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ERNDIM
Diagnostic Proficiency Testing
France 2013

ANNUAL REPORT 2013

In 2013, 23 labs participated to the Proficiency Testing Scheme France.
Organizing Centre: Dr Christine Vianey-Saban, Dr Cécile Acquaviva-Bourdain, Service Maladies Héréditaires du Métabolisme et Dépistage Néonatal, Centre de Biologie et de Pathologie Est, Lyon.

Geographical distribution of participants

Country	Number of participants
France	10
Italy	5
Spain	4
Portugal	2
Czech republic	1
Switzerland	1
TOTAL	**23**

Logistic of the scheme

- **2 surveys** 2013-1: patient A, B and C
  2013-2: patient D, E and F

Origin of patients:

- Patient A: NFU1 deficiency – Dr Encarnacio Riudor, Dr Jose Antonio Arranz, Barcelona
- Patient B: Mitochondrial Neuro-GastroIntestinal Encephalopathy (MNGIE) – Centre de Biologie Est, Lyon
- Patient C: Lysinuric protein intolerance – Dr Viktor Kozich, Prague. This sample has been sent to all labs participating to the DPT scheme in Europe
- Patient D: Mitochondrial acetoacetyl-CoA thiolase (MAT) – Centre de Biologie Est, Lyon
- Patient E: Morquio disease (MPS IV) – Centre de Biologie Est, Lyon
- Patient F: Glycerol kinase deficiency – Dr Begoña Merinero, Madrid

- Mailing: samples were aliquoted (when needed) and sent by CSCQ (Centre Suisse de Contrôle de Qualité) at room temperature. One mailing for the 2 surveys

Timetable of the schemes

- May 13: shipment of samples of Survey 1 and Survey 2 by CSCQ
- May 16: clinical data available on CSCQ website and start analysis of samples (Survey 1)
- June 7: deadline for result submission (Survey 1)
- June 24: clinical data available on the CSCQ website and start analysis of samples (Survey 2)
- July 19: deadline for result submission (Survey 2)
- August 23: report of Survey 1 and Survey 2 with temporary scoring by e-mail
- September 3: meeting in Barcelona
- April 7 2014: annual report with definitive scoring, as agreed by the SAB of ERNDIM, sent by e-mail

Date of receipt of samples

	Survey 1 + 2
+ 24 hours	21
+1 week	2 (custom problem in Spain)

CSCQ Website reporting

Since 2011, the website reporting system is compulsory for all centres.

Be careful: **don't enter results in the "Comments" section**: the CSCQ reporting program cannot incorporate these results in the reports.

Recommendations = **advice for further investigation**. Advice for further investigations is not anymore scored separately but it is scored together with the interpretation of results.

	Survey 1	**Survey 2**
Receipt of results	23 labs	22 labs
No answer	**0**	**1 lab**

Scoring of results

The scoring system established by the International Scientific Advisory Board (SAB) of ERNDIM has changed. Two criteria are evaluated:

A	Analytical performance	Correct results of the appropriate tests	2
		Partially correct or non-standard methods	1
		Unsatisfactory of misleading	0
I	Interpretation of results and recommendations	Good, diagnosis is established	2
		Helpful but incomplete	1
		Misleading / wrong diagnosis	0

The **total score** is calculated as the sum of these 2 criteria without weighting. The maximum that can be achieved is 4 for one sample. The scoring for each urine sample is discussed at the Scientific Advisory Board of ERNDIM in spring.

Meeting of participants

It took place in Barcelona on Tuesday 3 September 2013 from 8.30 to 10.00, before the SSIEM Meeting.

❖ Participants

Representatives from at least 17 labs were present (unfortunately, the attendance sheet was not filled by all participants: sorry for those who were present but not included in this list): JA Arranz, N Corral Gallego (Hospital Vall d'Hebron, Barcelona), J Garcia Villoria (Hospital Clinic, Barcelona), F Sabourdy (representing Bordeaux), S Funghini, E Pasquini (Florence), U Caruso (Genova), C Corne (Grenoble), O Boulat (Lausanne), G Briand (Lille), B Merinero, P Ruiz Sala (Madrid), M Chefrour, M Gastaldi (Marseille), G Polo (Padova), F Habarou, C Ottolenghi (Hôpital Necker, Paris), D Quelhas (Porto), P Jesina, K Peskova (Prague), C Rizzo (Rome), S Bekri (Rouen), MD Boveda, D Castañeiros (Santiago de Compostella).

❖ Information from the Executive Board and the Scientific Advisory Board

- **Scoring and certificate of participation**: scoring is done by 2 scheme organizers, who change every year. The results of DPT France 2013 have been also scored by Pr Jim Bonham from Sheffield. At the SAB meeting in March, the definitive scores have been finalized. The concept of critical error will be introduced in 2014. Certificate of participation for 2013 will be issued for participation and it will be additionally notified whether the participant has received a performance support letter. This performance support letter is sent out if the performance is less than 62% (score < 15 / 24). For 2013, sample B has been considered as educational, due to the low level of excretion of abnormal metabolites, and will not be scored. Therefore, the maximum score will be 20, and poor performance is considered for a score <12.
- Two warning letter will be sent for 2012, and two for 2013. One lab will not receive a certificate of participation in 2013, since this lab did not reply to one of the two surveys.
- **Reference materials** provided by SKML (mix of the four samples of the scheme) are still available, and can be ordered through the ERNDIM website. Participants are encouraged to use them as internal control, but they cannot be used as calibrants. The possibility of providing 2 levels with different concentrations has been accepted and will be available in 2015.
- **Training**: SSIEM Academy training courses.
  - The last SSIEM Academy has taken place in Paris on Tuesday and Wednesday 1st and 2nd April 2014. The program for biochemists included:
    - Purines and pyrimidines (Jörgen Bierau)
    - Mucopolysaccharides (George Ruijer)
    - Peroxisomes (Christine Vianey-Saban)
  - The lectures will be available on the SSIEM website
- **Urine samples**: we remind you that every year, each participant must provide to the scheme organizers at least 300 ml of urine from a patient affected with an established inborn error of metabolism or "normal" urine, together with a short clinical report. If possible, please collect 1500 ml of urine: this sample can be sent to all labs participating to one of the DPT schemes. Each urine sample must be collected from a single patient (don't send urine spiked with pathological compounds). Please don't send a pool of urines, except if urine has been collected on a short period of time from the same patient. For "normal" urine, the sample must be collected from a symptomatic patient (don't send urine from your kids!). Annex 1 gives the list of the urine samples we already sent.

  As soon as possible after collection, the urine sample must be heated at 50 °C for 20 minutes. Make sure that this temperature is achieved in the entire urine sample, not only in the water bath. Separate 4 aliquots in 10 ml plastic tubes, add stoppers, and freeze these aliquots and the rest of

the urine sample in a bulk. Send the bulk and the aliquots on dry ice by rapid mail or express transport to:

Dr Christine Vianey-Saban, Dr Cécile Acquaviva,
Service Maladies Héréditaires du Métabolisme et Dépistage Néonatal, 5ième étage,
Centre de Biologie et de Pathologie Est, Groupement Hospitalier Est,
59, Boulevard Pinel, 69677 Bron cedex, France.

