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QUALITY ASSURANCE IN LABORATORY TESTING FOR IEM

Diagnostic Proficiency Scheme UK

ERNDIM Workshop, October 2025

Joanne Croft and Claire Hart, Sheffield, UK

Agenda

- Welcome
- Comments for the Annual report 2024
- Certificate of participation in proficiency Testing for 2024
- Website reporting: recommendations
- Logistics
  - Participants
  - Tests required
  - Origin of samples
  - Shipment of samples
  - Common sample
- Evaluation of Reports
  - Deadlines of the results submission
  - Scoring system
- Survey 2025 – 1
- Survey 2025 – 2
- DPT scheme in 2026
- Contribution of samples
- Any other business
- Acknowledgements

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DPT UK 2024

- 20 participants
- 1 participant - letter for poor score
- 1 participant – letter for critical error
- 1 participant – letter for poor score and critical error
- All 3 responded informing me of investigations carried out and measures put in place

- Any comments/issues from participants?

- Did everyone receive their certificate of participation for 2024?

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Website reporting : recommendations

- Please ensure all metabolites you wish to be considered are recorded as a key metabolite in the results section and not entered in the comments – it is easy to miss things when scoring
- Please ensure your diagnosis is entered into the diagnosis section and not under the metabolites reporting section
- Participants recommendations/suggestions for improvements?

Logistics - 2025

- **Participants**
  - 20 in the UK DPT scheme
  - one request received for a short extension to the deadline for results submission for Round 1 which was granted (see further slide on rules)
  - **Tests required**
  - amino acids, organic acids, mucopolysaccharides, purines/pyrimidines, oligosaccharides and acylcarnitines
  - the use of a ‘send away’ laboratory for any tests you don’t perform in your laboratory is allowed but participants have to take ownership of the result they provide
  - collusion between laboratories is NOT allowed

Logistics cont.

- **Origin of samples**
  - Samples are either donated to us from other laboratories, donated to us from another scientific advisor or collected from laboratory staff
  - In 2025, samples used (excluding the common sample) had been donated to us from patients seen at the Sheffield Children's Hospital and the Northern General Hospital, Sheffield
- **Shipment of samples**
  - Sent in bulk from our laboratory to CSCQ in Switzerland
  - CSCQ aliquot the samples and ship to participants (and to us for checking)
- **Common sample**
  - Provided in 2025 by the French DPT scientific advisor (Christine Vianey Sabine)

Rules for requesting extensions

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- If the participant supplies results before the consensus results are published or the diagnoses are circulated (no later than 2 weeks after the deadline) and it is the first extension request, the Admin Office will make the decision to reject or accept the extension without contacting the Scientific Advisor.

- If multiple extensions are requested in a scheme year or if the Admin Office believe an extension request is not justified, then the request is discussed with the SA.

- The AO directs participants to read the participant guide and instructions closely, and it does say to contact the AO if a lab has difficulty meeting deadlines.

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Report format

Investigations

pre-investigation (quantitative and qualitative results: pH, protein, glucose, creatinine, urate, etc).

amino acids

organic acids

mucopolysaccharides

purines/pyrimidines

oligosaccharides

acylcarnitines

Conclusion **(diagnosis, the probability of an enzyme deficiency)**

Advice for further investigation

Advice for the attending clinician

Scoring

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A	Analytical Performance	Correct results of the appropriate tests	2
		Partially correct	1
		Unsatisfactory or mis-leading	0
I	Interpretation of results	Diagnosis established	2
		Helpful but incomplete	1
		Misleading/incorrect diagnosis	0

Maximum obtainable *24 points*
No return *0 points*

Minimum Acceptable Score

- The minimum acceptable score is now 17 (increased from 15 in 2022)
- This was agreed by the ERNDIM Scientific Advisory Board in 2021
- Previously a lab could score 0 for 2 samples and still gain an acceptable score

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Scoring and Critical Errors

- Laboratories who otherwise obtain an acceptable score (min. of 17) but who get a critical error are automatically sent a performance support letter
- What constitutes a critical error for the 2025 scheme will be discussed and confirmed at the Scientific Advisory Board meeting (held in Autumn)
- N.B. All scores given in this presentation will be moderated by another DPT scheme Scientific Advisor and are not, as yet, accepted as the final score

Samples in 2025

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- **Sample A**

Common sample – 15-year-old boy. Dysmorphic features, scoliosis, size -1.5 SD, normal intellectual development. Under treatment.

The sample was obtained from a 16-year old boy with mucopolysaccharidosis type VI due to arylsulfatase B deficiency.

- **Sample B**

47 year old male. Epilepsy since teenager. Adult onset leukoencephalopathy,

The sample was obtained from a 48 year old man with 3 methylglutaconyl-CoA hydratase deficiency.

- **Sample C**

Presented at 1 year of age with developmental delay. Liver pathology a later feature.

