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Diagnostic Proficiency Testing

Centre: France

Final Report 2024

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 the ERNDIM Privacy Policy on www.erndim.org.

1. Geographical distribution of participants

In 2024, 21 labs registered to DPT France. One lab withdrawn registration. Finally, 20 labs submitted results for the 2 surveys.

Country	Number of participants
France	8
Italy	5
Netherlands	1
Portugal	2
Spain	5

[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.

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 and Nicola Braik (erndim.survey@cscq.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: all urine samples have been provided by the scheme organizers, by Dr Déborah Mathis (DPT-Switzerland), and by Dr José Antonio Arranz (Barcelona).

Patient A: Malonyl-CoA decarboxylase deficiency
Patient B: L-2-hydroxyglutaric aciduria
Patient C: Citrullinaemia type I
Patient D: Adenylosuccinate lyase (ADSL) deficiency (ADSL gene).
Patient E: No IEM
Patient F: Multiple acyl-CoA dehydrogenase deficiency (MADD) due to ETF deficiency (ETFA gene)

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 7 — Shipment of samples of Survey 1 and Survey 2 by CSCQ
- March 12 — Clinical data available on CSCQ website and start analysis of samples A, B, C (Survey 1)
- March 26 — Reminder for website submission
- April 2 — Deadline for result submission (Survey 1)
- May 8 — Interim report of Survey 1 available on CSCQ website (sent to CSCQ by SA on May 2)
- June 3 — Clinical data available on the CSCQ website and start analysis of samples D, E, F (Survey 2)
- June 17 — Reminder for website submission
- July 1 — Deadline for result submission (Survey 2). Extension of the deadline by one week due to a maintenance of the CSCQ website
- August 6 — Interim report of Survey 2 available on CSCQ website (sent to CSCQ by SA on August 3)
- September 3 — Meeting of participants in Porto during the SSIEM Symposium
- November 29 — SAB meeting: definition of critical errors
- December 2024 — Annual Report with definitive scoring

5. Results

One lab withdrawn registration.

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

6. Web site reporting

The website reporting system is compulsory for all centres. Please read carefully the following advice:

- Selection of tests: **don't select a test if you will not perform it**, otherwise the evaluation program includes it in the report.
- Results
  - Give quantitative data as much as possible.
  - Enter the key metabolites with the evaluation **in the tables** even if you don't give quantitative data.
  - If the profile is normal: enter "Normal profile" in "Key metabolites".
  - **Don't enter results in the "comments" window**, otherwise your results will not be included in the evaluation program.
- Recommendations = **advice for further investigation**.
  - Scored together with the interpretative score.
  - Advice for treatment are 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 2024 have been also scored by Dr Petr Chrastina from DPT Czech Republic. At the SAB meeting in Leiden on November 29th, 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 2024, 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 2024. 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.

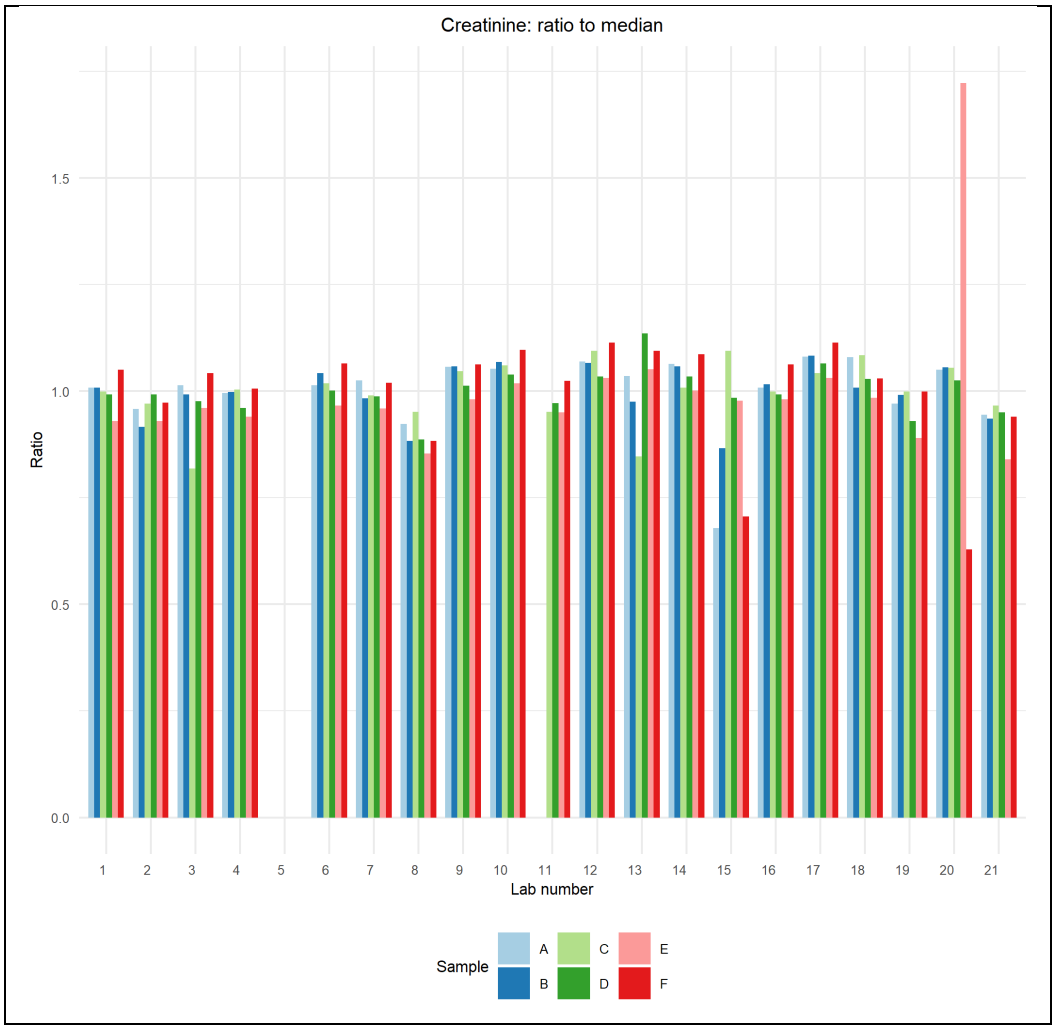
8. Results of samples and evaluation of reporting

8.1. Creatinine measurement for all samples

After exclusion of two wrong values, the CV for creatinine determination ranged from 5.3 % (sample D and F) to 9.2 % (sample F), which is satisfying. It is comparable to the interlab CV 2023 for Special Assays in Urine (5.9 %, n = 134).

The median values for creatinine determination were:
- Sample A: 8.25 mmol/L
- Sample B: 12.04 mmol/L
- Sample C: 2.10 mmol/L
- Sample D: 9.50 mmol/L
- Sample E: 9.60 mmol/L
- Sample F: 16.3 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
Ratio
1.5
1.0
0.5
0.0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
Lab number
Sample
A
B
C
D
E
F

8.2. Patient A

Malonic aciduria due to malonyl-CoA decarboxylase deficiency (MLYCD gene)

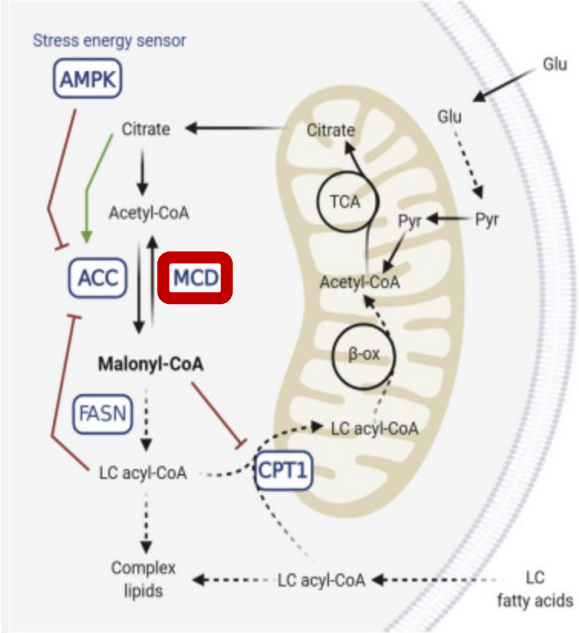
Patient details provided to participants

Diagnosed by family screening after sudden infant death of brother at 5 months of age in the context of an intercurrent viral infection. Dilated cardiomyopathy, normal development.

