# ERNDIM PROFICIENCY SCHEME (NORTHERN EUROPE)

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Dear Colleague

**Re: ERNDIM Proficiency Scheme Report – Samples 09.1, 09.2, 09.3, 09.4, 09.5, 09.6**

Six samples were distributed in one batch to 22 participants, returns were received from 22 participants for samples 09.1, 09.2 & 09.3 and from 21 participants for samples 09.4, 09.5 & 09.6.

## Patient 09.1

50 year old male, cerebellar syndrome, parents first cousins
**This sample was obtained from a patient with 3-methylglutaconic aciduria type 1 with undetectable 3-methylglutaconyl CoA hydratase activity and who was homozygous for a disease causing mutation in the AUH gene.**

**Findings**

21/22 laboratories identified an increased excretion of 3-methylglutaconate.

**Conclusions**

14/22 of these concluded that Type 1 methylglutaconic aciduria was the most likely diagnosis.

**Further investigations**

17/22 would have recommended measurement of hydratase acitivty and 11/22 would have suggested mutation analysis. Several laboratories also raised the possibility of Barth syndrome and suggested that the Tafazzin gene should be investigated. 3/22 laboratories recommended that any siblings should be tested.

**Comment**

It is reassuring that all laboratories except one identified an increased excretion of 3-methylglutaconate.

### *Patient 09.2*

*A 6 year old girl with prominent cerebellar ataxia and mild retardation and previous hypotonia. Only able to speak a few words.*

**This sample was the common sample and was obtained from a child with Salla disease.**

**Findings and Conclusions**

This was a challenging sample and only two laboratories identified an increase in sialic acid, one measured the compound but found it to be normal. 6/22 laboratories performed oligosaccharide analysis, all reporting normal findings. 4/22 participants commented on an increased excretion of lysine and/or basic aminoacids.

**Further investigations**

2/22 participants correctly identified Salla disease as a possibility. 17/22 reported no significant abnormality, one considered the clinical features consistent with an MPS disorder, one considered hyperlysinaemia as a possibility and one made no interpretative comment.

**Comment**

This was a difficult sample and it will be interesting to compare how participants in this DPT scheme performed versus those in the other schemes once they are reported. It is interesting that none of the six laboratories who undertook oligosaccharide analysis reported an abnormality. One laboratory observed a fourfold increase in GAG excretion but reported "No significant abnormality" as a conclusion.

### *Sample 09.3*

Adult female with severe learning difficulties

**This sample was obtained from an adult female with learning difficulties and fumarate hydratase deficiency**

**Findings**

21/22 laboratories noted an increased excretion of fumarate. 17 of these also commented on increased succinate excretion and 10 reported that the excretion of malate was increased.

**Conclusions**

19 of the 21 laboratories reporting an increased excretion of fumarate considered that fumarate hydratase deficiency was a possible or likely diagnosis. Of the remaining two, one considered a mitochondrial disorder and the other that an MPS disorder was indicated despite near normal GAG excretion and the identification of increased fumarate.

**Further investigations**

18/22 participants would have recommended measurement of fumarate hydratase activity and 9/22 mutation analysis. 4/22 suggested mitochondrial studies and 6/22 the measurement of plasma or blood lactate.

**Comment**

It is encouraging that almost all laboratories identified the increased excretion of fumarate and that 19 of these concluded that fumarate hydratase deficiency was likely or possible. A number of laboratories commented on the excretion of malate which would perhaps not be expected in fumarate hydratase deficiency however it is likely that this was generated by the cytosolic form of the enzyme not affected in this condition.

## *Sample 09.4*

3 year old male, unexplained pyrexia, failure to thrive

**This sample was obtained from a 3 year old boy who is a healthy child of a laboratory staff member**

**Findings**

Only two participants noted any abnormal findings. One reporting a marked increase in the excretion of homocystine although this was likely to have been a sample labelling or transcription error (see sample 9.5) and the other a slight increase in the excretion of urate, two other laboratories reported this as normal and the reference range used by the laboratory reporting an increase may have been inappropriate. One laboratory did not return any results.

**Conclusions**

19/22 participants clearly indicated that no inherited metabolic disorder could be detected on the basis of the sample provided. In view of the pyrexia outlined in the clinical details two laboratories commented that mevalonic acid or its metabolites were not increased. Two laboratories raised the possibility of other disorders.

**Further investigations**

10/22 participants would not have recommended any additional investigations. 4 participants would have advised immunological studies to exclude hyper-IgD syndrome. 7 recommended a variety of other investigations.

