C. VIANEY-SABAN, C. ACQUAVIVA-BOURDAIN
Service Maladies Héréditaires du Métabolisme
Centre de Biologie et de Pathologie Est
59, Boulevard Pinel
69677 Bron cedex
Tel 33 4 72 12 96 94
e-mail christine.saban@chu-lyon.fr
cecile.acquaviva-bourdain@chu-lyon.fr

ERNDIM
Diagnostic proficiency testing
2011
Southern Europe
Lyon Centre

ANNUAL REPORT 2011

In 2011, 22 labs participated to the Proficiency Testing Scheme Southern Europe.
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
Switzerland	1
TOTAL	**22**

Logistic of the scheme

- **2 surveys** 2011-1: patient A, B and C
  2011-2: patient D, E and F

Origin of patients: all urine samples have been provided by the scheme organizors

- Patient A : Molybdenum cofactor deficiency – Centre de Biologie Est, Lyon
- Patient B : Guanidinoacetate methyltransferase deficiency – Dr Ruijter, Rotterdam. This sample has been sent to all labs participating to the DPT scheme in Europe
- Patient C : Methylmalonic semialdehyde dehydrogenase deficiency – Centre de Biologie Est, Lyon
- Patient D : Mucopolysaccharidosis type IVA – Centre de Biologie Est, Lyon
- Patient E : Phenylketonuria – Centre de Biologie Est, Lyon
- Patient F : Citrullinemia type I – Centre de Biologie Est, Lyon

- Mailing: samples were sent by DHL at room temperature.

Timetable of the schemes

- May 3: shipment of samples of Survey 1 and Survey 2 by DHL and of the clinical data by e-mail
- May 27: deadline for result submission (Survey 1)
- June 23: analysis of samples of the second survey
- July 14: deadline for result submission (Survey 2)
- August 3: report of Survey 1 by e-mail
- August 12: report of Survey 2 by e-mail
- August 30: meeting in Geneva
- January 12: annual report with scoring by e-mail

Date of receipt of samples

	Survey 1 + 2
+ 24 hours	22

Date of reporting

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

Exceptionally this year, the website remained open at least one week after the deadline; therefore all labs could enter their results in time. This will not happen next year.

Scoring of results

The scoring system established by the International Scientific Advisory Board of ERNDIM is still the same. Three 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	Good, diagnosis is established	2
		Helpful but incomplete	1
		Misleading / wrong diagnosis	0
R	Recommendations for further investigations	Complete	1
		Unsatisfactory of misleading	0

Since most of the laboratories in Southern Europe don't give therapeutic advices to the attending clinician, this criteria is not evaluated.

The **total score** is calculated as the sum of these 3 criteria without weighting. The maximum that can be achieved is 5 for one sample.

Meeting of participants

It took place in Geneva on 30 August 2011 from 9.00 to 10.30, before the SSIEM Meeting.

❖ Participants

Representatives from 16 labs were present: E Riudor, JA Arranz (Barcelona), MH Read (Caen); E Pasquini (Florence), U Caruso (Genova), C Corne (Grenoble), O Boulat, C Roux (Lausanne), G Briand, M Joncquel (Lille), I Tavares de Almeida (Lisbon), B Merinero (Madrid), M Gastaldi (Marseille), E Jeannesson (Nancy), O Rigal (Robert Debré, Paris), M Del Rizzo (Padova), S Bekri (Rouen), JA Cocho (Santiago de Compostella), C Rizzo (Roma).