Patient details

The diagnosis of malonyl-CoA decarboxylase deficiency has been confirmed genetically in this 3-year old boy. Results from all labs participating to DPT has be presented during the ERNDIM meeting in Porto and are available on the ERNDIM website.

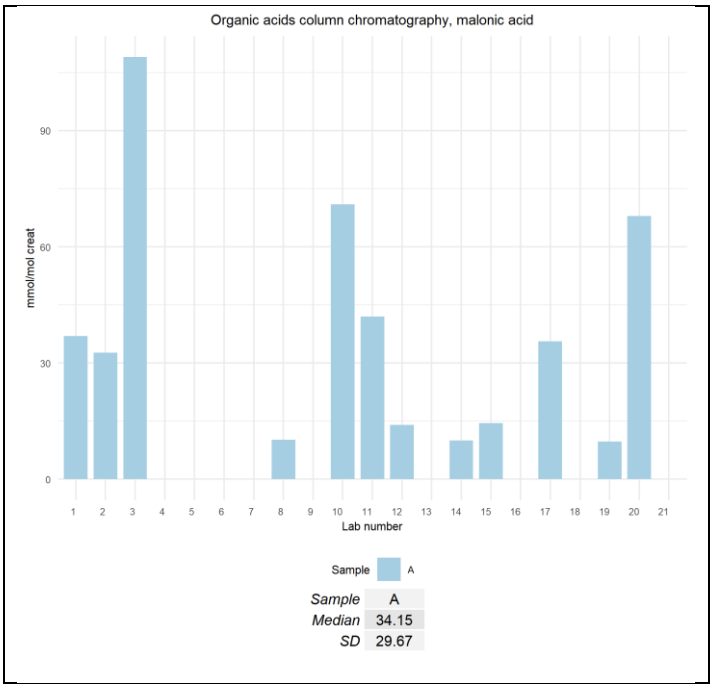
Malonic aciduria is a rare autosomal recessive inborn error of metabolism, due to malonyl-CoA decarboxylase deficiency (*MLYCD* gene) (OMIM # 248360). It can present in the neonatal period with progressive lethargy, hypotonia, hepatomegaly, metabolic acidosis, mild hyperammonaemia, sometimes associated with hypoglycaemia and hyperlactataemia. Cardiac failure due to cardiomyopathy can be present at birth. In the late-onset form, patients present with acute metabolic episodes secondary to infections, or non-specific psychomotor retardation. Cardiomyopathy is present in 40% of patients. The prognosis is variable, but the disease can be lethal in the neonatal period.
Malonyl-CoA decarboxylase is a cytosolic enzyme which regulates cytoplasmic malonyl-CoA concentration. Malonyl-CoA inhibits CPT I that is why the phenotype of patients is similar to FAOD but with a normal ketogenesis.

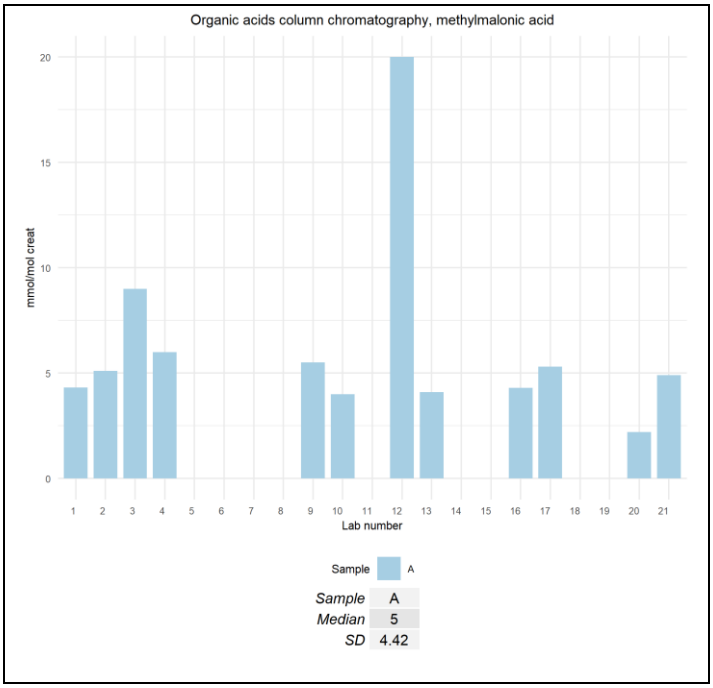


From Fadó R, Rodríguez-Rodríguez R, Casals N. Prog Lipid Res. 2021;81:101071

Analytical performance

All participants performed **organic acids analysis** (20/20) and all reported an increase in **malonic acid** excretion (median = 37.8 mmol/mol creatinine; range: 9.7 – 109 ; n = 12). Thirteen labs reported that methylmalonic acid excretion was normal (median = 6.22 mmol/mol creatinine; range: 2.2 – 20 ; n = 11), whereas one participant reported an increased excretion (4.31 mmol/mol creatinine) and concluded to combined methylmalonic and malonic aciduria (CMAMMA).





An increase in **C3DC-carnitine** was reported by the 9 participants (median = 4.07 mmol/mol creatinine; range: 0.30 – 13.34 ; n = 8) who performed **acylcarnitines** (9/20). Some of them are performing FIA-MS/MS without derivatisation and therefore measure the sum C3DC + C4OH: this probably explains the wide range of results.

Among the 17 labs who performed amino acids (17/20), 12 reported an increase in glycine (median = 369 mmol/mol creatinine; range : 260 – 369 ; n = 12), and 5 no significant abnormality.

Diagnosis / Interpretative proficiency

Most likely diagnosis

Malonic aciduria (malonyl-CoA decarboxylase deficiency)	19
Combined methylmalonic and malonic aciduria	1

Alternative diagnosis

Combined methylmalonic and malonic aciduria 2

Scoring

- **Analytical performance**
  - Increase in malonic acid or malonylcarnitine (score 2)

- **Interpretation of results**
  - Malonic aciduria as main diagnosis (score 2)
  - CMAMMA as main diagnosis (score 1)

- **Critical error:** failure to report malonic acid. Number of occurrences: 0

Overall impression

The overall proficiency (based on scores) was excellent: 99%

8.3. Patient B

L-2-hydroxyglutaric aciduria due to L-2-hydroxyglutarate dehydrogenase deficiency (L2HGDH gene)

Patient details provided to participants

Discovery of leukodystrophy during an MRI performed at 3 years of age following accidental head trauma. Psychomotor delay at 13 years old.

