



ERNDIM DIAGNOSTIC PROFICIENCY TESTING SCHEME

COMMON SAMPLE 2017

Joanne Croft
Sheffield, UK
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Sample A – Clinical Picture

- Male baby presented at A+E at 3 days of age
- Febrile - ? Infection
- Sample collected after commencing therapy
- Initial plasma ammonia = 542 $\mu\text{mol/L}$ (ref. < 40)

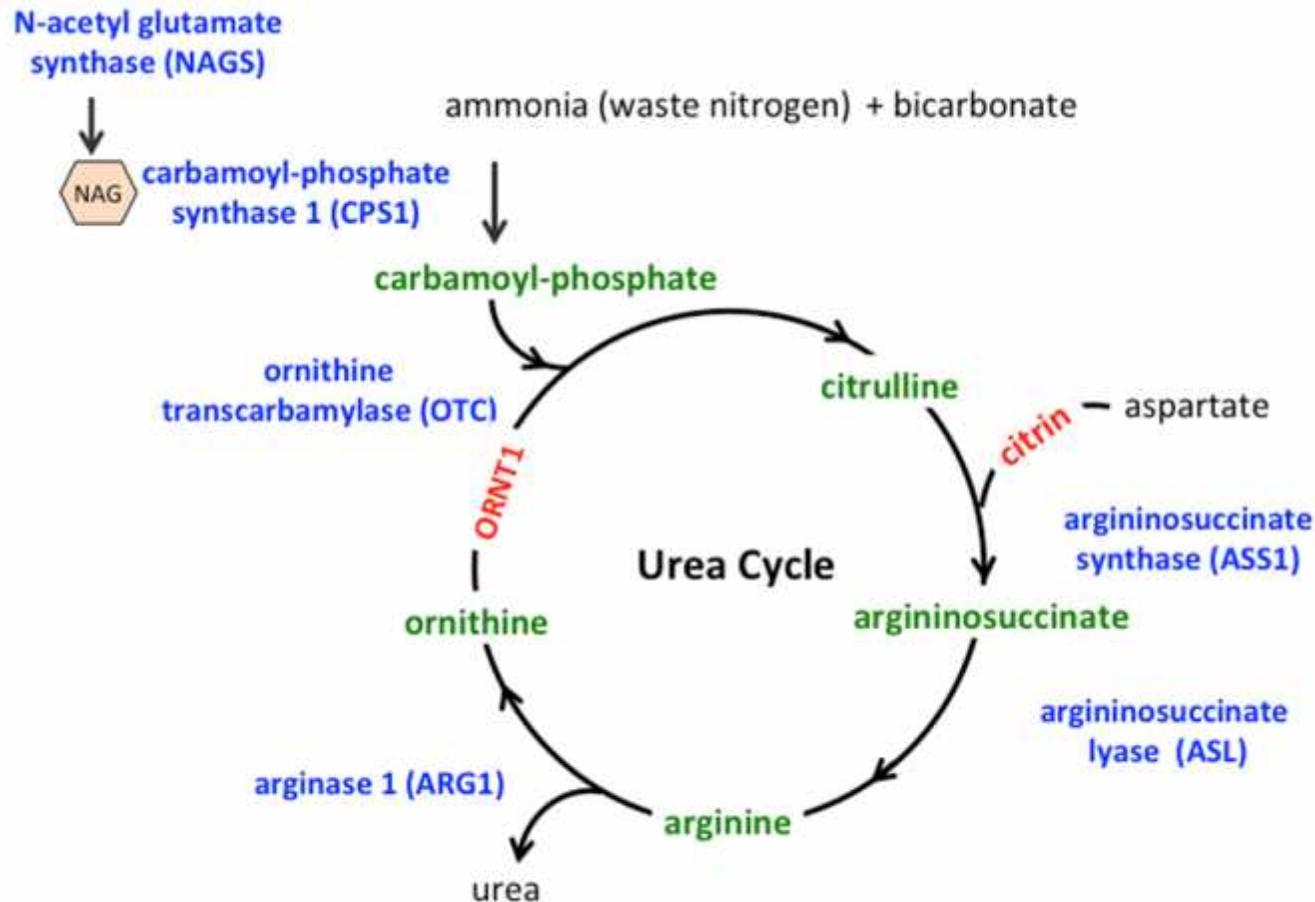
Results at time of diagnosis

- Urine:
 - orotic acid = 1801 $\mu\text{mol}/\text{mmol}$ creatinine (ref range <3)
 - citrulline = 3605 $\mu\text{mol}/\text{L}$ (++++)
 - arginine = 4 $\mu\text{mol}/\text{L}$ (low)
 - glutamine = 1172 $\mu\text{mol}/\text{L}$ (+)
- Plasma:
 - citrulline = 1401 $\mu\text{mol}/\text{L}$ (++++)
 - arginine = 35 $\mu\text{mol}/\text{L}$ (N)
 - glutamine = 2456 $\mu\text{mol}/\text{L}$ (+++)

