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Diagnostic Proficiency Testing (DPT) Scheme (United Kingdom) Annual Report 2014

1. Scheme Design

The scheme has been designed and planned by Prof Jim Bonham and Mrs Joanne Croft as Scientific Advisor/Scheme Organiser and deputy Scientific Advisor/Scheme Organiser, respectively, both appointed by and according to procedures laid down by the ERNDIM Board.

2. Geographical distribution of participants

Twenty-one laboratories from 5 countries participated in the 2014 scheme, for details see the table below.

Table 1: Geographical distribution of registered participants

Country	Number of participants
Ireland	1
Malaysia	1
New Zealand	2
Spain	1
United Kingdom	16

3. Samples and shipment

All samples are obtained following local ethical and consent guidelines. Two sets of three samples (numbered 14.1 to 14.6) were dispatched together in March 2014 to 21 participants by CSCQ (Geneva, Switzerland). Submission deadlines were 2nd May (samples 14.1, 14.2 and 14.3) and 13th June (samples 14.4, 14.5 and 14.6).

Table 2: Schedule for the 2014 scheme

Sample distribution	17th March 2014
Start of analysis of 1st round (samples 14.1, 14,2 & 14.3)	14th March 2014
1st round – results submission	2nd May 2014
Start of analysis of 2nd round (samples 14.4, 14.5 & 14.6)	26th May 2014
2nd round – results submission	13th June 2014
Annual meeting of participants	8th September 2014
Annual report 2014	April 2015

4. Submission of results

Laboratories were asked to analyse the sample sets at intervals during the year as if they were separate circulations. Twenty-one laboratories returned results for samples 14.1, 14.2 and 14.3 and 20 laboratories returned results for samples 14.4, 14.5 and 14.6.

All submitted results are treated as confidential information and are only shared with ERNDIM approved persons for the purposes of evaluation and reporting.

5. Samples

Patient 14.1

Clinical details provided: 'Neonate. 'Blue' episodes. ? septic. ? cause'.

Increased pyroglutamate was found on organic acid analysis. Mutation analysis has been performed and this patient has been shown to have 5-Oxoprolinase deficiency.

- **Findings**
  19/21 participants identified increased pyroglutamic acid on organic acid analysis.
- **Conclusions**
  All the laboratories that identified pyroglutamic acid identified this as a case of Pyroglutamic Aciduria. Most gave Oxoprolinase as either the diagnosis or alternative diagnosis and received 2 marks for interpretation. Those who only gave Glutathione synthetase or secondary Pyroglutamic Aciduira due to drugs e.g. paracetamol, as the possible diagnosis received 1 mark.
- **Further Investigations**
  Recommendations to follow up with a repeat urine and enzymatic and genetic testing are appropriate.
- **Comment**
  Proficiency for this sample was good with only 1 laboratory receiving 0 marks.

Patient 14.2

Clinical details provided: 'spasticity and mental retardation. On treatment'

This sample was obtained from a patient with Lesch Nyhan syndrome on Allopurinol treatment.

- **Findings**
  Purine analysis is performed by few laboratories. Those who did do purine analysis scored better. Many labs measured uric acid (15/21), with 9/15 deeming the concentration to be significant. There appears to be a discrepancy with the units used for reporting the uric acid concentration to the website (range was 1.0 – 1480).
  Laboratories who stated that they would send the sample away for purine analysis based on the increased uric acid concentration received full analytical marks.
- **Conclusions**
  Many of those labs who identified this patient as having Lesch Nyhan syndrome stated that the patient is on allopurinol.
- **Further investigations**
  Recommendations provided varied according to whether the diagnosis of Lesch Nyhan syndrome was reached or not. Many recommended plasma urate and follow up purine/pyrimidine analysis if not already done.
- **Comment**
  This sample had relatively poor participant performance with 10 laboratories scoring 0 marks. However, those that did do purine analysis all scored 4 marks (9 labs).

  Please note – following the Scientific Advisory Board (SAB) meeting in March 2015, due to the poor proficiency for this sample, this will be considered as educational and therefore not be scored.

Patient 14.3

Clinical details provided: 'Hypotonia and seizures'

This sample was obtained from a patient with proven Fumarase deficiency.

- **Findings**
  All laboratories successfully identified increased excretion of fumarate in this urine sample.

- **Conclusions**
  Most laboratories considered the diagnosis to be Fumarase deficiency. One laboratory did not mention Fumarase deficiency and one considered fumarase deficiency but decided that the presence of a malate peak went against this diagnosis.

Patient 14.4

Clinical details provided: 'Behavioural problems. Developmental regression'

This sample is from a healthy 11 year old.

- **Findings**
  Most laboratories did not detect any significant abnormality on this sample. However, a few did measure a low urate concentration (n=6) and made recommendations based on this finding.
- **Conclusions**
  Most laboratories reported this as having no significant abnormality. Many suggested further testing strategies. One lab gave a diagnosis of purine nucleoside phosphorylase deficiency based on the low urate concentration and another a diagnosis of MPS Type 3 based on a terrace amount of heparin sulphate by GAG 1D electrophoresis.
- **Further investigations**
  Recommendations ranges from 'no further follow up required' to quite extensive lists of further testing to be carried out (e.g. NCL testing, plasma amino acids, CSF amino acids, copper, lead, mercury, MRI brain, VLCFAs, white cell enzymes, neurogenetic conditions). Perhaps because this is a QA sample we are more reluctant to say it is 'normal'.
- **Comment**
  Overall this sample was analysed and reported successfully by the majority of participants.

Patient 14.5

Clinical details provided: 'Metabolic Acidosis, hyperammonaemia. On treatment.'

This sample was obtained from an 18 year old female with Methylmalonic Aciduria. We received this sample without any clinical details so are not able to provide further information.

