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Diagnostic Proficiency Testing

Centre: The Netherlands

Final Report 2018

prepared by
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Note: This annual report is intended for participants of the ERNDIM DPT Netherlands scheme. The contents should not be used for any publication without permission of the Scientific Advisor.

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The ERNDIM Diagnostic Proficiency Testing (DPT) Scheme is the ultimate external quality assessment scheme for biochemical genetics laboratories. In 2018, 21 labs participated to the Proficiency Testing Scheme NL.

1. Geographical distribution of participants

For both surveys, all 21 participants have submitted results.

Country	Number of participants
Australia	3
Belgium	5
France	1
Germany	2
Netherlands	8
South Africa	1
Switzerland	1

2. Design and logistics of the scheme including sample information

The scheme has been designed and planned by dr George Ruijter as Scientific Advisor and coordinated by Xavier Albe as scheme organiser (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. 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 samples: Samples used in 2018 have been provided by:

- UMC Radboud, Nijmegen
- VUMC, Amsterdam
- AMC, Amsterdam
- One sample was obtained with help of VKS, the Dutch patient organization

Patient A: DPD deficiency Common sample provided by DPT Czech
Patient B: ACY1 deficiency
Patient C: Cystinuria
Patient D: Glycerol kinase deficency
Patient E: Alfa-Mannosidosis
Patient F: Barth syndrome

Sample pre-treatment (heat-treatment) was performed in the Scientific Advisor's laboratory, while aliquoting and dispatch of the samples was done by the Scheme organiser. Before dispatch to participants one set of samples was sent to the Scientific Advisor and checked for quality. In all six samples the typical metabolic profiles were preserved.
Mailing: samples were sent by DHL; FedEx or the Swiss Post at room temperature.
The time allotted for submitting reports was 3 weeks after opening of the website. Clinical information on the samples was provided through the website.

3. Tests

The minimal required test panel for participation in any DPT scheme includes creatinine, dip stick, amino acids, organic acids, oligosaccharides and quantitative GAG. DPT-NL additionally requires the analysis of purines-pyrimidines. It is strongly recommended to have the following tests available for DPT-NL: GAG subtype analysis (by electrophoresis, TLC or LC-MS/MS), sialic acid, creatine-guanidinoacetate and polyols-sugars. Please note that in DPT schemes it is allowed to obtain results from neighboring laboratories when this is routine clinical practice. It is required to indicate in the report that results were obtained from a cluster lab.

4. Schedule of the scheme

- February 5, 2018: shipment of samples
- February 26, 2018: start analysis of samples of the first survey
- March 26, 2018: deadline for result submission (Survey 1)
- April 17, 2018: interim report with preliminary scores of Survey 1 published
- May 28, 2018: start analysis of samples of the second survey
- June 25, 2018: deadline for result submission (Survey 2)
- July 30, 2018: interim report with preliminary scores of Survey 2 published
- September 4, 2018: DPT workshop in Athens
- February 2019: annual report with final scoring published

5. Results

All participants submitted results for both surveys on time.

	Survey 1	Survey 2
Receipt of results	21	21
No results submitted	0	0

6. Web site reporting

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

- Selection of tests: please **don't select a test if you do not intend to perform it**, otherwise the evaluation program will include it in the report.
- Results: please
  - Give quantitative data as much as possible.
  - Enter the key metabolites with interpretation **in the tables** even if you don't provide 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 investigations**)
  - Recommendations are scored together with interpretation.
  - Advice for treatment is not scored.
  - **Please don't give advice for further investigations in "Comments on diagnosis"**: it will not be included in the evaluation program.

7. Scoring and evaluation of results

Information regarding procedures for establishment of assigned values, statistical analysis, interpretation of statistical analysis etc. can be found in generic documents on the ERNDIM website.
The scoring system has been established by the International Scientific Advisory Board of ERNDIM. Two aspects 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 the sum of these two aspects. The maximum score is 4 points per sample. The scores were calculated only for laboratories submitting results for both surveys.

Scoring and certificate of participation
Scoring is carried out by the scientific advisor as well as a second assessor from another DPT scheme who changes every year. The results of DPT NL 2018 have been scored additionally by Dr Joanne Croft, from DPT UK. At the SAB meeting in Leiden, November 29-30, 2018, the definitive scores have been set. 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. Details on critical errors in the 2018 samples are given under section 8 of this report.

ERNDIM provides a single certificate for all its schemes with details of participation and performance. In addition, performance support letters will be issued if the performance is evaluated as unsatisfactory. One performance support letters will be sent by the Scheme Advisor for 2018. Any

partial submitters will receive a letter from the ERNDIM Executive Administrator, Sara Gardner.