The sample was obtained from a 15 year old girl with Argininosuccinic aciduria due to arginine succinate lyase deficiency.

Sample A – MPS Type VI

Sample A (common sample)

— ***Returns were received from all 20 participants***

- Common sample – provided this year by the French DPT scheme Scientific Advisor
- Will be discussed in more depth by Christine at the meeting for all participants

Sample A – marking scheme

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(Marking scheme used by all the DPT scheme organisers)

- **Analytical**
- Increase of dermatan sulphate (score 2)
- Increase of glycosaminoglycans without GAGs fractionation (score 1)

- **Interpretation**
- Mucopolysaccharidosis type VI (score 2)
- Unspecified or wrong mucopolysaccharidosis, or diagnosis according to the clinical presentation (score 1)

Sample A (UK scheme participants performance)

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Analytical

- 17/20 participants scored 2 marks
- Identified presence of dermatan sulphate by GAG fractionation
- 3/20 participants scored 1 mark
- Identified increased GAG concentration but did not do GAG fractionation

Sample A – Interpretation

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- 17/20 participants scored 2 marks
- 3/20 participants scored 1 mark

- All the participants who scored 2 marks for analysis interpreted the result correctly.
- All the participants who scored 1 mark for analysis also scored 1 mark for interpretation

Sample A – Recommendations

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All participants gave helpful recommendations

- Enzyme assay to confirm the diagnosis – 18/20
- Genetic analysis – 16/20

MPS VI or Maroteaux-Lamy disease is due to N-acetylgalactosamine-4-sulfatase deficiency. Coded by the *ARSB* gene.

Samples in 2025

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Sample B – 3 methylglutaconyl-CoA hydratase deficiency

Sample B – Returns were received from all 20 participants

Marking scheme:

- Analytical
- Increased 3 methyl glutaconic acid – 1 mark
- Increased 3 OH IVA – 1 mark
- (there is also raised EMA in this sample – cause unknown in this case)

- Interpretation
- 3 methyl glutaconyl hydratase deficiency – 2 marks
- 3 methylglutaconic aciduria – 1 mark

Sample B - Organic acid chromatogram

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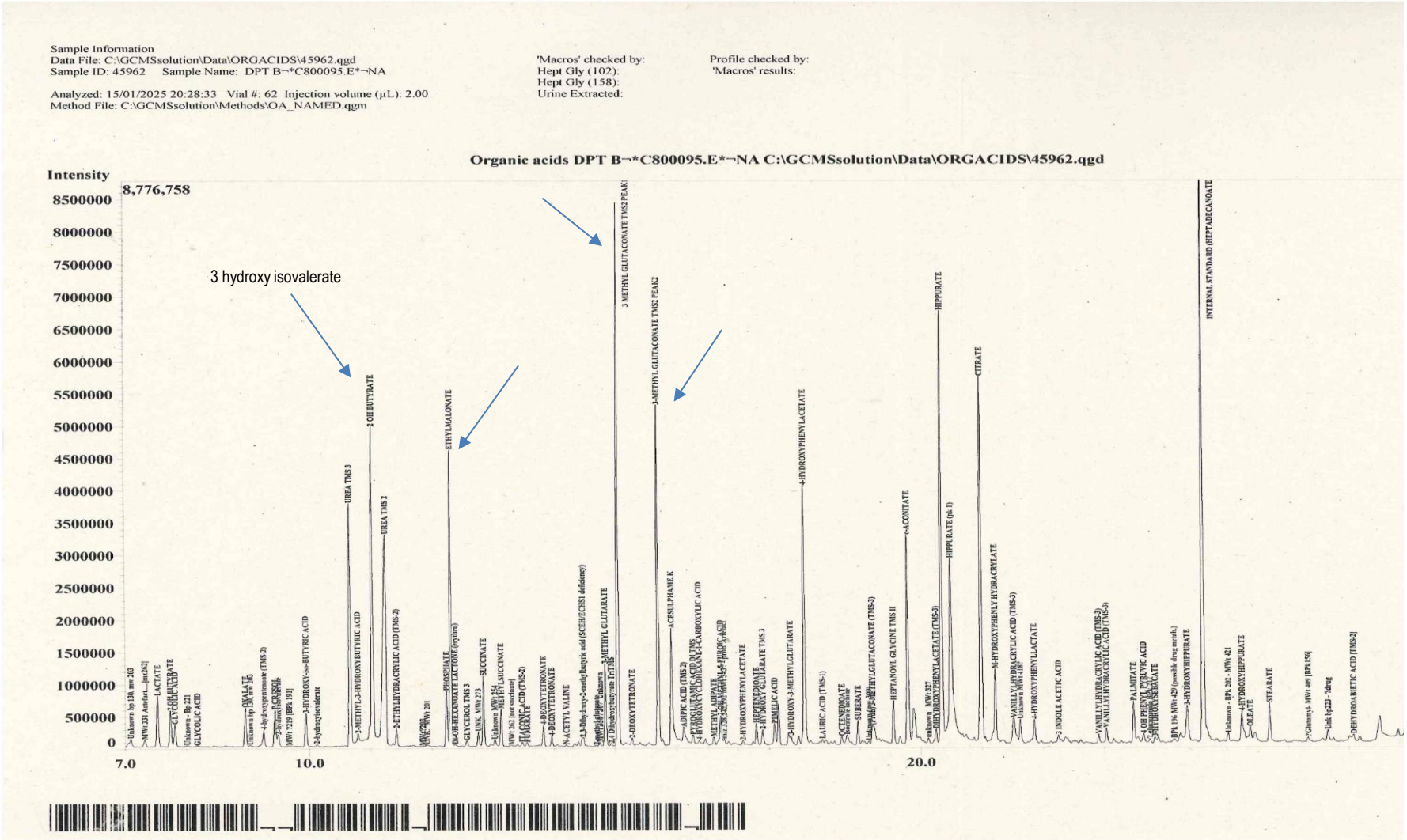

