** | 4 | 4 | 4 | 3 | 4 | 4 | 23 | 96 | |
| **12** | 4 | 4 | 2 | 4 | 4 | 4 | 22 | 92 | |
| **13** | 4 | 4 | 4 | 4 | 4 | 4 | 24 | 100 | |
| **14** | 4 | 4 | 2 | 2 | 4 | 4 | 20 | 83 | |
| **15** | 4 | 4 | 2 | 4 | 4 | 4 | 22 | 92 | |
| **16** | 4 | 4 | 4 | 4 | 4 | 4 | 24 | 100 | |
| **17** | 4 | 4 | 2 | 4 | 4 | 4 | 22 | 92 | |
| **18** | 4 | 4 | 4 | 4 | 4 | 4 | 24 | 100 | |
| **19** | 4 | 4 | 4 | 4 | 4 | 3 | 23 | 96 | |
| **20** | 4 | 3 | 4 | 4 | 4 | 3 | 22 | 92 | |
| **21** | 0 | 0 | 4 | 4 | 4 | 4 | 16 | 67 | CE |

**Performance**

| | Number of labs | % total labs |
|---|---|---|
| **Satisfactory performers (≥ 60 % of adequate responses)** | 18 | 86 |
| **Unsatisfactory performers (< 60 % adequate responses and/or critical error)** | 2 | 10 |
| **Partial and non-submitters** | 1 | 5 |

**Overall Proficiency**

| Sample | Diagnosis | Analytical (%) | Interpretation (%) | Total (%) |
|---|---|---|---|---|
| **DPT-FL-2022-A** | Barth syndrome | 90 | 88 | 89 |
| **DPT-FL-2022-B** | Propionic acidaemia due to propionyl-CoA carboxylase deficiency | 95 | 93 | 94 |
| **DPT-FL-2022-C** | MPS IVA | 85 | 85 | 85 |
| **DPT-FL-2022-D** | No IEM | 98 | 86 | 92 |
| **DPT-FL-2022-E** | 3MCC deficiency | 95 | 93 | 94 |
| **DPT-FL-2022-F** | AADC deficiency. | 83 | 93 | 88 |

## 10. Annual meeting of participants

This took place in Freiburg on August 30th 2022 from 9.00 to 10.30, before the SSIEM Meeting.

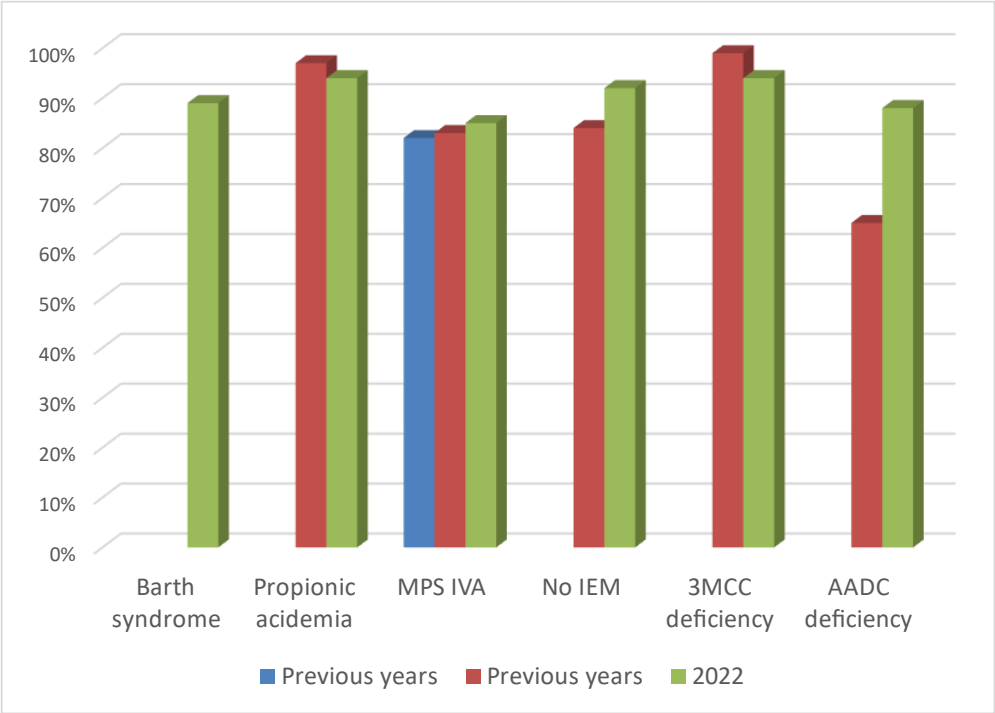
## Participants

Representatives from 10 labs were present: Maria Unceta (Bilbao), Judit Garcia (Hosp. Clinic, Barcelona), Jose Antonio Arranz (Vall d'Hebron, Barcelona), Silvia Funghini, Sabrina Malvaglia (Florence), Christelle Corne (Grenoble), Olivier Boulat, Clothilde Roux (Lausanne), Apolline Imbard, Clément Pontoizeau (Paris), Dulce Quelhas (Porto), Cristobal Colon (Santiago de Compostella), Cristiano Rizzo (Rome).

Interestingly, all participants to this meeting are using the organic acid standards developed by Amsterdam UMC.

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.

**Improvement of DPT France 2022**




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

- **Scoring policy for DPT scheme in 2023**: 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 SKML: 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 24th and 25th April 2023 in Manchester. The topics will be:
    - Organic acidaemias
    - Fatty acid oxidation defects
    - Metabolic cardiomyopathies
  - 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. Annex 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
- Purines / 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 enter the results on the website, as if the assay had been performed by your lab.
Please send quantitative data for amino acids and, as much as possible, for organic acids.

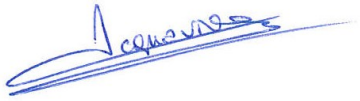
## 13. Tentative schedule and fee in 2023

| | |
|---|---|
| Sample distribution | 8 February 2023 |
| Start of analysis of Survey 2023/1 Website open | March 13 |
| Survey 2023/1 - Results submission | April 3 |
| Survey 2023/1 - Reports | May |
| Start of analysis of Survey 2023/2 | June 5 |
| Survey 2023/2 – Results submission | June 26 |
| Survey 2023/2 - Reports | July |
| Annual meeting of participants | August 29 Jerusalem SSIEM |
| Annual Report 2023 | 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.

Date of report, 2023-01-19



Christine Vianey-Saban Cécile Acquaviva

C. VIANEY-SABAN, C. ACQUAVIVA-BOURDAIN
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France
Tel +33 4 72 12 96 914
e-mail
christine.vianeysaban@gmail.com
cecile.acquaviva-bourdain@chu-lyon.fr

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

| Version Number | Published | Amendments |
|---|---|---|
| 1 | 20 January 2023 | 2022 annual report published |
| | | |
| | | |

**ANNEX 2**

***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 | MCC 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 |

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|---|---|---|
| | 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 |

**END**