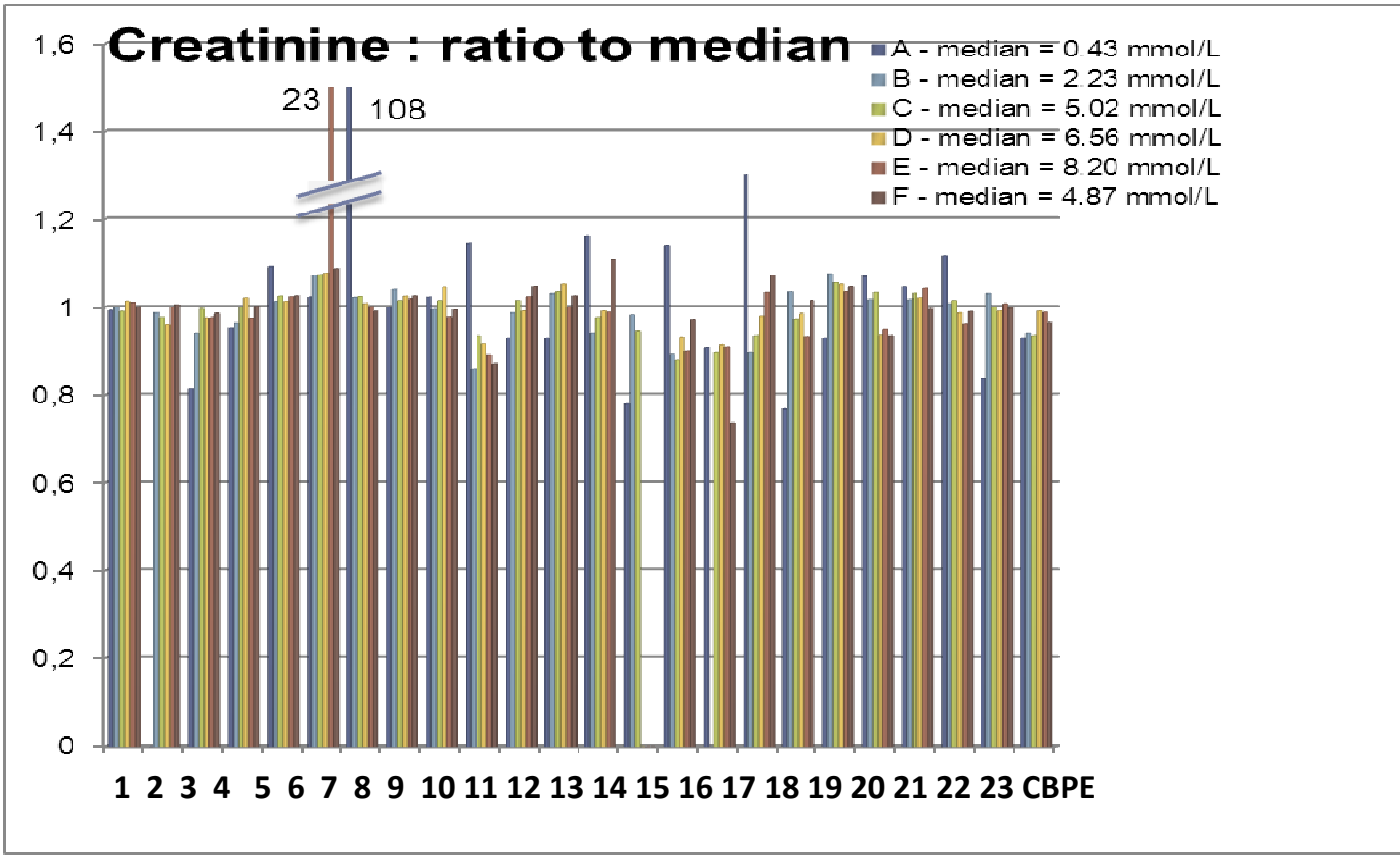
Please send us an e-mail on the day you send the samples.

- **Lab identification**: since 2007, it has been accepted that the ERNDIM number is used for "in centre" communication but anonymous identification is used for the Annual Report on the website or other purposes.

❖ Discussion of results

- **Creatinine measurement**

Creatinine determination was satisfying for most labs, except for lab 10, 15 and 16 who have systematically low values (lab 10 had the same problem last year). Lab 6 and 7 had one wrong value. Creatinine values are expressed in the figure as the ratio of each measurement over the median from all labs.
CV is < 7.5 % for all samples (4.3 – 7.5 %), except for sample A (13.5% - median = 0.43 mmol/L), and this is rather similar to the interlab CV 2012 for Special Assay in urine (6.5 %, n = 119), and the interlab CV 2012 for Quantitative organic acids (6.2 %, n = 73).



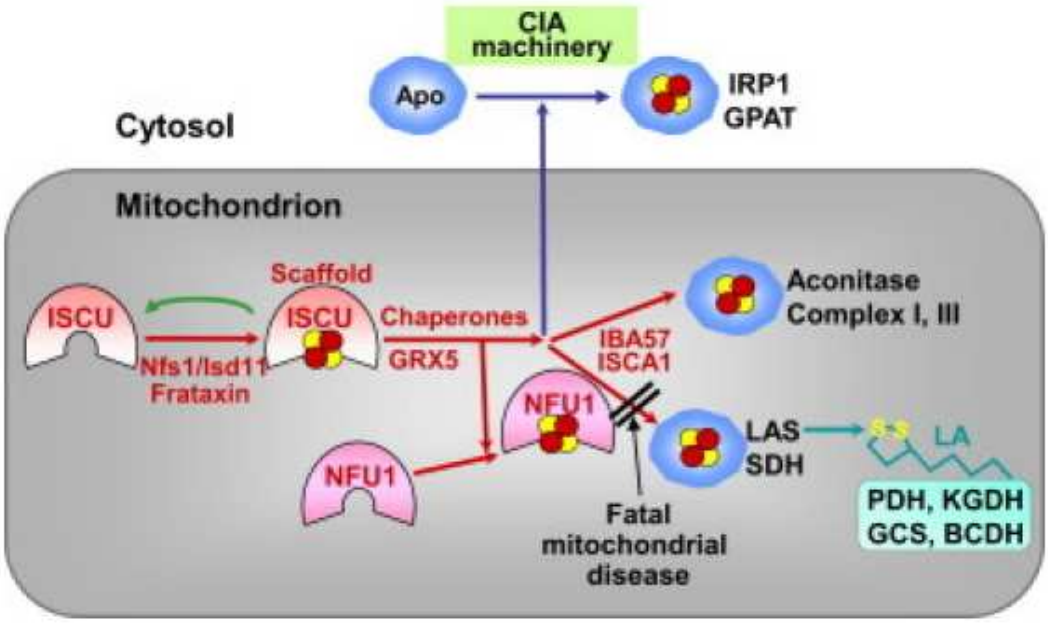
Patient A – Defect in lipoic acid synthesis due to defective NFU1 function

This 6-month old girl, without previous problems or familial history, presented with primary pulmonary hypertension and metabolic acidosis. She had no psychomotor retardation, no neurological regression. Treatment for hypertension and acidosis was immediately instituted, but despite treatment, the situation worsened and the child died a week later. Autopsy revealed extensive areas of white matter vacuolisation and astrocytosis.
This patient has been published in: Navarro-Sastre A, Tort F, Stehling O, Uzarska MA, Arranz JA, Del Toro M, Labayru MT, Landa J, Font A, Garcia-Villoria J, Merinero B, Ugarte M, Gutierrez-Solana LG, Campistol J, Garcia-Cazorla A, Vaquerizo J, Riudor E, Briones P, Elpeleg O, Ribes A, Lill R. A fatal mitochondrial disease is associated with defective NFU1 function in the maturation of a subset of mitochondrial Fe-S proteins. Am J Hum Genet. 2011 Nov 11;89(5):656-67. The biochemical investigation at diagnosis is summarized in the following tables.