❖ Information from the Executive Board and the Scientific Advisory Board

- **Scoring and certificate of participation**: scoring is done by 2 scheme organizers. For the Lyon Centre, the results have also been scored by Dr Viktor Kozich from Prague Centre. Certificate of participation for 2011 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 60% (score < 18 / 30; this year, score < 15 / 25).
- Two warning letters will be sent for 2010, and one for 2011.
- 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.
- **Training**: SSIEM Academy training courses.
  - A 2 days course has been organized on Monday and Tuesday 23 and 24 November in Amsterdam. The program for biochemists included disorders of:
    - Glycogen Storage Disorders (René Santer)
    - CDG Syndromes (Dirk Lefeber)
    - Mitochondrial Disease (Johannes Mayr)
  - The lectures will be available on the SSIEM website
  - The next SSIEM Academy will take place in Manchester in October 2012. Advertising will be available on the SSIEM website.
- A scientist, Sara Gardner, has been employed by ERNDIM for accreditation and training.
- The new **ERNDIM website** is now open: www.erndim.org
- **Urine samples**: we remind you that every year, each participant must provide to the scheme organizer 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. Then aliquot the sample in 10 ml plastic tubes (minimum 48 tubes), add stoppers and freeze. Be careful to constantly homogenize the urine while aliquoting the sample. Send 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.

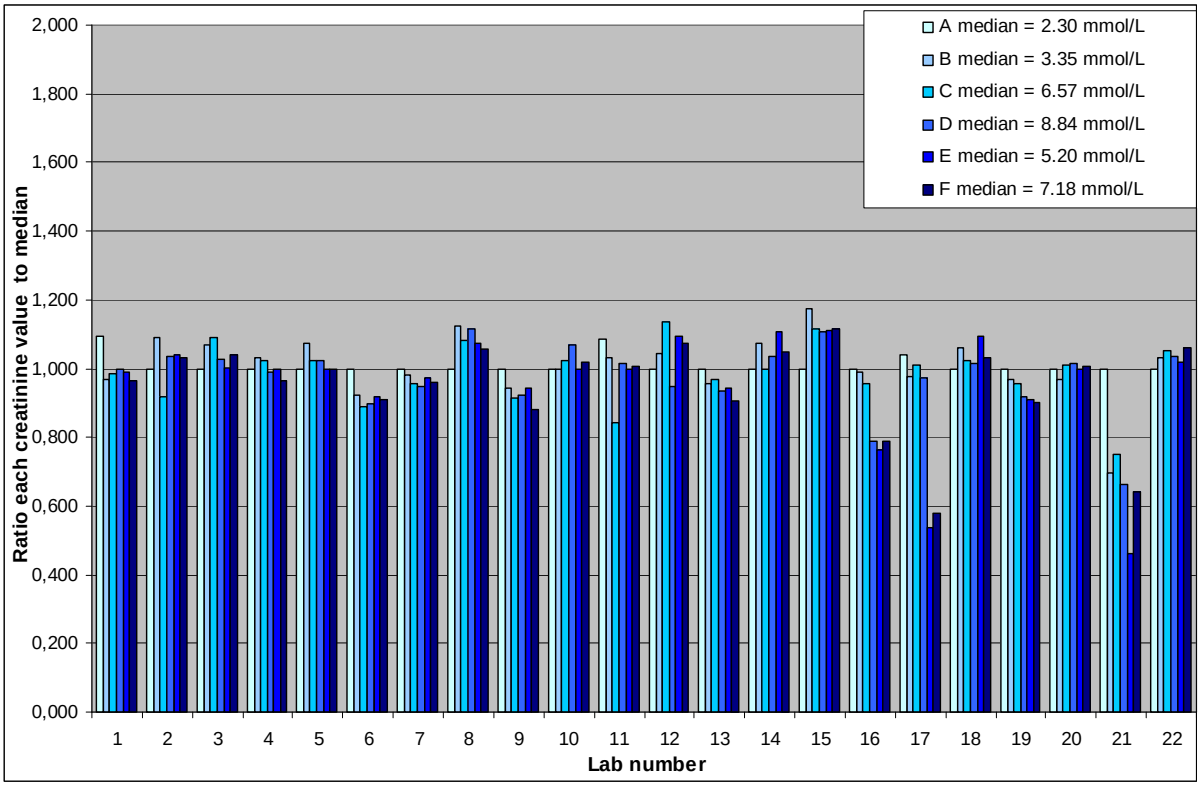
  Please send us an e-mail on the day you send the samples.