Sample B - Analytical

- 18/20 participants scored 2 marks for analysis
  - Noted the increased 3 methylglutaconic acid and the increased 3 hydroxy isovaleric acid
- 2/20 participants scored 1 mark for analysis
  - Did not report the increased excretion of 3 hydroxy isovaleric acid

Sample B – Interpretation

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20/20 participants scored 2 marks

- All participants correctly identified this sample as having come from a patient with 3 methylglutaconyl-CoA hydratase deficiency (aka 3 methylglutaconic aciduria type 1)

- Many participants wrote other 3 methylglutaconic acidurias as their alternate diagnosis with some saying this was unlikely given the level of excretion of 3 hydroxy isovaleric acid.

- Due to the increased excretion of ethylmalonic acid in this sample, a couple of participants also mentioned multiple acyl-CoA dehydrogenase deficiency, ethylmalonic acidaemia or SCADD as other alternate diagnoses but with the caveat that these were much less likely on clinical grounds.

Sample B – Recommendations

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- Molecular analysis of the AUH gene - 16/20
- Referral to adult metabolic consultant/team - 13/20
- Repeat organic acid analysis - 7/20
- 3 methyl glutaconyl enzyme assay (in leucocytes or fibroblasts)- 4/20
- Acylcarnitines (some mentioned to help determine significance of the increased EMA) - 9/20

Samples in 2025

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- **Sample A**

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Sample C – ASA

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Results were received from all 20 participants

Marking scheme:

- Analytical

Detection of ASA (argininosuccinic acid) – 2 marks

- Interpretation

ASA (argininosuccinic aciduria) – 2 marks

Sample C – Analytical

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- 20/20 participants scored 2 marks
- All detected increased argininosuccinic acid and its associated anhydrides
- Mean ASA concentration =842.4 umol/mmol (7 labs provided a quantitative result)(no SCH ref range)
- 9/20 commented on increased arginine – felt to be due to treatment
- Mean arginine concentration = 56.9 umol/mmol (SCH ref range 0 - 11)

