ERNDIM QC Schemes

Diagnostic Proficiency Scheme

Practice at Reporting and Interpretation

ERNDIM Proficiency Scheme: Design

Clinical picture

Lab results and interpretation

- Pre-investigations
- Amino acid analysis
- Organic acid analysis
- Purines/pyrimidines analysis
- Mucopolysaccharide analysis
- Oligosaccharide analysis
- Other analyses performed

Analytical Proficiency — 2 points

Interpretation(diagnosis)

Advice for follow up investigations

} 2 points

ERNDIM Proficiency Scheme: Errors

- Appropriate assay/method not used/available
- **Incorrect** analyte recognition
- **Incomplete** analyte recognition
- Correct analyte recognition BUT **incorrect** interpretation
- **Incorrect** confirmatory test

ERNDIM Proficiency Scheme: Errors

- Appropriate assay/method not used/available
  e.g. Guanidinoacetate methyltransferase deficiency

Sample F: GAMT deficiency
Patient: a 7-year old girl with developmental retardation, in particular speech delay. She has epilepsy, for which she is treated with valproic acid.
Analytic: elevated guanidinoacetic acid: 640 mmol/mol (ref. values <129) Guanidino-acetic acid in plasma 27.2 umol/L (ref values 0.5-3.6),
Interpretation: guanidino-acetic acid methyltransferase (GAMT, EC 2.1.1.2) deficiency (OMIM 612736)
Analytical performance: Measurement of guanidinoacetic acid and creatine was critical for this sample. Those labs (**11 of 19**) that performed these assays found the relevant abnormality.
Interpretative proficiency:. Interpretation is straightforward and was correct in all cases in which the relevant analysis was performed.
Recommendations: Measurements of GAA and creatine in plasma backed up by GAMT enzyme and / or mutation analysis (601240) was considered helpful.

	n	Points
Guanidino-acetate methyltransferase deficiency (GAMT)	11	**2**
Glycinuria secondary to valproate medication.	2	**0**
No diagnosis obtained	5	**0**
biotinidase deficiency	**1**	**0**

ERNDIM Proficiency Scheme: Errors

Incorrect analyte recognition

e.g. Arginino succinic aciduria

Patient: this sample came from a 20 year old male patient with ASAuria (OMIM 207900) who is under treatment with arginine. This sample was also distributed in 2009.

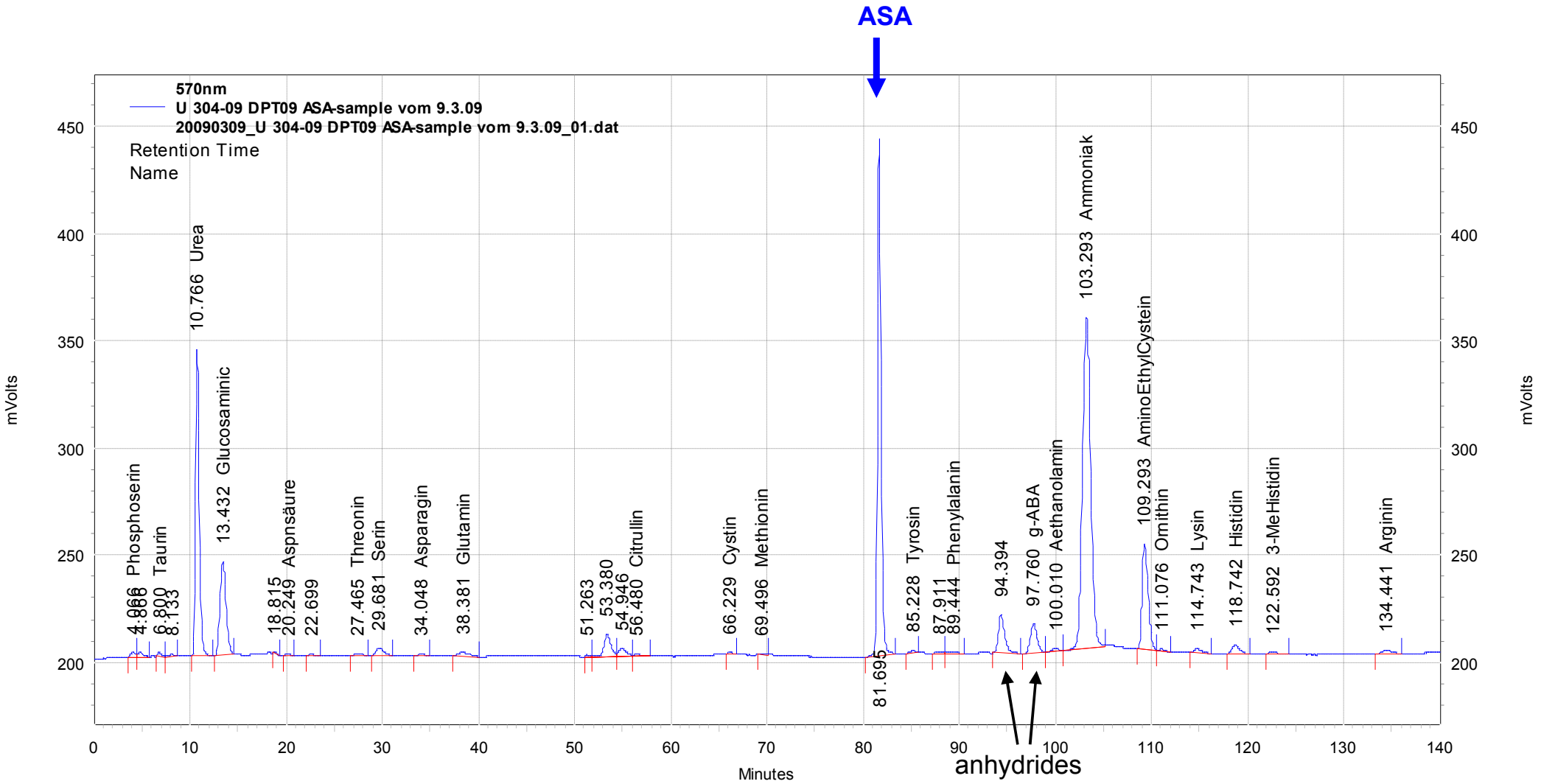
Analytical performance: Two points were given for identification of ASA and//or its anhydrides. **18 of 20** labs identified key metabolites pointing to the correct diagnosis.