- **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 16 and 17 who had low values for survey 2 (?); lab 16 had the same problem last year. Lab 21 has systematically low values, and had the same problem last year.



The CV is < 12.5% for all samples (6 – 12.5 %) and this is still higher than the interlab CV 2010 for Special Assay in urine (6.3 %, n = 108) and than the interlab CV 2010 for Quantitative Organic Acids (6.1 %, n = 68).

- **Patient A – Molybdenum cofactor deficiency (combined sulphite oxidase and xanthine oxidase deficiency)**

This 2-month old boy is the first child of non consanguineous parents of Chechen origin. A previous pregnancy led to a stillborn baby at 28 weeks of amenorrhea. From birth, this boy presented tremors, severe axial hypotonia with peripheral hypertonia and feeding difficulties. At 2 months of age, EEG was strikingly abnormal and MRI showed cavitation of the white matter, cerebral and cerebellar atrophy, and corpus callosum hypoplasia. Neurological examination revealed pyramidal syndrome, opisthotonos episodes, poor contact, and microcephaly. Biochemical investigation revealed a very low cystine value in plasma (Cys = 1 µmol/L - controls: 11 – 30) and the abnormal presence of sulfocystein in urines (Scys = 104 mmol/mol creat - controls: ND). Plasma uric acid was severely decreased (<12 µmol/L – controls: 120 – 210 µmol/L) and organic acid analysis allowed to identify a

peak of xanthine. Because of the severe clinical condition, no treatment was tempted and the mother returned to Chechnya with her son. Mutation analysis revealed that this child is homozygous for c.658_664del7insG in exon 6 of *MOCS2* gene, responsible for the deletion of 2 amino acids (p.Leu158_Lys159del)

Diagnosis

Most likely diagnosis

Nine labs concluded to molybdenum cofactor deficiency, 3 labs to sulphite oxidase deficiency (isolated or molybdenum cofactor), and 5 labs to isolated sulphite oxidase deficiency. But 5 labs (23 %) gave a wrong diagnosis.

