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Diagnostic Proficiency Testing

Centre: The Netherlands

Final Report 2019

prepared by
Dr. G.J.G. Ruijter and Dr. W. Onkenhout

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 2019, 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
Germany	2
Netherlands	8
South Africa	1
Switzerland	1
United Kingdom	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 2019 have been provided by:

- Erasmus MC, Rotterdam
- AmsterdamUMC, location AMC
- AmsterdamUMC, location VUmc

Patient A: APRT deficiency Common sample provided by DPT Switzerland
Patient B: CMAMMA
Patient C: MSUD
Patient D: MPS I
Patient E: MADD
Patient F: AGAT def

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 4, 2019: shipment of samples
- March 4, 2019: start analysis of samples of the first survey
- March 25, 2019: deadline for result submission (Survey 1)
- May 6, 2019: interim report with preliminary scores of Survey 1 published
- June 3, 2019: start analysis of samples of the second survey
- June 24, 2019: deadline for result submission (Survey 2)
- August 12, 2019: interim report with preliminary scores of Survey 2 published
- September 3, 2019: DPT workshop in Rotterdam
- January28, 2020: 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 2019 have been scored additionally by Dr Petr Chrastina, from DPT CZ. At the SAB meeting in Manchester, November 21-22, 2019, 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 2019 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 letter will be sent by the Scheme Advisor for 2019. 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 12 points out of the maximum of 20 (60%) 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 generally correct for all labs with acceptable CV's.

8.2. Patient A – Adenine phosphoribosyltransferase (APRT) deficiency (OMIM 614723

Patient details provided to participants
The female was admitted to hospital due to a history of pain on passing urine. Had been treated but urine collected off treatment.

Patient details

Sample A was the common sample distributed to participants of all 5 DPT centers and was discussed during the ERNDIM participant meeting in Rotterdam, September 3, 2019 by dr Alessio Cremonesi from Zurich. The presentation showing results and conclusions on this sample can be viewed on the ERNDIM website (erndim.org).

Analytical performance
Out of the 17 participants that have performed purine-pyrimidine analysis in the DPT Netherlands scheme, 15 reported abnormal purines, i.e. elevated adenine (n=12) and/or 2,8-diOH-adenine (n=13). Analytical performance was 64%. The reported concentrations of 2,8-diOH-adenine are shown in Fig. 1.