	Patient	Controls
Blood lactate (mmol/L)	3.3	0.5 – 2.0
Plasma glycine (µmol/L)	1 920	125 - 318
Urinary amino acids (mmol/mol creat)		
Glycine	9 631	144 - 445
Glutamate	6 646	0.2 - 30
2-aminoadipate	1 799	< 17
Urinary organic acids (mmol/mol creat)		
Lactate	> 24 000	13 – 102
2-ketoglutarate	3 033	10 - 271
2-ketoadipate	427	< 5
2-hydroxyadipate	733	Traces
Glutarate	137	1 - 8

	Patient
Pyruvate dehydrogenase activity	9 % of controls
E3 component (dihydrolipoyl dehydrogenase)	Normal
Glycine cleavage system	Undetectable
Mutation analysis *NFU1* gene	p.Gly208Cys / p.Gly208Cys

NFU1 has a late-acting function in the pathway of Fe-S protein maturation. NFU1 is preferentially needed for Fe-S cluster assembly of succinate dehydrogenase (SDH) and lipoic acid synthase (LAS), but not of other proteins such as aconitase. An NFU1 functional defect results in defective SDH and LAS and hence in decreased synthesis of lipoic acid (LA) and a lack of lipoylation of the E2 subunits of PDH, α-KGDH, and BCDH and the H protein of GCS.



LAS: lipoic acid synthase; SDH: succinate dehydrogenase (From Navarro-Sastre et al. Am J Hum Genet. 2011;89:656-67)

Diagnosis

Most likely diagnosis

- Defect in lipoic acid synthesis (probably NFU1 deficiency) 12

- Mitochondriopathy 2
- Lactic acidosis 2
- Dihydrolipoyl dehydrogenase (E3) deficiency 1
- 2-ketoglutarate dehydrogenase deficiency 1
- Pyruvate carboxylase deficiency 1
- Non ketotic hyperglycinemia 1
- 2-aminoadipic aciduria to be defined 1

- No or wrong diagnosis 2

Other possible diagnosis

- Other causes of lipoic acid synthesis defect 7
- Mitochondriopathy 3
- Pyruvate dehydrogenase deficiency 2
- Multiple acyl-CoA dehydrogenase deficiency 2
- Pyruvate carboxylase deficiency 1

- Neuroblastoma 1

All labs but one performed **amino acid** analysis. They reported an increase of:

- **Glycine**: 20 labs (median = 7 803 mmol/mol creat – range: 3 225 – 11 217 – CV = 28.5%)
- **2-aminoadipate**: 18 labs (median = 1 830 mmol/mol creat – range: 83* – 2 950 – CV = 41.7%)
- **Glutamic acid**: 17 labs (median = 7 564 mmol/mol creat – range: 238* – 10 647 – CV = 31.3%)
- Alanine: 10 labs
- Glutamine: 7 labs

* wrong creatinine : 10.31 mmol/L (median all labs = 0.43)

All labs but one also performed **organic acid** analysis, and all of them reported a very high increase of **lactic acid** (median = 27 803 mmol/mol creat – range: 3 000 – 104 362, n = 8). They also reported an increase of:

- **2-hydroxyadipic acid**: 14 labs (median = 376 mmol/mol creat – range: 19 – 737, n = 5)
- **2-ketoadipic acid**: 12 labs (median = 451 mmol/mol creat – range: 190 – 663, n = 5)
- **2-ketoglutaric acid**: 12 labs (median = 1 788 mmol/mol creat – range: 1 127– 4 260, n = 7)

Scoring

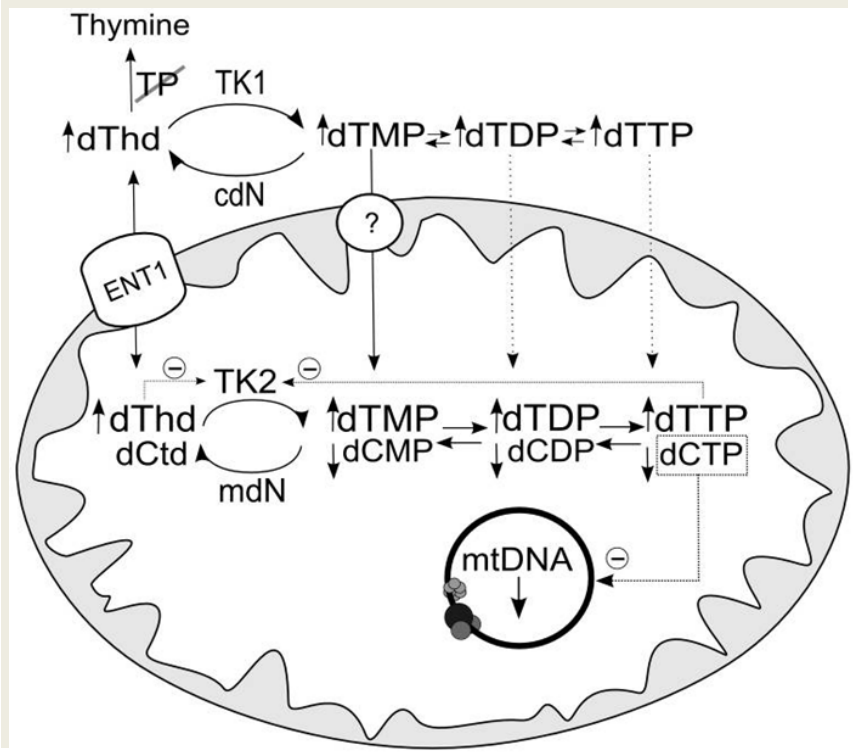
- Analytical: Increase of 2-aminoadipic, 2-ketoadipic or 2-hydroxyadipic acids (score 1), Increase of glycine, glutamic acid, lactic acid or 2-ketoglutaric acid (score 1)

- Interpretation of results: Defect of lipoic acid biosynthesis due to *NFU1* gene mutation(s) (score 2), Mitochondriopathy, 2-ketoglutarate dehydrogenase deficiency, pyruvate carboxylase deficiency, E3 deficiency, lactic acidosis, non ketotic hyperglycinemia, 2-aminoadipic aciduria (score 1)

- **Patient B – Mitochondrial neuro-gastrointestinal encephalopathy (MNGIE) due to thymidine phosphorylase deficiency (TYMP gene, OMIM 603041)**

The patient is a 14 year-old girl. From 7 years of age she presented with important loss of weight, vomiting (at night and in the morning), and osteoporosis ascribed to mental anorexia. She was referred to the neuropediatry unit because MRI revealed abnormality of white matter. She subsequently developed acute renal insufficiency because of dehydration due to severe vomiting, with rapid favourable evolution. Diagnosis was confirmed by measurement of thymidine phosphorylase activity in leukocytes; mutation analysis of *ECGF1* gene is still pending.

Thymidine phosphorylase deficiency leads to mtDNA deletions or mtDNA depletion.