Sample C – amino acid trace

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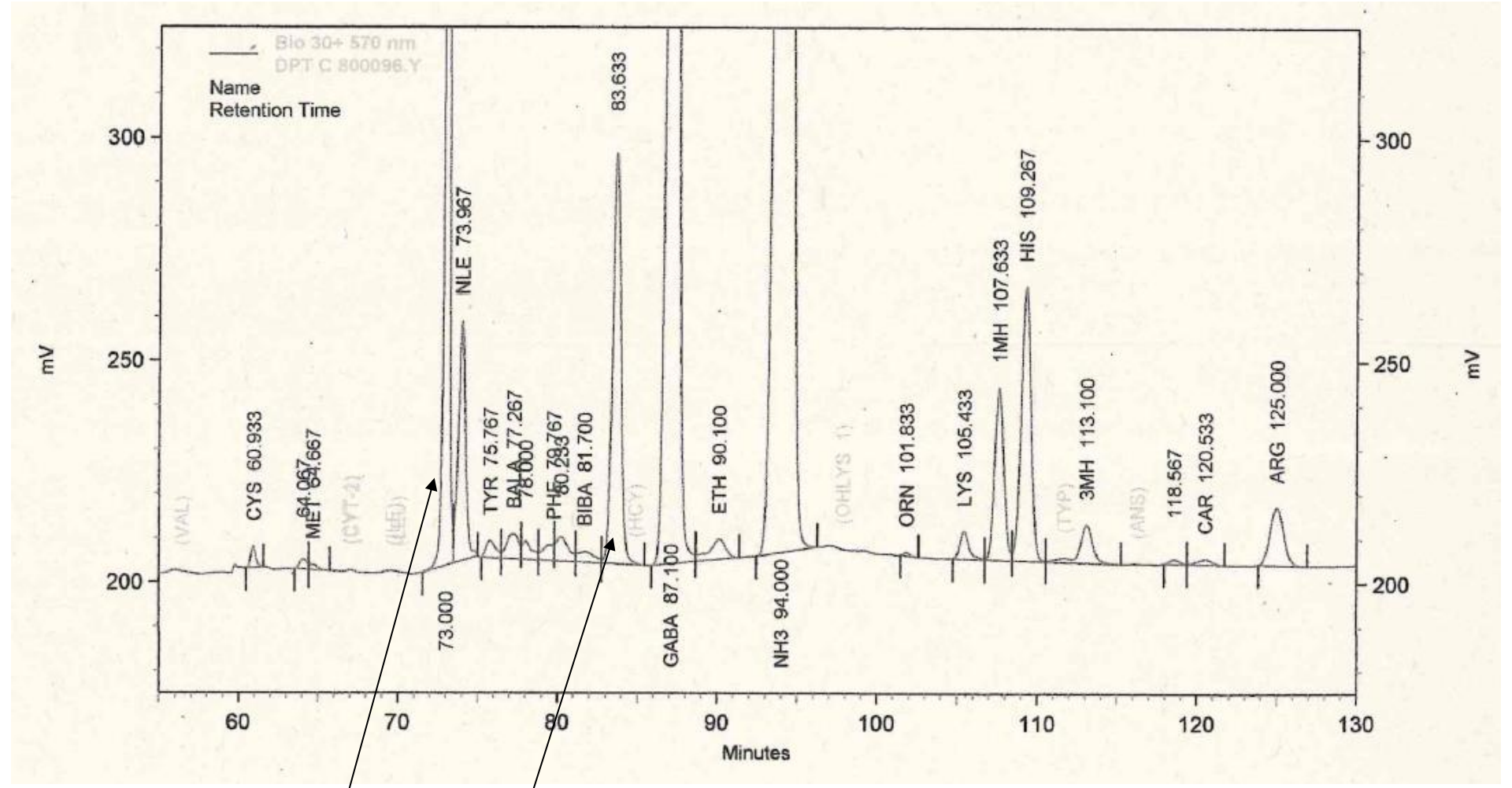

ASA

ASA anhydride

Sample C – Interpretation

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- 20/20 scored 2 marks
- All participants concluded that this sample was from a patient with Argininosuccinic aciduria
- Compare this to the ASA sample that was sent as the common sample in 2023 when 6/20 participants scored 0 marks (though concentration of ASA in that sample was much less – mean value 46 umol/mmol)

Sample C – Recommendations

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- Urgent blood ammonia - 20/20
- Urgent plasma amino acids - 18/20
- Mutation analysis of ASL gene to confirm diagnosis - 18/20
- Genetic testing (no gene named) – 2/20
- Testing of siblings/family members – 7/20
- Liver function tests – 7/20
- Urine orotic acid – 3/20 (10 participants commented on the fact that excretion of orotic acid was normal/not detected)

Samples in 2025

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- **Sample D**

Failure to thrive in infancy. Presented acutely unwell later in life with hypoglycaemia, acidosis and requiring ventilatory support. Diagnosed aged 1 year. Sample collected aged 29 years.
Sample was obtained from a female patient with glutaric aciduria type 3.

- **Sample E**

Skeletal dysplasia, diagnosed aged 8 years. Sample collected aged 15 years.
Sample was obtained from a male patient with alpha mannosidosis.

- **Sample F**

Poor feeding and drowsiness, Diagnosed aged 2 weeks. Sample collected aged 32 years.
Sample was obtained from a male patient with isovaleric acidaemia.

Sample D – Glutaric Aciduria Type 3

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Results were received from all 20 participants

Marking scheme:

Analytical

- Increased glutarate on OAs – 2 marks
- Increased lactate and TCA metabolites, with no mention of increased glutarate – 1 mark

Interpretive

- Increased glutaric acid with appropriate further tests (acylcarnitines, fatty acid oxidation flux) – 2 marks
- MADD – 1 mark
- Mitochondrial disorder – 1 mark

Sample D – Analytical

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- 14/20 participants commented on the increased glutarate in this sample.

- Most participants also commented on the increased excretion of lactate, malate, fumarate and 3 hydroxy butyrate.