 - did not present at Sheffield

Citrullinaemia Type 1;
Argininosuccinate
Synthase deficiency

The Urea Cycle



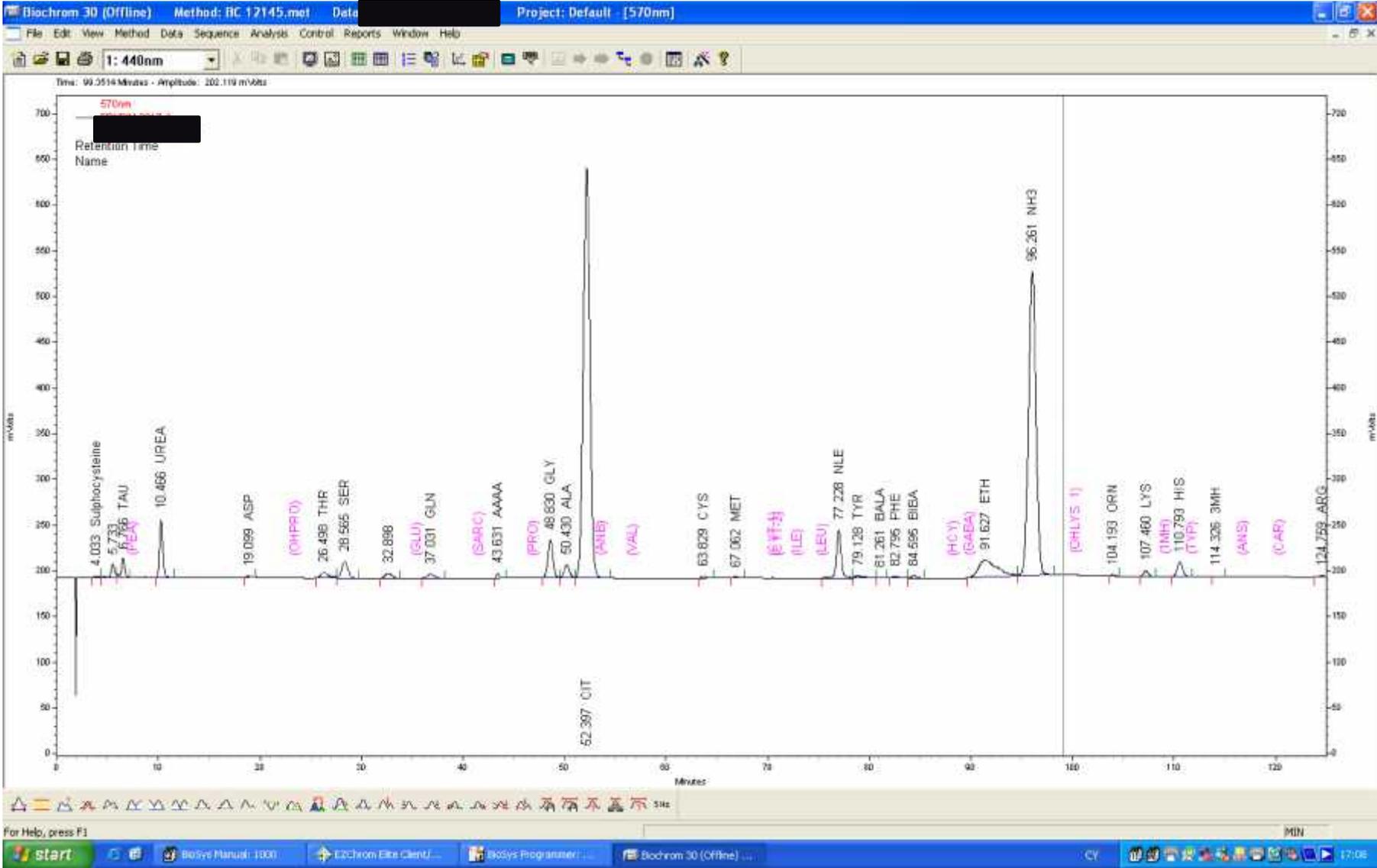
Sample used in the scheme

- The sample sent out was collected after commencing therapy
 - Sodium benzoate and arginine
- Citrulline remained high
 - $>11,000 \mu\text{mol}/\text{mmol creat}$ (as measured in Sheffield)