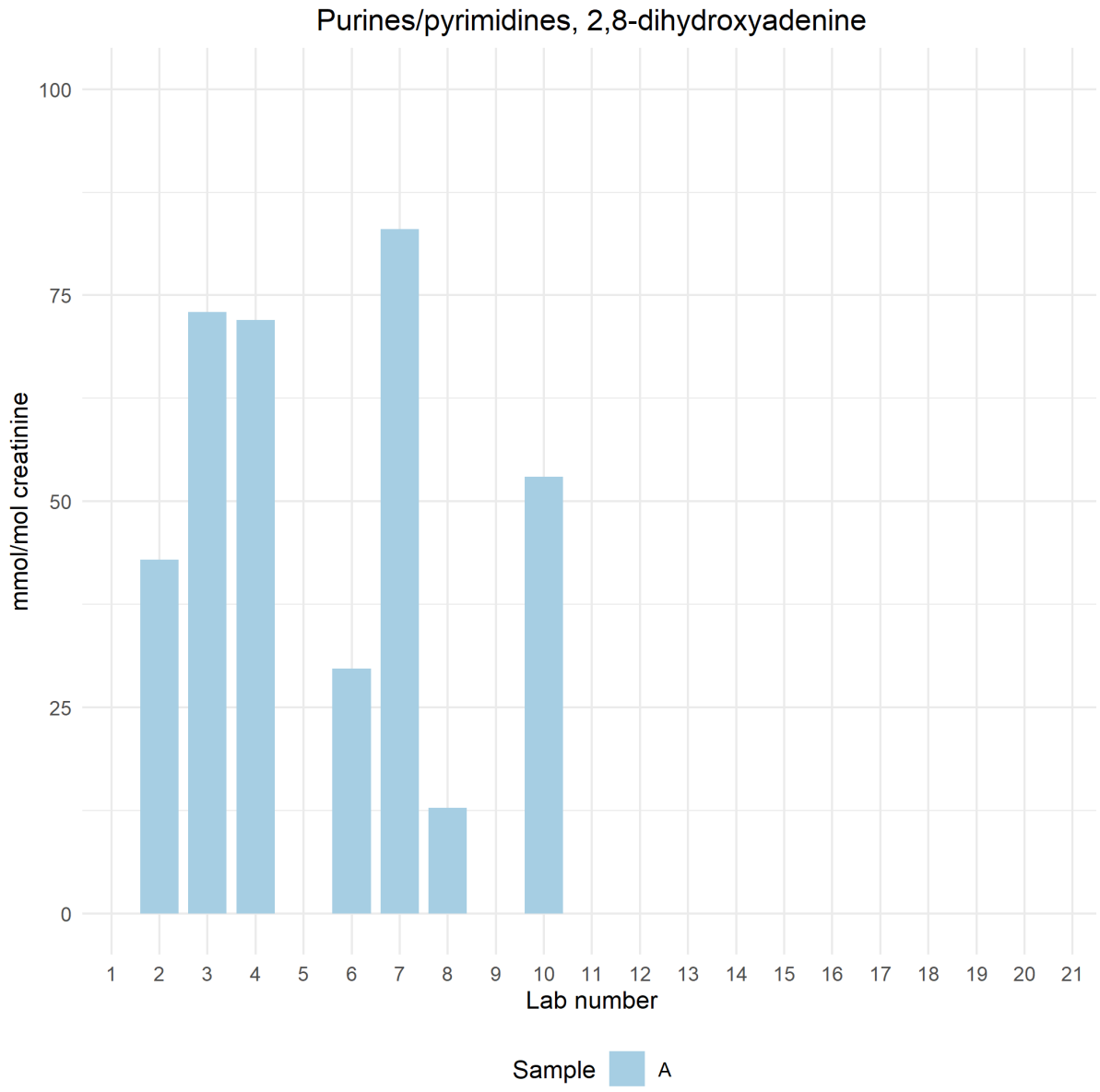

Fig 1

Diagnosis / Interpretative proficiency
As expected all 15 laboratories that detected abnormal adenine/2,8-diOH-adenine correctly concluded APRT deficiency. Four laboratories have not performed purine-pyrimidine analysis, but did recommend this test. Interpretative proficiency was 79%.

Recommendations
Recommendations for further analysis included APRT activity testing (n=9) and APRT mutation testing (n=12). Regarding patient management, a purine-restricted diet, high fluid intake and allopurinol were suggested. Four participants also suggested testing of sibs.

Scoring

- Analytical results: elevated adenine and elevated 2,8-diOH-edanine were each scored 1 point
- Interpretation of results: APRT deficiency: score 2, recommendation to perform purine-pyrimidine analysis: score 1
- Critical error: sample not eligible

Overall impression
Moderate overall proficiency of 71% due to lack of purine-pyrimidine analysis in 4/21 laboratories and

missed key metabolites in 2/21 labs.

Multiple distributions of similar samples
-

8.3. Patient B – Combined malonic and methylmalonic aciduria (CMAMMA; OMIM 614265)

Patient details provided to participants
A 42-year old male referred for peripheral polyneuropathy.

Patient details
The initial finding in this patient was elevated plasma MMA (12 umol/L). Vitamin B12 deficiency was suspected, but supplementation did not result in a decrease in plasma MMA. Subsequent metabolic investigations revealed elevated MA and MMA in urine leading to the diagnosis CMAMMA, which was confirmed by two ACSF3 mutations. Plasma MMA was elevated (12.3 umol/L), but total homocysteine was normal.

Analytical performance
All 21 participants reported elevated methylmalonic acid, whereas only 5 reported elevated malonic acid. Identification of MA either by chromatographic separation from MMA or by SIM (Fig. 2) was key in this sample. Many laboratories use a CP-Sil19 column for their organic acid screening. TMS-derivatised MA and MMA co-elute on this column. Columns with a less polar stationary phase, such as CP-Sil8, will separate MA and MMA (Fig. 3). A SIM of m/z 233 (for TMS-derivatised organic acids) will reveal the presence of MA and enable quantification (Fig. 2). When MA and MMA are not separated by chromatography, a m/z 233 SIM is mandatory to investigate the possibility of malonic aciduria and CMAMMA.
Analytical proficiency was 62%.

