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Diagnostic Proficiency Testing Centre: The Netherlands Final Report 2020

prepared by
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Published: 17 February 2021[1]

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.

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 performance of your laboratory, unless ERNDIM is required to disclose performance data by a relevant government agency. For details, please see the terms and conditions in the EQA Schemes Catalogue and Participant Guide and the ERNDIM Privacy Policy on www.erndim.org.

The ERNDIM Diagnostic Proficiency Testing (DPT) Scheme is the ultimate external quality assessment scheme for biochemical genetics laboratories. In 2020, 19 labs participated to the Proficiency Testing Scheme NL.

1. Geographical distribution of participants

For both surveys, all 19 participants have submitted results.

Country	Number of participants	Country	Number of participants
Australia	2	Netherlands	8
Belgium	5	South Africa	1
Czech Republic	1	Switzerland	1
Germany	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 and Anthony Barrozo 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

[1] If these scheme instructions are not Version 1 for this scheme year, go to APPENDIX 1 for details of the changes made since the last version of this document

2 surveys	Round 1: patients A, B and C
	Round 2: patients D, E and F

Origin of samples: Samples used in 2020 have been provided by:

- Radboud UMC, Nijmegen
- UZA, Antwerpen

Patient A: PKU Common sample provided by DPT France
Patient B: AGU
Patient C: GA I
Patient D: Hyperoxaluria type 1
Patient E: HMG-CoA-lyase deficiency
Patient F: MNGIE

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 normally allotted for submitting reports is 3 weeks after opening of the website. Due to COVID-19, the submission deadline of survey 1 was extended (see item 4). 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, quantitative GAG and 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 11, 2020: shipment of samples
- March 9, 2020: start analysis of samples of the first survey
- June 1, 2020: extended deadline (due to COVID-19) for result submission of survey 1
- June 24, 2020: interim report with preliminary scores of survey 1 published
- June 8, 2020: start analysis of samples of the second survey
- June 29, 2020: deadline for result submission of survey 2
- August 6, 2020: interim report with preliminary scores of survey 2 published
- September 1, 2020: DPT discussion (online meeting)
- December 22, 2020: annual report with final scoring published

5. Results

Due to COVID-19, results were submitted late by 2 participants for survey 1. One participant submitted results 1 week after the original deadline. Another participant could not submit results online due to closure of the website and submitted results of survey 1 by email two weeks after the deadline of June 1st. For survey 2 all participants submitted results on time.

	Survey 1	**Survey 2**
Receipt of results	19	19
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 2020 have been scored additionally by Dr Deborah Mathis and Dr Brian Fowler, from DPT Switzerland. At the SAB meeting, November 19-20, 2020, 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 2020 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 2020. 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.

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.

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 (5-10%). CV's were relatively high for the 2 samples with low creatinine (2020-E, median value 0.6 mmol/L, CV 10% and 2020-F, median 1.6 mmol/L, CV 7.5%). One clearly incorrect value was noticeable in sample C (6.9 mmol/L, median 3.7), but no systematic errors were present.

8.2. Patient A – Phenylketonuria due to PAH mutations.

Patient details provided to participants
Adult patient investigated due to spastic paraparesis, leukodystrophy and hemolytic uremic syndrome

Patient details
Sample A was the common sample distributed to participants of all 5 DPT centers and provided by Dr Begoña Merinero and Dr Pedro Ruiz-Sala from Madrid, Spain. The urine samples was obtained from a previously undiagnosed (and untreated) patient with phenylketonuria (PKU). He did not benefit from neonatal screening.

Analytical performance
Elevated phenylalanine was reported by 17 of the 19 participants and all but one participant reported abnormal organic acids characteristic of PKU. The following abnormal organic acids were mentioned: phenyllactic, phenylpyruvic, phenylacetic, mandelic, 4-OH-phenyllactic and 2-OH-2-phenylacetic. Less commonly mentioned compounds were phenylacetylglutamine and N-acetyl-phenylalanine, which were reported by only 2 participants. N-acetyl-phenylalanine elutes in the range of azelaic acid - hippuric acid and the spectrum of TMS-derivatised N-acetyl-phenylalanine is shown in Fig. 1.
One laboratory mentioned a normal result for pterin analysis.
Analytical proficiency was 92%