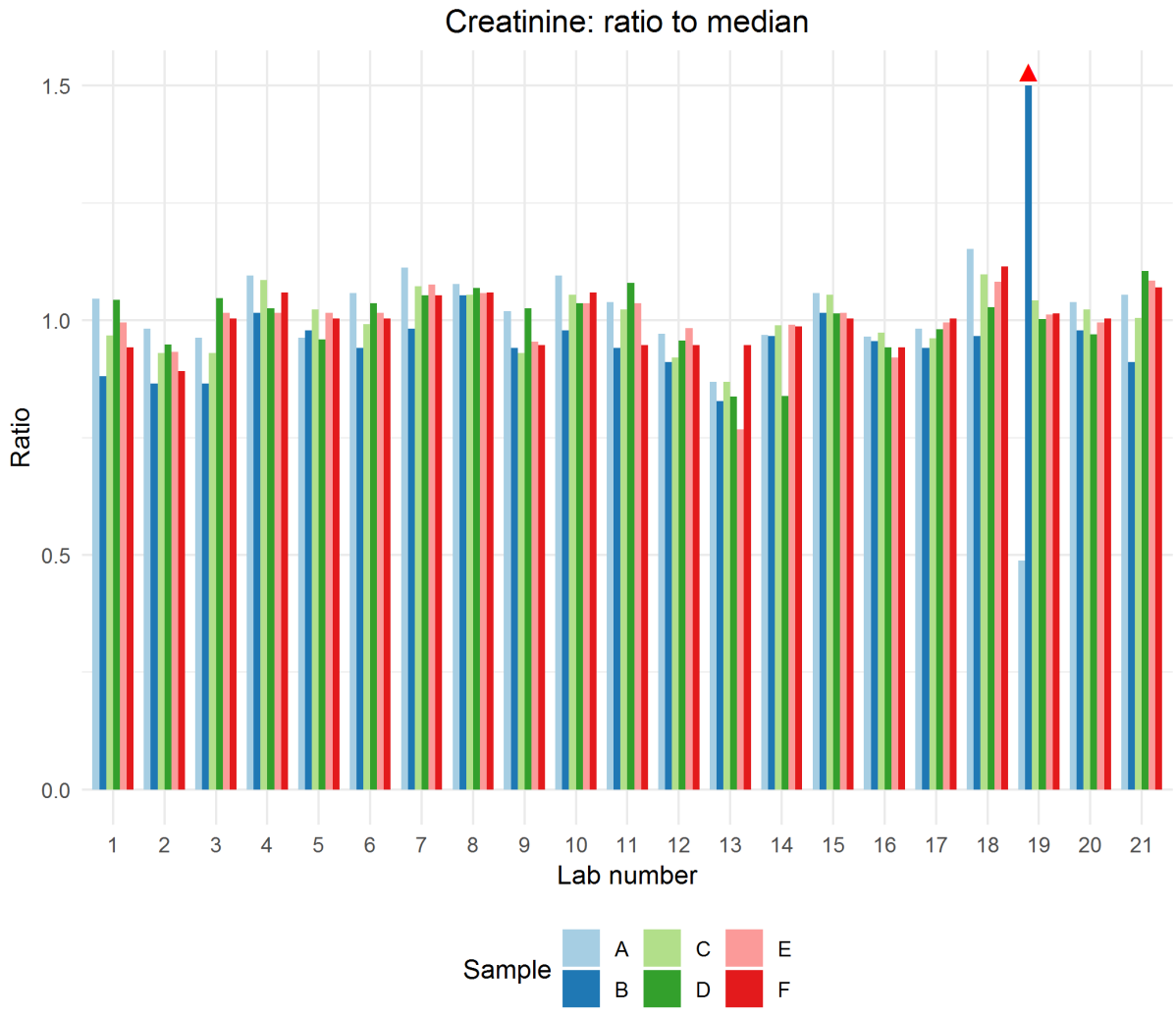
7.1. Score for satisfactory performance

A total score of at least 15 points out of the maximum of 24 (62%) and absence of critical errors must be achieved for satisfactory performance.

8. Results of samples and evaluation of reporting

8.1. Creatinine measurement for all samples

Creatinine determination was mostly correct for all labs. Two clearly incorrect values were noticeable, but no systematic errors were present. Creatinine values are expressed in Figure 1 as the ratio of each measurement over the median for all labs. CV's are <8 % for samples C-F, but slightly higher in samples A and B due to 2 outliers.



Sample	A	B	C	D	E	F
Mean	5.29	2.66	3.22	9.07	4.82	1.79
Median	5.50	2.54	3.24	9.30	4.90	1.80
SD	0.71	0.68	0.20	0.63	0.33	0.10

Figure 1

8.2. Patient A – DPD deficiency (OMIM 274270)

Patient details provided to participants
This female patient was referred at the age of 18 years with suspicion for multiple sclerosis based on MRI scan. Since the age of 5 years mental retardation and cognitive impairment was observed. Urine was collected at the age of 20 years.

Patient details
The sample was obtained from a 20 years old woman with dihydropyrimidine dehydrogenase deficiency. The diagnosis was confirmed by enzymatic and molecular genetic analyses.

Sample A was the common sample distributed to participants of all 5 DPT centers and was discussed during the ERNDIM participant meeting in Athens, September 4, 2018 by dr Chrastina from Prague. The presentation showing results and conclusions on this sample can be viewed on the ERNDIM website (erndim.org).

Analytical performance
All 21 participants detected elevations of thymine and uracil. Twelve labs specifically reported normal levels of dihydrothymine an dihydrouracil.

Diagnosis / Interpretative proficiency
All labs mentioned DPD as the most likely diagnosis.

Recommendations
Most laboratories suggested DPD enzyme testing and all recommended DPYD DNA testing. 5-Fluoro-uracil toxicity was mentioned by 11 participants.

Scoring
- Analytical results: increases of uracil and thymine were each scored with 1 point
- Interpretation of results: DPD deficiency (score 2)
- Critical error: Failure to report elevated uracil. Number of occurrences: 0

Overall impression
High overall proficiency (99%).

Multiple distributions of similar samples
Another DPD urine sample has been distributed in 2017. The overall performance is slightly higher in 2018.

	2017	2018
Analytical performance	93 %	100 %
Interpretative performance	90 %	98 %
Overall performance	91 %	99 %

8.3. Patient B – Aminoacylase 1 deficiency (OMIM 609924) receiving L-DOPA treatment

Patient details provided to participants
Adult female patient with childhood-onset generalised dystonia for which she is treated. Age at diagnosis is unknown, the sample was taken at adult age.

Patient details
A cognitively normal 63-year-old woman who around the age of 12 years had developed dystonic symptoms that gradually evolved into generalized dystonia. Extensive investigations, including metabolic diagnostics and diagnostic exome sequencing, were performed to elucidate the cause of dystonia. Findings were only compatible with a diagnosis of ACY1 deficiency: the urinary metabolite

pattern with N-acetylated amino acids was characteristic, there was decreased ACY1 activity in immortalized lymphocytes, and two compound heterozygous ACY1 mutations were detected, one well-characterized c.1057C>T (p.Arg353Cys) and the other novel c.325A>G (p.Arg109Gly).
She received L-DOPA. See also: Sass et al, Metab Brain Dis (2016) 31:587-592

Analytical performance
Eight labs reported the presence of 1 of one or more N-acetylated amino acids. NAc-Ala and NAc-Glu were mentioned most frequently, i.e. by 5 participants. Except one (semi-)quantitative result for NAcGlu, no quantitive data on NAcAA were reported. During discussion at the DPT meeting in Athens it was suggested to use selected ion monitoring of NAcGlu to screen for ACY1 deficiency. An organic acid chromatogram and the mass-spectrum (TMS) of NAcAla is depicted below (Fig 2 and 3; kindly provided by dr Leo Kluijtmans, Radboud UMC, Nijmegen, Netherlands). Mass spectra have also been described by Gerlo et al.
Almost all labs reported elevated levels of VLA (18/21) and HVA (19/21). Increased DOPAC, VMA, dopamine, L-DOPA, 3MT, and 3OMD were mentioned as well, while some labs specifically reported normal levels of 5HTP, 5HIAA and pterins. Slightly elevated propionylglycine was mentioned by 6 participants.

Metabolite	reported elevated (n)	median value	(range; n)
HVA	19	123	(96-362; 9)
VLA	18	52	(18-233; 8)
Propionylglycine	6	14	(4-14; 3)