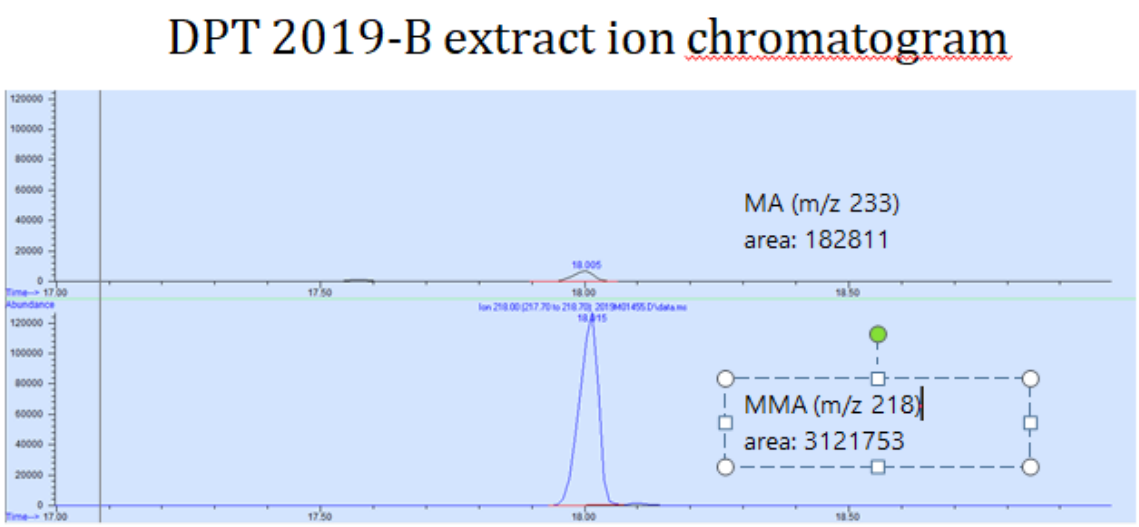

Figure provided by K van Baal, B Prinsen, M de Sain UMC Utrecht

Fig 2

Patient B; organic acids (TMS, CP-Sil 8)