Interpretative proficiency: The correct diagnosis was arginino-succinic aciduria due to ASA-lyase deficiency (EC 4.3..21). 18/20 labs made the correct diagnosis.

Overall impression: All labs should be able to identify arginino-succinic acid and its anhydrides, there appear to be some difficulties in identification on some amino acid analysers.

	n	Points
Argininosuccinic aciduria due to argininosuccinate lyase deficiency)	**18**	**2**
Hyperprolinaemia	**1**	**0**
VinylGABA therapy	**1**	**0**

Amino acid analysis by Ion exchange chromatography



ERNDIM Proficiency Scheme: Errors

Incomplete analyte recognition

e.g. Combined malonic and methylmalonic aciduria due to mutations in the ACSF3 gene.

Patient: At 20 y. of age investigated for bowel problems and serum methylmalonate was elevated. Urinary organic acid analysis showed methylmalonate, 73 mmol/mol creat. and malonate, 13 mmol/mol creat. Two mutations in the ACSF3 gene were identified.

Analytical performance*:* The finding of increased methylmalonic acid was scored with one point (20 labs) and increased malonic acid with one point (10 labs).

Interpretative proficiency: The correct diagnosis was combined malonic acid and methylmalonic aciduria scoring two points (9 labs). Other diagnoses based on finding methylmalonic acid alone were scored with 0 points.

Overall impression: This was a fairly difficult sample but it was clearly possible to detect increased malonic acid as reported by ten labs pointing to the correct diagnosis.

Combined malonic and methylmalonic aciduria	**9**	**2**
Malonic aciduria	1	**0**
Mild MMA/B12 deficiency	**10**	**0**