- This was a dilute urine sample

(mean creatinine conc. of participants results = 0.77mmol/L)

Sample D – organic acid chromatogram

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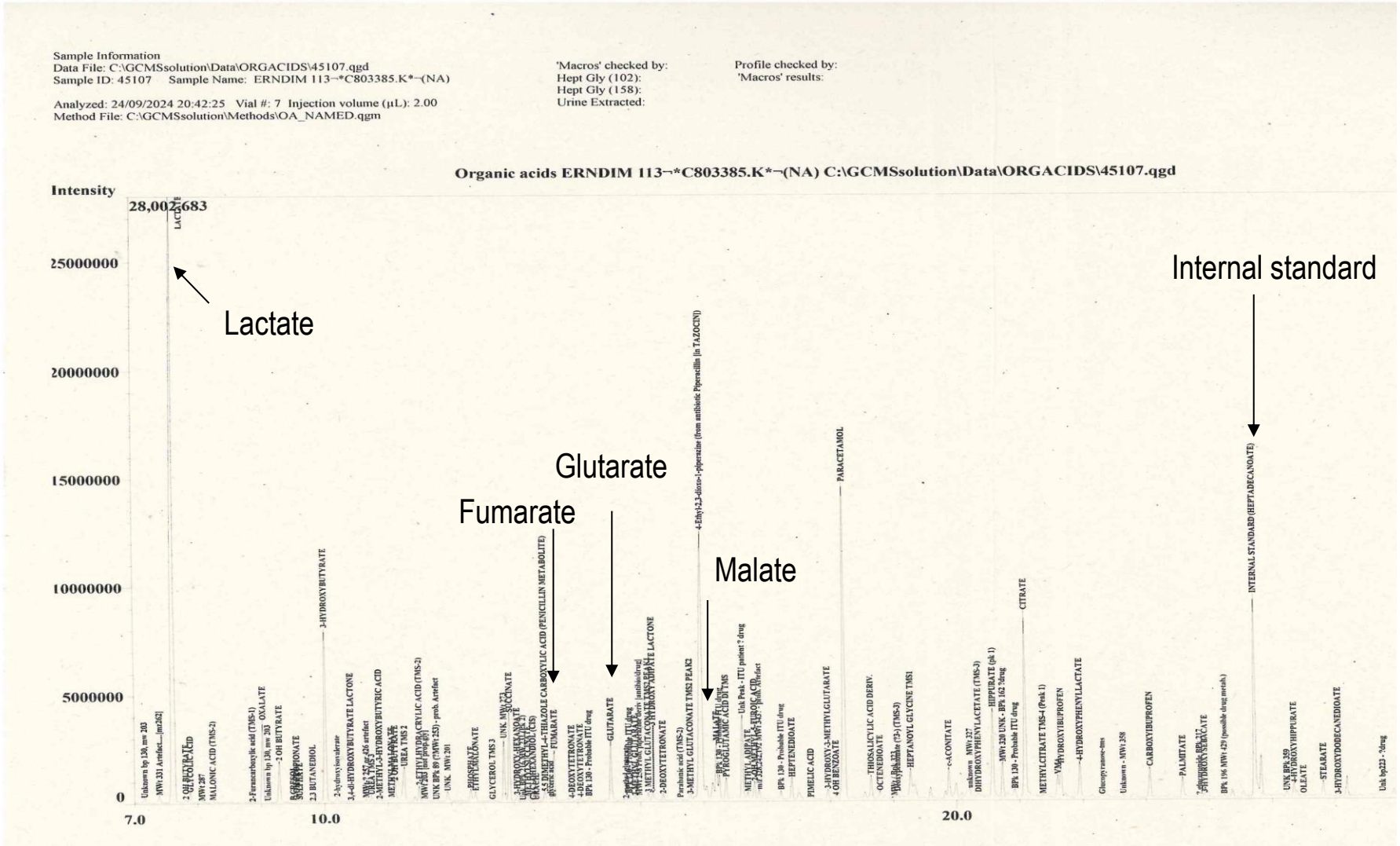

Sample D – Interpretation

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- No participants gave glutaric aciduria type 3 as either the diagnosis or the alternate diagnosis.
- Most laboratories mentioned that the pattern of results on organic acid analysis (increased lactate, malate and fumarate) could be suggestive of a mitochondrial disorder.
- Made scoring difficult.

Sample D – Recommendations

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- Plasma lactate – 19/20
- Acylcarnitines – 13/20
- Plasma amino acids – 15/20
- Mitochondrial genetics panel – 8/20

- Many other recommendations provided due to the non-specific findings

Sample D

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- This sample was obtained from a patient with biochemically and genetically confirmed Glutaric aciduria type 3 (GA3)
- Succinate-hydroxymethylglutarate-CoA transferase deficiency, encoded by C7orf10 (converts glutarate to glutaryl-CoA)
- The patient presented acutely unwell at the age of 29 years, following a brief vomiting illness, and was admitted to the ICU requiring ventilation.
- Urine organic acids showed increased excretion of glutarate, lactate, fumarate and malate without increased acylglycines suggestive of a possible mitochondrial disorder. High dose riboflavin was administered which was followed by a rapid clinical recovery.

Sample D

- It was subsequently found that the patient had been the first described case of GA3 (Bennett et al, JIMD (1991) 14:165-173) but had been lost to follow up.
- This case was presented as a poster at the SSIEM meeting in September 2014 and has also been used in the Sheffield QLOU scheme in 2014 (sample 221).