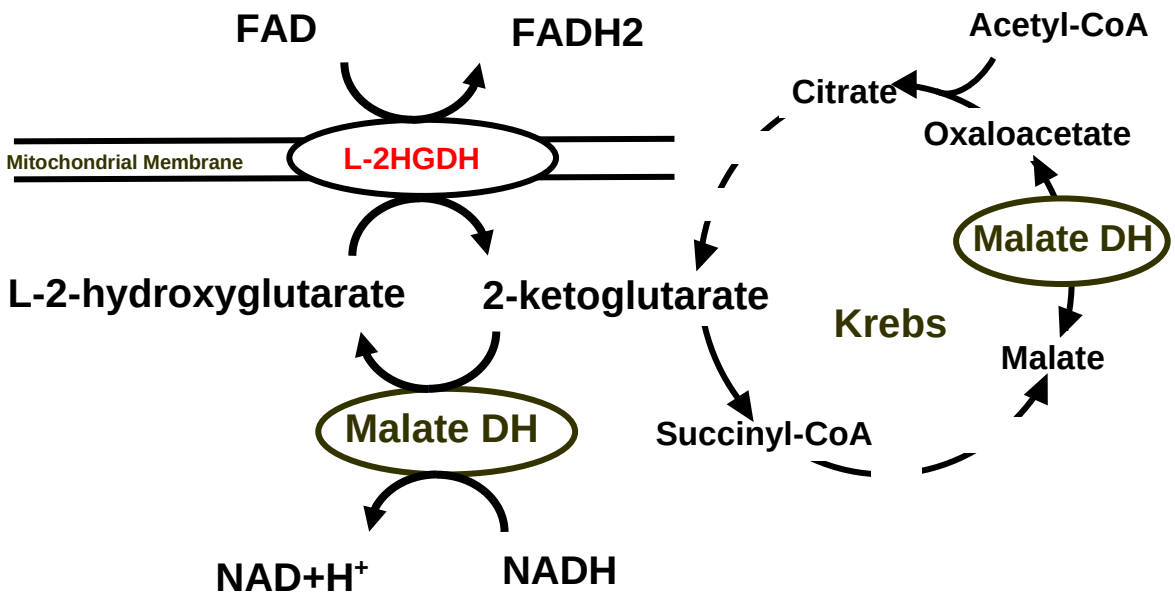
Patient details

This 13-year-old male patient is the 3rd child of consanguineous parents. At 3 years of age, he suffered hyperthermia with oral and labial vesicular eruption and left parietal cranial trauma from a fall on a table corner. He was hospitalized for drowsiness. The CT-scan showed a pathological appearance of supratentorial white matter without hemorrhage. MRI confirmed leukodystrophy with T2 hypersignal of subcortical white matter, putamen, caudate nuclei and dentate nuclei suggestive of an IEM. Biochemical investigation revealed a herpes infection (herpes PCR positive) and urinary organic acids, an increase in 2-hydroxyglutaric acid excretion. At 13 years of age, he is mentally retarded but can speak slowly. He has spasticity with steppage when walking, without clear cerebellar syndrome. Diagnosis of L-2-hydroxyglutaric aciduria (OMIM # 238792) has been confirmed by mutation analysis of *L2HGDH* gene.

Affected patients present with a characteristic disease course: in infancy and early childhood, the mental and psychomotor development appears normal or only slightly retarded. Thereafter seizures, progressive ataxia, pyramidal tract signs, slight extrapyramidal signs and progressive mental retardation become the most obvious clinical findings. Progressive macrocephaly is present in about half of the patients. The IQ in teenagers is about 40–50. The neuroimaging findings are very specific. In some patients, different types of malignant brain tumours, such as medulloblastoma, glioblastoma multiforme, astrocytoma, and primitive neuroectodermal tumour, have been reported.

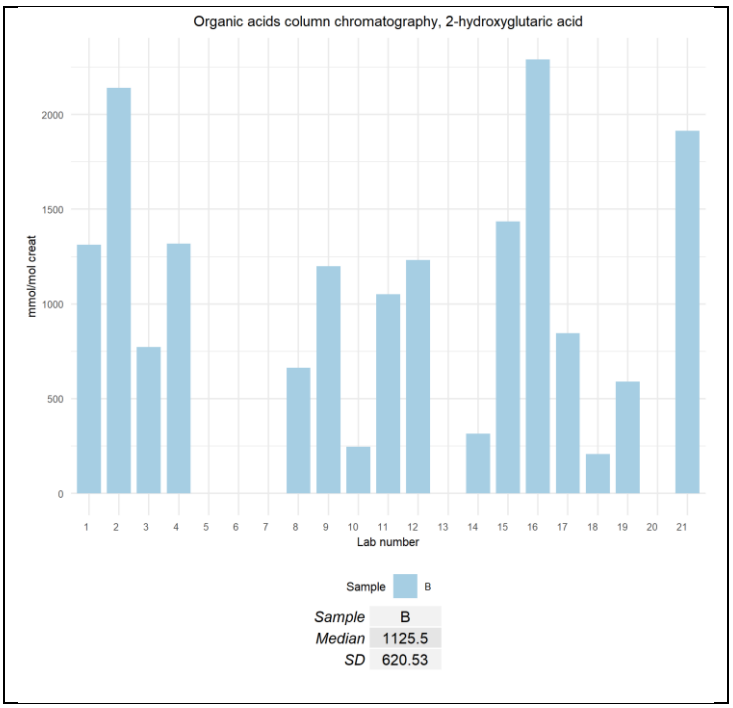
L-2-hydroxyglutaric aciduria is due to L-2-hydroglutarate dehydrogenase deficiency, a membrane bound FAD dependent enzyme (inner mitochondrial membrane) which catalyses the dehydrogenation of L-2-hydroxyglutarate into 2-ketoglutarate (*L2HGDH* gene). It had been demonstrated that urinary excretion of L-2-hydroxyglutaric acid (L2OHGA) was independent of feeding and came exclusively from endogenous production (muscle: 75%, liver: 25%).The toxicity of L-2-hydroxyglutaric (L2OHGA) is due to its excitoxic effect (increases uptake of glutamate), the oxidation of lipids and proteins (mainly in cerebellum), the reduction of brain capacity to regulate the production of free radicals. But no inhibitory effect on the mitochondrial respiratory chain have been identified. These effects are emphasized by the low permeability of blood brain barrier (BBB) to this compound (dicarboxylic acid). In 2007, Rzem et al (J Inher Metab Dis 2007;30:681) demonstrated that the production of L2OHGA has no metabolic function, but is due to the lack of specificity of malate dehydrogenase. Degradation of L2OHGA by L-2-

hydroxyglutarate dehydrogenase is a repair mechanism, and therefore this enzyme belongs to the group of « house-cleaning » enzymes.



Analytical performance

All participants identified an increase in **2-hydroxyglutaric acid** (20/20) (median = 1125.5 mmol/mol creatinine; range : 208 – 2290 ; n = 16), and 13 of them mentioned an increase in **2-hydroxyglutaric lactone.**



Among the 14 labs who performed amino acids (14/20), 11 reported no significant abnormality, and 3 an increase in lysine.

Diagnosis / Interpretative proficiency

Most likely diagnosis *

L-2-hydroxyglutaric aciduria	16
D-2-hydroxyglutaric aciduria	5
L&D-2-hydroxyglutaric aciduria	2
2-hydroxyglutaric aciduria	2
L- or D-2-hydroxyglutaric aciduria	1

Alternative diagnosis *

D-2-hydroxyglutaric aciduria	14
L&D-2-hydroxyglutaric aciduria	10

* Some participants proposed more than 1 diagnosis

Scoring

- **Analytical performance**
  - Increase in 2-hydroxyglutaric (score 2)

- **Interpretation of results**
  - L-2-hydroxyglutaric aciduria based on clinical presentation or on chiral identification of the enantiomer (score 2)
  - D-2-hydroxyglutaric aciduria as only diagnosis (score 1)

- **Critical error:** failure to report 2-hydroxyglutaric acid. Number of occurrences: 0

Overall impression

The overall proficiency was 99 %.

Multiple distributions of similar samples

Two similar urine samples have been distributed in 2008 and 2014: the overall performance was similar.

	2008	2014	**2024**
Analytical performance	**100 %**	**100 %**	100 %
Interpretative performance	**100 %**	**100 %**	98 %
Overall performance	**100 %**	**100 %**	99 %

8.4. Patient C

Citrullinaemia type I due to argininosuccinate synthetase deficiency (ASS1 gene)

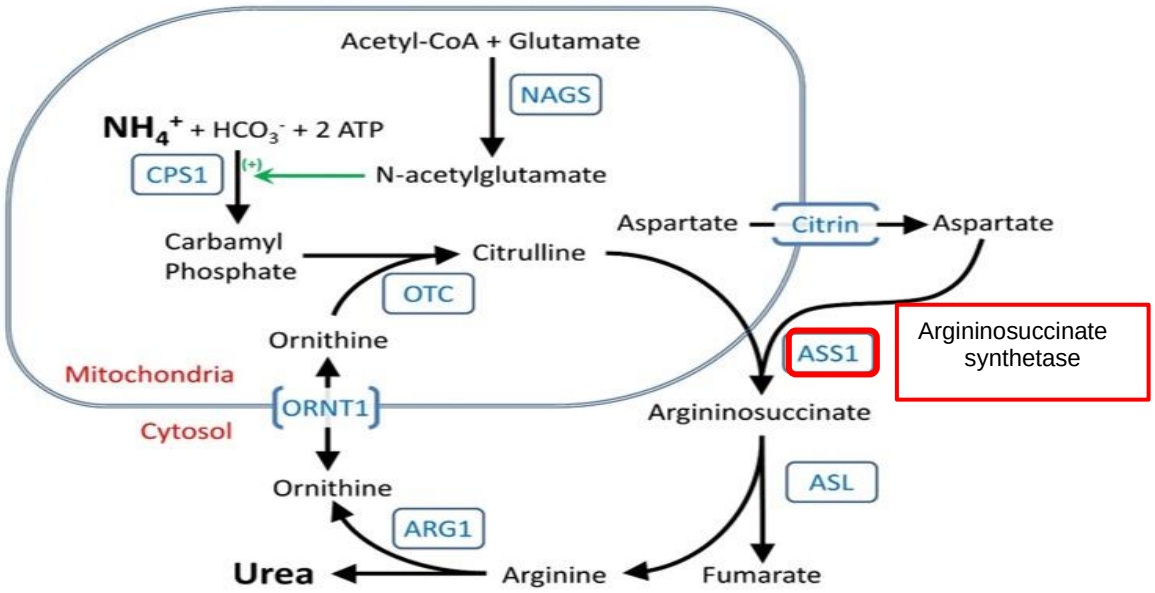
Patient details provided to participants

This girl presented at 2 days of life with clonic movements and respiratory distress. Blood ammonia was 1000 mmol/L. The urine sample was collected at age 23, under treatment.