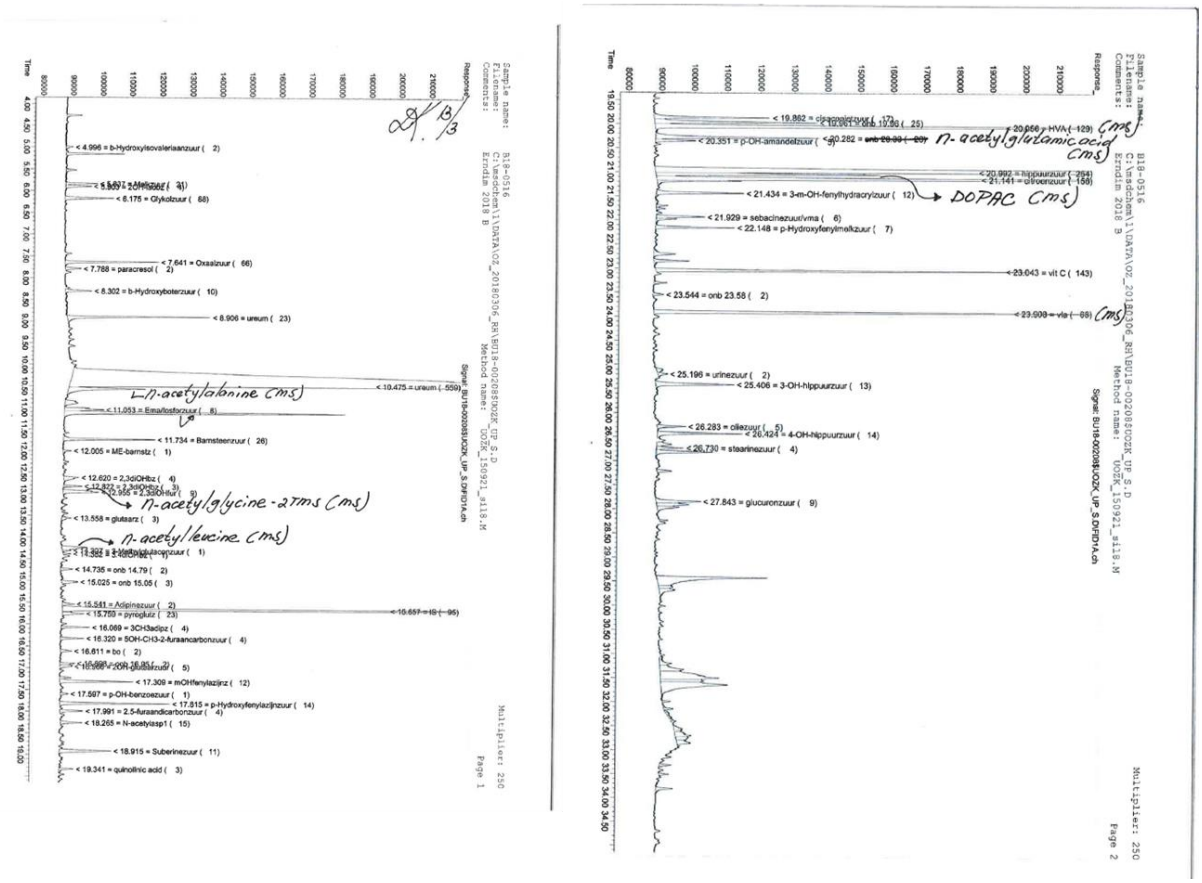


Figure 2. Chromatogram of TMS-derivatised organic acids in sample B

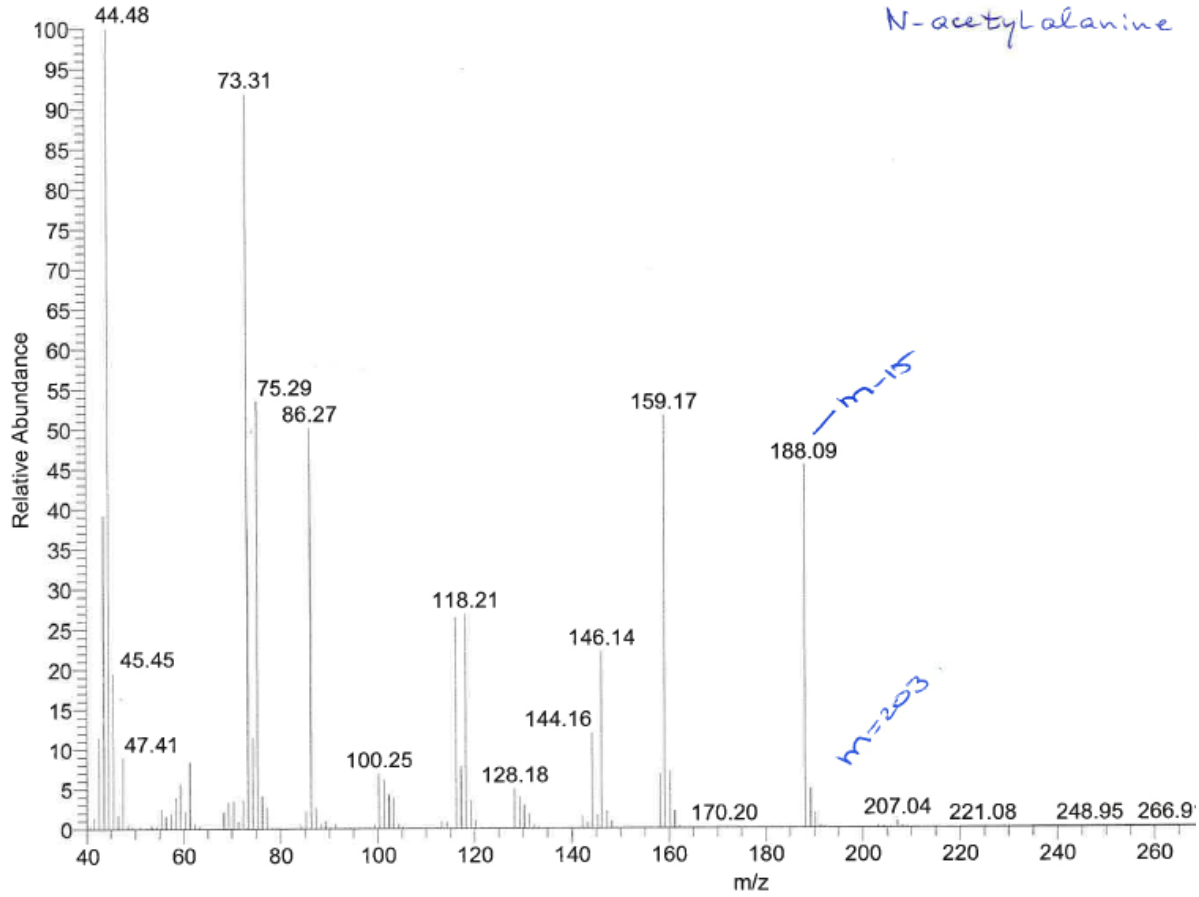


Figure 3. Fragmentation spectrum of N-acetyl-alanine.

Diagnosis / Interpretative proficiency

Only 5 labs (24%) reported the correct diagnosis, ACY1 deficiency. Three participants that have observed N-acetylated amino acids did not interpret this as aminoacylase 1 deficiency.

Many participants reported DOPA treatment (n=15). Various diagnoses were reported in relation to the elevations of HVA and VLA. DOPA-responsive dystonia, with or without different genetic causes mentioned, was reported by 6 participants. This conclusion is probably based on the clinical details in combination with the metabolite signature of DOPA treatment. Pterin analysis might be useful to investigate e.g. GTPCH deficiency. Normal pterin results in urine would exclude GTPCH deficiency as a cause of DOPA-responsive dystonia (reported by 1 participant). AADC deficiency was reported by 5 participants as the most likely diagnosis. However, in that case one would expect normal HVA, 5HTP and 5HIAA. Two labs suggested Tyrosine hydroxylase deficiency, but this possibility would be hard to establish in the sample, since the treatment by L-DOPA would conceal this defect. Other suggestions for most likely diagnosis made by single participants were: neuroblastoma (unlikely because of elevated VLA), Salla disease (unlikely because of normal free sialic acid), Propionic academia (see below) and no IEM.