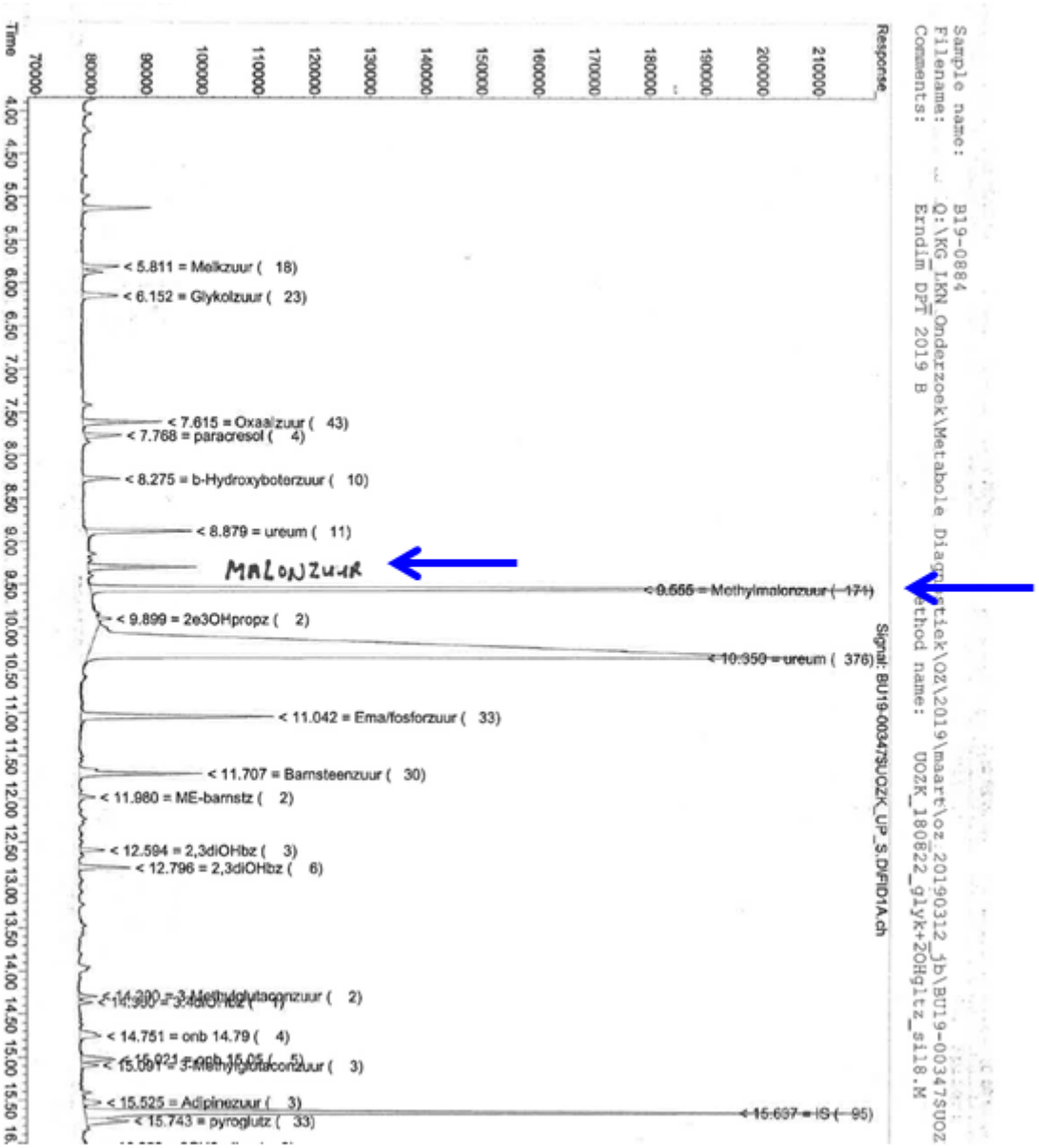

Figure provided by L Kluijtmans, UMC Radboud - Nijmegen

Fig 3

Diagnosis / Interpretative proficiency

Four laboratories concluded combined malonic and methylmalonic aciduria (CMAMMA) as the most likely diagnosis, while one other lab mentioned CMAMMA among the possible explanations for mildly elevated MMA. Vitamin B12 deficiency due to diet or uptake/transport defects was reported by 19 labs. Inborn errors of MMA metabolism (mut, cbl, sucl, epimerase) were considered by 14 participants. In CMAMMA urine samples the ratio MMA/MA typically is 5-10, but may be higher/lower. Plasma homocysteine is not elevated and also propionyl-carnitine is normal in both plasma and urine. In this sample the median concentration values of MA and MA were 20 and 150 mmol/mol, respectively.

An overview of various defects leading to elevated MMA in urine is given in Fig. 4. The ACSF3 protein converts MA to MA-CoA and MMA to MMA-CoA, but the exact role in metabolism is unknown. A function in protein malonylation or metabolite repair are putative roles of this protein (Fig. 5). The clinical relevance of an ACSF3 defect is unclear (e.g. see Levtova et al, J Inherit Metab Dis 2019 Jan;42(1):107-116).