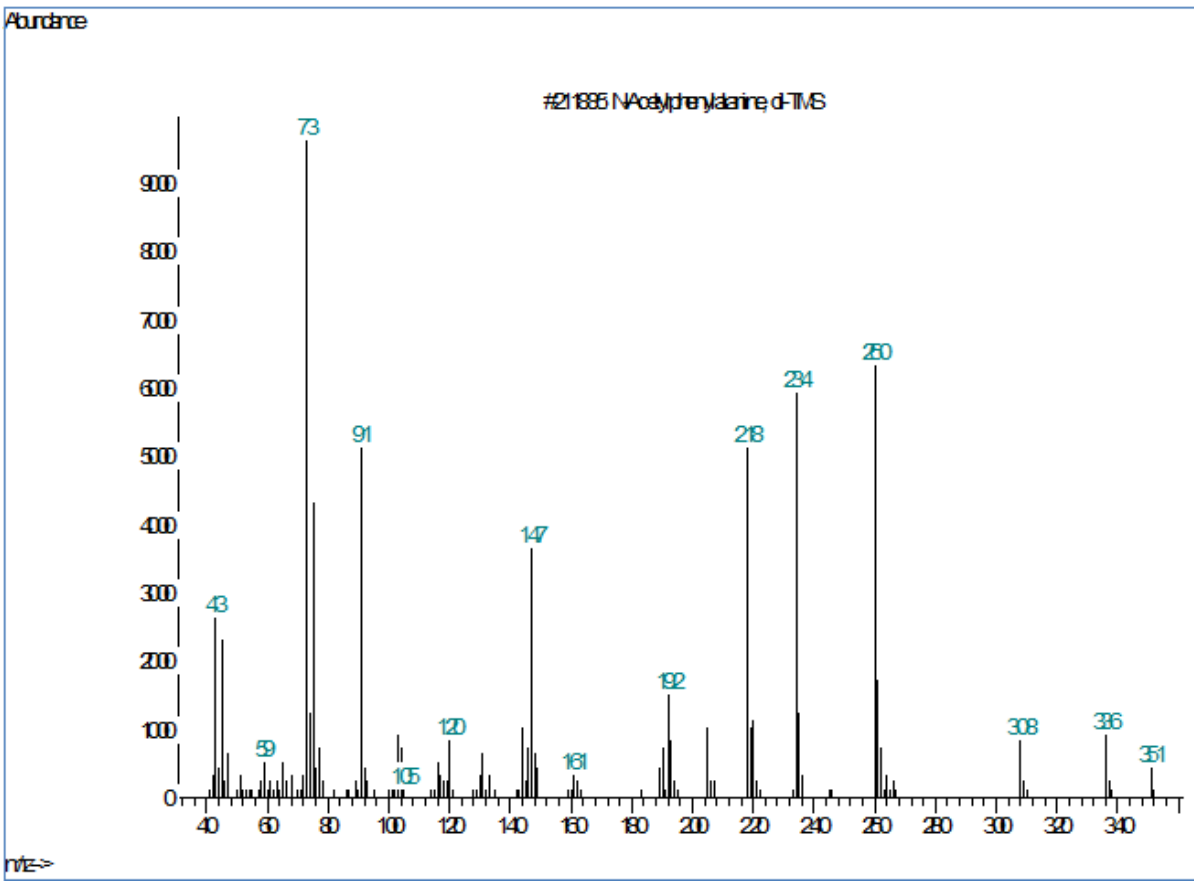

Fig. 1. MS-spectrum of TMS-derivatised NAc-pehnylalanine (provided by Dr Merinero and Dr

Ferrer, Madrid).

Diagnosis / Interpretative proficiency
PKU was concluded by 18 participants. Various 'other possible' diagnoses were mentioned such as pterin defects and, the recently described, DNAJC12 deficiency.
HUS is probably not explained by PKU, so the patient may have suffered from another disease. A possible relation between hemolysis and PKU has been described by Anand et al, Sci Rep (2017) 7(1):11146. doi: 10.1038/s41598-017-10911-z2017).
Interpretative proficiency was 97%.

Recommendations for further analysis
Only 12 out of 19 labs advised to measure plasma/serum amino acids. Other recommendations mentioned were: analysis of pterins in urine or CSF (13), a BH4 loading test (7), DHPR enzyme activity test (8) and mutation testing of PAH (9), genes of pterin metabolism (5) and DNAJC12 (4).

Scoring
- Analytical results: Increase of phenylalanine: score 1; increase of at least one organic acid present in PKU: score 1
- Interpretation of results: PKU as a first or alternative diagnosis: score 2; hyperphenylalaninemia: score 1
- Critical error: failure to report elevated phenylalanine, abnormal organic acids and PKU. Number of occurrences: 1

Overall impression
Easy DPT sample with high overall proficiency of 95%.

Multiple distributions of similar samples
None

8.3. Patient B – Aspartylglucosaminuria (OMIM 208400)

Patient details provided to participants
A 6 year old, slightly dysmorphic, male with delayed development, in particular speech and fine motor skills, abnormal behaviour and frequent upper airway and inner ear infections. He currently is 29 years old and severely retarded.

Patient details
The diagnosis was confirmed by deficiency of AGA enzyme activity in WBC.

