ERNDIM Diagnostic Proficiency Testing is an important Tool in Determining Quality of Laboratory Diagnosis in a wide Range of Inborn Errors of Metabolism

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Background & Discussion

Introduction

ERNDIM (www.erndim.org) aims to improve the quality of diagnosis and monitoring in patients with inborn errors of metabolism (IEM) through quality assurance programmes and educational activities. Diagnostic proficiency testing schemes focus on the ability of laboratories to identify and interpret abnormalities in natural urine samples reflecting a wide range of IEMs.

Aims & Method

- 273 samples from 83 different conditions (some no IEM), sent to up to 105 laboratories, mainly European but also worldwide.
- Organising centres - Czech Republic, France, Netherlands, Switzerland, and United Kingdom, now sent centrally (CSCQ, Switzerland).
- Six samples / year, one common to all centres, sent with clinical information.
- Laboratories choose and perform tests (limited amount of urine) needed to reach a diagnosis using analysis of one or more of amino acids, organic acids, mucopolysaccharides, oligosaccharides and purines and pyrimidines

Conclusions

- Overall performance is fairly good, emphasising that a definitive diagnosis is not always possible with urine alone.
- Evidence of improved performance repeat distributions
- ERNDIM diagnostic proficiency testing valuable for:
  - informing accreditation
  - assessing individual laboratory performance
  - identifying methodological and technical challenges
  - contributing to improved diagnostic approaches.
- Clinicians must be aware that laboratory testing for IEM can be difficult and results need to be viewed with caution.

Ask your lab "Do you participate in ERNDIM"

Results

Performance criteria: analysis and interpretation scores and lack of critical error (defined as an error that would be unacceptable to the majority of labs and would have a serious adverse effect on patient management).

Diagnostic proficiency: overall combined scores for analytical findings and interpretation, ranged widely from below 50% for challenging samples to 100% for more straightforward ones.

Participant performance: (figure) diagnostic proficiency (average % of total points possible for all participating laboratories within all schemes for all samples) was:
amino acid disorders, range 14-100 ; organic acid disorders, range 44-100; mucopolysaccharide disorders, range 67-93
oligosaccharide disorders, range 28-99: purine/pyrimidine disorders, range 12-93; miscellaneous disorders, range 17-91; no IEM, range 65-95.

Re-distributed samples within the same centre – improved performance 21 cases (average 15%): no clear improvement seen in 13

Table: Overall diagnostic proficiency in individual IEMs: #Common Sample;

Amino Acid disorders (26) – 79 samples distributed

Disorder	n	Range	Mean	Change on Repeat
alpha-AA semialdehyde synthase deficiency #	1	70		
Aminoacylase 1 deficiency	3	35-58	51	
argininosuccinate lyase deficiency	12	75-100	88	25+ / 0 / 26+
Aromatic L-Aminoacid Decarboxylase deficiency	2	14-65	40	
branched chain aminoaciduria intermittent #	1	88		
branched chain aminoaciduria (MSUD)	2	93-100	97	
Citrullinaemia	4	94-99	97	1+
Cystine / dibasic aminoaciduria	6	89-100	94	11- / 7+
Cystinosis	1	61		
Formiminoglutamic aciduria	2	33-46	40	13+
Hartnup disease	2	76		
Hawkinsinuria	1	64		
HHH syndrome (treated with citrulline) #	3	50-80	70	4- / 5+
Homocystinuria due to CBS deficiency #	5	67-96	87	5+ / 4+ / 21+
Homocystinuria mild	1	26		
Hypermethioninaemia /0 (MAT1A gene).	2	62-76	69	
Hypophosphatasia (one sample juvenile form) #	4	51-100	79	27+
Iminodipeptiduria	6	48-86	70	9+ / 38+
LPI / Dibasic amino aciduria #	4	82-96	90	4-
Non-Ketotic Hyperglycinaemia	2	87-98	92	
Ornithine Amino Transferase deficiency	3	92	92	
Ornithine Carbamyl Transferase deficiency	3	77-85	81	
Phenylketonuria	2	87-98	93	11-
Taurinuria (Red Bull intake)	1	88		
Tyrosinaemia type 1	1	98		
Tyrosinaemia type II	1	100		