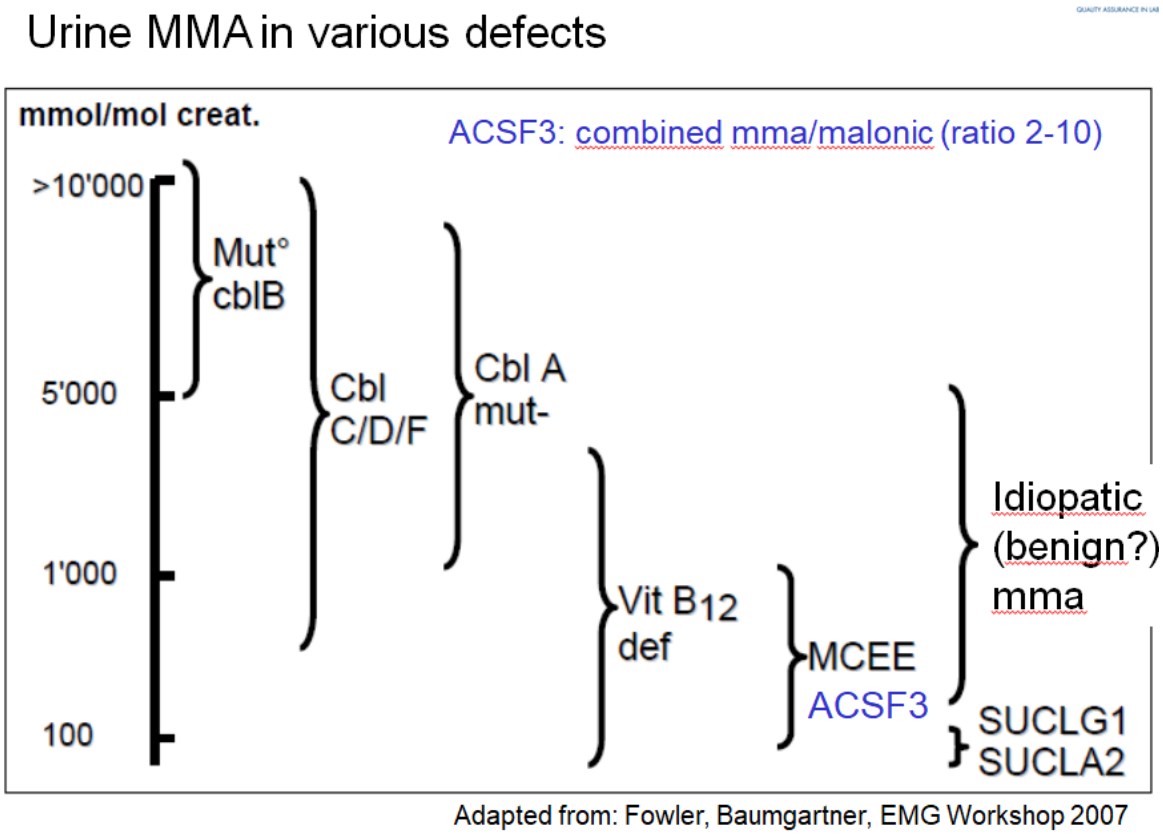

Fig 4

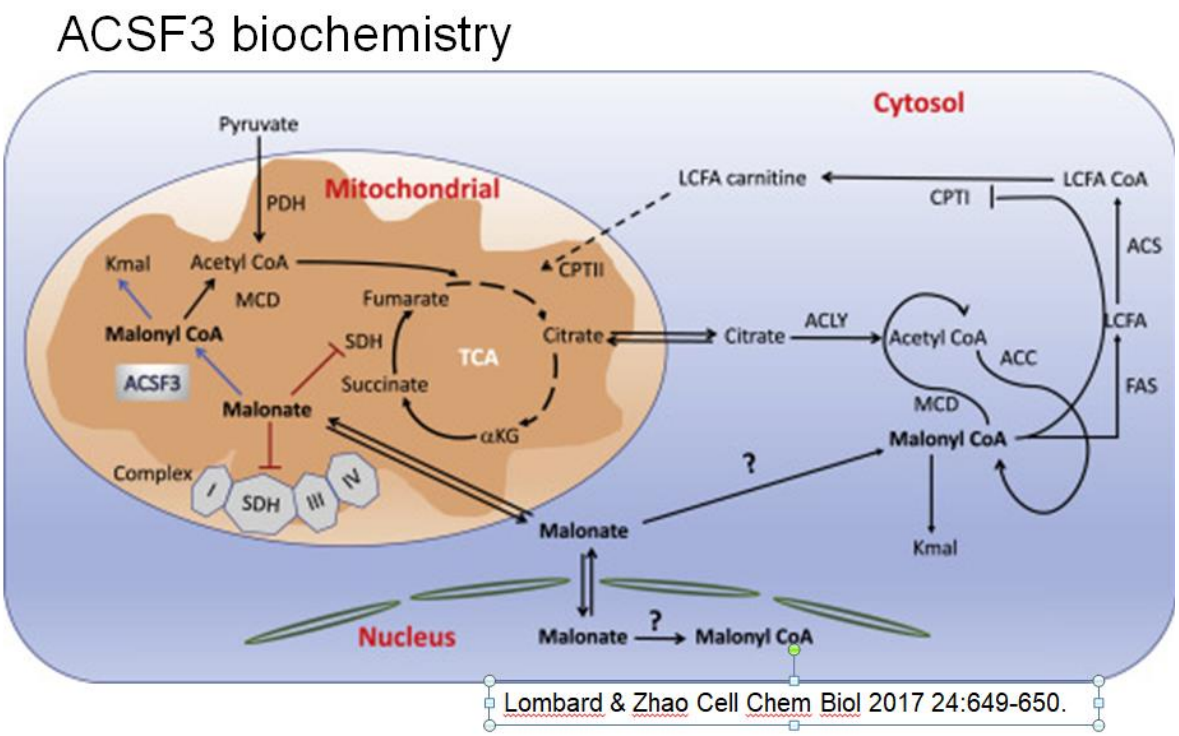

Fig 5

Recommendations

Only 2 participants suggested molecular testing of the ACSF3 gene. During the DPT meeting, September 3, 2019 in Rotterdam, most participants considered ACSF3 mutation testing necessary in this case. Many recommendations were given to further investigate the mild MMA-uria and B12 status.

Scoring

- Analytical results: elevated methylmalonic acid: score 1, elevated malonic acid: score 1
- Interpretation of results: CMAMMA: score 2, vitamin B12 deficiency and/or MMA due to mut/cbl: score 1
- Critical error: sample not eligible

Overall impression

This CMAMMA sample was challenging. Overall proficiency was 62%. Possible explanations are limited knowledge of CMAMMA, co-elution of MMA and MA in most organic acid analysis methods and the relatively low level of MA in this sample. It was debated at the DPT meeting whether this is a representative sample. Given the concentrations and the MMA/MA ratio, it is. The MMA/MA ratio may depend on the exact method used. It must be noted that the DPT remains an artificial situation compared to routine diagnostics. In routine diagnostics MMA and MA may be measured in plasma and ACSF3 gene analysis may be performed.
The ERNDIM SAB has decided, during its meeting November 21-22, 2019, that sample 2019-B will be scored despite the relatively low proficiency.

Multiple distributions of similar samples

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8.4. Patient C – MSUD (OMIM 248600)

Patient details provided to participants

Female admitted in the first week of life with vomiting, poor feeding, hyperventilation and hypertonia.

Patient details

Initial metabolic investigations of this MSUD patient showed increased branched-chain amino acids in plasma and urine, including allo-isoleucine, and very high levels of typical 2-hydroxy-acids, 2-keto acids, lactate and 2-ketoglutarate in urine. The first urine sample of the patient was used in this DPT survey. Deficiency of BCKDH was confirmed on both enzyme and DNA level.

Analytical performance

Clear abnormalities could be detected in both amino acid and organic acid profiles. All participants reported abnormal leucine/valine and 2-keto-/2-hydroxy-acids. The metabolites reported most were lactate, 2-OH-isovaleric acid, 2-keto-3-methylvaleric acid and 2-keto-4-methylvaleric acid. Nine participants reported elevated allo-isoleucine. Elevated 2-keto-glutaric acid was reported by 3 labs, while another 5 reported that 2KG was normal. At the DPT meeting it was mentioned that 2KG is degraded during DPT sample preparation (heating for 1 h at 60 deg C). When 2KG is elevated, this may be suggestive for E3 def, but enzyme testing or mutation analysis is required to establish diagnosis.
Analytical proficiency 100%.