From Gonzalez-Vioque et al, Plos1 2011; 7:e1002035

Diagnosis

Most likely diagnosis

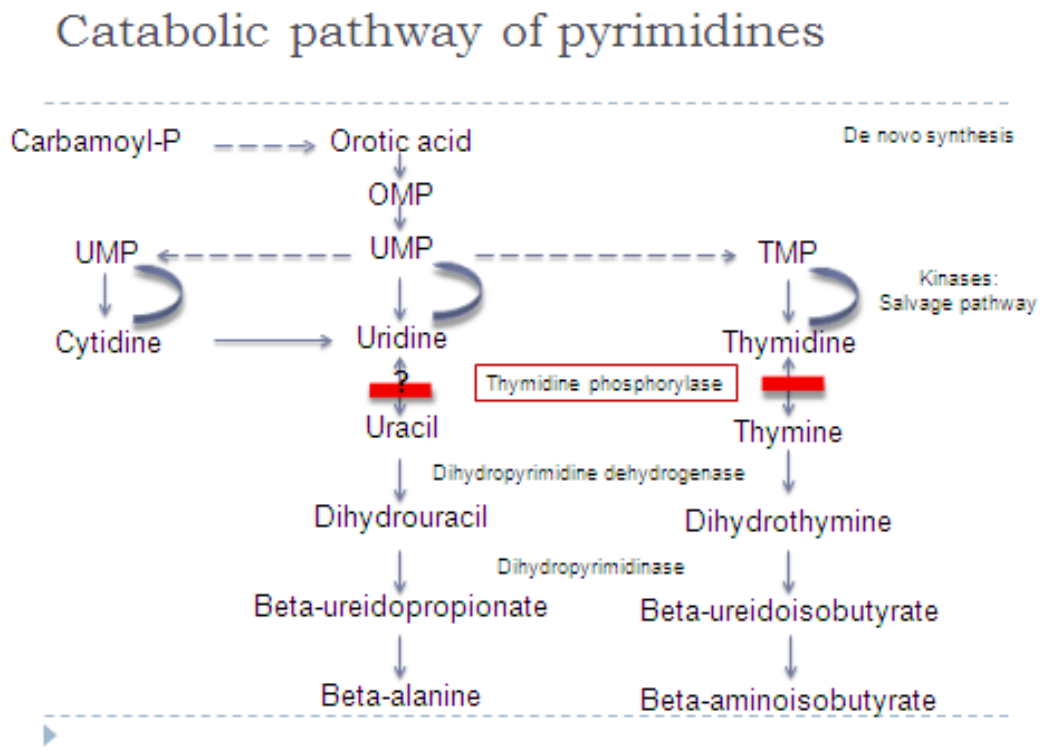
- MNGIE 3
- Dihydropyrimidine dehydrogenase deficiency 7
- Dihydropyrimidinase deficiency 1
- No significant abnormality 7
- Wrong diagnosis 5

Other possible diagnosis

- Other mitochondriopathy / POLG deficiency 2
- Dihydropyrimidine dehydrogenase deficiency 1
- Dihydropyrimidinase deficiency 1
- No significant abnormality 1
- Other 2

Seventeen labs performed **amino acid** analysis: an increase of glycine was reported by 15 of them, (median = 686 mmol/mol creat, range: 500 – 862, CV = 14%), possibly secondary to poor nutrition or to a poor storage of the urine sample (pH = 8, but nitrites were negative). Some labs reported an increase of alanine (9 labs), taurine and threonine (7 labs).

All labs but one performed **organic acids**, and 11 of them reported an increase of thymine, and 7 an increase of uracil. A dicarboxylic aciduria, evocating MCT supplementation, was reported by 18 labs.



Among the 6 labs who performed **purines / pyrimidines analysis,** 5 reported an increase of **thymine** (median = 30.1 mmol/mol creatinine, range: 20.5 - 65), and of **uracil (**median = 68 mmol/mol creatinine, range: 45 - 88); the sixth lab specified that the excretion of thymine and thymidine was in the control range.

Scoring: although the clinical information was suggestive of MNGIE, this sample was challenging because of the low excretion of metabolites, and misleading because of MCT supplementation. Therefore, the SAB of ERNDIM decided that this sample is educational, and will not be scored.

- **Patient C – Lysinuric protein intolerance**

The patient is a 4-year old boy who presented with splenomegaly (known since 6 months of life), failure to thrive and a special eating behaviour. The sample was collected at the age of 17 years during a routine check-up while receiving specific treatment. **This sample has been distributed to all labs in Europe**. Details for this patient are on the ERNDIM website.

Diagnosis

Most likely diagnosis

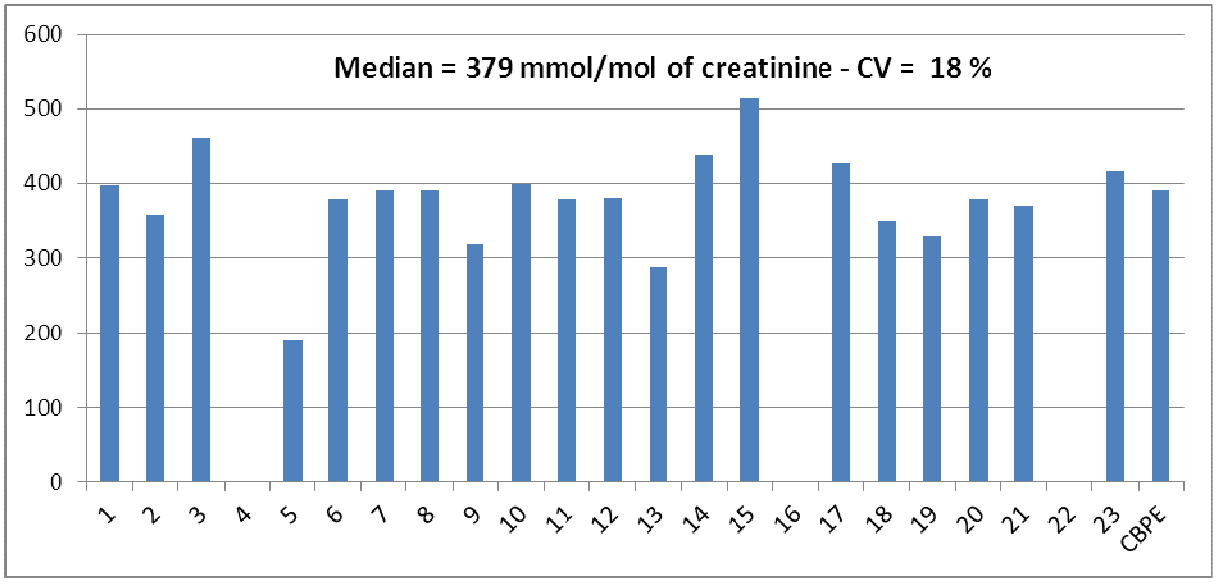
- Lysinuric protein intolerance 19
- Argininosuccinic aciduria 1
- OTC deficiency 1
- Wrong diagnosis 2

Other possible diagnosis

- LPI 1
- Other urea cycle deficiency 3
- Wrong diagnosis 1

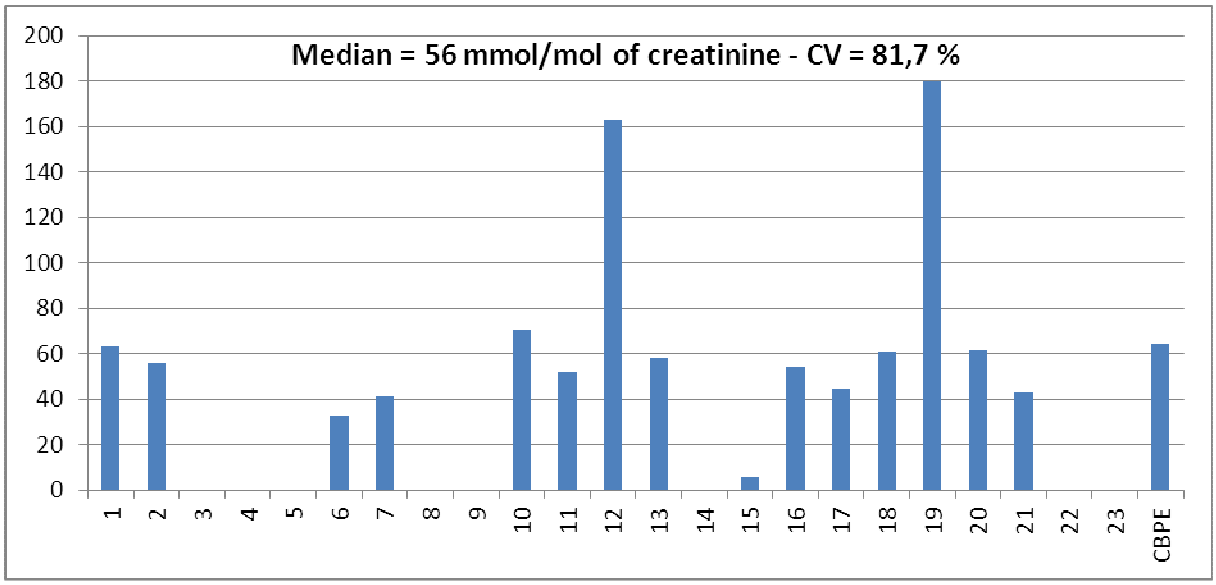
All labs but one performed **amino acid analysis**, and all of them except one reported an increase of **lysine** (median = 379 mmol/mol creatinine; range: 288 – 574). Eighteen labs also reported an increase of arginine (median = 88 mmol/mol creatinine; range: 67 – 119), fifteen labs an increase of ornithine (median = 15 mmol/mol creatinine; range: 8 – 24).