Sample D

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- This was a difficult sample. The disorder is rare (and often thought of as benign) but one which metabolic laboratories need to be aware of. Biochemically it is difficult to distinguish between glutaric aciduria type 3, generalised mitochondrial dysfunction or riboflavin responsive glutaric aciduria type 2 on riboflavin. One of the key differences is the lack of acylglycines in GA3. Participants that failed to follow up on the increased glutarate appropriately scored lower.
- At the Scientific Advisory Board meeting to be held later in the year I will recommend that this be made an educational sample.

Samples in 2025

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- **Sample D**

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- **Sample E**

Skeletal dysplasia, diagnosed aged 8 years. Sample collected aged 15 years.
Sample was obtained from a male patient with alpha mannosidosis.

- **Sample F**

Poor feeding and drowsiness, Diagnosed aged 2 weeks. Sample collected aged 32 years.
Sample was obtained from a male patient with isovaleric acidaemia.

Sample E – Alpha mannosidosis

Results were received from all 20 participants

Marking scheme

- **Analytical**

Abnormal oligosaccharide pattern - 2 marks

- **Interpretation**

Alpha mannosidosis – 2 marks

Suggesting oligosaccharide analysis if not done (or results not yet back) - 1 mark

Sample E – Analytical

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- 14/20 laboratories reported an oligosaccharide result
- 13/14 laboratories identified an abnormal pattern
- 1/14 reported a normal pattern
- 6/20 did not report an oligosaccharide result

- 1 laboratory reported that they had sent the sample away for oligosaccharide analysis but did not receive the result before the deadline. I am not aware that this laboratory asked for an extension.

Sample E – oligosaccharide TLC

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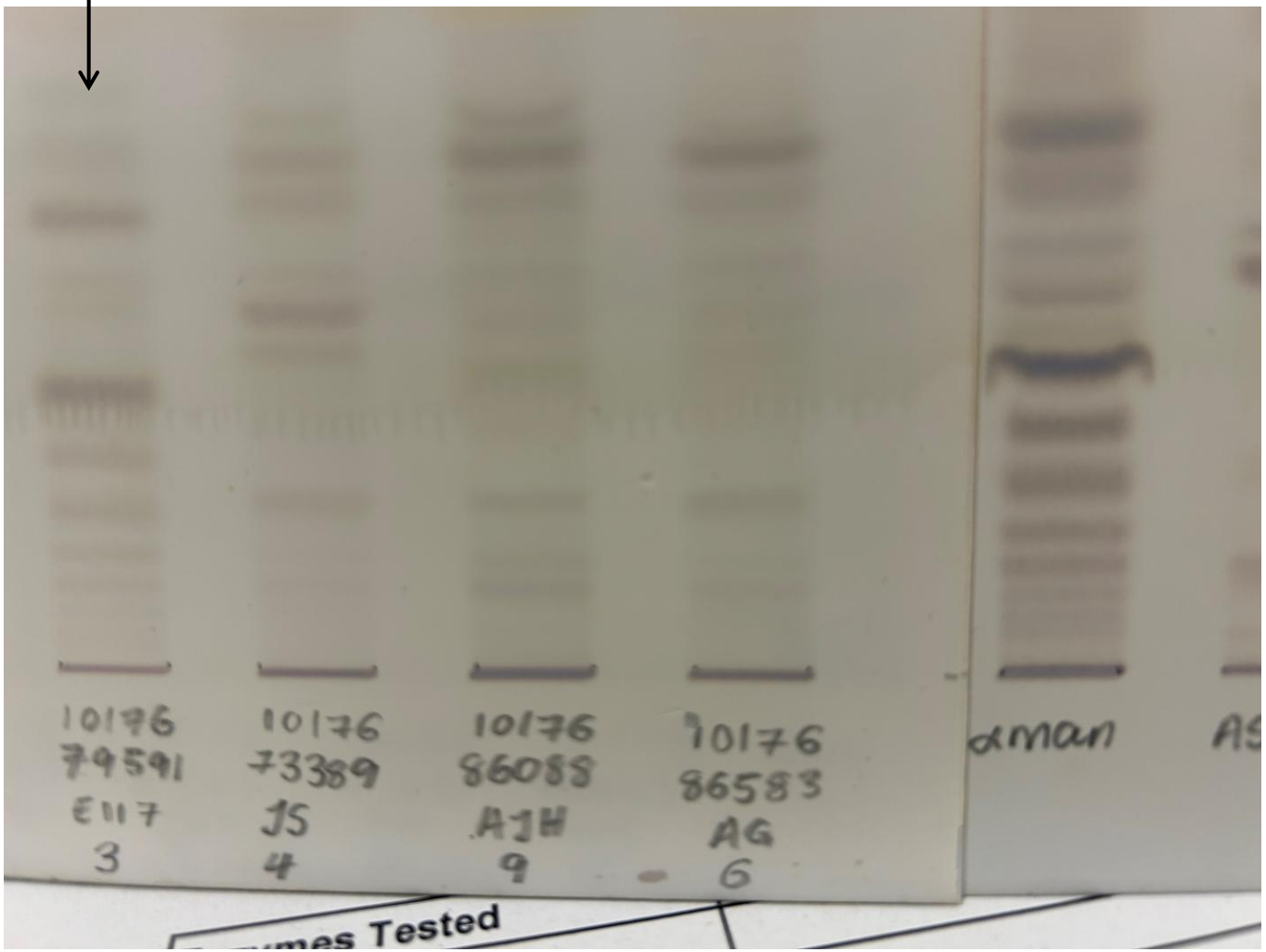