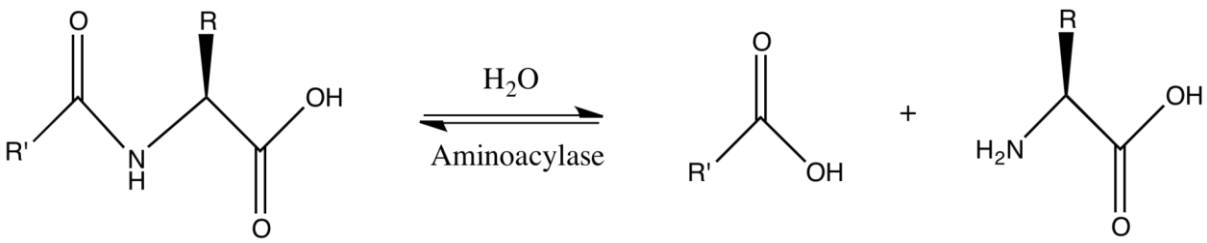


Figure 4

The chemical reaction catalyzed by aminoacylase 1 is shown above (Fig 4). Substrates are NAc-amino acids. NAc-aspartate is not a substrate of ACY1, but is hydrolysed by aminoacylase 2, which is deficient in Canavan's disease.

Propionylglycine was reported elevated by 6 participants and this observation has also been reported in the literature. An explanation is currently not established. Perhaps also propionylglycine is a substrate of ACY1.
The role of aminoacylase 1 in metabolism is presently not clear. Moreover, aminoacylase 1 deficiency may be a non-disease and not related to the symptoms of the patient (e.g. see Alessandri et al Brain and Development 40 (2018) 570-575).

Recommendations
The labs that concluded ACY1 deficiency suggested mutation analysis of the gene, enzyme testing in lymphocytes and to repeat urine organic acid analysis. Many labs suggested to follow-up on the abnormal VLA and HVA levels and DOPA-responsiveness by specific gene analysis, such as GCH1 and DDC, analysis of biogenic amines in CSF and pterins in CSF.

Scoring
- Analytical results: elevated N-acetyl-amino acids: score 1, elevated HVA, VLA or L-DOPA treatment: score 1
- Interpretation of results: aminoacylase 1 deficiency (score 2)
- Critical error: no potential critical errors were identified for this sample

Overall impression
Overall proficiency (based on points) was 45%. Clearly, not many labs include N-acetylated amino acids in their organic acid analysis. Moreover, some of the labs that do detect N-acetylated amino acids, did not report on the significance of this finding. The L-DOPA treatment apparently complicated analysis and interpretation in this sample. This proved to be a challenging sample, for analysis as well as interpretation. Although the overall proficiency was rather low, the SAB decided not to classify it as an educational sample.

8.4. Patient C – Cystinuria (OMIM 220100)

Patient details provided to participants
9 year-old boy with kidney stones.

Patient details
Patient under treatment for cystinuria.

Analytical performance
All participants reported increases of cystine, ornithine, lysine and arginine. Quantitative data of cystine are depicted in Fig 5.

Amino acid	median (mmol/mol)	range
Cystine	305	218-633
Ornithine	183	157-319
Lysine	567	318-639
Arginine	133	93-183

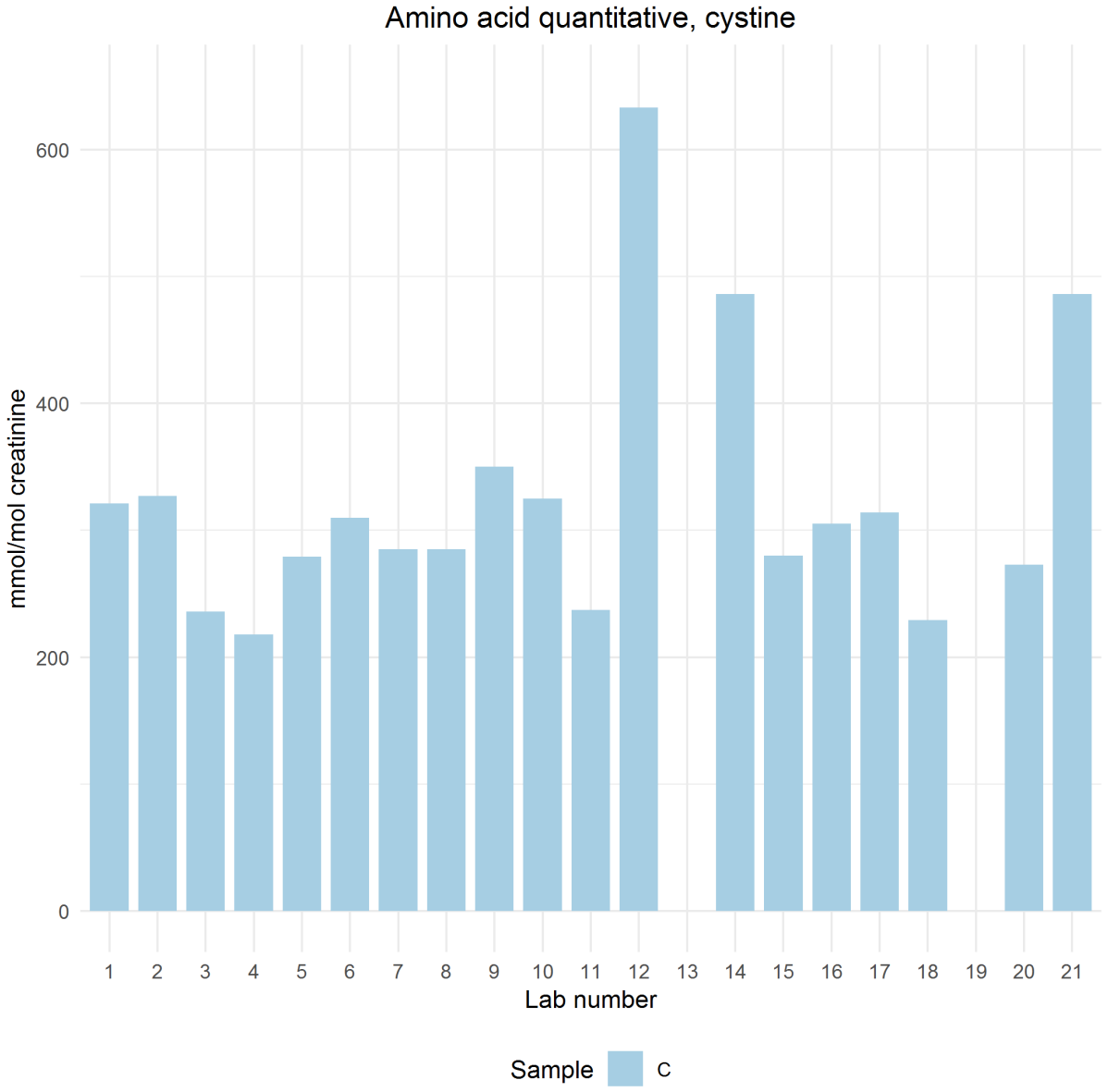


Figure 5

Diagnosis / Interpretative proficiency

Metabolic causes of kidney stones include: cystinuria, xanthine DH, APRT, hyperoxaluria types 1, 2, and 3, uric acid overproduction/hyper excretion, orotic acid overproduction and low citrate excretion. All participants correctly concluded the diagnosis cystinuria in sample 2018-C.

One participant reported the cysteine-homocysteine mixed disulfide (Fig 6). Its elevated level in urine may be explained if transport also occurs via SLC3A1/SLC7A9, the 'cystine' transporter. During discussion at the DPT meeting in Athens it was confirmed by several participants that the mixed disulfide is often present in cystinuria urine samples.