- Orotate had decreased
 - $96.1 \mu\text{mol}/\text{mmol creat}$ (as measured in Sheffield)

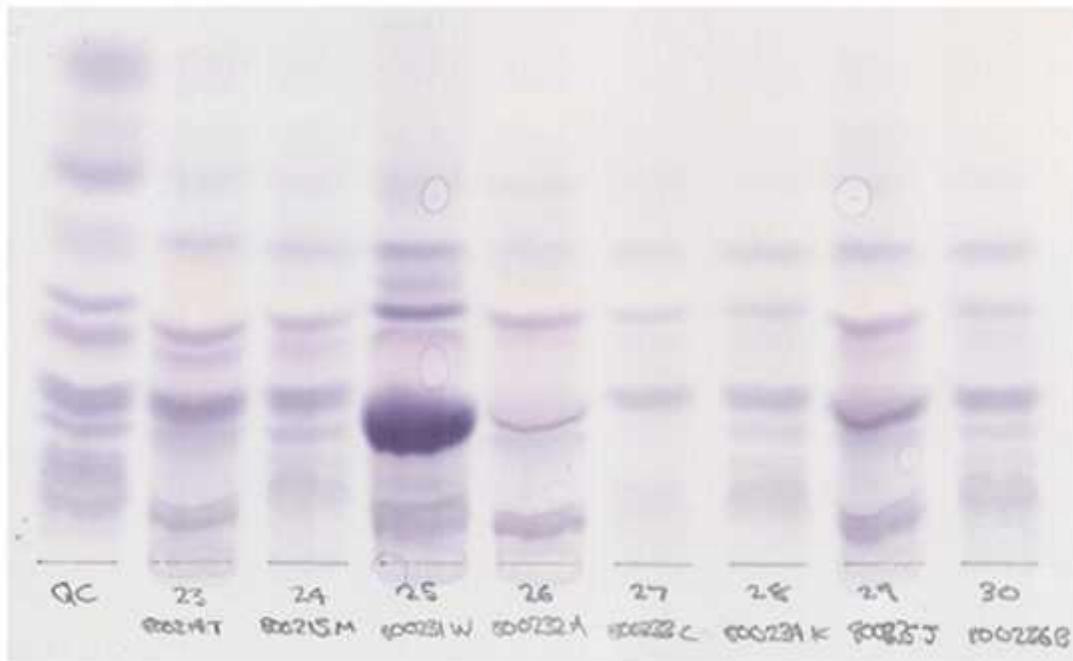
Marking Scheme

- Analytical
 - 1 mark - detecting increased orotic acid
 - 1 mark - detecting increased citrulline
- Interpretative
 - 2 marks – Citrullinaemia Type 1
 - 1 mark - Other urea cycle defect