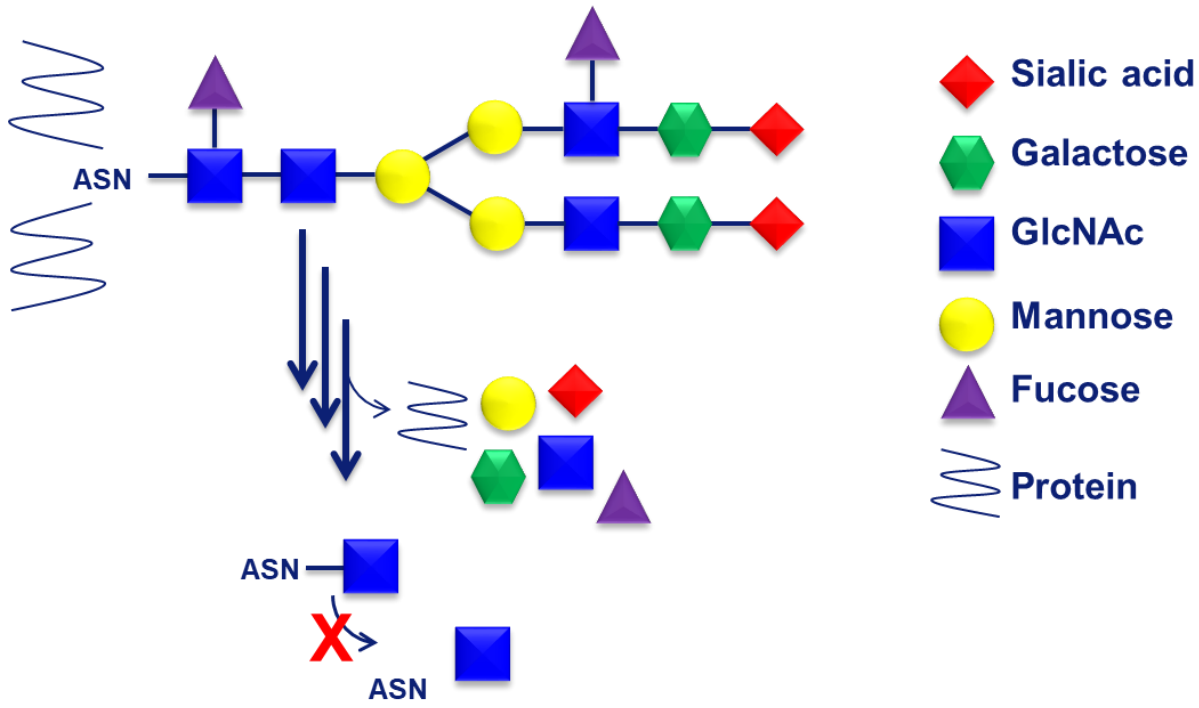

Fig.2. Oligosaccharide metabolism in aspartylglucosaminuria.

Analytical performance
Aspartylglucosamine is the primary storage compound in aspartylglucosaminuria (Fig. 2). Elevated aspartylglucosamine in amino acid analysis (see Fig. 3) was reported by 15 participants. Oligosaccharide analysis (see Fig. 4) was performed by 18 labs and 17 reported an abnormal result, while one participant interpreted the oligosaccharide pattern as borderline. Two participants mentioned abnormal results after ninhydrin-staining of the TLC plate. Three labs reported results from oligosaccharide analysis by LC-MS. Elevated conjugated sialic acid can be expected in aspartylglucosaminuria and was report by 2 participants.
Analytical proficiency was 95%.

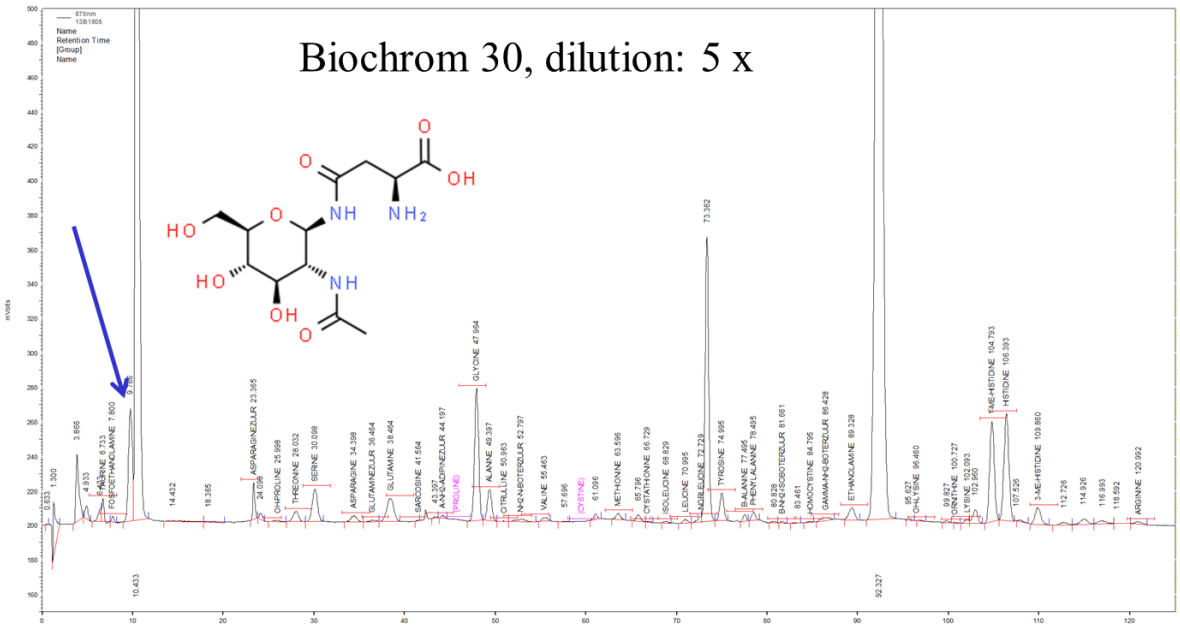

Fig. 3. Aspartylglucosamine elutes before urea using Biochrom30 amino acid analysis.