Sample E

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- Oligosaccharide analysis performed by the Willink laboratory to check sample both before and after aliquoting by CSCQ
- Reported ‘trisaccharide band and ‘ladder’ formation detected on oligosaccharide chromatography, strongly suggestive of alpha-mannosidosis’.
- At time of patient’s diagnosis, enzyme analysis was undertaken
  - Leucocyte alpha mannosidase = < 10 nmol/mg/hr (ref range 55 – 340)

Sample E - interpretation

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- Of those 14 laboratories who performed oligosaccharide analysis, 13 gave the correct diagnosis and scored full marks for this sample
- 3 laboratories scored 1 mark for recommending oligosaccharide analysis
- 1 laboratory performed oligosaccharide analysis and reported a normal profile (?critical error) – scored 0 for this sample
- 3 laboratories did not perform nor suggest oligosaccharide analysis therefore scored 0 marks for this sample

Sample E – Recommendations

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- Genetic confirmation (MAN2B1 gene) - 9/20
- Genetic confirmation (no gene named) - 3/20
- Enzyme assay - 13/20 (including one lab who did not reach the correct diagnosis but felt, on clinical info provided, alpha mannosidosis needed investigating)
- Repeat urine for oligos – 3/20
- Oligos if not already done – 3/20 (different 3 to those above)
- Refer to metabolic consultant/team - 8/20

- Not all labs who scored 4 marks for this sample suggested both genetic and enzyme analysis but did suggest at least one of these follow up tests.

Samples in 2025

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- **Sample D**

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Sample was obtained from a female patient with glutaric aciduria type 3.

- **Sample E**

Skeletal dysplasia, diagnosed aged 8 years. Sample collected aged 15 years.
Sample was obtained from a male patient with alpha mannosidosis.

- **Sample F**

Poor feeding and drowsiness, Diagnosed aged 2 weeks. Sample collected aged 32 years.
Sample was obtained from a male patient with isovaleric acidaemia.

Sample F – Isovaleric acidaemia

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Results were received from all 20 participants

Marking scheme

- Analytical

Increased isovalerylglycine on OAs – 2 marks

- Interpretation

Isovaleric acidaemia – 2 marks

Sample F - analytical

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- All participants identified the markedly increased excretion of isovalerylglycine, with many commenting on the absence of increased excretion of 3 hydroxy isovaleric acid, likely to be due to this being a non-crisis sample taken from a patient under treatment.
- All participants scored 2 marks for analysis