Diagnosis / Interpretative proficiency

The presence of 2-hydroxy-acids, 2-keto acids and elevated leucine/valine suggested MSUD, but because of strongly elevated lactate many participants included DLD/E3 deficiency in their differential diagnosis. MSUD was reported as the most likely diagnosis by 12 participants. Six of these labs considered DLD/E3 deficiency as another possible diagnosis. Eight labs concluded DLD/E3 as the most likely diagnosis with MSUD also possible. Either MSUD or DLD/E3 was scored with 2 points. One participant concluded pyruvate carboxylase as the most likely diagnosis, which is incorrect. Please note that a BCKDH-phosphatase deficiency may mimic BCKDH def.
Interpretative proficiency was high: 95%.

Recommendations

Most participants (18/21) suggested to perform activity and/or mutation testing of the BCKDH complex. Plasma amino acid analysis to confirm MSUD/DLD deficiency was recommended by 17 labs.

Scoring

- Analytical results: elevated leucine/valine: score 1, elevated 2-keto-/2-OH-acids: score 1
- Interpretation of results: MSUD or DLD/E3 deficiency: score 2
- Critical error: failure to conclude MSUD/DLD (n=1)

Overall impression
Sample 2019-C was a clearly abnormal sample with high overall proficiency (98%).

Multiple distributions of similar samples
In 2012 the common sample was a MSUD sample, with mild abnormalities. Overall proficiency was 90% in 2012-F.

8.5. Patient D – Mucopolysaccharidosis type I (OMIM 607015/607016)

Patient details provided to participants
Male, 55 years of age, with skeletal dysplasia, corneal clouding and carpal tunnel syndrome.

Patient details
This MPS I patient with an attenuated phenotype was not under ERT treatment at the time of urine sampling. The diagnosis was confirmed by IDUA enzyme testing.

Analytical performance
All participants reported abnormal GAG test results. Abnormal electrophoresis results (elevated DS or DS+HS) were reported by 12 labs. Six labs used LC-MS/MS to investigate GAGs and reported elevated DS+HS or MPS I-specific oligosacharides. Literature references describing LC-MS/MS analysis of GAG are:

1. Langereis et al PLoS One 2015 10:e0138622 (enzymatic GAG hydrolysis, followed by LC-MS/MS of disaccharides)
2. Zhang et al Mol Genet Metab 2015 114:123-128 (methanolytic GAG hydrolysis, followed by LC-MS/MS of disaccharides)
3. Saville et al Genet Med 2019 21:753-757(LC-MS/MS of GAG-derived (oligo)saccharides derivatised by PMP).

Analytical proficiency was 93%.

Diagnosis / Interpretative proficiency
A number of different combinations of MPS were reported (including I, II, I/II, I/II/VII, VI) for most likely diagnosis. Most participants did mention MPS I (either in most likely diagnosis or in other possible diagnoses) based on GAG/metabolite abnormalities. During the DPT meeting it was discussed whether the HS/DS ratio was discriminative between MPS I and II. Using the methanolysis method the ratio is different, but with some overlap between the 2 disorders. The ratio is not discriminative with the enzymatic hydrolysis-LC-MS method. The Saville method appears superior and able to distinguish all MPS types. Mucolipidosis (type 2/3) and multiple sufatase deficiency were mentioned as other possible diagnosis. Mucolipidosis seems less likely, since in mucolipidosis type 2 abnormalities in oligosacharides are expected and in mucolipidosis type 3, GAG are usually not strongly abnormal. Multiple sulfatase deficiency is very rare; it is not clear whether mild presentations exist which show elevated GAG in urine.
Interpretative proficiency was 90%.

Recommendations
IDUA enzyme testing was proposed by 18 labs, while 17 suggested (IDUA) mutation testing.

Scoring

- Analytical results: Elevated total GAG, established by e.g. the DMB-test, was scored 1. Abnormal GAG results in electrophoresis/TLC: score 1. MS tests: elevated DS+HS or MPS I-specific oligosacharides: score 2.
- Interpretation of results: MPS I: score 2, Mucopolysacharidosis unspecified or wrong type MPS: score 1.
- Critical error: failure to report abnormal GAG or MPS (n=0)

Overall impression
Obvious MPS sample with high overall proficiency (92%).

Multiple distributions of similar samples
Sample 2015-A was obtained from an adult MPS II. Overall proficiency in 2015-A was 90%, which is similar to the score of 2019-D.

8.6. Patient E – Multiple acyl-CoA dehydrogenase deficiency (MADD; glutaric aciduria type II) subtype ETFA (OMIM 231680)

Patient details provided to participants
A girl, born in hospital after a normal pregnancy. She was investigated at age 2 days because of lethargy. No obvious dysmorphic features were observed. The sample was collected at age 8 y.