Patient details

This 23-year-old lady, is the first child of non-consanguineous parents, born after a normal pregnancy and delivery. At 48 hours of life, she presented clonic movements of upper limbs and poor feeding. On day 3, she had an episode of respiratory distress with whining and hemicorporeal clonia. She was transferred to the intensive care unit of a peripheral hospital. Ammonaemia was 1000 µmol/L, and went up to 2000 µmol/L. She had 3 exchange transfusions, IV arginine, oral sodium benzoate, and gardenal. Transfontanelle ultrasonography showed cerebral oedema. On day 5, she was transferred to intensive care unit. She had axial hypotonia, peripheral hypertonia, and no reaction to stimuli. She received glucido-lipidic enteral feeding, hyperglucidic parenteral feeding, and oral phenylbutyrate. Ammonaemia normalized, and her neurological status progressively improved. She was discharged from hospital on day 11 with hypoprotidic diet, oral arginine and sodium benzoate. Diagnosis was confirmed by mutation analysis of *ASS1* gene (OMIM # 215700). At 23 years of age, she

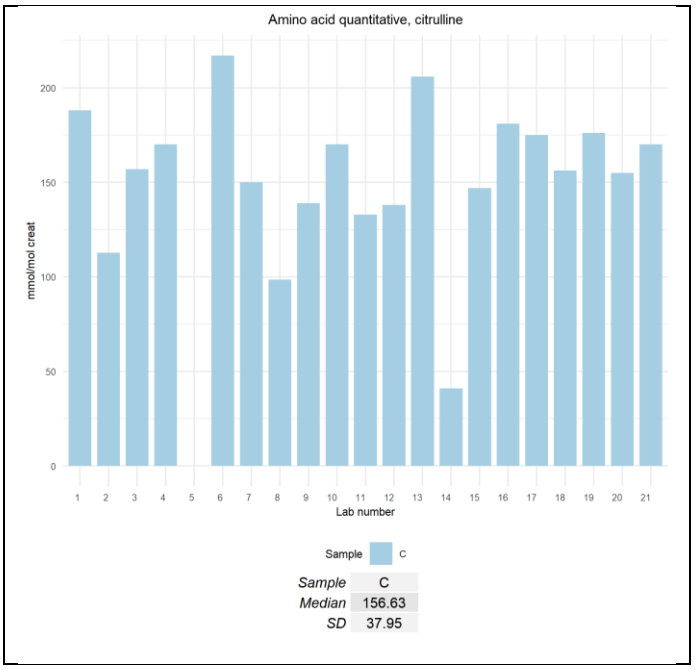
has mental retardation. She lives in a structure for disabled people but can prepare meals. Her treatment is hypoprotidic diet, oral arginine, sodium phenylbutyrate and benzoate.



GeneReviews® Internet

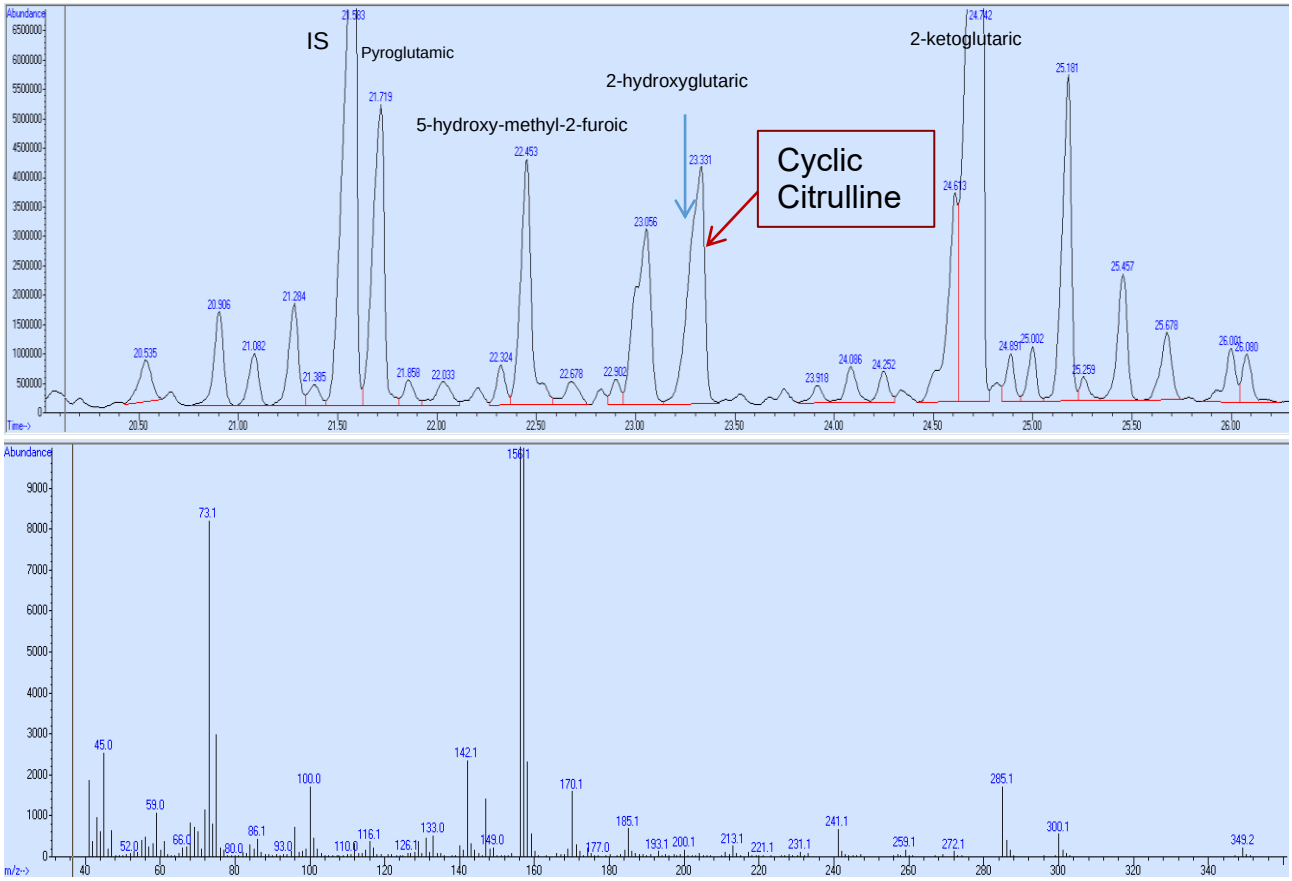
Analytical performance

All participants identified an increase in **citrulline** (20/20) (median = 154 mmol/mol creatinine; range : 41.0 – 217 ; n = 20). Some mentioned a normal excretion of argininosuccinic acid (n = 7), arginine (n = 6), glutamine (n = 4) and alanine (n = 1).



Eighteen labs performed organic acids and identified an increase in citrulline cyclic derivative (n = 5) (whereas 8 mentioned that it was undetectable – see spectrum below), hippuric acid (n = 15), benzoylalanine (n = 9), and benzoic acid (n = 8).

Orotic acid excretion was reported as normal using organic acids chromatography (n = 8) or a specific assay (n = 11). Only 2 participants mentioned an increased excretion.