ERNDIM Proficiency Scheme: Errors

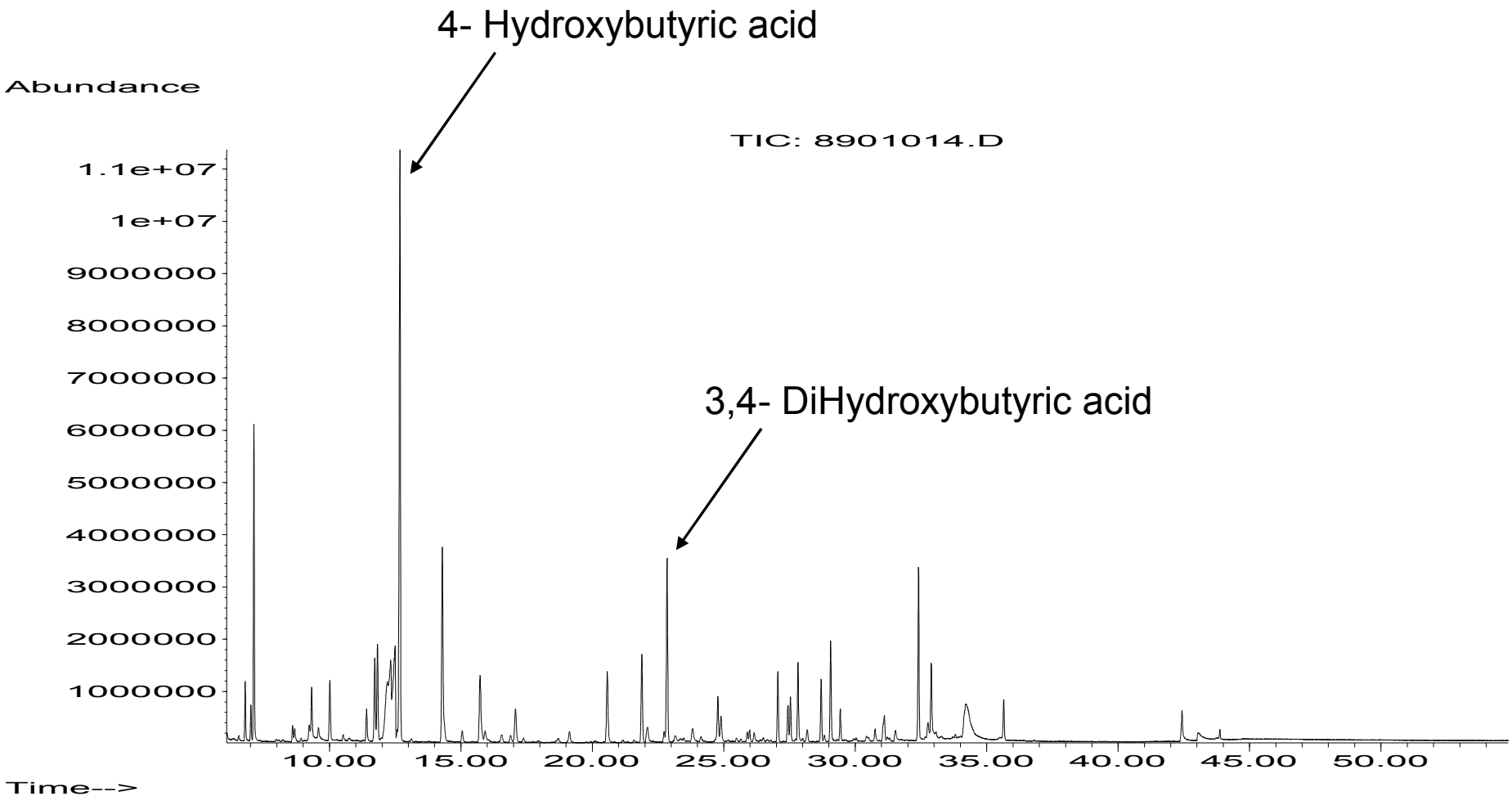
Correct analyte recognition BUT incorrect interpretation
e.g. 4-Hydroxybutyric aciduria

Patient: The urine was obtained from a 7 months old patient with confirmed 4-hydroxybutyric aciduria (succinate-semialdehyde dehydrogenase deficiency, EC 1.2.1.16).
Analytical performance: The finding of 4-hydroxybutyric acid with or without other key metabolites such as 3,4-dihydroxybutyric acid was considered to be correct. Overall performance was high at 95%.
Interpretative proficiency: The correct diagnosis was considered to be 4-hydroxybutyric aciduria due to SSADH deficiency (OMIM 271980). Proficiency for interpretation for this sample was also good at 90%.

Lab X

Analytical:4-Hydorxybutyric acid 71 mmol/mol Creat. (Ref <10)	2 points
Interpretation: Mucopolysaccaridosis (tentative)	
Clinical suggestion	0 point

Sample D:
Total Ion Chromatogram



ERNDIM Proficiency Scheme: Errors

Incorrect confirmatory test

e.g. Non-ketotic hyperglycinaemia

Patient:
The patient was diagnosed with non-ketotic hyperglycinaemia (OMIM 605899) due to high CSF and plasma Glycine, subsequently confirmed by enzyme assay
Analytical performance*:* All but one lab found greatly elevated glycine. Overall analytical performance was 95 %.

Interpretative proficiency: a diagnosis of non-ketotic hyperglycinaemia (glycine encephalopathy) was considered correct. Overall performance in interpretation was 85 %.

Recommendations*:* Analysis of glycine in **both** plasma and CSF was considered essential and glycine cleavage enzyme (EC 2.1.2.10) and mutation analysis (*GLDC*, 238300) as helpful.

	n	points
Plasma and CSF glycine	**15**	**1**
Plasma glycine	**2**	**0**

High Voltage Electrophoresis