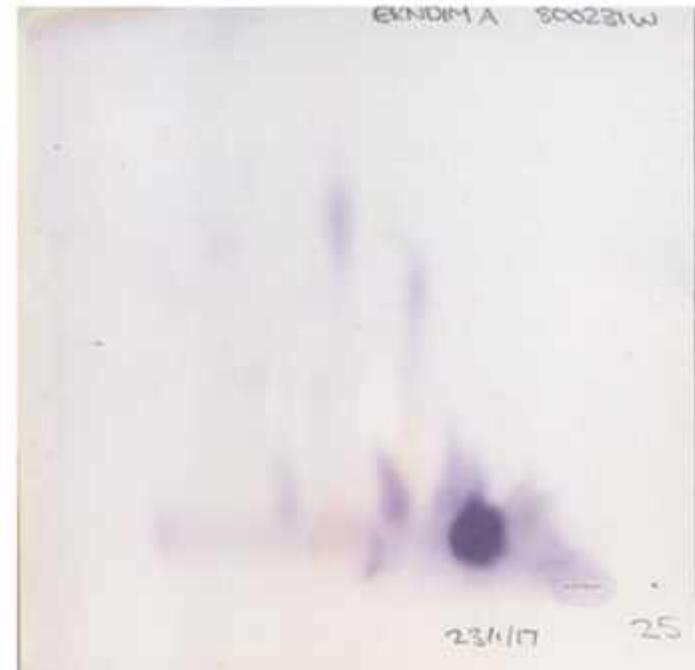
Sample A - Biochrom trace



Sample A – AA TLC



1D



2D

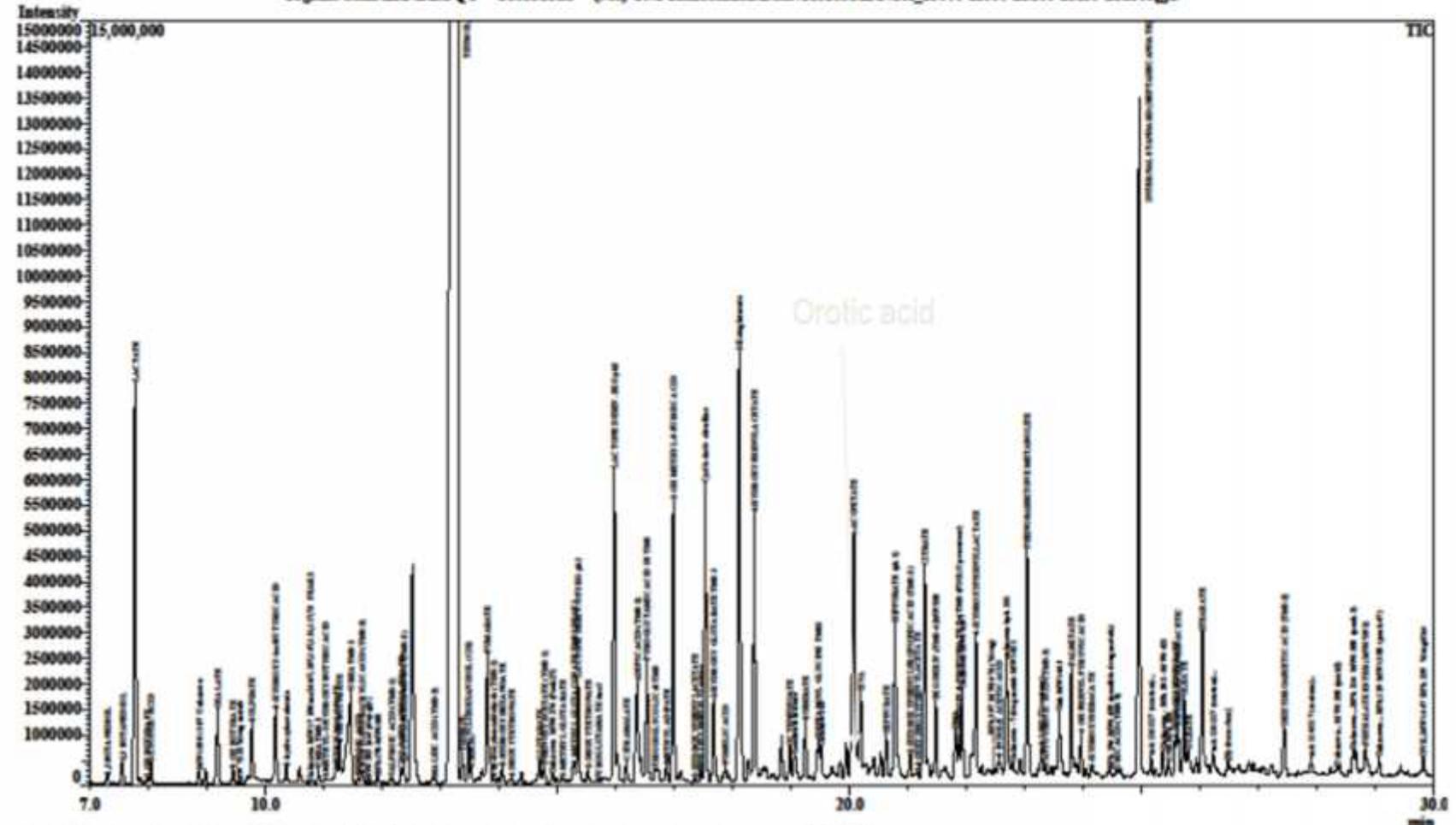
Citrulline concentration

- 96 of 108 participants provided a quantitative result for citrulline
- Median = 14404 $\mu\text{mol}/\text{mmol}$ creatinine
- Range = 681 – 2,583,416 (?units error)
- All participants reported increased citrulline

Sample Information
 Data File: C:\GCMSolution\Data\ORGACIDS\OA_23000-23999\23100-23199\23130.ggd
 Sample ID: 23130 Sample Name: ERNDIM QC-C803328.A*- (NA)
 Analyzed: 9/14/2014 9:01:36 PM Val# 30 Injection volume (µL): 2.00
 Method File: C:\GCMSolution\Method\OA_NAME.D.ggd