Diagnosis / Interpretative proficiency

Most likely diagnosis

Citrullinaemia type I (argininosuccinate synthetase deficiency)	19
Carbamyl-phosphate synthetase I deficiency (seems to be treated by benzoate and citrulline)	1

Alternative diagnosis

Citrullinaemia type I	1
Other urea cycle defect	6
Citrullinaemia type II	3
Argininosuccinic aciduria	1

Scoring

- **Analytical performance**
  - Increase in citrulline (score 2)

- **Interpretation of results**
  - Citrullinaemia type I as 1st diagnosis (score 2)
  - Citrullinaemia type I as alternative diagnosis (score 1)

- **Critical error:** failure to report citrulline. Number of occurrences: 0

Overall impression

The overall proficiency was 98 %.

Multiple distributions of similar samples

Similar urine samples have been distributed in 2011, 2017 and 2020: the overall performance slightly improved.

	2011	2017	**2020**	**2024**
Analytical performance	**94 %**	**96 %**	98 %	100 %
Interpretative performance	**95 %**	**100 %**	96 %	95 %
Overall performance	**95 %**	**98 %**	97 %	98 %

8.5. Patient D

Adenylosuccinate lyase (ADSL) deficiency (ADSL gene).

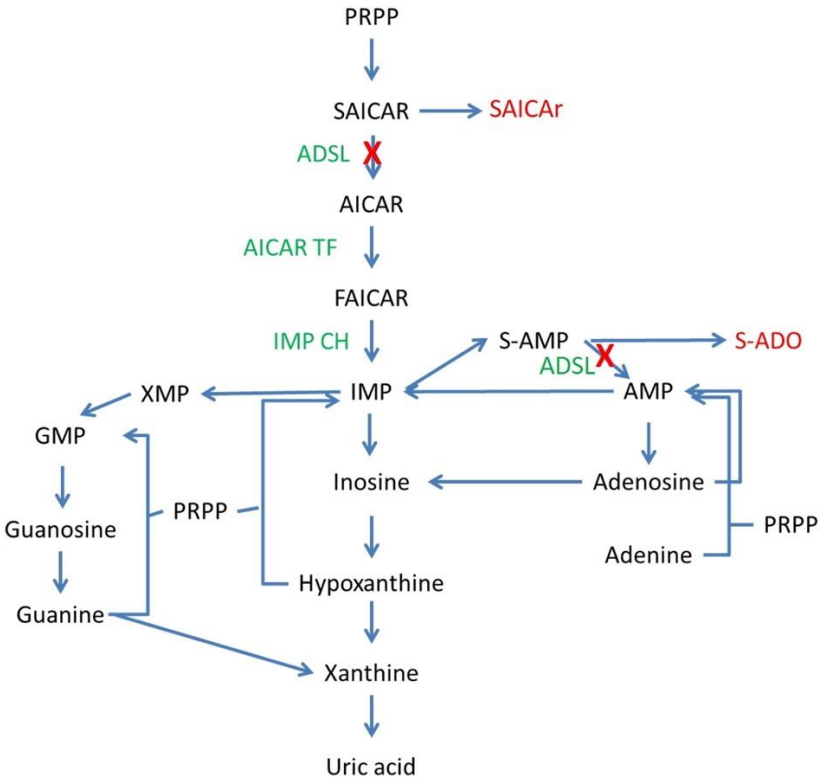
Patient details provided to participants

Boy, 5 years. He presents severe psychomotor retardation with stereotypies since 10 months old. His brother also presents the same clinical picture.

Patient details

This 5-year-old boy, born from unrelated parents, had normal gestation and delivery. At 10 months of age, the parents consulted for evident motor retardation, absent communication skills and frequent stereotypies. This picture is quite similar to his brother's, 2 years older, who also have suffered some epileptic crises. The diagnostic workout included basic biochemistry without alterations, a normal CGH array 60k, no evident alterations of brain NMR, and a normal karyotype. Whole exome sequencing identified a homozygous mis-sense variant in *ADSL* gene, considered as a VUS. His brother had the same alteration.
He was reinvestigated at 5 years of age. Organic acid, amino acid, and acylcarnitine profiles and redox metabolites were without significant alterations, but Bratton-Marshall test was positive. Purine and pyrimidine profile exhibited a high increase in succinyladenosine (S-Ado = 268.1 mmol/mol creat, controls : ND) and succinyl-aminoimidazolecarboxamide riboside (SAICAr = 144.8 mmol/mol creat, controls: ND). This profile, together with the clinical picture and previous genetic information (probably pathogenic homozygous variant in the *ADSL* gene) and recurrence in his brother, is highly compatible with adenylosuccinate lyase deficiency (OMIM # 103050).

Adenylosuccinate lyase (ADSL) deficiency is a rare autosomal recessive IEM, with a broad clinical spectrum, varying from intractable convulsions, severe hypotonia in the neonatal period, to moderate to severe psychomotor retardation, epilepsy after the first years, autistic features, growth retardation later in life. Microcephaly is often present. Some patients are only mildly retarded. Prognosis for survival is variable. ADSL catalyses 2 steps in purine synthesis: the conversion of SAICAR into AICAR in the *de novo* pathway and that of S-AMP into AMP, leading to the accumulation of SAICAr and S-Ado by dephosphorylation of SAICAR and S-AMP. SAICAr/S-Ado ratio has been reported to be around 1 in severe form, and between 2 and 3 in milder forms, but this ratio in not reliable.



From Donti et al. Mol Genet Metab Rep. 2016. 27;8:61-6

Analytical performance

Fourteen participants reported an increase in **succinyladenosine** (S-Ado) (median = 79.3 mmol/mol creat, range : 19.6 – 113 ; n=6), and 13 an increase in **SAICAr** (median = 57.5 mmol/mol creat, range : 22 – 92 ; n=5). A SAICAr calibrator is now commercially available from Sigma. It is too expensive to include in the ERNDIM quantitative purine-pyrimidine (PPU) scheme, but its analogue AICAr is included in the PPU scheme. S-Ado can be prepared easily from adenylosuccinate (succinyl-AMP, available from Sigma). Reference values of S-Ado are age-dependent. Urine from young children usually does contain some S-Ado, which makes quantitative analysis imperative to identify ADSL patients. The **Bratton-Marshall test** to detect SAICAr was reported positive by three participants. Less reliable than quantitative purine analysis, this test has been reported to have an LOD of 1 µmol/l. Analytical proficiency was 80 %.
Nine participants reported an increase in cystathionine (median = 86 mmol/mol creat, range: 73.0 – 107.6), and 4 of them, who did not perform purine analysis, concluded to cystathionuria. There is apparently no link with ADSL deficiency, but it can be speculated that this increase is secondary to B6 deficiency, possibly caused by anti-epileptic drugs.

Diagnosis / Interpretative proficiency

<u>Most likely diagnosis</u>	
Adenylosuccinate lyase deficiency (adenylosuccinase deficiency, ADSL deficiency)	16
Cystathioninuria (cystathionine gamma-lyase deficiency)	4
<u>Alternative diagnosis</u>	
Cystathionine gamma-lyase deficiency	2
Other deficiency of purine metabolism	2
Remethylation defects	1

Scoring

- **Analytical performance**
  - Increase in succinylaminoimidazole carboxamide riboside (SAICAr) or AICAr or positive Bratton-Marshall test (score 1)

- Increase in succinyladenosine (S-Ado) (score 1)

- **Interpretation of results**
  - Adenylosuccinate lyase deficiency (score 2)
  - Recommendation to perform purines & pyrimidines or Bratton-Marshall test (score 1)

- **Critical error:** sample not eligible

Overall impression

The overall proficiency was 80 %.

8.6. Patient E

No IEM

Patient details provided to participants

52-year-old woman. Severe muscle pain after cross fit.

Patient details

This urine sample was from Cécile, the Deputy of DPT-France.

Analytical performance

Twelve participants reported no significant abnormality in organic acid profile, while one mentioned a slight increase in conjugated glycines (isobutyrylglycine, 2-methylbutyrylglycine, isovalerylglycine). Seven labs reported a normal acylcarnitine profile but two identified an increase in decadienoyl-carnitine (C10:2 = 0.35 ; 0.7 mmol/mol creatinine), concluding to 2,4-dienoyl-CoA reductase deficiency. No significant abnormality in the amino acid profile was reported by 12 labs.