Excretion of lysine



Among the 20 labs who performed **organic acids, 15 detected an abnormal peak of orotic acid.** Fifteen labs also performed quantification of orotic acid either using purine and pyrimidine analysis or using specific measurement of orotic acid.

Excretion of orotic acid

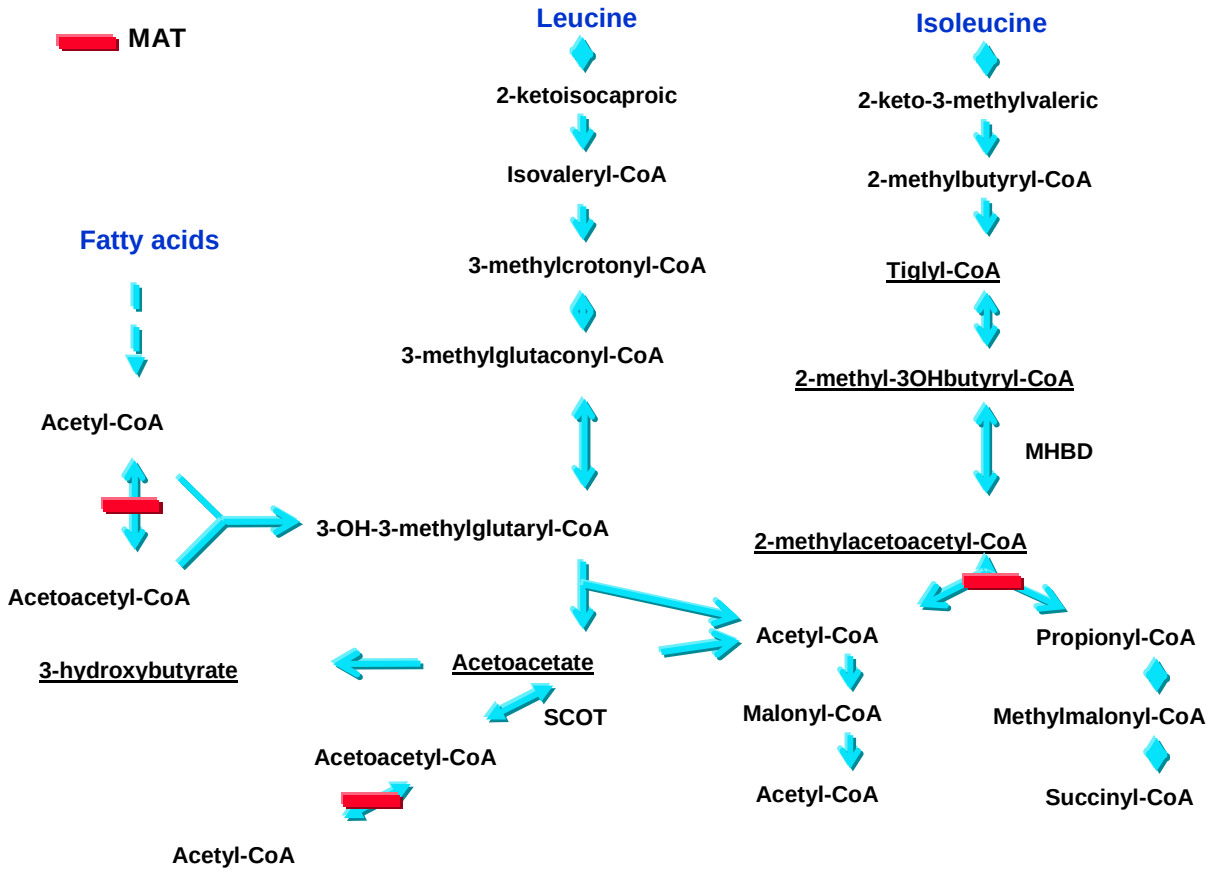


Scoring

- Analytical performance: increase of lysine (ornithine and arginine) (score 1), increase of orotic acid (score 1)
- Interpretation of results: lysinuric protein intolerance (as first or alternative diagnosis) (score 2)

- **Patient D – Mitochondrial acetoacetyl-CoA thiolase (MAT) deficiency**

The patient is the first child of non-consanguineous parents. He presented, during the first week of life, with vomiting, tachypnea, metabolic acidosis with ketonuria, but no hypoglycemia, and no hyperammonemia. Diagnosis has been immediately suspected on organic acid analysis. The urine sample has been collected at 12 years of age. He has a normal psychomotor development under treatment with low protein diet (1.4 kg/day), low lipids (7% of caloric intake), 1940 kcal/day, and L-carnitine supplementation (3g/day).
Patients with MAT deficiency rarely present symptoms in the neonatal period. Diagnosis has been confirmed by measurement of enzyme activity in cultured skin fibroblasts with and without addition of KCl, to differentiate the mitochondrial isoform from the cytoplasmic one.



Diagnosis

Most likely diagnosis

- Mitochondrial acetoacetyl-CoA thiolase deficiency 20
(3-oxothiolase, beta-ketothiolase, 3-ketothiolase, 2-methylacetoacetyl-CoA thiolase)
- 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency 1
- No diagnosis 1

Other possible diagnosis

- 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency 2
- 3-ketothiolase deficiency 1

No significant abnormality was reported by 18 out of the 19 labs who performed **amino acid** analysis.

All labs but two performed **organic acids**. They reported an increase of:

- **Tiglylglycine**: 20 labs (median = 353 mmol/mol creatinine; range: 93 – 1457)
- **2-methyl-3-hydroxybutyric acid**: 18 labs (median = 256 mmol/mol creatinine; range: 128 – 515)
- **2-methylacetoacetic acid**: 11 labs (3; 23 mmol/mol creatinine)
- 3-hydroxybutyrate, and acetoacetate: 2 labs
- 2-methylglutaconic acid : 1 lab

Excretion of 2-methylacetoacetic acid was low in this treated patient, but this metabolite was present. Oximation of urinary organic acid allows detecting more accurately ketone derivatives. Another clue for the differential diagnosis between MAT deficiency and 2-methyl-3-hydroxybutyryl-CoA dehydrogenase (2MHBDH) deficiency is the ocurrence of only one peak for 2-methyl-3-hydroxybutyric acid in MAT deficiency, whereas there are two peaks for this compound in 2MHBDH deficiency (Pr Brian Fowler, personal communication).

The 2 labs who performed acylcarnitines reported an increase of tiglylcarnitine (C5:1) and of 2-methyl-3-hydroxybutyrylcarnitine (C5OH).