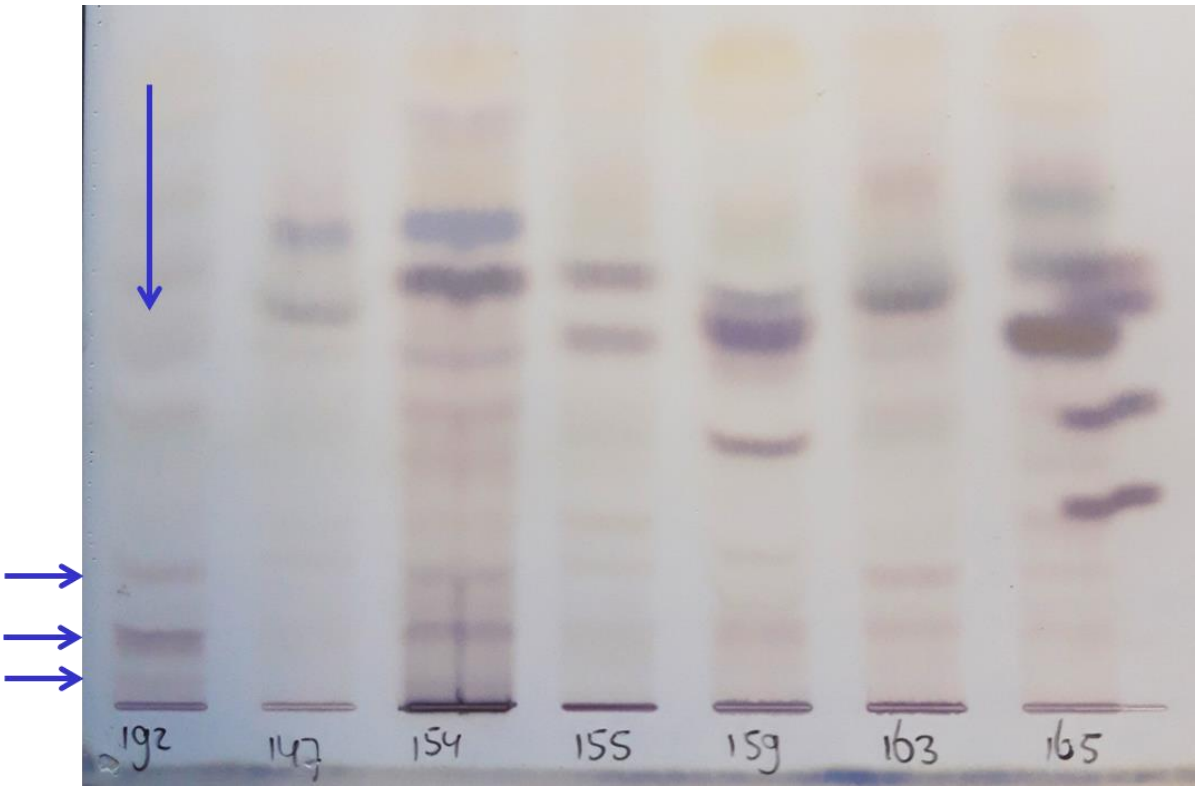

Fig. 4. Oligosacharide analysis by TLC. Arrow indicates sample 2020-B.

Diagnosis / Interpretative proficiency
Aspartylglucosaminuria was reported as the most likely diagnosis by 17 out of 19 participants. GM1 gangliosidosis was concluded by one lab, while another concluded MPS III as a diagnosis. The GAG level was, however, borderline in this sample and probably secondary to lysosomal dysfunction. Interpretative proficiency was 89%.

Recommendations
Aspartylglucosaminidase testing in WBC/fibroblasts was suggested by 11 participants, while 17 adviced AGA mutation testing.

Scoring
- Analytical results: Elevated aspartylglucosamine and/or AGU oligosaccharide pattern: score 2; Abnormal oligosaccharide pattern (incorrect/not specified): score 1
- Interpretation of results: Aspartylglucosaminuria : score 2
- Critical error: no critical errors were identified for this sample

Overall impression
Surprisingly high overall proficiency, 92%, for this extremely rare disorder.

Multiple distributions of similar samples
In 2013 proficiency was 83% in a similar sample.

8.4. Patient C – Glutaric aciduria type I (OMIM 231670)

Patient details provided to participants
This boy presented at age 1 year with dystonic movements after an upper airway infection. The urine was sampled at age 9 y when he received specific treatment.

Patient details
Patient with the classic biochemical phenotype of glutaric aciduria type I. He is treated with carnitine supplementation.

Analytical performance
All participants reported increased urinary excretion of glutaric acid and 18/19 reported elevated 3-OH-glutaric acid. Elevated glutaryl-carnitine was reported by 8 participants. Glutaryl-carnitine in urine is a very good biomarker for GA I (Tortorelli et al, 2005, Mol Gen Metab 84, 137-143).

Diagnosis / Interpretative proficiency
As expected, glutaric aciduria type I was concluded by all participants.
The differential diagnosis of IEM's causing dystonia in infancy is rather short and includes: Pelizaeus-Merzbacher, L-2-OH-glutaric aciduria, Glutaric acidemia type I, MMA/cbl and propionic academia. In most cases organic acid analysis is required to establish diagnosis.
Upon finding elevated glutaric acid, 3 different disorders are possible: GA I, II and III. GA II (MADD) is unlikely with no other abnormalities in the organic acids (such as ethylmalonic acid and 2-OH-glutaric acid). In GA III (SUGCT deficiency) only glutaric acid is elevated and C5DC and 3-OH-glutarate are normal.