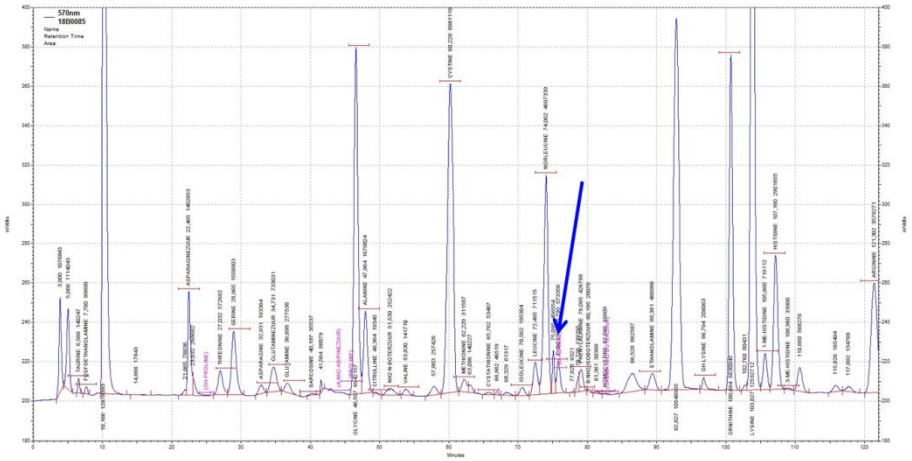


Figure 6. Amino acid chromatogram of sample C showing cys-hcys mixed disulfide (arrow).

The current classification of cystinuria is as follows: type A is a defect of SLC3A1, type B is a defect of SLC7A9. Heterozygotes of the B type may develop kidney stones; they often have an increased urine excretion of cystine and lysine.
The following comments were made:

- LPI is unlikely (n=2)
- Hyperlysinemia and hyperornithinemia are unlikely (n=1)
- PREPL is possible (n=1)

Recommendations
Recommendations for further investigations included mutation analysis of SLC3A1 and SLC7A9 (n=18) and testing of (asymptomatic) sibs (n=3).

Scoring

- Analytical results: increases of cysteine, lysine, ornithine and arginine (score 2)
- Interpretation of results: cystinuria (score 2)
- Critical error: Failure to report cystinuria as a diagnosis. Number of occurrences: 0

Overall impression
As expected overall proficiency (based on points) was high: 100%. This was an easy sample to investigate.

Multiple distributions of similar samples
This sample was also circulated in 2010 (sample P). Overall proficiency in 2010 was 98%.

8.5. Patient D – Glycerol kinase deficiency (OMIM 307030)

Patient details provided to participants
Adult male patient treated for many years because of hypertriglyceridemia.

Patient details
This forty-six year-old patient was treated for many years because of hypertriglyceridemia. He had no other symptoms. The lab in charge of his follow-up measured urinary triglycerides which were found elevated: 73 g/L. Organic acids were performed at that time. His brother has the same problem.

Analytical performance
Analytical performance was very good (95%). Twenty participants reported elevated glycerol (median 524 mmol/mol, range 50-21168, n=7). Increased lactate was reported by 4 labs, while 2 participants reported normal lactate. Low uric acid was mentioned by 8 labs. Although slightly elevated lactate might be consistent with F1,6BPase deficiency, the lactate may also be produced by bacteria. High pH and the presence of nitrite suggest bacterial contamination.

Diagnosis / Interpretative proficiency

Glycerol kinase deficiency (Fig 7) was reported as the most likely diagnosis by 20 participants. One participant concluded GSD I A. However, in that case lactate and uric acid are expected to be higher. In fact low uric acid level was reported by 8 participants.

Many participants (16) commented on the hypertriglyceridemia, which is actually in this case a 'pseudohypertriglyceridemia'. The common assay for triglycerides is based on determination of glycerol after triglyceride hydrolysis and the high glycerol concentration in blood of the GK patient causes a false-positive result. For marking interpretation, the correct diagnosis was scored with 1 point. The SAB decided that reporting pseudohypertriglyceridemia as the explanation for the hypertriglyceridemia was required to score 2 points.

The following other comments were made:

- Xp21 deletion possible (n=6)
- Xp21 deletion unlikely (n=3)
- F1,6BPase deficiency possible (n=1)
- F1,6BPase deficiency unlikely (n=4)
- F1,6BPase deficiency excluded (n=1; based on normal glycerol 3-P, 2KG)
- Glycerol may originate from exogenous sources, e.g. cosmetic cream (n=4)

Interpretative proficiency (86%) was slightly lower than analytical proficiency.

There is no clear consensus regarding the clinical relevance of glycerol kinase deficiency. Four participants noticed that GK deficiency is a benign condition, while 4 others stated that this condition may present with symptoms.