Patient details
This girl was diagnosed shortly after birth with a severe form of MADD. Mutations were detected in ETFA.

Analytical performance
All participants reported abnormal organic acids. Organic acids reported included glutaric acid, 2-OH-glutaric acid, ethymalonic acid, adipic acid, suberic acid, sebacic acid, hexanoylglycine, (iso)butyrylglycine, isovalerylglycine, methylsuccinate, 5-OH-hexanoic acid, octanoic acid, 3-OH-isobutyric acid and 3-OH-isovaleric acid, Since the patient was decompensated during urine sampling also lactate and 3-OH-butyric acid were slightly elevated.
Sarcosine dehydrogenase also requires ETF for electron transfer, but sarcosine was not reported by participants.

Diagnosis / Interpretative proficiency
All participants correctly interpreted the OA profile as characteristic for MADD. In other possible diagnoses several participants mentioned riboflavin metabolism/transport defects (n=5), SCADD (n=2) and MCADD (n=1). Given the organic acid profile, SCADD and MCADD are very unlikely. A riboflavin defect cannot be excluded based on the test results, but is less likely with the clinical symptoms of the patient.

Recommendations
Most participants recommended acylcarnitine analysis in plasma and mutation analysis of ETFA, ETFB and ETDH genes. Six labs suggested to investigate fatty acid oxidation flux in fibroblasts. Riboflavin therapy was suggested by 13 participants, while 3 recommended SLC52A1-3, SLC25A32 and FLAD1 mutation analysis.

Scoring
- Analytical results: abnormal organic acids typical for MADD: score 2.
- Interpretation of results: MADD: score 2
- Critical error: failure to report abnormal organic acids and MADD (n=0)

Overall impression
Sample with grossly abnormal organic acid profile. Overall proficiency was 100%.

Multiple distributions of similar samples
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8.7. Patient F – L-arginine:glycine amidinotransferase (AGAT) deficiency (OMIM 612718, Cerebral Creatine Deficiency Syndrome 3; CCDS3)

Patient details provided to participants
A boy with delayed mental and motor development apparent since the age of 15 months. Diagnosis was made at age 7 y, while the sample was collected at age 8 y.

Patient details
AGAT deficiency was confirmed in this patient by undetectable enzyme activity and homozygosity for a null mutation in the GATM gene. The patient was not on creatine supplementation during collection

of the sample.

Analytical performance
Guanidinoacetate and creatine were measured by 13/21 participants and all these labs reported low/decreased guanidinoacetate. The median concentration of guanidinoacetate was 0.1 mmol/mol (range 0–3, n=11). Creatine median value was 46 mmol/mol (range 0–53, n=12). Creatinine, which is a degradation product of creatine, was relatively low in this sample (2.83 mmol/L), but is not a reliable biomarker for creatine biosynthesis disorders.
Many laboratories commented on increased concentrations of amino acids, uric acid, GAG and sialic acid. This is due to the relatively low creatinine concentration and the resulting elevated values of other metabolites normalised to creatinine (see e.g. Verhoeven et al Clinica Chimica Acta 2005, 361; 1-9).

Diagnosis / Interpretative proficiency
AGAT deficiency was reported as the most likely diagnosis by 12 labs. Other diagnoses reported were: carnosinase def (n=1), Sandhoff disease (n=1), defects in purine metabolism (HPRT, PRPS), isobutyrylCoA DH deficiency (n=1), SSADH deficiency (n=1), ETFDH deficiency(n=1) and MPS (n=3). These are probably related to the secondary abnormalities in various metabolites due to the low creatinine.
Secondary causes of low guanidinoacetate excretion include hyperornithinemia (OAT deficiency) and UCD defects when arginine is low. Low urine guanidinoacetate is not uncommon. Further testing includes measurement of plasma guanidinoacetate.

Recommendations
AGAT enzyme testing and GATM mutation analysis were the suggestions made for further testing. Two participants, that did not measure guanidinoacetate and creatine, suggested to do this test.

Scoring
The ERNDIM SAB has decided, during its meeting November 21-22, 2019, that sample 2019-F will be educational and will NOT be scored.

Overall impression
Moderate overall proficiency, mainly because a number of participants did not measure creatine and guanidinoacetate. We recommend to include creatine and guanidinoacetate tests in metabolic screening. A lower limit of the guanidinoacetate reference range (i.e. not zero) is required to detect AGAT deficiency. Elevated values of many unrelated metabolites should prompt testing of creatine biosynthesis disorders.