Recommendations
Mutation analysis of the GCDH gene was adviced by all participants, while 12 also suggested to measure glutaryl-CoA dehydrogenase activity in lymphocytes/fibroblasts. Only 10 participants recommended to analyse/monitor carnitine in plasma/DBS.

Scoring
- Analytical results: Glutarate + 3-OH-glutarate and/or C5DC-carnitine elevated: score 2
- Interpretation of results: GA I: score 2
- Critical error: Failure to report elevated glutarate, 3-OH-glutarate, C5DC and GA I. Number of occurrences: 0

Overall impression
Overall proficiency was 100%.

Multiple distributions of similar samples
In 2015 a urine sample obtained from a GA I 'low excretor' was circulated (2015-F). Overall proficiency was 95% for that sample.

8.5. Patient D – Hyperoxaluria type 1 (OMIM 259900)

Patient details provided to participants
Male, 26 y, presenting with kidney stones.

Patient details
This patient was known since the age of 3 with calcium oxalate stones, but was diagnosed in adulthood with hyperoxaluria type I. AGT activity was decreased in liver: 7.2 nmol/mg/min; control 93, confirming the diagnosis.

Analytical performance
Oxalic acid was reported by 17 participants; 15 found elevated oxalate, while 2 labs reported a normal and borderline oxalate level. Glycolic acid (n=17) was reported to be elevated by 16 labs and normal by one laboratory. Six participants explicitly reported normal glyceric acid (typically elevated in hyperoxaluria type II / GRHPR deficiency), while 2 labs reported normal 4-OH-glutamate/4-OH-2-ketoglutarate (elevated in hyperoxaluria type III / HOGA deficiency). Oxalate metabolism is depicted in Fig. 5.
Some comments on methodology: the following techniques were reported for oxalic acid analysis: organic acid screening (n=10), GC-MS (n=7), ion chromatography (n=1) and 'other' (n=1). From the 10 labs that used organic acid screening, 8 reported elevated oxalate and 2 normal level. Users of other methods all reported elevated oxalate. This may suggest that GC-MS (with isotope dilution?) or specific methods give superior results.

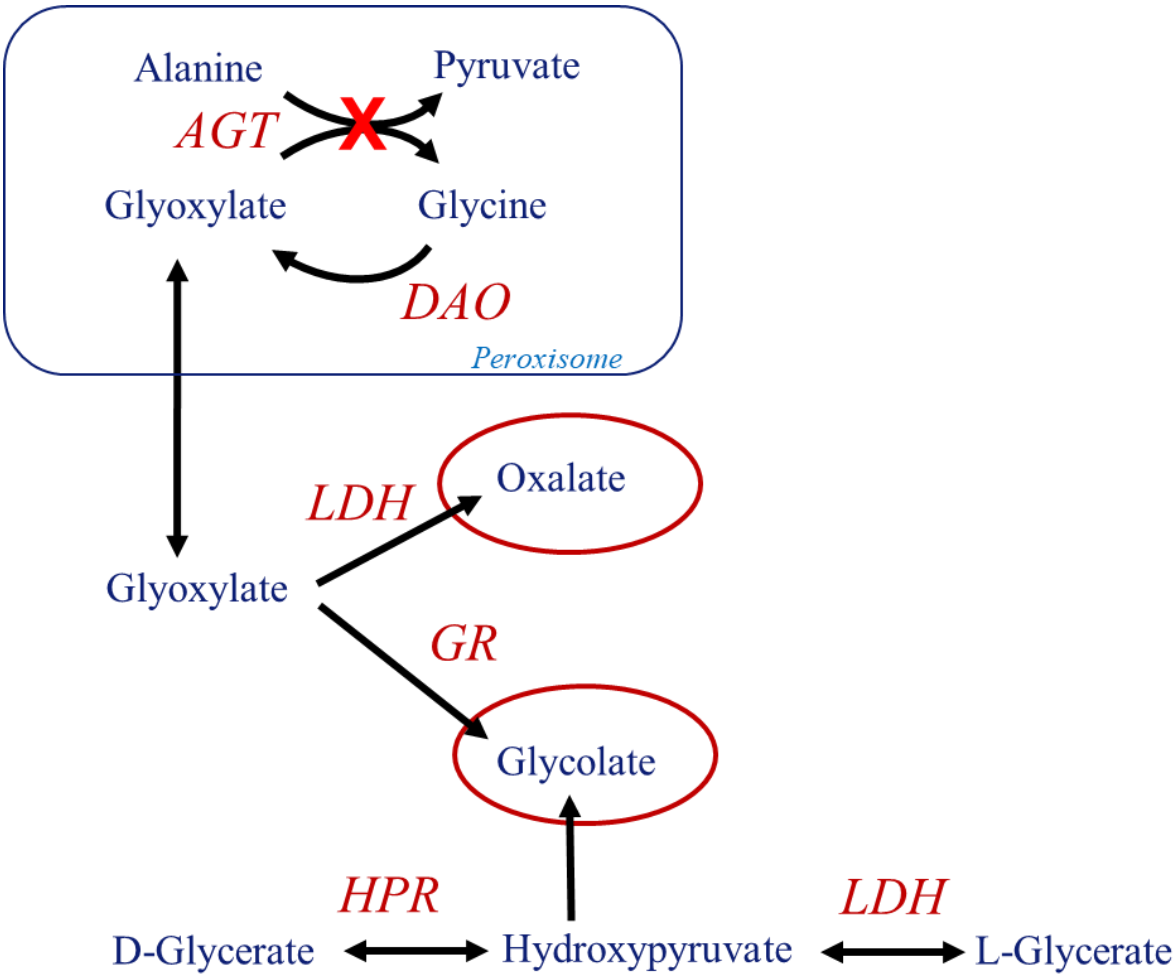

Fig. 5. Oxalate metabolism in hyperoxaluria type I.