Scoring

- Analytical: increase of tiglylglycine, 2-methyl-3hydroxybutyric and 2-methylacetoacetic acids (score 2), increase of only 2 metabolites (score 1)

- Interpretation of results: mitochondrial acetoacetyl-CoA thiolase as first or alternative diagnosis (score 2)

Critical error: MAT deficiency is a treatable disorder, whereas 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency is not. Misidentification of this sample has been considered by the SAB of ERNDIM as a **critical error**. The two labs who did not conclude to MAT deficiency should have been considered as poor performers. But the concept of critical error will be introduced only in 2014.

- **Patient E – Morquio A disease (mucopolysaccharidosis type IVA)**

The patient, a boy, is the second child of non-consanguineous parents. He was born at 34 weeks of amenorrhea by caesarean delivery because of pre-eclampsy, with macrosomy, and oedemas. During the first year of life, he presented with an accelerated growth, but a normal psychomotor development. At 2 years of age, the rapid growth stopped but he had pectus carinatum, lumbar kyphosis, and genu valgum. X ray revealed multiple dysostosis. The first biochemical investigation was performed at 2.5 years of age: an increase of GAG's (harmine) (196 mg/g creat - controls: 68 -188), and an abnormal band of keratane sulfate at electrophoresis were observed. Morquio A disease was confirmed by measurement of galactose-6-sulfate sulfatase activity (< 0.1 nmol/h/mg prot - controls: 1.13 – 4.48). Mutation analysis of *GALNS* gene revealed a compound heterozygote genotype: c.901G>T / c.1482+2dup. At 10 years of age, his weight is 24.4 kg, his height 1.00 m. He is good at school but he has a severe muscle weakness, and a severe walk handicap (wheel chair). He experienced several surgical interventions, and has been recently included in an enzyme replacement assay.

Diagnosis

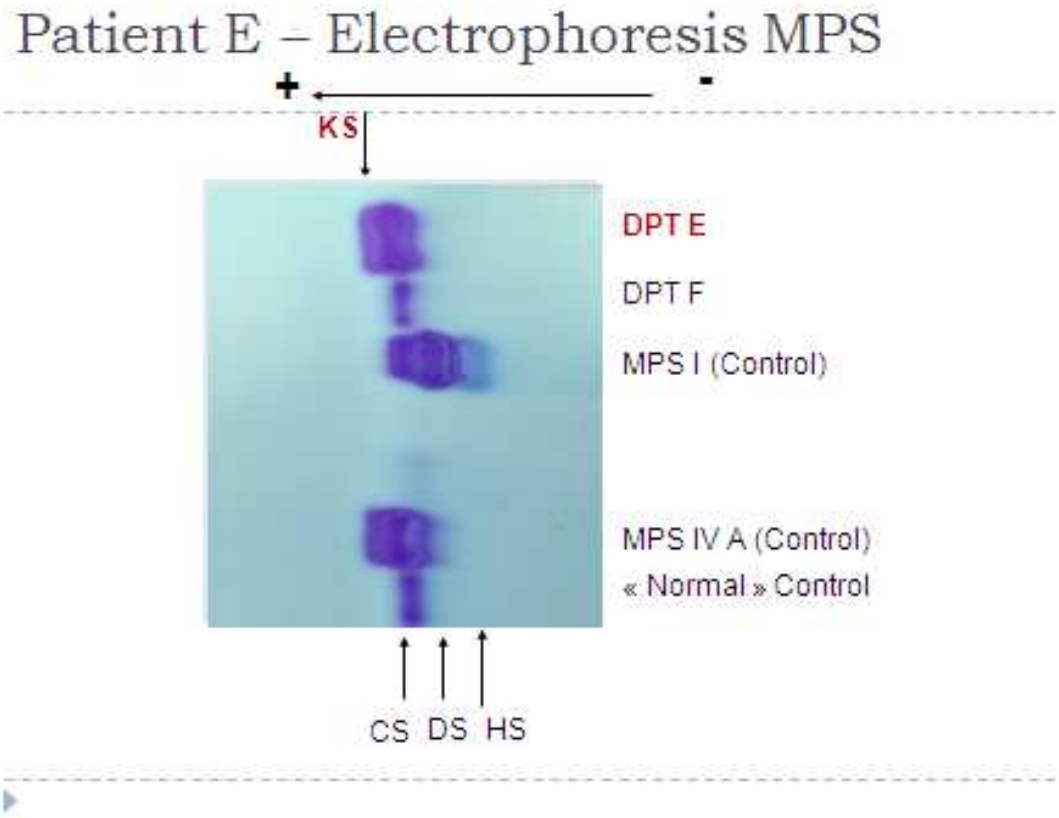
Most likely diagnosis

- Mucopolysaccharidosis type IV 19
(Morquio, Morquio A, Morquio B, MPS IVA, MPS IVB)
- Mucopolysaccharidosis 2
- Mucopolysaccharidosis type VI 1

Other possible diagnosis

- Other mucopolysaccharidoses 2
- Galactosialidose 1
- Cystathionine synthase 1

Sixteen labs reported an increase of **glycosaminoglycans**, while the 3 labs who used the harmine test reported a normal excretion of GAG's. Fractionation of GAG's was performed by 18 labs: all except two observed an abnormal band of keratan (and chondroitin) sulphate; one reported a normal profile and one an increase of dermatane (and heparane) sulphate. Despite their lack of sensitivity, screening tests were positive (4 labs).



Among the 12 labs who performed **oligosaccharides**, 8 reported a normal profile, 3 a borderline profile and 1 an abnormal profile.

Scoring

- Analytical: increase of keratan sulphate (score 2), increase of GAG's, abnormal profile (score 1)
- Interpretation of results: MPS IV (score 2), MPS IV on clinical information (no fractionation of GAG's) or non-characterized mucopolysaccharidosis or wrong mucopolysaccharidosis (score 1)

- **Patient F – glycerol kinase deficiency**

The patient is a male referred at 2.5 years of age because of psychomotor delay, hypotonia, myopathy, vomiting, and increased LDH, CK (18 838 UI/L), and transaminases. He also had a pseudo-hypertriglyceridemia (3.51 g/L). He presented deletion of all exons of dystrophin gene. He had no clinical or analytical signs of adrenal insufficiency at 6 years of age. A short clinical description has been published by Duart-Rodriguez et al, in Rev Neurol 2010;50 (30):192 (in Spanish). The urine sample has been collected at 9 years of age.