Sample F – organic acid chromatogram

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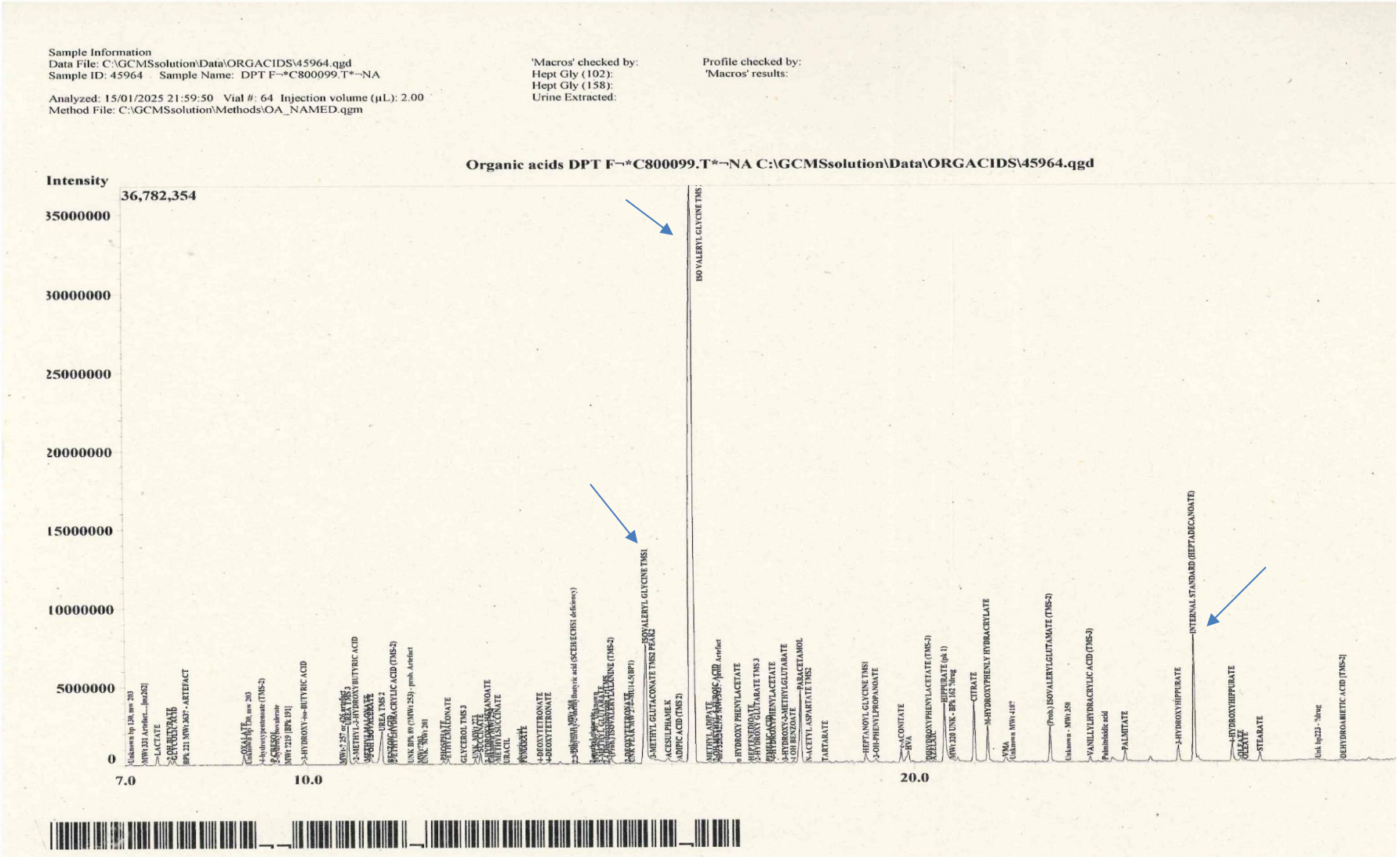

Sample F – Interpretation

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- All participants correctly gave isovaleric aciduria/isovaleric acidaemia as the most likely diagnosis with no suggestions for alternative diagnoses provided given the clear nature of the analytical findings.
- All participants scored 2 marks for interpretation.

Sample F – Recommendations

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- Acylcarnitines (DBS or plasma) - 19/20
- Urgent ammonia (given clinical details of drowsiness) - 10/20
- Mutation analysis (IVD gene) - 18/20
- Mutation analysis (gene not named) - 2/20
- Referral to metabolic consultant/team - 15/20
- Testing of siblings/family members - 5/20
- Repeat sample for repeat organic acid analysis - 5/20
- Blood glucose (given clinical details of poor feeding) - 2/20

Sample F – Recommendations (cont.)

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- Acylcarnitines to monitor free carnitine status and to help confirm the diagnosis (increased C5 acylcarnitine). Given clinical details of drowsiness and poor feeding an urgent ammonia and glucose should be requested.
- Genetic confirmation of isovaleric acidaemia caused by homozygous or compound heterozygous mutations in the isovaleryl CoA dehydrogenase gene (IVD; 607036) on chromosome 15q15.1 with appropriate family studies.
- Referral to specialist metabolic consultant/team for
- immediate management (emergency regimen) and long term dietary therapy (low protein diet, glycine and carnitine supplementation) and testing of siblings/family members.

Overall performance

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Sample	Analytical performance	Interpretive performance
MPS VI	92.5%	92.5%
3 methylglutaconyl-CoA hydratase deficiency	95%	100%
Argininosuccinic aciduria	100%	100%
Glutaric aciduria Type 3	87.5%	70%
Alpha mannosidosis	65%	72.5%
Isovaleric acidaemia	100%	100%

Annual plea for samples

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- We can only send what we have stored
  - samples may not be ideal for use
  - samples deteriorate
  - diagnostic metabolite may be OK but others might not be
    - may lead to diagnostic confusion

- We will struggle to continue providing this EQA scheme without your input

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Sample Donations

- Labs that provide a sample that is used in the scheme receive a 20% discount on cost of the DPT scheme for the next scheme year

- Requirements: 200 ml urine, creatinine >1, pH 5-9

- Please contact the Scientific Advisors if you have a sample that you think may be suitable
  - Joanne.Croft4@nhs.net
  - Claire.Hart10@nhs.net

Acknowledgements

- Louisa Smith, Chief BMS, Sheffield Children's Hospital Clinical Chemistry
- Stephen McSweeney, Chief BMS, Sheffield Children's Hospital Clinical Chemistry
- Olivia Edmondson, Senior BMS, Sheffield Children's Hospital Clinical Chemistry
- Willink laboratory (for kindly checking Sample E)