Diagnosis / Interpretative proficiency
Hyperoxaluria type I was mentioned as the most likely or possible diagnosis by 16 participants. Since the oxalate concentration was not very high in this sample, increased glycolic acid was important to come to the correct diagnosis. No diagnosis was concluded by 3 participants. Under 'other possible' diagnoses, 7 labs suggested hyperoxaluria's type II/III or secondary causes of high oxalate/glycolate.

Recommendations
The following recommendations were frequently reported: genetic analysis of the AGT gene (n=15), repeat analysis of oxalate/glycolate in another urine sample with acidification (n=6), crystal/stone analysis (n=5), analysis of oxalate/glycolate in plasma (n=4) and investigation of B6 responsiveness (n=8). Testing of sibs was suggested by 3 participants. The latter seems to be a valuable advice in this case of mild PH I.

Scoring
- Analytical results: Elevated oxalic and glycolic acid: score 2; elevated oxalic or glycolic acid: score 1
- Interpretation of results: Hyperoxaluria type 1: score 2; advice to measure oxalate: score 1
- Critical error: no potential critical errors were identified for this sample

Overall impression
Overall proficiency was 86%.
The questions remains whether a spot urine sample is sufficient for hyperoxaluria screening. The results suggest that screening of just oxalate in urine samples is not sufficiently sensitive to find all PH I patients. During the DPT discussion a suggestion was made to always measure glycolate and glycerate in addition to oxalate, preferably quantitatively, i.e. by isotope dilution methodology. Another remark was that urine must be acidified before analysis, since this improves oxalate solubility. It is,

however, NOT crucial to acidify directly at sampling (Van Woerden et al, 2007, Clin Chim Acta 384, 184-185).

Multiple distributions of similar samples
This sample was also circulated in 2015 and 2008 (samples 2008-C, 2015-C). In 2008 the proficiency was 71% and in 2015 73%. Strikingly, the median oxalate concentration in 2020 (approx. 200 mmol/mol) was double the value calculated in 2015 (approx. 100 mmol/mol). This may be related to heating of the sample to 37 deg before aliquoting by the scheme organizer. In 2020, 15/17 labs reported high oxalate, while in 2015 this ratio was 11/18. Glycolate median values were similar in 2020 (240 mmol/mol) and 2015 (251) , but still a larger number of labs reported an elevated value in 2020 (16/17) compared to 2015 (13/15). In conclusion, higher proficiency in 2020 may be explained by a higher oxalate concentration and by a larger number of labs measuring the relevant compounds.

8.6. Patient E – 3-Hydroxy-3-methylglutaryl coenzyme A lyase (HMG-CoA-lyase) deficiency (OMIM 246450)

Patient details provided to participants
This girl started to vomit at the age of 3 days. She developed lethargy and convulsions with acidosis and hypoglycemia. The urine sample was taken at age 1 month when she was in stable condition.

Patient details
Patient with neonatal presentation of HMG-CoA lyase deficiency. She is treated with carnitine supplementation.

Analytical performance
All participants reported increased urinary excretion of the expected organic acids, i.e. HMG, 3-methylglutaric acid, 3-methylglutaconic acid, 3-OH-isovaleric acid and 3-methylcrotonylglycine.

Diagnosis / Interpretative proficiency
As expected, HMG-CoA lyase deficiency was concluded by all participants.

Recommendations
Mutation analysis of the HMGCL gene was adviced by 16 participants, while 11 suggested to measure HMG-CoA lyase activity in lymphocytes/fibroblasts. Only 9 participants recommended to analyse/monitor carnitine in plasma/DBS.

Scoring
- Analytical results: Elevated level of at least 3 of the typical organic acids (HMG, 3-methylglutarate, 3-methylglutaconate, 3-OH-isovalerate, 3-methylcrotonylglycine): score 2
- Interpretation of results: HMG-CoA lyase deficiency: score 2
- Critical error: Failure to report any of the typical OA and HMGCL deficiency. Number of occurrences: 0

Overall impression
Overall proficiency was 100%.

Multiple distributions of similar samples
None

8.7. Patient F - Mitochondrial NeuroGastroIntestinal Encephalopathy (MNGIE) due to thymidine phosphorylase deficiency (OMIM 603041)

Patient details provided to participants
A 15 year-old female with myopathy, severe cachexia, leukodystrophy and slight psychomotor retardation.

Patient details
Diagnosis was confirmed by two TYMP mutations. Treatment by BMT was unsuccesful.