Diagnosis

Most likely diagnosis

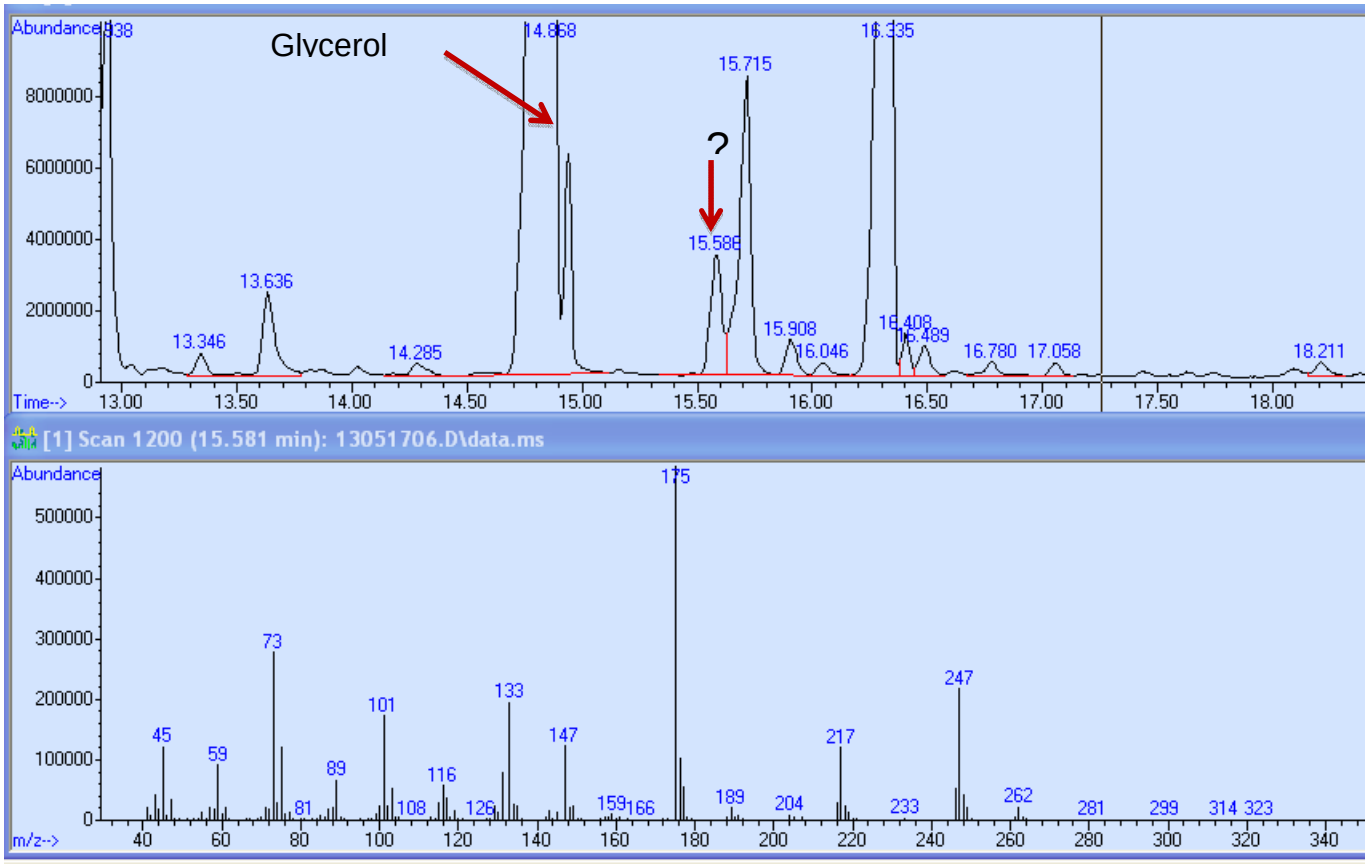
- Glycerol kinase deficiency (chromosome Xp21 deletion syndrome, complex form) 20
- 3-methylglutaconic aciduria (Barth syndrome) 1
- No diagnosis 1

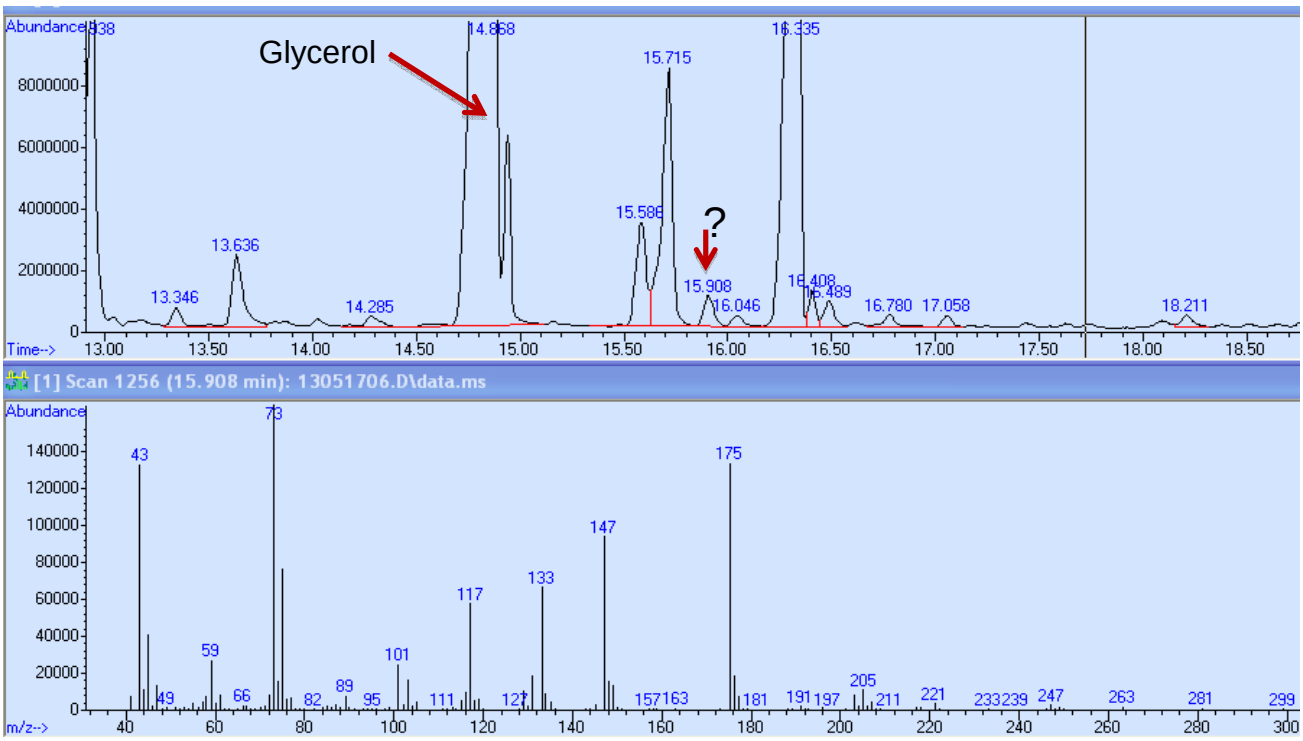
Other possible diagnosis

- Exogenous glycerol contamination 3
- Glyceroluria due to mutations in *AQP7* gene 1
- Fructose-1,6-diphosphatase deficiency 1

Twenty one labs performed **organic acid analysis**, and all but one reported an increase of glycerol (median = 1 168 mmol/mol creatinine; range: 151 – 4 000; n = 6).

Interestingly, one lab reported the occurrence of two unknown peaks that we observed in all patients with glycerol kinase deficiency.





Scoring

- Analytical: increase of glycerol (score 2)
- Interpretation: glycerol kinase deficiency (score 2)

Scores of participants

- **Survey 2013-1**

Lab n°	Patient A NFU1			Patient B MNGIE			Patient C LPI		
	A	I	Total	A	I	Total	A	I	Total
1	2	1	3	Educational sample No score			2	2	4
2	2	1	3				2	2	4
3	2	2	4				2	2	4
4	2	2	4				0	0	0
5	2	2	4				2	2	4
6	2	0	2				2	2	4
7	1	1	2				2	0	2
8	2	2	4				2	2	4
9	2	2	4				1	2	3
10	1	1	2				2	2	4
11	1	1	2				2	2	4
12	2	2	4				2	2	4
13	2	2	4				2	2	4
14	2	2	4				2	2	4
15	2	1	3				2	2	4
16	2	2	4				2	2	4
17	2	1	3				2	2	4
18	1	1	2				2	2	4
19	2	2	4				2	2	4
20	2	2	4				2	2	4
21	2	2	4				2	2	4
22*	0	0	0				0	0	0
23	2	1	3				2	2	4