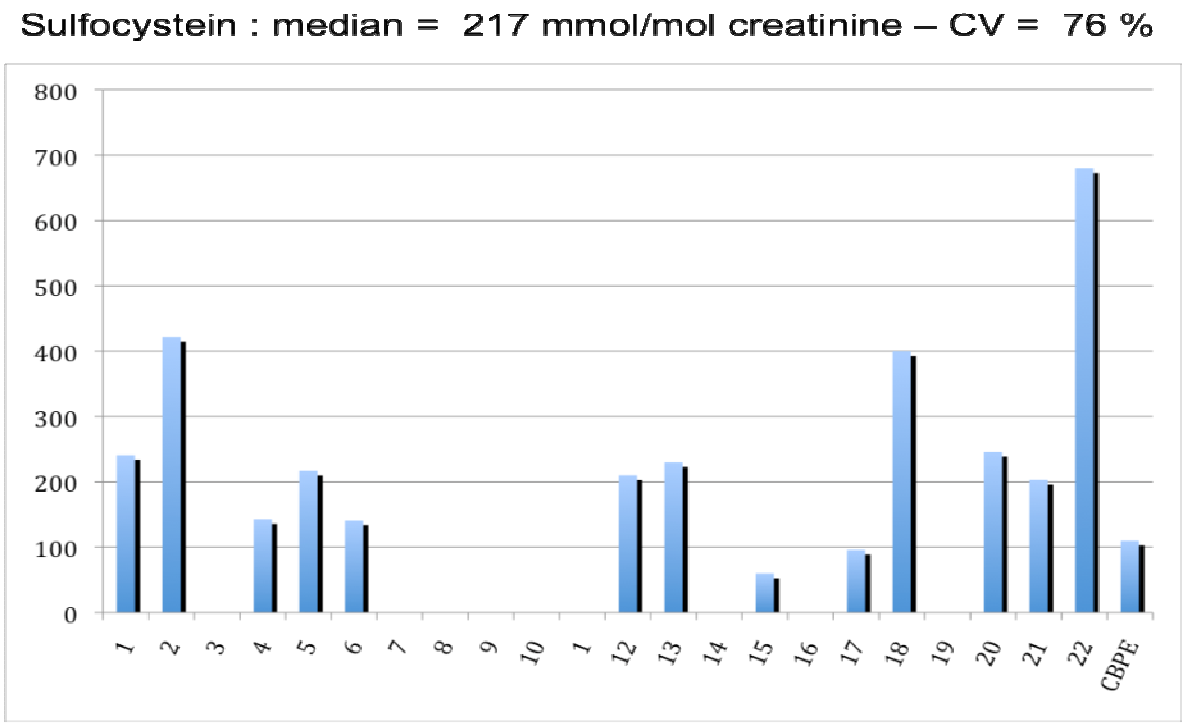
Other possible diagnosis

Four labs gave molybdenum cofactor deficiency and one lab gave isolated sulphite oxidase deficiency as an alternative diagnosis.

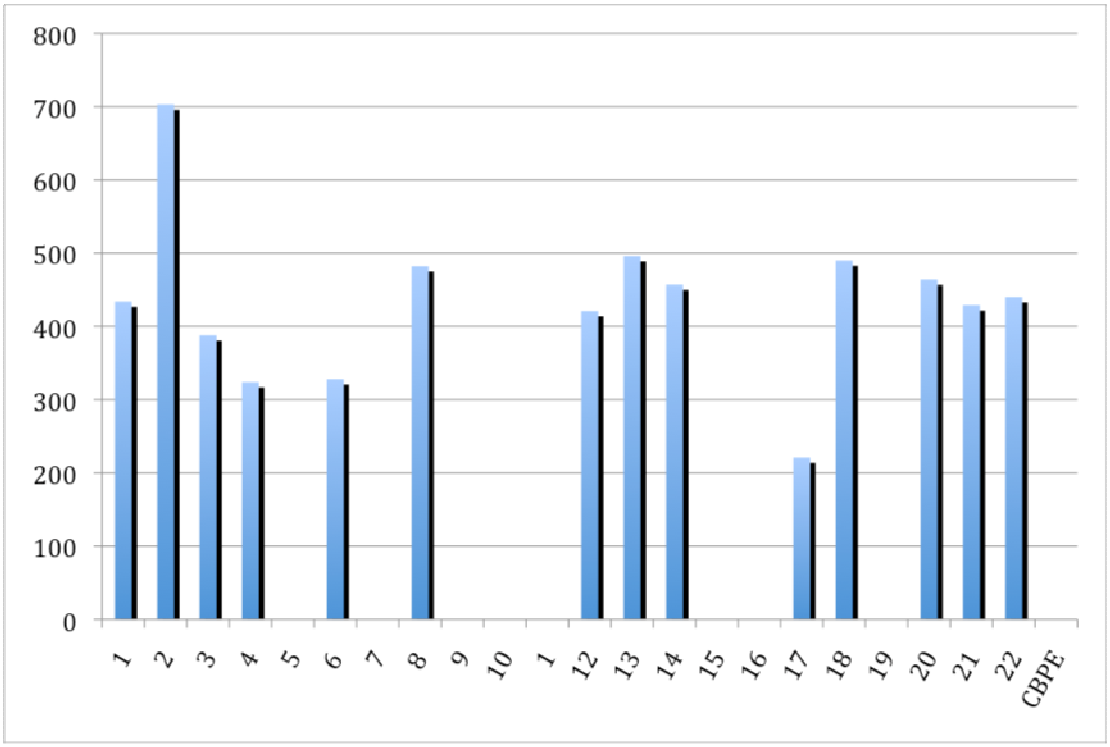
Diagnostic reliability

Score	Significance	Number of labs
1	Certain	8
2	Fairly certain	12
3	Tentative	1
-1	To be entered	0
-2	Not performed	1