**Comment**

While 19 of the 21 laboratories returning results concluded that no metabolic disorder could be identified around half would have recommended additional investigations in this normal child with vague and common clinical details. It is likely that this is because the sample was analysed as part of an EQA scheme but it would be worrying if this reflected everyday practice.

## *Sample 09.5*

7 year old male, family history of early onset cardiovascular disease

**This sample was obtained from a 28 year old male receiving treatment for homocystinuria**

**Findings**

19/22 participants identified an increased excretion of homocystine. Two reported normal findings although one of these was likely to have been a sample labelling or transcription error (see sample 9.4). One laboratory did not return any results. The mean concentration of homocystine reported was 44 µmol/mmol creatinine (range 25-60). 9/22 commented specifically on a normal excretion of methylmalonate on organic acid analysis.

**Conclusions**

On this basis 19/22 described homocystinuria as a conclusion. 11/19 considered that cystathionine ß-synthase deficiency was the most likely cause. One participant felt that another defect of S-aminoacid metabolism was more likely and 7 laboratories did not suggest an etiology.

**Further investigations**

All participants (19) who identified an increased excretion of homocystine would have recommended that plasma total homocysteine should be measured. 18/19 would have also suggested the measurement of plasma aminoacids in whole or part. Only two laboratories felt that quantitative excretion of methylmalonate should be undertaken. Five participants

suggested measurement of cystathionine ß-synthase activity and 12/19 the assessment of B12/folate status.

**Comment**

It is concerning that one laboratory failed to identify an increased excretion of homocystine or other relevant metabolites and it is a little surprising that a number of laboratories (n=9) failed to comment on the lack of excretion of MMA or suggest its measurement.

### *Sample 09.6*

A male aged 4 years with facial dysmorphia and speech delay
**This sample was obtained from a boy with Hunter disease, MPS type 2. It was previously circulated as sample 7.1**

**Findings**

20/22 participants identified an increased excretion of glycosaminoglycans. Where this was quantitated (n=18) the mean excretion was 63.8 mg/mmol cr. 15/20 laboratories commented on an increased excretion of key metabolite such as deramatan and heparan sulphate. One laboratory did not return any results.

**Conclusions**

All 20 laboratories who identified an increased excretion of glycosaminoglycans concluded that an MPS disorder was likely. 16/20 participants concluded that Hunter disease (type 2) was likely or possible in this patient.

**Further investigations**

19/20 participants who identified an increased excretion of glycosaminoglycans recommended enzyme confirmation and 3/20 would have arranged testing in siblings.

**Comment**

It is reassuring that all laboratories who assessed MPS excretion identified an increase and that 19/20 of these would have recommended lysosomal enzyme assay for confirmation.

**Overall comment**

It is interesting that a small number of laboratories miss significant and quite prominent findings on an occasional basis so in the current circulation one laboratory failed to identify the increased excretion of 3-methylglutaconate on organic acid analysis and another failed to identify the increased excretion of fumarate. One laboratory was also unable to identify the increased excretion of homocystine in sample 9.5. From 22 labs offering specialist diagnostic services in this area and working with EQA samples, this is food for thought.

The common sample, 9.2, caused real problems for most participants and it will be interesting to discuss the results in the context of the larger group with all participating centres at the meeting in Basel.

The normal sample, 9.4, highlighted the over enthusiasm of participants to suggest additional investigations (approximately one third did so) in normal patients, perhaps this is likely to be influenced by the context as part of an EQA scheme and may not be reflected in normal clinical practice. The scores are attached.

**Sample receipt and results return**

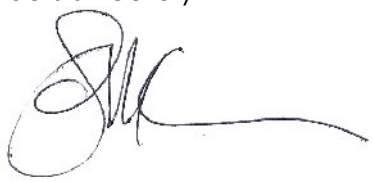
*Circulation 9.1,9.2,9.3,9.4,9.5,9.6*

Nine participants received the samples on the day following dispatch; one, 2 days later; two, 3 days later; three, 8 days later; one 9 days later; one 14 days later and one mysteriously 2 days before they were sent. 4 laboratories did not report the date of receipt.

For samples 9.1,9.2,9.3 19 reported on time, one was 1 day late, one was 7 days late and one was 6 weeks overdue.

For samples 9.4,9.5,9.6 19 reported on time, one was 1 day late and one was 6 days late. One did not return results.

Yours sincerely



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