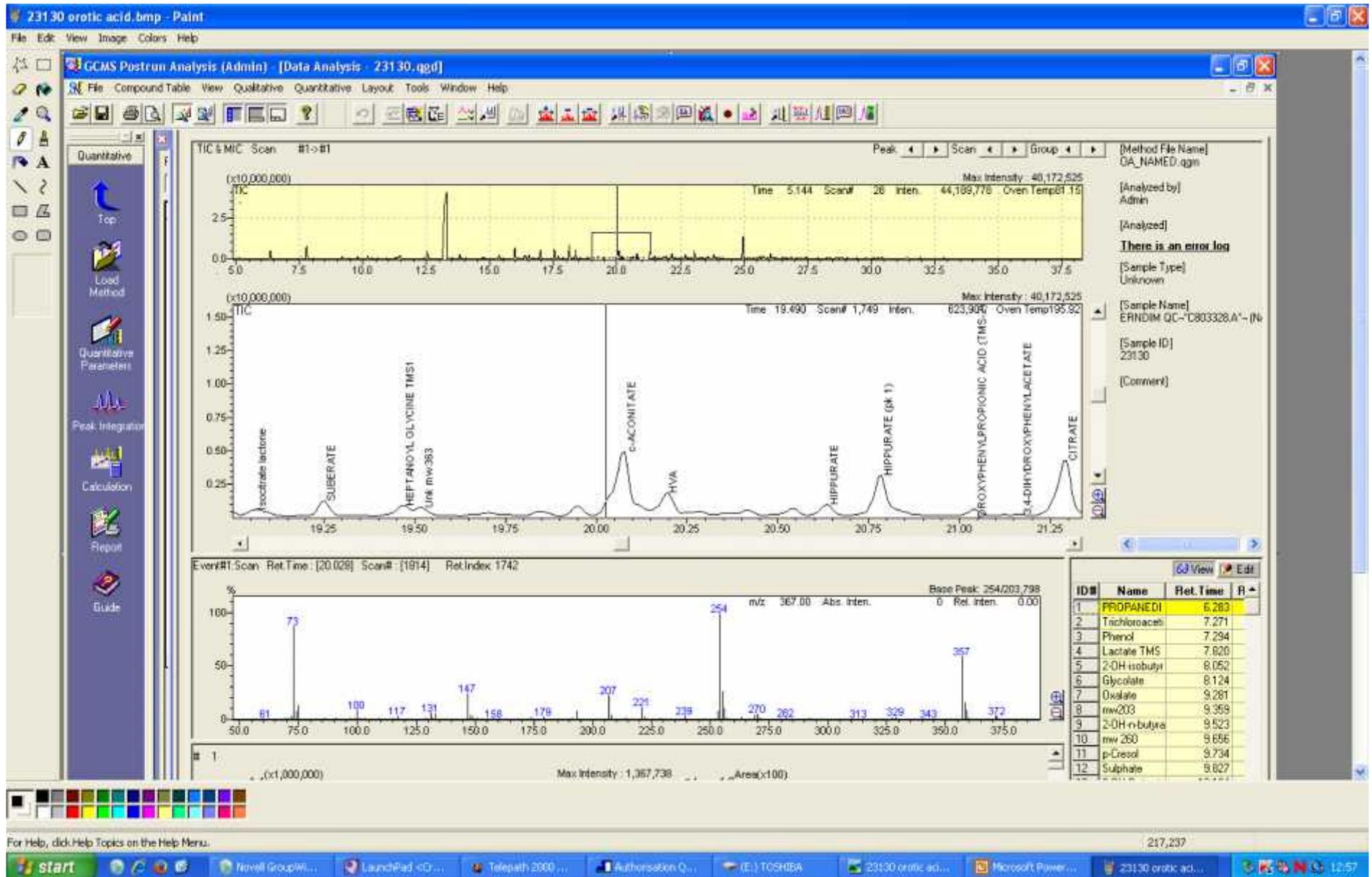
'Macro' checked by: _____
 Hapt Qty (102)
 Hapt Qty (138)
 Profile checked by: _____
 'Macro' results: _____

Organic acids ERNDIM