Diagnosis / Interpretative proficiency

<u>Most likely diagnosis</u>	
No IEM detected (no abnormality detected, no diagnosis, …)	18
2,4-dienoyl-CoA reductase deficiency	2
<u>Alternative diagnosis</u>	
Mc Ardle	4
Fatty acid oxidation defect	4
Myoadenylate deaminase deficiency	2
Late-onset Pompe disease	2
Riboflavin-responsive exercise intolerance, RR-MADD	1

Scoring

- **Analytical performance**
  - No significant abnormality in organic acid and/or acylcarnitine profile (score 2)
  - Wrong result for one test (e.g. increase of C10:2 acylcarnitine), amino acids analysis as only performed test (score 1)

- **Interpretation of results**
  - No indication for an IEM as first or alternative diagnosis (score 1)
  - Recommendation to perform plasma CK, plasma/DBS acylcarnitines or to ask for more detailed clinical information (score 1)

- **Critical error:** sample not eligible

Multiple distributions of similar samples

Two similar urine samples have been distributed in 2017 and 2022: the overall performance has slightly improved.

	2017	2022	2024
Analytical performance	**84 %**	**98 %**	95 %
Interpretative performance	**84 %**	**86 %**	95 %
Overall performance	**84 %**	**92 %**	95 %

8.7. Patient F

Multiple acyl-CoA dehydrogenase deficiency (MADD) due to ETF deficiency (ETFA gene)

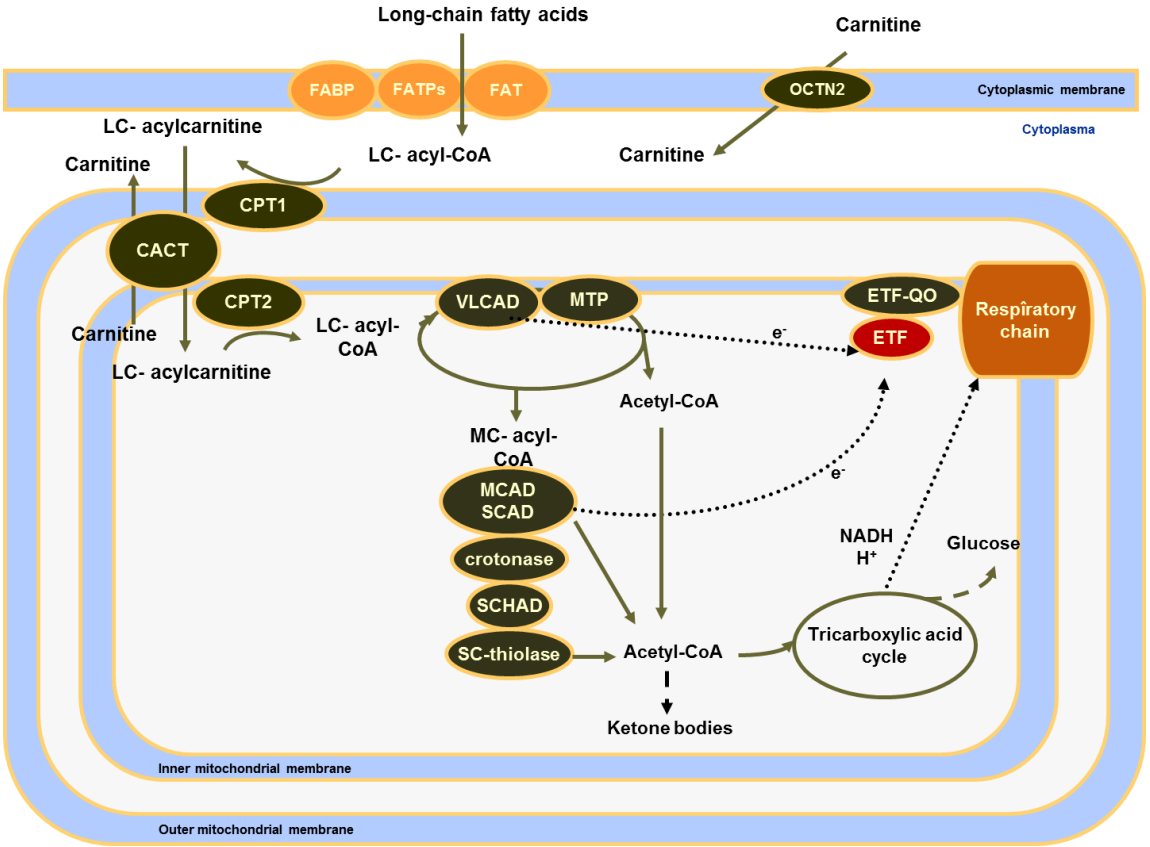
Patient details provided to participants

31-year-old boy. His elder brother died from “Reye-like” syndrome at 9 months of age. Almost asymptomatic under treatment.

Patient details

The patient’s mother was pregnant at the time his brother died. Multiple acyl-CoA dehydrogenase deficiency (MADD) was diagnosed at birth by analysis of plasma acylcarnitines and urinary organic acids. Diagnosis of ETF deficiency was determined by measurement of ETF activity in cultured skin fibroblasts and by mutation analysis of *ETFA* gene. He is now 31-year-old and is almost asymptomatic under treatment. Plasma acylcarnitine profile was strikingly abnormal when the urine sample was collected, with an increase of all chain-length acylcarnitines.

Multiple acyl-CoA dehydrogenase deficiency (OMIM # 231680) is due either to a deficiency of electron transfer flavoprotein (ETF – genes *ETFA* and *ETFB*) or to a deficiency of ETF ubiquinone oxidoreductase (ETF-QO – gene *ETFDH*), the 2 electron transporters which transfer electrons from acyl-CoA dehydrogenases to respiratory chain.



Simplified scheme of mitochondrial fatty acid oxidation

There are 11 ETF-dependent dehydrogenases, involved in 5 metabolisms:

- Fatty acid oxidation: VLCAD, LCAD, MCAD, SCAD
- Branched-chain metabolism: isovaleryl-CoA dehydrogenase, isobutyryl-CoA dehydrogenase, 2-methylbutyryl-CoA dehydrogenase
- Lysine metabolism: glutaryl-CoA dehydrogenase
- Choline metabolism: sarcosine dehydrogenase, dimethylglycine dehydrogenase
- 2-hydroxyglutarate dehydrogenase

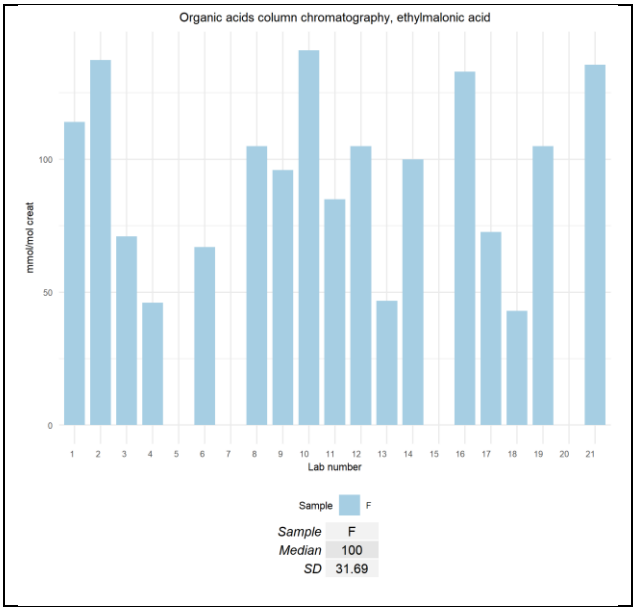
MADD is sometimes called glutaric aciduria type II: this name is **misleading and must be abandoned.**