MPS & Lipid Storage disorders (11) - 53 samples distributed

Disorder	n	Range	Mean	Change on Repeat
Mucopolysaccharidosis type 1	7	81-93	87	6+ / 10-
Mucopolysaccharidosis type 4A	9	73-86	80	10+ / 0 / 6+
Mucopolysaccharidosis type 2	7	83-92	87	9+ / 1-
Mucopolysaccharidosis type 3 #	7	67-90	77	12+ / 30- / 12+ / 19+
Mucopolysaccharidosis type 6	4	72-88	76	4+
alpha-mannosidosis	5	74-99	88	
Aspartylglucosaminuria	5	45-83	62	
Fucosidosis	2	62-80	71	
GM1 gangliosidosis	3	59-79	68	7-
Salla disease #	1	28		
Sialidosis due to neuraminidase deficiency #	3	55-85	74	0

Purine & Pyrimidine disorders (8) – 22 samples distributed

Disorder	n	Range	Mean	Change on Repeat
Adenylosuccinate lyase deficiency	4	37-62	42	
Dihydropyrimidine dehydrogenase deficiency	1	93		
Dihydropyriminidase deficiency	1	80		
Lesch-Nyhan Disease	5	12-81	50	29+
MNGIE / Thymidine phosphorylase deficiency	6	50-91	73	
Molybdenum cofactor deficiency	3	51-82	70	
Purine nucleoside phosphorylase deficiency	1	74		
Xanthine Oxidase deficiency	1	74		

Organic Acid disorders (32) – 89 samples distributed

Disorder	n	Range	Mean	Change on Repeat
2-hydroxyglutaric aciduria	6	91-100	97	5-
3-Me-glutaconyl hydratase deficiency	1	80		
3-methylcrotonyglycinuria	2	99-100	99.5	
Beta-ketothiolase deficiency (*ACAT1)*	5	83-97	91	2+ / 7-
Ethylmalonic encephalopathy (*ETHE1*)	1	98		
Fumarase deficiency	4	78-98	90	7+
Glutaric acidaemia type I	8	89-100	96	0
Glyceroluria Xp21 contiguous gene deletion	4	80-96	92	16+
HMG-CoA-lyase deficiency	2	96-100	98	
Homocystinuria /Methylmalonic / cblC	4	72-97	84	6- / 8-
homogentisic acid oxidase deficiency	3	94-100	94	
Hyperoxaluria type 2 #	1	87		
Hyperoxaluria type I	2	72-80	76	
Isovaleric acidaemia	4	95-100	97.5	
long chain acylCoA dehydrogenase deficiency	2	56-71	63	
Malonic and MMA / *ACSF3* gene	2	54-67	60	
Malonyl CoA decarboxylase deficiency	1	97		
MCAD deficiency	3	93-96	95	
Methylglutaconic aciduria/ Barth Syndrome	4	66-79	73	1-
methylmalonic aciduria Isolated /cblA	6	92-100	96	1-
Methylmalonic semialdehyde dehydrogenase def.	1	81		
Mevalonic aciduria	3	78-99	85	21+
2-Methyl-3-hydroxybutyryl-CoA dehydrogenase def.	1	44		
Multiple acyl-CoA dehydrogenase def.	3	85-99	90	
N-acetylaspartic aciduria	2	95	95	
NFU1 deficiency	1	79		
Oxoprolinase def.	1	91		
Propionic aciduria	3	96-100	99	4-
Short chain acyl CoA dehydrogenase deficiency	3	83-91	88	
Short chain hydroxyl acyl CoA dehydrogenase def.	1	89		
Short/branched-chain acyl-CoA dehydrogenase def.	1	79		
Succinate semialdehyde dehydrogenase def. (4HB)	4	81-92	86	8+

Miscellaneous disorders (6) – 7 samples distributed

Disorder	n	Range	Mean	Change on Repeat
DOPA therapy	1	91	91	
Essential fructosuria	1	17	17	
Ethylene glycol intake	1	91	91	
Galactosemia	2	51-100	75	49+
GAMT deficiency #	1	52	52	
Adenine phosphoribosyltransferase def. + MPS 4	1	50	50	
No evidence of an IEM	23	65-95	87	

Figure