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QUALITY ASSURANCE IN LABORATORY TESTING FOR IEM

Diagnostic Proficiency Scheme UK –Common Sample

ERNDIM Workshop,
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Sample A – Common Sample

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- ***Provided by UK DPT scheme organisers***
- ***Returns were received from all 97 participants***

Common Sample (A)

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- *14 year old male*
- *Pre-natal growth concerns. Monitored throughout life for poor growth (height and weight < 2nd centile)*
- *Presented at 4 years of age due to lips going blue during exercise – found to have cardiomyopathy*
- *Diagnosed at 14 years when genome sequencing became available, confirmed by bloodspot cardiolipin*

This sample came from a patient with BARTH SYNDROME.

Sample A – marking scheme

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(Marking scheme used by all the DPT scheme organisers)

- Analytical
  - Detecting increased concentration of 3 methyl glutaconate: 2 marks
- Interpretation
  - Barth syndrome (as primary or alternate diagnosis): 2 marks
  - Any secondary 3 methyl glutaconic aciduria (as primary or alternate diagnosis): 2 marks
  - Primary 3 methylglutaconic acidurias (either HMG CoA lyase or 3 methylglutaconyl CoA hydratase deficiency) with no mention of Barth syndrome: 1 mark only
  - 3 methylglutaconic aciduria as diagnosis only (i.e. no mention of primary or secondary): 1 mark only

Analytical Performance

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- Returns were received from all participants in all schemes

Marks	UK (20)	France (20)	Czech R (19)	Switzerland (20)	Netherlands (18)	Total (97)
2	20	18	18	20	18	94 (97%)
1	0	0	0	0	0	0
0	0	2	1	0	0	3 (3%)

Interpretative Performance

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Marks	UK (20)	France (20)	Czech R (19)	Switzerland (20)	Netherlands (18)	Total (97)
2	19	15	17	19	18	88 (91%)
1	1	3	1	1	0	6 (6%)
0	0	2	1	0	0	3 (3%)

- Those that scored zero for interpretation were those that did not recognise the raised 3-methylglutaconate

Types of 3-methylglutaconic aciduria

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- Primary
  - 3-methylglutaconyl –CoA hydratase deficiency (AUH gene, Type 1 MGA) – increased 3-hydroxyisovaleric acid in addition to 3MGA
  - HMG-CoA lyase deficiency (HMGCL gene) – increased 3-hydroxy-3-methylglutarate and usually 3-hydroxy IVA

These disorders should be distinguishable from each other and from secondary causes

Types of 3-methylglutaconic aciduria

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- Secondary Causes (3-methylglutaconic and 3-methylglutarate only)
  - Barth Syndrome (TAZ gene, MGA Type 2)
  - Costeff syndrome (OPA3 gene, MGA Type 3)
  - MEGDEL Syndrome (SERAC1 gene)
  - THEM70 deficiency (THEM70 gene)
  - DCMA syndrome (DNAJC19 gene, MGA Type 5)
  - Various others, e.g. ECHS1 deficiency, mtDNA depletion (POLG, SUCLA2), MELAS, other mitochondrial disorders, CPS1 deficiency, Smith-Lemli-Opitz, GSD Type1A

Recommendations

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	UK	France	Czech R	Switzerland	Netherlands	Total (of 97)
Cardiolipin	17	6	2	7	11	43
General genetics	10	14	11	9	9	53
TAZ gene	15	10	13	11	14	63
FBC	8	8	4	7	8	35
Refer to metabolic	16	2	0	4	5	27
Refer to cardiology	5	3	1	5	6	20
Repeat Organic acids	6	2	0	0	3	11
Genetic counselling / sibling testing etc	6	0	0	7	1	14