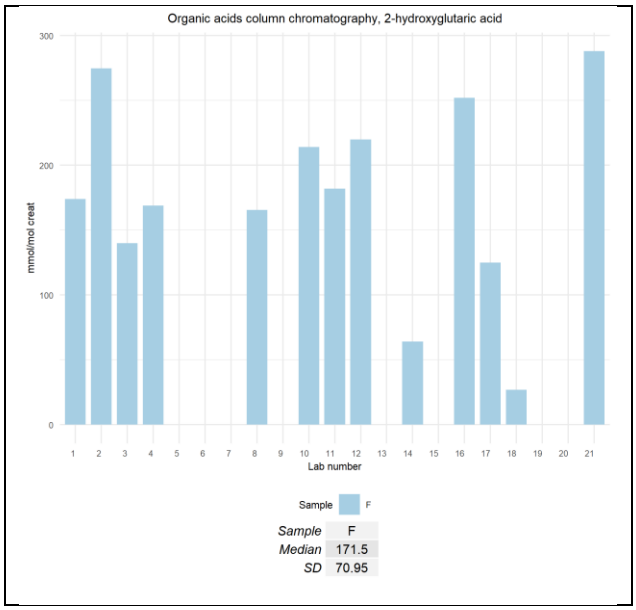
Analytical performance

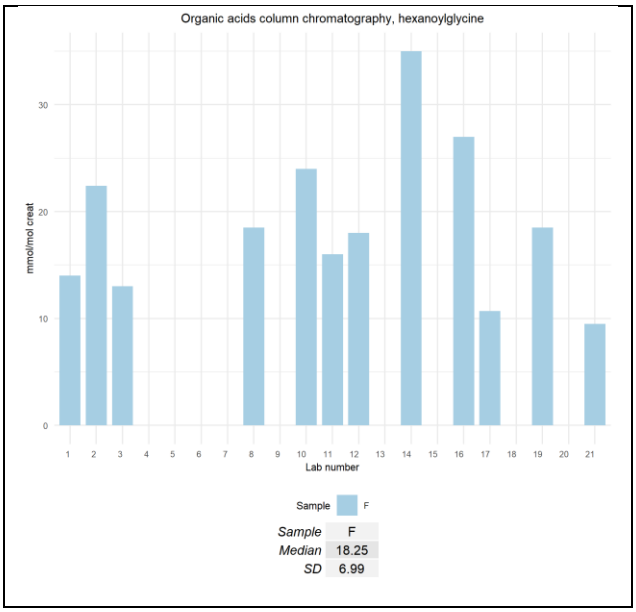
All participants performed organic acids and identified an increase in:

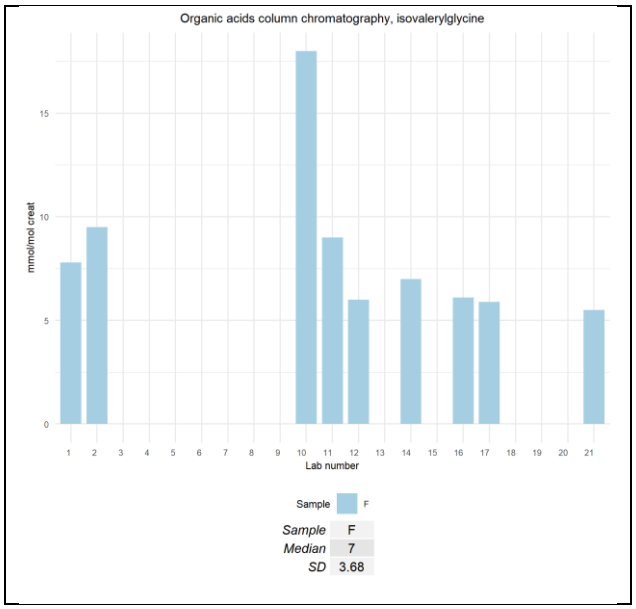
- **Ethylmalonic acid** (n=20): median = 100 mmol/mol creatinine; range : 43 – 141 ; n=17
- **2-hydroxyglutaric acid** (n=20): median = 171.5 mmol/mol creatinine; range : 27.0 – 288 ; n=16
- **Hexanoylglycine** (n=15): median = 18.88 mmol/mol creatinine; range : 9.5 – 35.0 ; n=12
- **Isovalerylglycine** (n=9): median = 7.0 mmol/mol creatinine; range : 5.5 – 18 ; n=9
- **Isobutyrylglycine** (n=9): median = 12.28 mmol/mol creatinine; range : 2.0 – 33.9 ; n=5
- Glutaric acid (n=7): 7.0 ; 7.5; 8.9 ; 10.1 mmol/mol creatinine ; n=4

But 4 labs mentioned a normal excretion of glutaric acid (1.7 ; 12.0 mmol/mol creatinine)




Organic acids column chromatography, 2-hydroxyglutaric acid
mmol/mol creat
Lab number
Sample F
Sample F
Median 171.5
SD 70.95


Organic acids column chromatography, hexanoylglycine
mmol/mol creat
Lab number
Sample F
Sample F
Median 18.25
SD 6.99


Organic acids column chromatography, isovalerylglycine
mmol/mol creat
Lab number
Sample F
Sample F
Median 7
SD 3.68

Nine labs performed acylcarnitines and identified an increase in:

- **Butyryl/isobutyrylcarnitine** (C4; n=6): median 15.7 mmol/mol creatinine; range: 12.4 – 42.8; n=5
- **Isovalerylcarnitine** (C5 ; n=6): 4.27 ; 4.49 ; 5.0 ; 13.8 mmol/mol creatinine; n=4
- **Glutarylcarnitine** (C5DC ; n=5): 4.5 ; 7.4 ; 38.25 mmol/mol creatinine; n=3
- **Octanoylcarnitine** (C8 ; n=5): 1.19 ; 1.5 ; 2.04 mmol/mol creatinine; n=3
- **Hexanoylcarnitine** (C6 ; n=1): 0.38 mmol/mol creatinine

Using tandem mass spectrometry for amino acid analysis, the scientific advisors identified an increase in **dimethylglycine** (= 128 mmol/mol creat - controls <10), which is frequent in MADD, but not specific. Conversely, sarcosine was undetectable.

Diagnosis / Interpretative proficiency

Most likely diagnosis

MADD	19
MADD secondary to riboflavin deficiency	1

Alternative diagnosis

MADD type 2A	2
MADD	1
Defects in riboflavin metabolism	5
Riboflavin deficiency	1
Ethylmalonic encephalopathy	1

Scoring

- **Analytical performance**
  - Increase in ethylmalonic or 2-hydroxyglutaric (score 1)
  - Identification of at least one acylglycine derivative (isovalerylglycine, hexanoylglycine, 2-methylbutyrylglycine, isobutyrylglycine or suberylglycine) or one acylcarnitine derivative (C5DC, C4, C5, C6, C8) (score 1)
  - A normal acylcarnitine profile limits the total score to 1 point

- **Interpretation of results**
  - Multiple acyl-CoA dehydrogenase deficiency as first or alternative diagnosis with the recommendation to perform plasma/DBS acylcarnitines and/or mutation analysis of ETFA, ETFB and ETFDH genes (score 2)

- **Critical error:** failure to report any metabolite typical of MADD. Number of occurrences: 0

Overall impression

The overall proficiency was 95%.

Multiple distributions of similar samples

Similar urine samples have been distributed in 2005, 2009 and 2019: the overall performance was almost similar.

	2011	2017	**2020**	**2024**
Analytical performance	**95 %**	**100 %**	94 %	95 %
Interpretative performance	**100 %**	**98 %**	88 %	95 %
Overall performance	**97 %**	**99 %**	91 %	95 %

9. Scores of participants

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

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

Detailed scores – Round 1

Lab n°	Patient A Malonyl-CoA decarboxylase deficiency			Patient B L-2-hydroxyglutaric aciduria			Patient C Citrullinaemia type I			
	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	1	3	11
4	2	2	4	2	2	4	2	2	4	12
5	--	--	--	--	--	--	--	--	--	0
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	1	3	11
10	2	2	4	2	2	4	2	2	4	12
11	2	1	3	2	1	3	2	2	4	10
12	2	2	4	2	2	4	2	2	4	12
13	2	2	4	2	2	4	2	2	4	12
14	2	2	4	2	2	4	2	2	4	12
15	2	2	4	2	2	4	2	2	4	12
16	2	2	4	2	2	4	2	2	4	12
17	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	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