Analytical performance
Seventeen labs performed purine-pyrimidine analysis and all reported elevated thymidine and/or deoxyuridine (and thymine, uracil); see Fig. 6 for thymidine values. Deoxyuridine values (median 57 mmol/mol) were slightly higher than thymidine values (22). Two participants reported pyrimidines based on organic acid analysis. One of these 2 labs reported increased deoxyuridine, thymine and uracil and another reported increased thymine and uracil only. Analytical proficiency was 97%.
Many labs reported elevated excretion of various organic acids

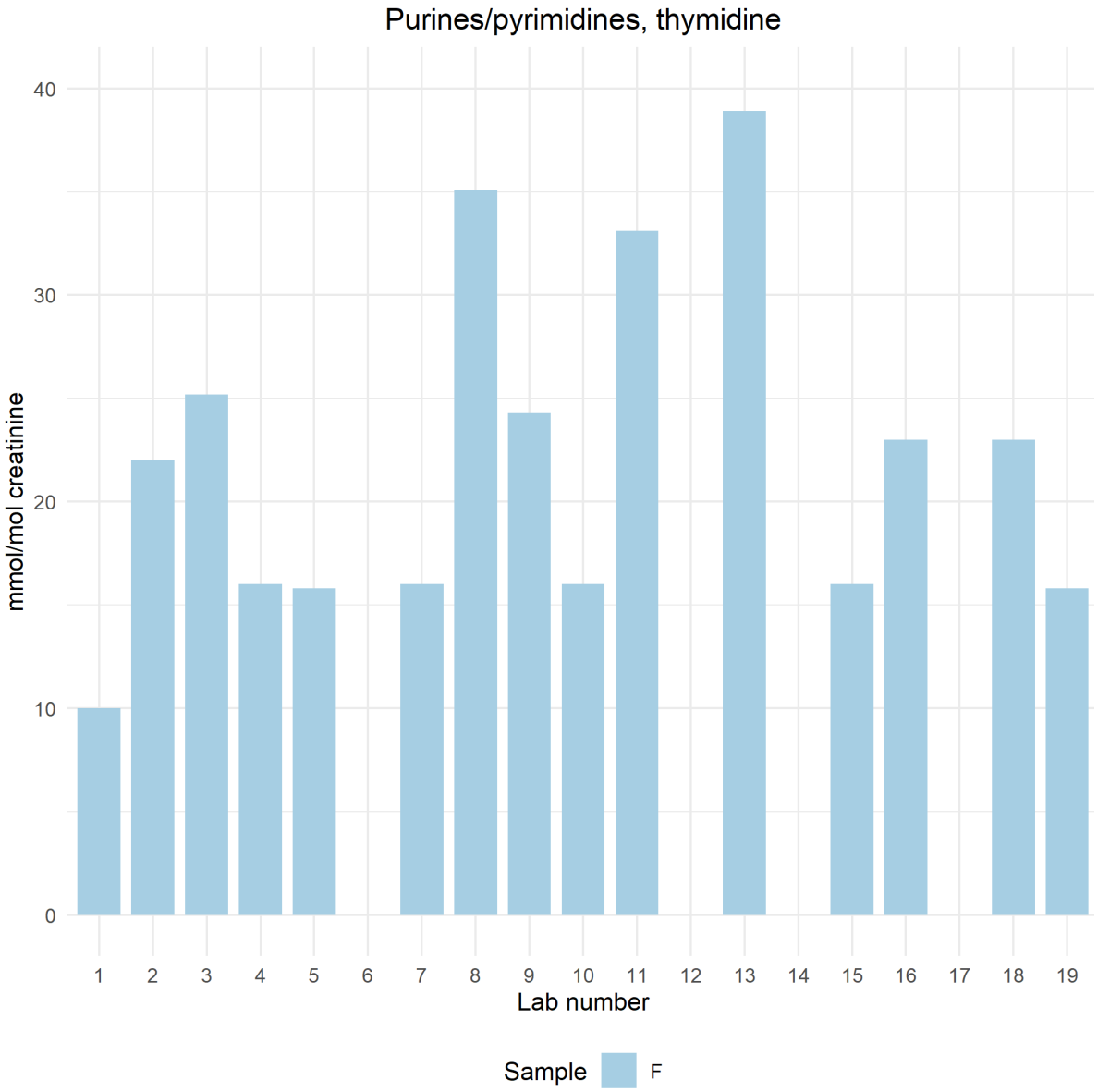

Fig. 6

Diagnosis / Interpretative proficiency
Seventeen participants reported MNGIE, one concluded mitochondriopathy, and one dihydropyrimidine dehdyrogenase deficiency. Interpretative proficiency was 92%.
Elevated thymidine and deoxyuridine are key to establish biochemical diagnosis of MNGIE. Elevated thymine and/or uracil is not sufficient, since these latter metabolites are not specific for MNGIE and may indicate defects in pyrimidine degradation, i.e.: Dihydropyriminidase or Dihydropyrimidine dehydrogenase deficiency. The source of uracil and thymine, products of the Thymidine Phosphorylase reaction, is not completely clear. Possibly Uridine Phosphorylase acts on thymidine/deoxyuridine at high concentrations. Since thymine and uracil appear to be normal in

plasma, spontaneous or bacterial degradation of the accumulating metabolites in urine may be the most likely explanation.
Many labs reported increased levels of various organic acids: in particular lactate, 3-OH-isobutyric acid and various krebs cycle intermediates. These abnormalities are secondary to mitochondrial failure (see Bennett et al 1993 JIMD 16:560-562).
In this patients various other abnormalities are secondary to TP deficiency: low creatinine can be explained by cachexia/muscle wasting, while glucosuria and hyperaminoaciduria are probably due to tubulopathy.