All labs performed **aminoacid** analysis, but only 16 of them reported the abnormal presence of sulfocystein (CV 76%, versus an interlab CV of 33% for the ERNDIM QA Amino acids 2008). Five of them reported an increase of taurine (CV 26%, versus an interlab CV of 10% for the ERNDIM QA Amino acids 2010), and 5 labs, a decrease of cystine.

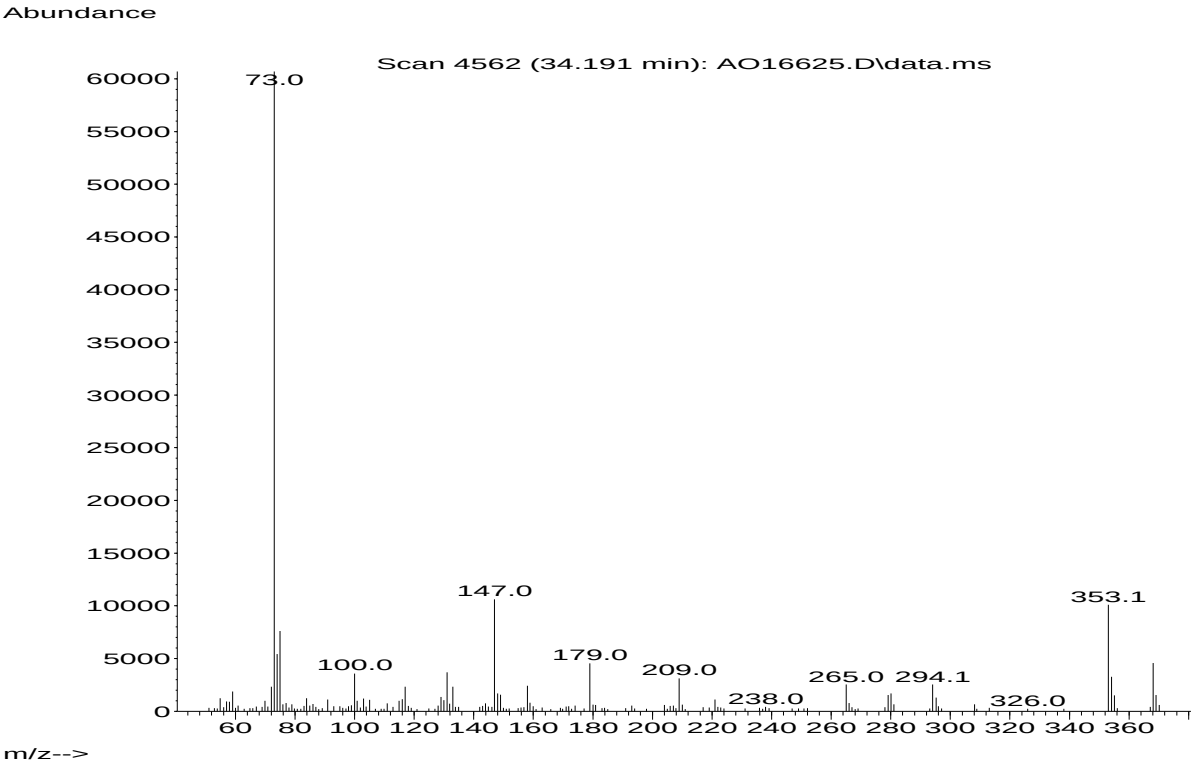


Taurine : median = 437 mmol/mol creatinine – CV = 26 %

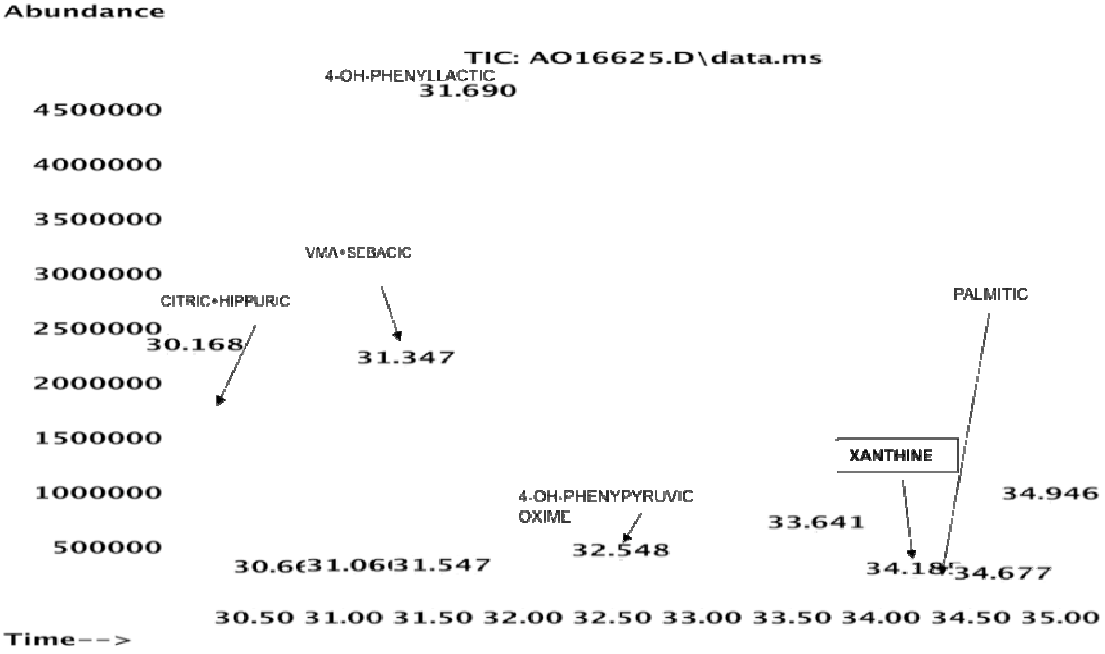


All labs but one also performed **organic acid** analysis. Very interestingly, 3 labs reported the presence of a peak of xanthine. Metabolites of paracetamol were mentioned by 6 labs, and metabolites of phenobarbital by one of them. Retrospectively, trace amounts of hypoxanthine were also identified. Thanks to Dr Rizzo from Roma and to Dr Caruba from Nice who provided the spectrum of both compounds.

Spectrum of xanthine



Profile of elution of xanthine



Spectrum of hypoxanthine (eluted 0.3 min later than azelaic acid)

Seven labs performed **purines and pyrimidines** determination: all of them reported an increase of xanthine and 5 of them an increase of hypoxanthine together with a decrease of uric acid.

Recommendations was OK for the labs who reached a correct diagnosis

Scoring

- Analytical: increase of sulphocystein (score 2), increase of xanthine or decrease of uric acid (score 1)
- Interpretation of results: Molybdenum cofactor deficiency or isolated sulphite oxidase deficiency (score 2)
- Recommendations: Sulphite oxidase activity in fibroblasts and/or mutation analysis *MOCS1, MOCS2, GPHN* genes and/or uric acid in serum (score 1).