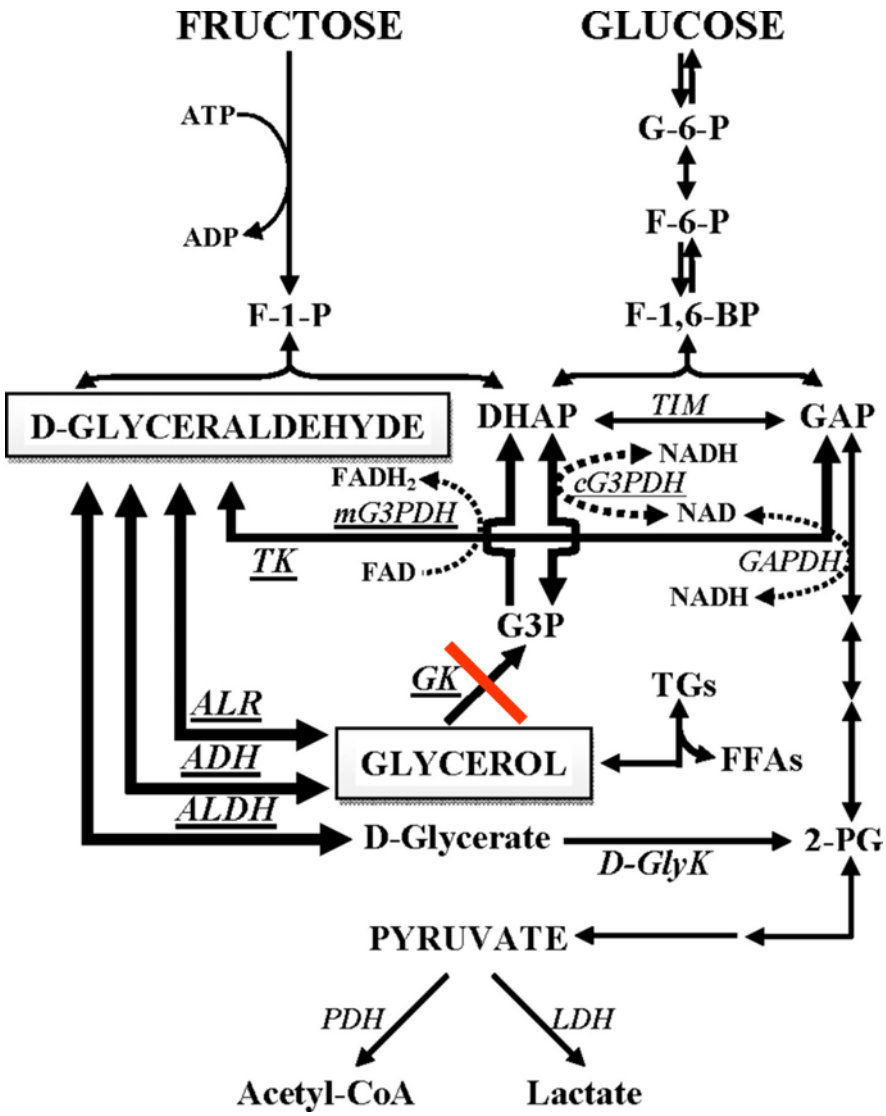


Figure 7

Recommendations
Most participants suggested to perform mutation analysis of the GK gene (n=19). Testing of sibs was suggested by 1 participant. The possibility of a contiguous gene deletion on Xp21 inclusing the GK, DMD and DAX1 genes was mentioned and participants suggested a SNP array to test this.

Scoring
- Analytical results: elevated glycerol (score 2)
- Interpretation of results: Glycerol kinase deficiency and reporting that the hypertriglyceridemia is in fact a pseudo-hypertriglyceridemia (score 2), while correct diagnosis without mentioning pseudo-hypertriglycerdemia was scored with 1 point
- Critical error: no potential critical errors were identified for this sample

Overall impression
Overall proficiency (based on points) 90%
Reaching the correct diagnosis in this sample proved to be rather straightforward. Most labs noted high glycerol and suggested the correct diagnosis.

Multiple distributions of similar samples
This sample was also circulated in DPT France in 2016 with an overall proficiency of 96%

8.6. Patient E – Alfa-mannosidosis (OMIM 248500)

Patient details provided to participants
This boy was referred at the age of 4 years for psychomotor retardation, sleep disturbances, recurrent respiratory tract infections and abdominal swelling. The urine sample was obtained at the age of 6 years.

Patient details
This sample was acquired with help of the Dutch IEM patient society: VKS. No detailed patient information is available.

Analytical performance
Oligosaccharide analysis was performed by 20/21 labs and all but one reported an abnormal profile. Analytical proficiency was 90%. Interestingly, two labs reported the use of LC-MS/MS for oligosaccharide analysis (see Piraud et al, Rapid Commun Mass Spectrom 2017, 31:951-963). GAG screening results were reported as normal by 13 participants. Five participants reported abnormal GAG screening. Three of these 5 labs analysed GAGs by electrophoresis and found normal results. GAGs may be abnormal in a sample of an α-mannosidosis patient (or another non-MPS lysosomal storage disorder), but this is most probably secondary to the primary defect.

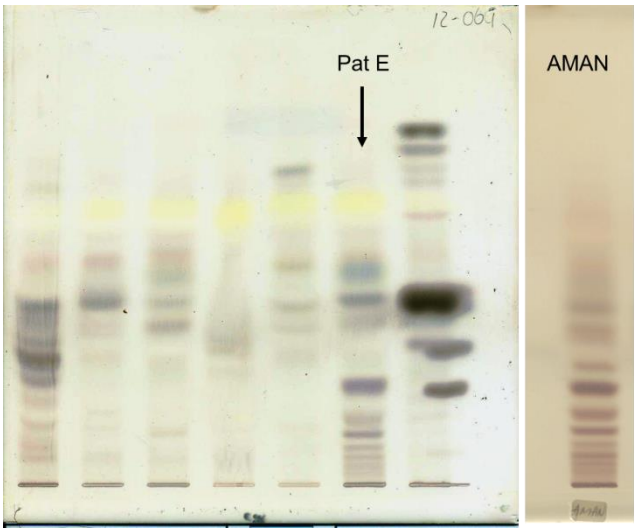


Figure 8. TLC analysis showing alfa-mannosidosis pattern of oligosaccharides in sample E.

Diagnosis / Interpretative proficiency
All 19 participants reporting an abnormal oligosaccharide pattern concluded α-mannosidosis as the most likely diagnosis. One participant suggested MPS as a diagnosis and another MPS/oligosaccharidosis. Interpretative proficiency was 93%.
Please note that an oligosacharide kit, containing different urine samples of oligosaccharidosis patients is available at MCA laboratory (Winterswijk, NL).

Recommendations
Recommendations for further investigations included α-mannosidase activity testing in WBC/fibroblasts (n=14) and MAN2B1 mutation analysis (n=19).

Scoring
- Analytical results: abnormal oligosaccharide pattern (score 2)
- Interpretation of results: alfa-mannosidosis (score 2)
- Recommendations: suggestion to investigate oligosaccharides (score 1)
- Critical error: Failure to detect abnormal oligosaccharides or failure to perform oligosaccharide analysis and no recommendation to do so. Number of occurrences: 1

Overall impression
Overall proficiency (based on points) 92%. Overall proficiency was 92%. An alfa-mannosidosis TLC pattern is one of the easier-to-interpret oligosaccharidosis patterns.

Multiple distributions of similar samples
Sample 2018-E was also circulated in 2012 (sample E). Overall proficiency in 2012 was 86%

8.7. Patient F – Barth syndrome (3-methylglutaconic aciduria type 2; OMIM 302060)

Patient details provided to participants
A boy, aged one month, hospitalised for infection. Tachypneu was noticed and ultrasound revealed dilated congestive heart failure. His motor milestones were slightly delayed.

Patient details
This boy was diagnosed with Barth syndrome.

Analytical performance
Elevated 3-methylglutaconic acid, the key compound to reach diagnosis in this sample, was reported by 18/21 participants, while 13 mentioned an abnormal value of 3-methylglutaric acid. Various other abnormalities in organic acid excretion were reported (see table below), which reflected the catabolic condition of the patient at the time of urine collection.

The 3-methylglutaconic acid (3MGA) concentration was not very high (see Table below, Fig. 9). When quantitative analysis is performed on this sample, the result; median value 36 mmol/mol, is clearly higher than the reference values (commonly 0-20 mmol/mol). 3-Methylglutaconic acid is commercially available (e.g. Sigma-Aldrich) to use as a calibrator.
Analytical proficiency was 93%.