Multiple distributions of similar samples
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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 APRT deficiency			Patient B CMAMMA			Patient C MSUD			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	2	4	1	2	3	2	2	4	11
2	2	2	4	1	1	2	2	2	4	10
3	2	2	4	1	1	2	2	2	4	10
4	2	2	4	1	1	2	2	2	4	10
5	2	2	4	2	2	4	2	2	4	12
6	2	2	4	1	1	2	2	2	4	10
7	2	2	4	2	2	4	2	2	4	12
8	2	2	4	1	1	2	2	2	4	10
9	2	2	4	1	1	2	2	2	4	10
10	2	2	4	2	2	4	2	2	4	12
11	0	0	0	1	1	2	2	2	4	6
12	1	2	3	1	1	2	2	2	4	9
13	0	1	1	2	1	3	2	2	4	8
14	1	2	3	1	1	2	2	2	4	9
15	0	1	1	2	2	4	2	0	2	7
16	0	0	0	1	1	2	2	2	4	6
17	0	0	0	1	1	2	2	2	4	6
18	2	2	4	1	1	2	2	2	4	10
19	0	1	1	1	1	2	2	2	4	7
20	1	2	3	1	1	2	2	2	4	9
21	2	2	4	1	1	2	2	2	4	10

Detailed scores – Round 2

Lab n°	Patient D MPS I			Patient E MADD			Patient F AGAT def			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	2	4	2	2	4	--	--	--	8
2	2	2	4	2	2	4	--	--	--	8
3	2	2	4	2	2	4	--	--	--	8
4	2	2	4	2	2	4	--	--	--	8
5	2	2	4	2	2	4	--	--	--	8
6	1	1	2	2	2	4	--	--	--	6
7	2	2	4	2	2	4	--	--	--	8
8	2	2	4	2	2	4	--	--	--	8
9	2	2	4	2	2	4	--	--	--	8
10	2	2	4	2	2	4	--	--	--	8
11	1	1	2	2	2	4	--	--	--	6
12	2	2	4	2	2	4	--	--	--	8
13	1	1	2	2	2	4	--	--	--	6
14	2	2	4	2	2	4	--	--	--	8
15	2	2	4	2	2	4	--	--	--	8
16	2	2	4	2	2	4	--	--	--	8
17	2	1	3	2	2	4	--	--	--	7
18	2	2	4	2	2	4	--	--	--	8
19	2	2	4	2	2	4	--	--	--	8
20	2	2	4	2	2	4	--	--	--	8
21	2	2	4	2	2	4	--	--	--	8

Total scores

Lab n°	A	B	C	D	E	F	Cumulative score	Cumulative score (%)	Critical error
1	4	3	4	4	4	--	19	95	
2	4	2	4	4	4	--	18	90	
3	4	2	4	4	4	--	18	90	
4	4	2	4	4	4	--	18	90	
5	4	4	4	4	4	--	20	100	
6	4	2	4	2	4	--	16	80	
7	4	4	4	4	4	--	20	100	
8	4	2	4	4	4	--	18	90	
9	4	2	4	4	4	--	18	90	
10	4	4	4	4	4	--	20	100	
11	0	2	4	2	4	--	12	60	
12	3	2	4	4	4	--	17	85	
13	1	3	4	2	4	--	14	70	
14	3	2	4	4	4	--	17	85	
15	1	4	2	4	4	--	15	75	CE
16	0	2	4	4	4	--	14	70	
17	0	2	4	3	4	--	13	65	
18	4	2	4	4	4	--	18	90	
19	1	2	4	4	4	--	15	75	
20	3	2	4	4	4	--	17	85	
21	4	2	4	4	4	--	18	90	

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 (%)
DPT-NL-2019-A	APRT deficiency	64	79	71
DPT-NL-2019-B	CMAMMA	62	62	62
DPT-NL-2019-C	MSUD	100	95	98
DPT-NL-2019-D	MPS I	93	90	92
DPT-NL-2019-E	MADD	100	100	100
DPT-NL-2019-F	AGAT def	--	--	--

10. Annual meeting of participants

The annual DPT workshop was organised in Rotterdam, September 3rd 2019. Representatives from 12 participating labs were present.

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
- For the Neurotransmitters in CSF, Pterins in Urine and Cystine in WBC pilots for scoring of interpretation will be introduced in the 2020 schemes.
- **Training**: SSIEM Academy training courses. A 2-day course will be organized on 21 and 22 April 2020 in Amsterdam. The program includes: Aminoacidopathies, Hyperammonaemia and Urea Cycle Defects.
- **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:

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

12. Tentative schedule in 2020

Sample distribution	February 11, 2020
Start of analysis of Survey 2020/1 (website open)	March 9, 2020
Survey 2020/1 - Results submission deadline	March 30, 2020
Survey 2020/1 – Interim report available	April/May 2020
Start of analysis of Survey 2020/2 (website open)	June 8, 2020
Survey 2020/2 – Results submission deadline	June 29, 2020
Survey 2020/2 – Interim report available	July/August 2020
Annual meeting of participants	September 1, 2020 (Freiburg)
Annual Report 2020	January 2021

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, 2020-02-04
Name and signature of Scientific Advisor

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