- **Findings**
  All laboratories correctly detected increased Methylmalonic acid excretion by organic acid analysis.
- **Conclusions**
  All labs correctly stated that this was due to Methylmalonic Aciduria, and many commented that this could be due to methylmalonyl-CoA mutase deficiency or a cobalamin disorder, and may be Vitamin B12 responsive.
- **Further investigations**
  All laboratories gave useful recommendations. Only 12 laboratories suggested measuring plasma total homocysteine. This may be due to the fact that the patient is already diagnosed and on treatment. If this was a diagnostic sample, the presence of increased MMA should be followed up with monitoring plasma ammonia and measuring total homocysteine.
- **Comment**
  Overall this sample was analysed and reported very well.

Patient 14.6

Clinical details provided: 'Following uneventful pregnancy and birth this male child showed mild hypotonia at 6 months of age. A few months later, developmental delay and failure to thrive with elevated transaminases was observed. The urine was collected at the age of 8.75 years whilst receiving specific treatment'.

The child showed the first symptoms at 6 months, then at 14 months liver dysfunction when increased ammonia (200), increased ornithine, orotic acid and mild increase of homocitrulline was found leading to diagnosis of HHH.

This sample came from a patient with Hyperammonaemia, hyperornithinaemia, homocitrullinuria (HHH) syndrome. Mutation in exon 2 of SLC25A15 found – c.208_209delGCinsTT. Treatment is with low protein diet and citrulline. Sample provided by Brian Fowler.

This was the common sample sent to all the DPT scheme participants.

- **Findings**
  Only a few laboratories detected homocitrulline in this sample.
- **Conclusions**
  All laboratories gave a diagnosis of a urea cycle disorder (1 mark) with only a few giving the diagnosis of HHH syndrome (2 marks).
- **Further investigations**
  Most laboratories gave helpful recommendations including analysis of plasma ammonia and amino acids. Some commented that diagnosis of a urea cycle disorder requires plasma amino acids and cannot be diagnosed on urine alone.
- **Comment**
  This sample was not performed particularly well, with only 4 laboratories scoring the full 4 marks. Many commented that it is difficult to provide a definitive diagnosis as patient is on treatment.

6. Scoring of results

ERNDIM are being encouraged by the European Society of Human Genetics to harmonise scheme performance assessments with the other European genetic laboratory EQA providers. ERNDIM has defined criteria for critical error (i.e. an error that would be unacceptable to the majority of labs and would have a serious adverse effect on patient management), which has been implemented for DPT 2014 evaluation. The summary of scoring criteria is given below:

A	Analytical performance	Correct results of the appropriate tests	2
		Partially correct or non-standard methods	1
		Unsatisfactory or misleading (in some instances will be evaluated also as a critical error)	0
I	Interpretative proficiency	Good (diagnosis was established and appropriate further tests were recommended)	2
		Helpful but incomplete	1
		Misleading/wrong diagnosis (will be most likely evaluated also as a critical error)	0

The total score is calculated as a sum of these two criteria. The maximum score that can be achieved is 4 points per sample. As sample 14.2 has been classed as an Educational sample, the maximum score for the 1st survey is 8 points and for the 2nd survey is12 points giving a maximum total of 20 points in 2014.

Scores assigned by the Scientific Advisor and agreed at the Annual Meeting have been reviewed by an independent advisor from another DPT Centre and the scoring was finalized after any possible discrepancies had been resolved at the March 2015 ERNDIM Scientific Advisory Board meeting.

Following the SAB meeting in Prague in March 2015 it was decided that any laboratory failing to identify an increased concentration of orotic acid in sample 14.6 would receive a critical error for this sample. As sample 14.6 was the common sample sent to all participants of the DPT scheme, this ruling applies to all laboratories in the scheme. For DPT UK this critical error applies to 4 participating laboratories.

7. Detailed scores for submitting laboratories

The total maximum score was 20 points, with 12 or more points being deemed satisfactory.

Anonymised Laboratory number	Sample number						Total score
	14.1	14.2*	14.3	14.4	14.5	14.6	
1	4	-	4	4	4	2	**18**
2	4	-	4	4	4	2	**18**
3	4	-	4	4	4	2	**18**
4	4	-	4	4	4	4	**20**
5	4	-	4	2	4	1	**15**
6	2	-	4	4	4	2	**16**
7	4	-	4	4	4	2	**18**
8	4	-	4	4	4	1	**17**
9	4	-	4	4	4	4	**20**
10	4	-	4	4	4	4	**20**
11	4	-	4	4	4	2	**18**
12	4	-	3	NR	NR	NR	**7**
13	4	-	4	4	4	2	**18**
14	4	-	4	4	4	2	**18**
15	0	-	4	4	4	1	**13**
16	4	-	4	0	4	1	**13**
17	4	-	4	4	4	2	**18**
18	4	-	3	4	4	3	**18**
19	4	-	4	4	4	2	**18**
20	4	-	4	4	4	2	**18**
21	4	-	4	4	4	1	**17**

* = sample 14.2 was classed as an Educational Sample
NR = no return

8. Proficiency per sample

Sample	Diagnosis	No of returns	Analytical performance (%)	Interpretative proficiency (%)	Total (%)
14.1	5-Oxoprolinase deficiency	21	93%	93%	**93%**
14.2*	Lesch-Nyhan syndrome (HPRT deficiency)	21	33%	49%	**41%**
14.3	Fumarate Hydratase deficiency	21	100%	95%	**98%**
14.4	A healthy child	20	90%	86%	**88%**
14.5	Methylmalonic Acidaemia	20	95%	95%	**95%**
14.6	HHH syndrome	20	43%	57%	**50%**

* = sample 14.2 was classed as an Educational Sample

Yours sincerely

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