***** This lab could only perform oligosaccharides and mucopolysaccharides in 2013

❖ **Survey 2013-2**

Lab n°	Patient D MAT deficiency			Patient E Morquio A			Patient F Glycerol kinase def.		
	A	I	Total	A	I	Total	A	I	Total
1	1	2	3	2	2	4	2	2	4
2	2	2	4	2	2	4	2	2	4
3	2	2	4	2	2	4	2	2	4
4	2	2	4	2	2	4	2	2	4
5	2	2	4	2	2	4	2	2	4
6	2	2	4	1	1	2	2	2	4
7	1	2	3	1	1	2	0	0	0
8	2	2	4	2	2	4	2	2	4
9	2	2	4	2	2	4	2	2	4
10	1	0	1	2	2	4	2	2	4
11	2	2	4	2	2	4	2	2	4
12	2	2	4	2	2	4	2	2	4
13	2	2	4	2	2	4	2	2	4
14	No answer to the second survey								
15	1	2	3	0	1	1	2	2	4
16	1	2	3	1	1	2	2	2	4
17	2	2	4	1	1	2	2	2	4
18	2	2	4	2	2	4	2	2	4
19	1	2	3	2	2	4	2	2	4
20	2	2	4	2	2	4	2	2	4
21	2	2	4	2	2	4	2	2	4
22*	0	0	0	2	2	4	0	0	0
23	2	2	4	1	1	2	2	2	4

* This lab could only perform oligosaccharides and mucopolysaccharides in 2013

❖ **Total scores**

Lab n° ERN	Survey 2013-1	Survey 2013-2	Cumulative score (max = 20)	Cumulative score (%)
1	7	11	18	90%
2	7	12	19	95%
3	8	12	20	100%
4	4	12	16	80%
5	8	12	20	100%
6	6	10	16	80%
7	4	5	9	45%
8	8	12	20	100%
9	7	12	19	95%
10	6	9	15	75%
11	6	12	18	80%
12	8	12	20	100%
13	8	12	20	100%
14	8	No answer	8	40%
15	7	8	15	75%
16	8	9	17	85%
17	7	10	17	85%
18	6	12	18	90%
19	8	11	19	95%
20	8	12	20	100%
21	8	12	20	100%
22*	0	4	4	20%
23	7	10	17	85%

Performance

	Number of labs	% total labs
Excellent performers (100 % of good responses)	7	30 %
Poor performers (< 60 % good responses)	2	9 %
Partial non responders (will not receive certificate of participation)	1	4 %

❖ **Summary of scores**

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Total (%)
Patient A	NFU1	**87%**	**72%**	**79%**
Patient B	MNGIE	**Educational sample**		
Patient C	LPI	**89%**	**87%**	**88%**
Patient D	MAT deficiency	**78%**	**87%**	**83%**
Patient E	Morquio A	**80%**	**83%**	**82%**
Patient F	Glycerol kinase	**87%**	**87%**	**87%**

DPT-scheme in 2014

- Two surveys of 3 urines, including “normal” patients, sent by CSCQ in March
- Results have to be sent within 3 weeks
- **Reporting** on CSCQ (Centre Suisse de Contrôle de Qualité) website, before the deadline.
- **Scoring**: performed by two different scheme organizers.

We remind you that to participate to the DPT-scheme, you must perform at least:

- Amino acids
- Organic acids
- Oligosaccharides
- Mucopolysaccharides

If you are not performing one of these assays, or if purine and pyrimidine analysis is required, you can send the samples to another lab (cluster lab) but you are responsible for the results.

Please send quantitative data for amino acids and, as much as possible, for organic acids.

Meeting in 2014

It will take place during the ICIEM meeting in Innsbruck **Tuesday 2 September 2013**, at 8.30 am.

We remind you that attending this meeting is an important part of the proficiency testing. The goal of the program is to **improve** the competence of the participating laboratories, which includes the critical review of all results with a discussion about improvements.

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ANNEX 1

PROFICIENCY TESTING – SOUTHERN EUROPE, LYON CENTER
URINE SAMPLES ALREADY SENT

• **1998 : 1**	**A**	**OCT**	
	B	**Propionic**	
• **1999 : 1**	**C**	**MPS I or II**	
	E	**Cystinuria**	SKZL
• **1999 : 2**	**D**	**CblC**	
	F	**HMG-CoA lyase**	
• **2000 : 1**	**G**	**Iminodipeptiduria**	SKZL
	H	**Glutathion synthetase**	
• **2001 : 1**	**P1**	**Mevalonate kinase**	
	P2	**L-2-OH glutaric**	
• **2001 : 2**	**P3**	**Methylmalonic**	SKZL
	P4	**MPS IIIA San Fillippo**	
• **2002 : 1**	**P1**	**LCHAD**	
	P2	**Sulphite oxidase**	
• **2002 : 2**	**P3**	**Biotinidase**	SKZL
	P4	**MPS I**	
• **2003:1**	**P1**	**Tyrosinemia type I**	

	P2	**SC-BCAD deficiency**	
	P3	**Argininosuccinic aciduria**	
• **2003:2**	**P4**	**MCC deficiency**	
	P5	**Sialidosis**	SKZL
	P6	**MSUD**	
• **2004:1**	**P1**	**Tyrosinemia type I, treated patient**	
	P2	**Propionic acidemia**	
	P3	**Non metabolic disease, septic shock**	
• **2004:2**	**P4**	**Mevalonic aciduria (common sample)**	
	P5	**Fucosidosis**	
	P6	**Alkaptonuria**	
• **2005:1**	**P1**	**Isovaleric acidemia**	
	P2	**Tyrosinemia type II (common sample)**	
	P3	**Disorder of peroxysome biogenesis**	
• **2005:2**	**P4**	**Multiple acyl-CoA dehydrogenase deficiency**	
	P5	**Alpha-mannosidosis**	
	P6	**4-hydroxybutyric aciduria**	
• **2006:1**	**P1**	**Aromatic amino acid decarboxylase deficiency**	
	P2	**Hyperoxaluria type I**	
	P3	**Mucopolysaccharidosis type VI**	
• **2006:2**	**P4**	**Hypophosphatasia (common sample)**	
	P5	**Lysinuric protein intolerance**	
	P6	**MCAD deficiency**	
• **2007:1**	**P1**	**Mitochondrial acetoacetyl-CoA thiolase (MAT)**	
	P2	**Homocystinuria due to CBS deficiency**	
	P3	**Hyperlysinemia (common sample)**	
• **2007:2**	**P4**	**Aspartylglucosaminuria**	
	P5	**Phenylketonuria**	
	P6	**SCAD deficiency**	

• **2008:1**	**P1**	**Cbl C/D**
	P2	**Mucopolysaccharidosis type III (common sample)**
	P3	**2-hydroxyglutaric aciduria**
• **2008:2**	**P4**	**Glycerol kinase deficiency**
	P5	**α-mannosidosis**
	P6	**3-methylcrotonyglycinuria**
• **2009:1**	**P1**	**Mucopolysaccharidosis type III**
	P2	**Salla disease (common sample)**
	P3	**No metabolic disorder**
• **2009:2**	**P4**	**Glutaric aciduria type I**
	P5	**Iminodipetiduria**
	P6	**Multiple acyl-CoA dehydrogenase deficiency**
• **2010:1**	**P1**	**Mevalonic aciduria**
	P2	**Aminoacylase I deficiency**
	P3	**No metabolic disorder**
• **2010:2**	**P4**	**Sialidosis type I (common sample)**
	P5	**Glutaric aciduria type I**
	P6	**Aspartylglucosaminuria**
• **2011:1**	**A**	**Molybdenum cofactor deficiency**
	B	**GAMT deficiency (common sample)**
	C	**Methylmalonic semialdehyde dehydrogenase def.**
• **2011:2**	**D**	**Mucopolysaccharidosis type IVA (Morquio)**
	E	**Phenylketonuria**
	F	**Citrullinemia type I**
• **2012:1**	**A**	**Intermittent MSUD (common sample)**
	B	**HHH syndrome**
	C	**Mucopolysaccharidosis type I**
• **2012:2**	**D**	**“RedBulluria”**
	E	**CblC**
	F	**SCAD deficiency**