Abnormal metabolite	n	median (mmol/mol)	range
3-Methylglutaconic acid	18	36	0-85
3-Methylglutaric acid	13	6	3-21
Lactate	17	375	172-5796
3-OH-butyric acid	20	1358	431-2247
3-OH-isovaleric acid	10	92	42-207
Free carnitine	7	219	46-283

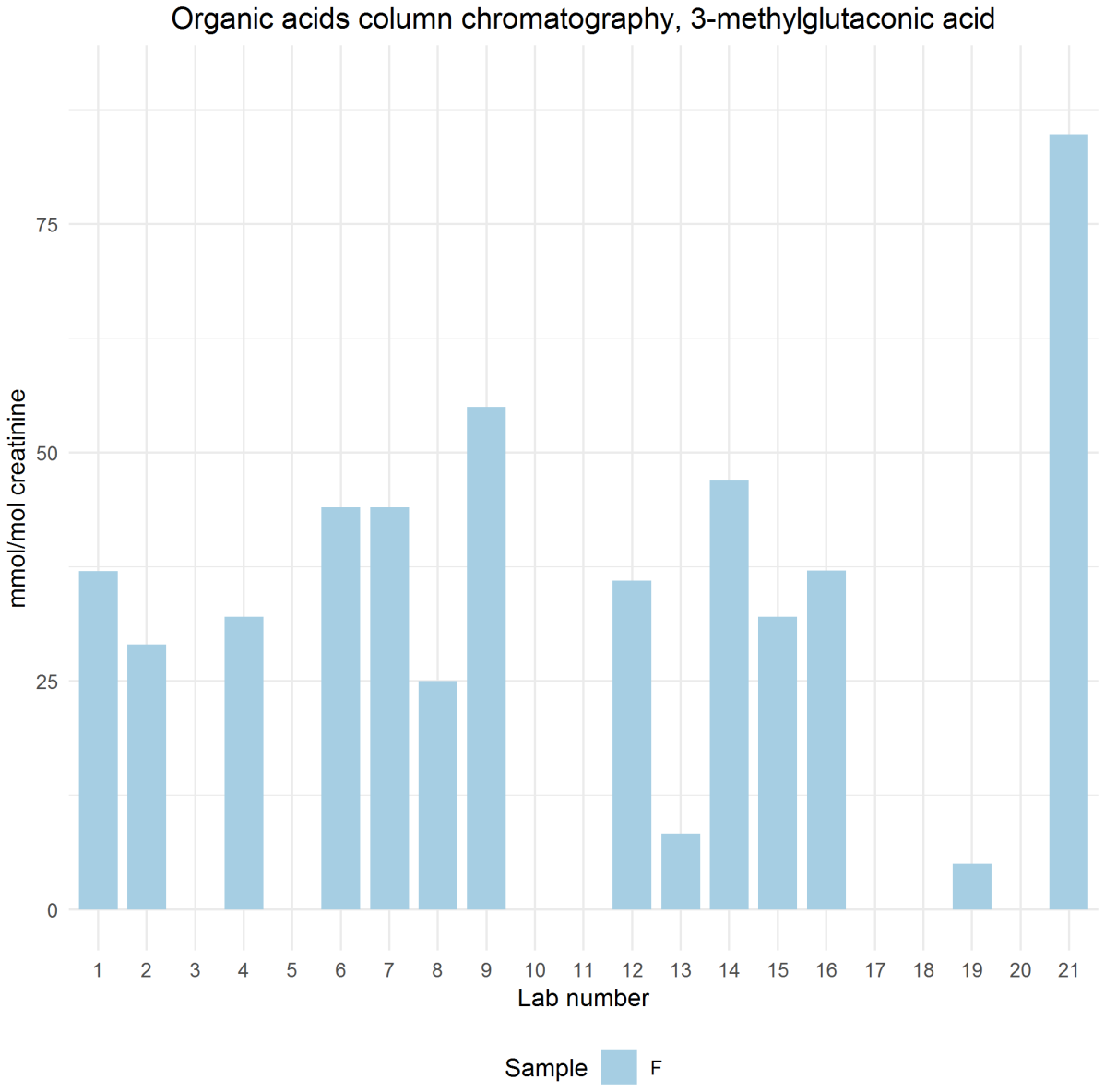


Figure 9

Diagnosis / Interpretative proficiency
Fifteen participants concluded Barth syndrome, 3MGA-uria type II, as the most likely diagnosis and one participant mentioned this diagnosis in the section 'other possible diagnoses'. Two labs did

observe elevated 3MGA, but did not interpret this finding as one of the 3MGA-urias and concluded another diagnosis. This resulted in a relatively large difference between analytical proficiency (93%) and interpretative proficiency (79%). 3MGA-uria is observed in several different IEM and more investigations are required to establish the precise diagnosis (see Figure below and Wortmann et al J Inherit Metab Dis 2013, 36:923-928 for a review). The specific type of 3MGA-uria in sample 2018-F was most probably concluded by most participants on the basis of the clinical symptoms. In fact, 9 participants mentioned that other types of 3MGA-uria were possible.
During discussion at the DPT meeting in Athens it was suggested that MEGDEL syndrome would also be a valid diagnosis on the basis of the metabolite pattern. MEGDEL syndrome was not specifically mentioned by any of the participants.
Carnitine transporter deficiency (OCTN2 def) was suggested by 3 participants. Indeed, the free carnitine level in the urine sample was high. It is unknown whether the patient was treated by carnitine suppletion at the time of urine collection. During discussion at the DPT meeting in Athens it was mentioned that elevated free carnitine may be secondary during ketosis. Other diagnoses reported were: 'ketolysis defect possible (n=1) and mitochondrial disease (n=1). Ketothiolase deficiency is unlikely based on organic acid results. Mitochondrial disease was scored with 1 point. One participant reported 'no diagnosis'.

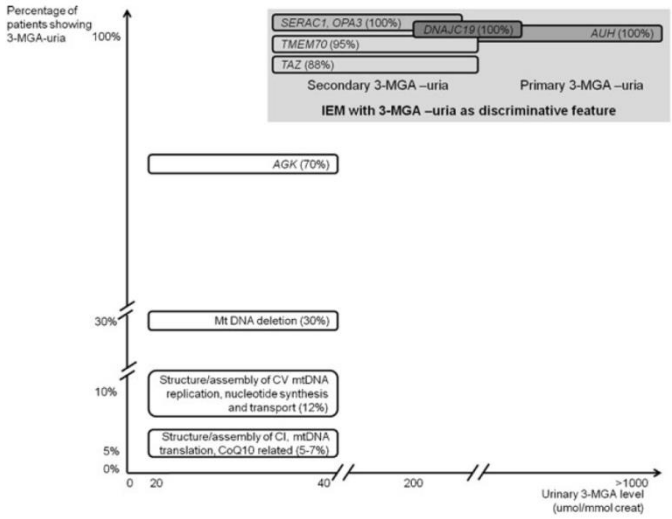


Figure 10. The interpretation of elevated 3-methylglutaconic acid (from Wortmann et al).

Recommendations
Recommendations for further investigations included: determination of monolyso-cardiolipins or cardiolipins in DBS/WBC (n=15), analysis of TAZ mutations (n=15) and measuring lactate/pyruvate (n=4)

Scoring
- Analytical results: elevated 3-methylglutaconic acid (score 1), elevated lactate (score 1)
- Interpretation of results: Barth syndrome/3MGAuria type II (score 2), 3MGAuria other/unspecified or mitochondrial disease (score 1)
- Critical error: no potential critical errors were identified for this sample

Overall impression
Overall proficiency (based on points) was 86%

Multiple distributions of similar samples
This sample was also circulated in 2009 (sample H). Proficiency in 2009 was 66%, which indicates a significant improvement in proficiency from 2009 to 2018 in this sample.

9. Scores of participants

All data transfer, i.e. submission of results as well as viewing and downloading of reports proceed via the DPT-CSCQ results website. The results of participants are confidential and only accessible using username and password on the CSCQ website. Anonymised scores of all laboratories are provided in the annual report. Your results are indicated by an arrow in the leftmost column.