Recommendations
The following recommendations were frequently made: thymidine phosphorylase activity in leu/lym/fib/dbs (11), TYMP mutation analysis (15) and analysis of pyrimidines (thymidine) in plasma (4).

Scoring
- Analytical results: elevated thymidine and/or deoxyuridine (and thymine, uracil): score 2; elevated thymine and/or uracil (without mentioning thymidine and deoxyuridine): score 1
- Interpretation of results: MNGIE: score 2, mitochondriopathy: score 1
- Critical error: no potential critical errors were identified for this sample

Overall impression
High overall proficiency of 95%.

Multiple distributions of similar samples
This sample was also circulated in 2013 (sample 2013-B). In 2013 overall proficiency was 63%. Higher proficiency in 2020 is related to more labs performing purine-pyrimidine analysis, 17 in 2020 compared to 13 in 2013.

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 PKU			Patient B AGU			Patient C GA 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	2	4	12
4	0	1	1	2	2	4	2	2	4	9
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	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	1	0	1	2	2	4	9
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	1	2	3	2	2	4	2	2	4	11
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	2	2	4	2	2	4	12
19	2	2	4	2	2	4	2	2	4	12

Detailed scores – Round 2

Lab n°	Patient D Hyperoxaluria type 1			Patient E HMG-CoA-lyase deficiency			Patient F MNGIE			
	A	I	Total	A	I	Total	A	I	Total	Total
1	2	2	4	2	2	4	2	2	4	12
2	2	2	4	2	2	4	2	2	4	12
3	2	2	4	2	2	4	2	2	4	12
4	2	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	1	0	1	2	2	4	2	2	4	9
9	2	2	4	2	2	4	2	2	4	12
10	2	2	4	2	2	4	2	2	4	12
11	2	0	2	2	2	4	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	1	1	2	10
15	1	2	3	2	2	4	2	2	4	11
16	0	1	1	2	2	4	2	0	2	7
17	1	2	3	2	2	4	2	2	4	11
18	2	2	4	2	2	4	2	2	4	12
19	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	4	4	4	4	24	100	
4	1	4	4	4	4	4	21	88	CE
5	4	4	4	4	4	4	24	100	
6	4	4	4	4	4	4	24	100	
7	4	4	4	4	4	4	24	100	
8	4	4	4	1	4	4	21	88	
9	4	4	4	4	4	4	24	100	
10	4	4	4	4	4	4	24	100	
11	4	1	4	2	4	4	19	79	
12	4	4	4	4	4	4	24	100	
13	4	4	4	4	4	4	24	100	
14	4	4	4	4	4	2	22	92	
15	3	4	4	3	4	4	22	92	
16	4	1	4	1	4	2	16	67	
17	4	4	4	3	4	4	23	96	
18	4	4	4	4	4	4	24	100	
19	4	4	4	3	4	4	23	96	

Performance

	Number of labs	% total labs
Satisfactory performers (≥ 60 % of adequate responses)	18	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-2020-A	PKU	92	97	95
DPT-NL-2020-B	AGU	95	89	92
DPT-NL-2020-C	GA I	100	100	100
DPT-NL-2020-D	Hyperoxaluria type 1	84	87	86
DPT-NL-2020-E	HMG-CoA-lyase deficiency	100	100	100
DPT-NL-2020-F	MNGIE	97	92	95

10. Annual meeting of participants

The annual DPT workshop was organised online on September 1st 2020 from 9.00 to 10.30. Representatives (22) from 18 participating labs were present. This is much more than usually seen at physical meetings planned along the SSIEM symposium. Apparently, participants find it easier to attend an online meeting. It was noted by the scientific advisor that discussion is less easy in an online 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

- **Control materials** for internal QC are now provided by MCA/SKML. Latest addition is control materials for pterins in urine. 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.

- **Other schemes**: For the following schemes scoring of interpretation will be included in the 2021 schemes: Neurotransmitters in CSF (NCSF), Pterins in Urine (PTU), Lysosomal enzymes in fibroblasts (LEFB) and Cystine in WBC (CWBC).
- **Training**: The SSIEM Academy training course was canceled in 2020 and postponed to 2021. Please go to the SSIEM website to find details on organization of this event The program includes: Aminoacidopathies, Hyperammonaemia and Urea Cycle Defects.
- **ERNDIM meeting 2021**: In 2021 there will be an international ICIEM meeting in Sydney, Australia. ERNDIM will organize a separate meeting in Rome, Italy, on October 21-22, 2021. An invitation and programme will follow early 2021. DPT discussions will be held during this meeting.
- **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.

12. Tentative schedule 2021

Sample distribution	February 9, 2021
Start of analysis of Survey 2021/1 (website open)	March 8, 2021
Survey 2021/1 - Results submission deadline	March 29, 2021
Survey 2021/1 – Interim report available	April/May 2021
Start of analysis of Survey 2021/2 (website open)	June 7, 2021
Survey 2021/2 – Results submission deadline	June 28, 2021
Survey 2021/2 – Interim report available	July/August 2021
Annual meeting of participants	October 21, 2021 (Rome)
Annual Report 2021	December 2021

13. ERDIM 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, 17.02.21

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

Version Number	Published	Amendments
1	18 January 2021	2020 annual report published
2	8th February 2021	Page 5, Poor Performance Policy, information for appeal of poor performance added.

END