QC-C803328.A*- (NA) C:\GCMSolution\Data\ORGACIDS\OA_23000-23999\23100-23199\23130.ggd

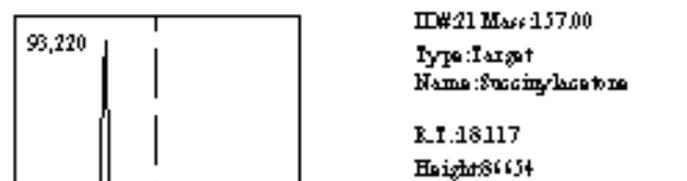
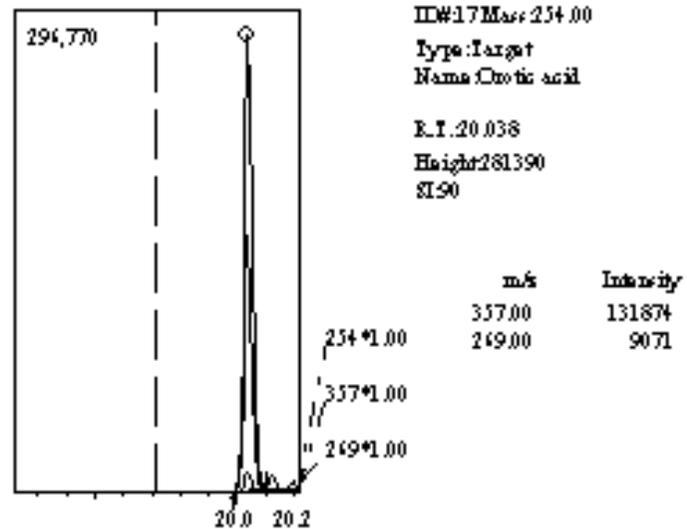
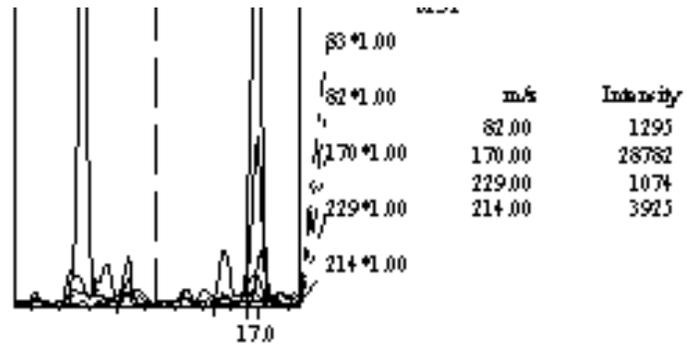