Detailed scores – Round 1

Lab n°	Patient A DPD deficiency			Patient B ACY1 deficiency			Patient C Cystinuria			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	2	4	0	0	0	2	2	4	8
2	2	2	4	2	2	4	2	2	4	12
3	2	2	4	2	2	4	2	2	4	12
4	2	2	4	1	0	1	2	2	4	9
5	2	2	4	1	0	1	2	2	4	9
6	2	2	4	2	2	4	2	2	4	12
7	2	1	3	2	2	4	2	2	4	11
8	2	2	4	2	0	2	2	2	4	10
9	2	2	4	2	0	2	2	2	4	10
10	2	2	4	1	0	1	2	2	4	9
11	2	2	4	1	0	1	2	2	4	9
12	2	2	4	1	0	1	2	2	4	9
13	2	2	4	1	0	1	2	2	4	9
14	2	2	4	2	0	2	2	2	4	10
15	2	2	4	1	0	1	2	2	4	9
16	2	2	4	1	0	1	2	2	4	9
17	2	2	4	2	2	4	2	2	4	12
18	2	2	4	1	0	1	2	2	4	9
19	2	2	4	1	0	1	2	2	4	9
20	2	2	4	1	0	1	2	2	4	9
21	2	2	4	1	0	1	2	2	4	9

Detailed scores – Round 2

Lab n°	Patient D Glycerol kinase deficency			Patient E Alfa-Mannosidosis			Patient F Barth syndrome			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	1	3	2	2	4	2	2	4	11
2	2	2	4	2	2	4	2	2	4	12
3	2	2	4	2	2	4	2	2	4	12
4	2	2	4	2	2	4	2	2	4	12
5	2	2	4	2	2	4	2	2	4	12
6	2	2	4	2	2	4	2	2	4	12
7	2	2	4	2	2	4	2	2	4	12
8	2	2	4	2	2	4	2	0	2	10
9	2	2	4	2	2	4	2	2	4	12
10	2	2	4	2	2	4	1	0	1	9
11	2	2	4	2	2	4	1	1	2	10
12	0	0	0	2	2	4	2	2	4	8
13	2	2	4	0	0	0	2	2	4	8
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	0	1	1	2	2	4	9
17	2	1	3	2	2	4	2	0	2	9
18	2	1	3	2	2	4	2	2	4	11
19	2	2	4	2	2	4	2	2	4	12
20	2	2	4	2	2	4	1	0	1	9
21	2	1	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	0	4	3	4	4	19	79	
2	4	4	4	4	4	4	24	100	
3	4	4	4	4	4	4	24	100	
4	4	1	4	4	4	4	21	88	
5	4	1	4	4	4	4	21	88	
6	4	4	4	4	4	4	24	100	
7	3	4	4	4	4	4	23	96	
8	4	2	4	4	4	2	20	83	
9	4	2	4	4	4	4	22	92	
10	4	1	4	4	4	1	18	75	
11	4	1	4	4	4	2	19	79	
12	4	1	4	0	4	4	17	71	
13	4	1	4	4	0	4	17	71	CE
14	4	2	4	4	4	4	22	92	
15	4	1	4	4	4	4	21	88	
16	4	1	4	4	1	4	18	75	
17	4	4	4	3	4	2	21	88	
18	4	1	4	3	4	4	20	83	
19	4	1	4	4	4	4	21	88	
20	4	1	4	4	4	1	18	75	
21	4	1	4	3	4	4	20	83	

Performance

	Number of labs	% total labs
Satisfactory performers (≥ 60 % of adequate responses)	20	95
Unsatisfactory performers (< 60 % adequate responses and/or critical error)	1	5
Partial and non-submitters	0	0

Overall Proficiency

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Total (%)
Sample 2018-A	DPD deficiency	100	98	99
Sample 2018-B	ACY1 deficiency	67	24	45
Sample 2018-C	Cystinuria	100	100	100
Sample 2018-D	Glycerol kinase deficency	95	86	90
Sample 2018-E	Alfa-Mannosidosis	90	93	92
Sample 2018-F	Barth syndrome	93	79	86

10. Annual meeting of participants

The annual DPT workshop was organised in Athens on September 4th 2018 from 9.00 to 10.30. Representatives from 10 participating labs were present. Three participants have notified their absence prior to the meeting.

Please note 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 critical review of all results with a discussion on interpretation of results and, if possible, to reach a consensus on best practice.

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

- New **control materials** are now provided by SKML. These are no longer related to EQA materials and have been produced separately. Two concentration levels for each group of analytes are available. The most suitable low and high concentration levels are defined by the scientific advisors of the schemes. Analytes and their concentrations will be similar in consecutive batches of control material. These reference materials can be ordered at MCA laboratory (https://www.erndimqa.nl/) or through the ERNDIM website. Participants are encouraged to use them as internal control samples, but they cannot be used as calibrators. On the ERNDIMQA 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 mixtures** has been developed by Dr Herman ten Brink in Amsterdam, following request and advice from ERNDIM. These mixtures are intended to use as calibrators for organic acid analysis in urine. The product is currently available at: hj.tenbrink@vumc.nl
- **Training**: SSIEM Academy training courses.
  - A 2 days course will be been organized on Monday and Tuesday 29 and 30 April 2019 near Zurich. The program for biochemists includes:
    - Glycogen Storage Disorders
    - CDG Syndromes
    - Mitochondrial Disease
    - Neurotransmitters disorders
  - The lectures will be available on the SSIEM website
- **Urine samples**: To be able to continue this scheme we need a steady supply of new and interesting patient samples. Several laboratories have donated samples in the past, for which they are gratefully acknowledged. If you have one or more samples available and are willing to donate these to the scheme, please contact us at g.ruijter@erasmusmc.nl.

  For the DPT scheme we need at least 300 ml of urine from a patient affected with an established inborn error of metabolism, accompanied by a short clinical report. If possible, please collect 1500 ml of urine: this sample can be used as the common sample and be circulated to all labs participating to the DPT schemes. Each urine sample must be collected from a single patient. Please don't send a pool of urines, except if urine has been collected during a short period of time from the same patient.

  When a donated sample is used, the participating lab donating the sample will have a 20% discount on the DPT scheme fee in the next scheme year.

  Please send samples on dry ice courier to:

  Dr. G.J.G. Ruijter
  Erasmus Medical Center
  Dep Clinical Genetics
  P.O. Box 2040
  3000 CA Rotterdam
  The Netherlands
  Email: g.ruijter@erasmusmc.nl

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

12. Tentative schedule and fee in 2018

Sample distribution	February 5, 2019
Start of analysis of Survey 2019/1 (website open)	March 4, 2019
Survey 2019/1 - Results submission deadline	March 25, 2019
Survey 2019/1 – Interim report available	April/May 2019
Start of analysis of Survey 2019/2 (website open)	June 3, 2019
Survey 2019/2 – Results submission deadline	June 24, 2019
Survey 2019/2 – Interim report available	July/August 2019
Annual meeting of participants	September 3, 2019 (Rotterdam)
Annual Report 2019	December 2019

13. ERNDIM certificate of participation

A combined certificate of participation covering all EQA schemes will be provided to all participants who take part in any ERNDIM scheme. For the DPT scheme this certificate will indicate if results were submitted and whether satisfactory performance was achieved in the scheme.

Date of report, 2019-02-27
Name and signature of Scientific Advisor
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