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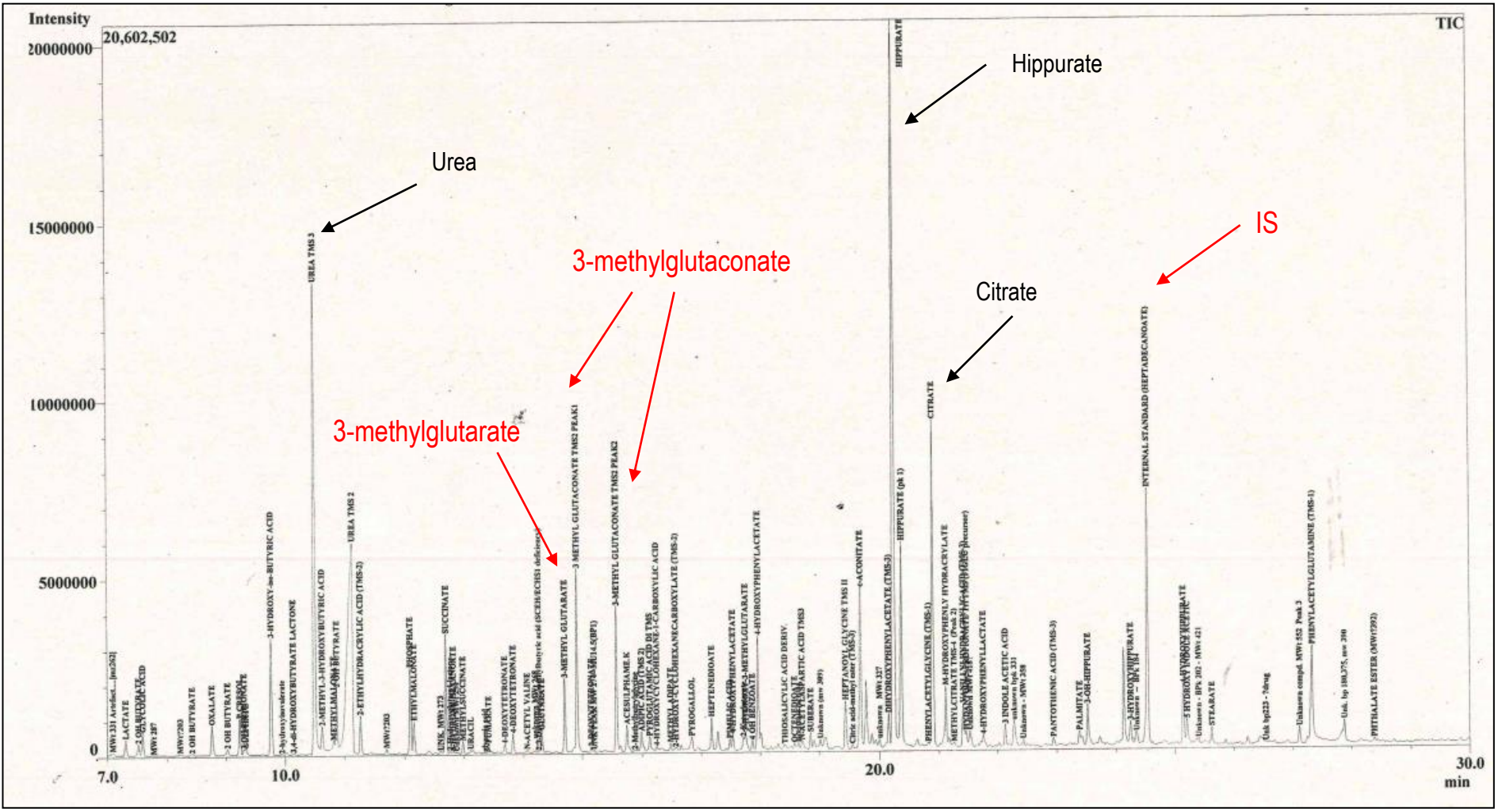

Overall performance

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Sample	Analytical performance	Interpretive performance
Barth Syndrome	97%	91%

Acknowledgements

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