AA2212A ERNDIM QC *C803328 A* (NA)

Sample A – orotic acid



Sample A – Extracted ions



Ions m/z:
254
357
269

Orotic acid

- Of those participants who gave a quantitative result:
 - Mean = 71.9 $\mu\text{mol}/\text{mmol}$ creatinine
 - Median = 72
 - (Sheffield result = 96 $\mu\text{mol}/\text{mmol}$ creatinine - ref. < 3.5)
 - Range = 0 – 289 $\mu\text{mol}/\text{mmol}$ creatinine
 - n = 79

Overall performance

	Number of laboratories scoring x points					
DPT scheme	4	3	2	1	0	Total
UK	21	1	0	0	0	22
France	23	1	0	0	0	24
Swiss	19	2	0	0	0	21
Netherlands	18	2	0	0	1 (no report)	21
Czech	19	1	0	0	0	20
Total	100	7	0	0	1	108

Where were marks lost?

Scheme	Did not detect orotic acid	Gave OTC deficiency as diagnosis	No report submitted
UK	1		
France	1		
Swiss	1	1	
Netherlands	1	1	1
Czech		1	

Orotic acid

- 4 laboratories out of a total of 108 did not detect orotic acid
- Of those participants who gave a quantitative result:
 - Mean = 71.9 $\mu\text{mol}/\text{mmol}$ creatinine
- All except 1 lab who gave a quantitative result stated that this was increased
- Concerning that orotic acid not detected when at such a high concentration

Orotic acid detection

- Known to be a problem metabolite

DPT UK experience

- 2016 – Lysinuric Protein Intolerance
 - 2 of 22 participants did not detect orotic acid
 - median value = 238.5 mmol/mol, range 30 – 500, n = 6
- 2015 – Argininosuccinic aciduria
 - 5 of 23 participants did not detect orotic acid
 - mean value = 13.9 mmol/mol, range 9.3 – 20, n = 7

Orotic acid detection

- Do all participants make use of extracted ion searches?
- Would use of QC material (such as 'Control Special Assays in Urine' from MCA) to check extraction/detection help?

OTC deficiency?

- 3 laboratories gave OTC deficiency as the diagnosis
- Of these 3, 2 gave Citrullinaemia Type 1 as an alternative diagnosis
- All 3 had detected the increased citrulline
- In OTC deficiency expect to see low citrulline concentration
- Give citrulline (or arginine) as treatment for OTC deficiency

Recommendations

- Majority of participants suggested:
 - Plasma ammonia (urgent)
 - Plasma amino acids
 - ASS1 gene mutation analysis
- Other suggestions:
 - Enzyme activity using cultured fibroblasts
 - Referral to a metabolic team/centre (urgent)
 - Treatment options mentioned – low protein diet/correction of hyperammonaemia

Acknowledgements

- Jennifer Watkinson
- John Hamilton for organising the donation of the sample

Sample Donations

- Labs that provide a sample that is used in the scheme receive a 20% discount on the cost of the DPT scheme for the next scheme year
- **We need your help to run the scheme**
- Requirements: 200 ml urine, creatinine >1, pH 5-9
- Please contact the ERNDIM office if you have a sample that you think may be suitable