Detailed scores – Round 2

Lab n°	Patient D Adenylosuccinate lyase (ADSL) deficiency (ADSL gene).			Patient E No IEM			Patient F Multiple acyl-CoA dehydrogenase deficiency (MADD) due to ETF deficiency (ETFA gene)			
	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	0	0	0	2	1	3	2	2	4	7
5	--	--	--	--	--	--	--	--	--	0
6	2	2	4	2	2	4	1	2	3	11
7	0	1	1	1	2	3	2	2	4	8
8	2	2	4	2	2	4	2	2	4	12
9	2	2	4	2	2	4	2	2	4	12
10	2	2	4	2	2	4	2	2	4	12
11	2	2	4	2	2	4	2	2	4	12
12	2	2	4	2	2	4	2	2	4	12
13	2	2	4	2	2	4	2	2	4	12
14	2	2	4	2	1	3	2	0	2	9
15	0	1	1	1	2	3	2	2	4	8
16	2	2	4	2	2	4	2	2	4	12
17	1	2	3	2	2	4	2	2	4	11
18	0	0	0	2	2	4	2	2	4	8
19	2	2	4	2	2	4	2	2	4	12
20	2	2	4	2	2	4	1	2	3	11
21	1	2	3	2	2	4	2	2	4	11

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	4	24	100	
3	4	4	3	4	4	4	23	96	
4	4	4	4	0	3	4	19	79	
5	--	--	--	--	--	--	0	0	
6	4	4	4	4	4	3	23	96	
7	4	4	4	1	3	4	20	83	
8	4	4	4	4	4	4	24	100	
9	4	4	3	4	4	4	23	96	
10	4	4	4	4	4	4	24	100	
11	3	3	4	4	4	4	22	92	
12	4	4	4	4	4	4	24	100	
13	4	4	4	4	4	4	24	100	
14	4	4	4	4	3	2	21	88	
15	4	4	4	1	3	4	20	83	
16	4	4	4	4	4	4	24	100	
17	4	4	4	3	4	4	23	96	
18	4	4	4	0	4	4	20	83	
19	4	4	4	4	4	4	24	100	
20	4	4	4	4	4	3	23	96	
21	4	4	4	3	4	4	23	96	

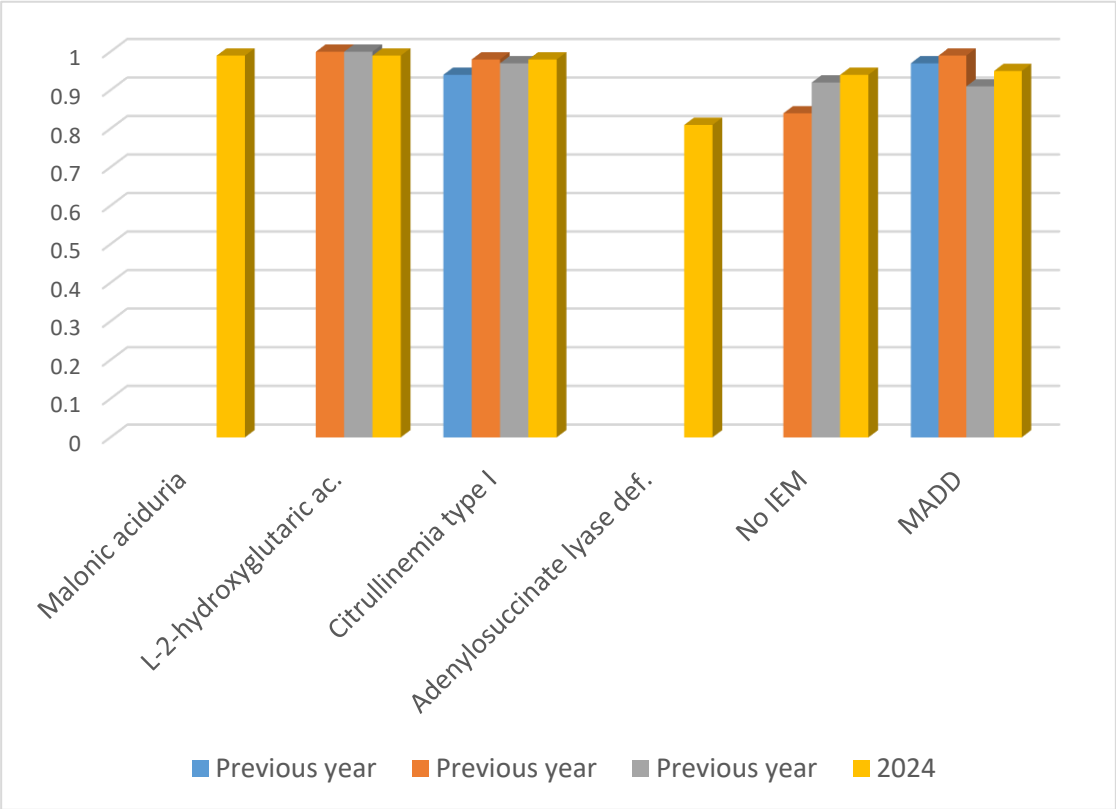
Performance

	Number of labs	% total labs
Satisfactory performers (≥ 70 % of adequate responses)	20	95
Unsatisfactory performers (< 70 % adequate responses and/or critical error)	0	0
Partial and non-submitters	1	5

Overall Proficiency

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Total (%)
DPT-FL-2024-A	Malonyl-CoA decarboxylase deficiency	100	98	99
DPT-FL-2024-B	L-2-hydroxyglutaric aciduria	100	98	99
DPT-FL-2024-C	Citrullinaemia type I	100	95	98
DPT-FL-2024-D	Adenylosuccinate lyase (ADSL) deficiency (ADSL gene).	75	85	80
DPT-FL-2024-E	No IEM	95	95	95
DPT-FL-2024-F	Multiple acyl-CoA dehydrogenase deficiency (MADD) due to ETF deficiency (ETFA gene)	95	95	95

Improvement DPT France



10. Annual meeting of participants

It took place in Porto on September 3rd, 2024 from 9.00 to 10.30, before the SSIEM Meeting.

Participants

Participants: 17 people from 10 labs:
Judith Garcia Cazorla, Sonia Pajores (Hospital Clinic, Barcelone), José Antonio Arranz (Vall d'Hebron, Barcelone), Giancarlo La Marca, Sabrina Malvaglia (Florence), Clara Rodriguez Fraga (Madrid), Marguerite Gastaldi (Marseille), Alberto Burlina (Padova), Apoline Imbart, Clément Pontoizeau (Paris), Carla Caseiro, Celia Ferreira, Cristina Florindo (Porto), Cristiano Rizzo (Rome), Jörgen Bierau, Augustyn Dieuwertje, Marne Hagermeijer (Rotterdam).

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 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 28th and 29th April 2025 in Prague. The topics will be:
  - Mitochondrial diseases
  - Glycogen storage disorders
  - Neurotransmitter disorders
  - Congenital disorders of glycosylation

  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:

  Dr C. Acquaviva, Dr D.P. de Brauwere, Dr C. Vianey-Saban,
  Maladies Héréditaires du Métabolisme
  Centre de Biologie et de Pathologie Est
  59, Bd Pinel
  69322 Lyon cedex (by post)
  69500 Bron (by transporter)
  Tel : + 33 4 72 12 96 94
  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 send quantitative data for amino acids and, as much as possible, for organic acids.

13. Tentative schedule in 2025

Sample distribution	February 5
Start of analysis of Survey 2025/1 Website open	March 17
Survey 2025/1 - Results submission	April 7
Survey 2025/1 - Reports	April
Start of analysis of Survey 2025/2	June 2
Survey 2025/2 – Results submission	June 23
Survey 2025/2 - Reports	July
Annual meeting of participants	October: details will follow
Annual Report 2025	Jan-Mar 2026

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, 2024-12-09
Name and signature of Scientific Advisor and Deputy

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cecile.acquaviva-bourdain@chu-lyon.fr

APPENDIX 1.

DIAGNOSTIC PROFICIENCY TESTING (DPT) FRANCE

URINE SAMPLES ALREADY SENT

• 1998 : 1	P1	OCT
	P2	Propionic acidemia
• 1999 : 1	P1	MPS I or II
	P2	Cystinuria (common sample)
• 1999 : 2	P3	CblC
	P4	HMG-CoA lyase deficiency
• 2000 : 1	P1	Iminodipeptiduria (common sample)
	P2	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
• 2023:1	A	Argininosuccinic aciduria (common sample)
	B	2-methylbutyryl-CoA dehydrogenase deficiency
	C	Isovaleric acidemia
• 2023:2	D	Combined MCAD and OCTN2 deficiency
	E	Fucosidosis
	F	Phenylketonuria

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

Version Number	Published	Amendments
1	21 January 2025	2024 annual report published

END