- **Patient B – Guanidinoacetic acid methyltransferase (GAMT) deficiency**

This sample, provided by Erasmus MC in Rotterdam, has been distributed to all labs in Europe: the complete report is available on the ERNDIM website. The patient is a 7-year old girl with developmental retardation, in particular speech delay. She has epilepsy, for which she is treated with valproic acid. Initial metabolic screening in urine revealed elevated guanidinoacetic acid: 640 mmol/mol creatinine (ref. values <129), and relatively low creatine: 15 mmol/mol creatinine (ref. values <754). Guanidinoacetic acid in plasma was 27.2 µmol/L (ref values 0.5-3.6), which was strongly elevated. These results indicated guanidinoacetic acid methyltransferase (GAMT) deficiency. Enzyme and mutation analysis is pending. The patient is currently on treatment (creatine, ornithine, benzoate, low protein).

Diagnosis

Most likely diagnosis

Only 12 labs concluded to GAMT deficiency. Other labs concluded to a normal urine sample or gave a wrong diagnosis.

Other possible diagnosis

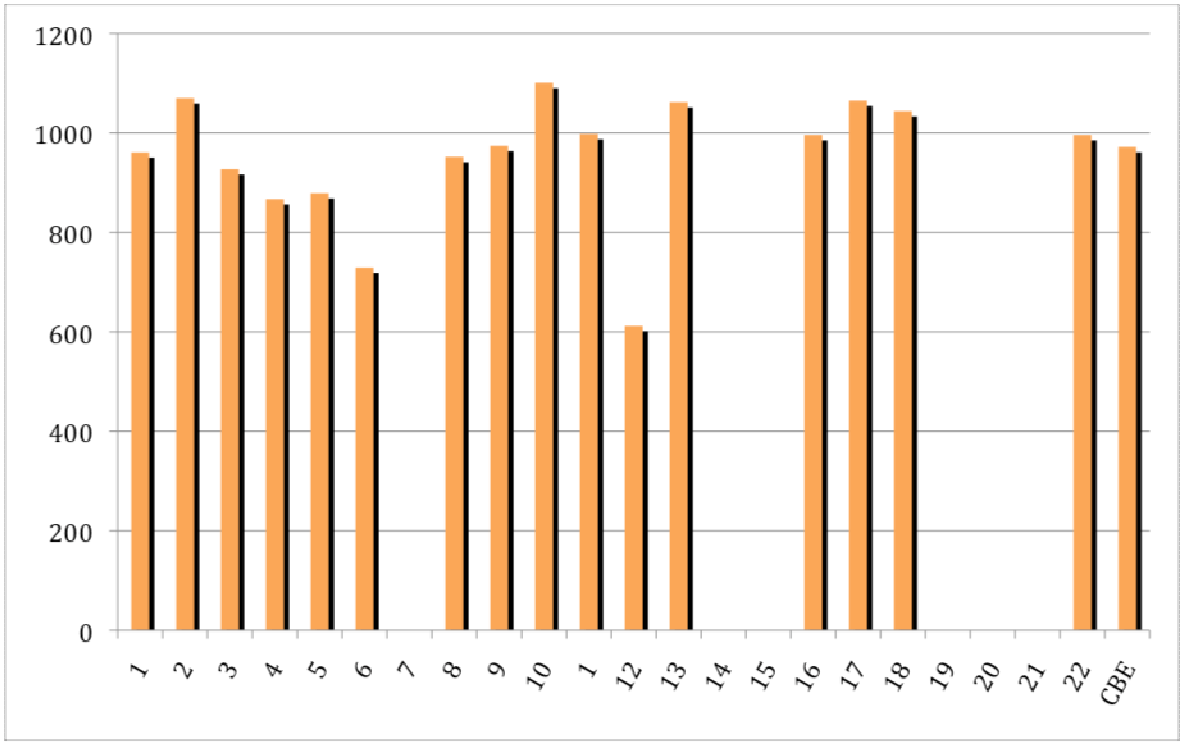
Two labs evoked a possible secondary increase of guanidinoacetate, and 2 labs evoked a creatine deficiency on the clinical presentation.

Diagnostic reliability

Score	Significance	Number of labs
1	Certain	8
2	Fairly certain	5
3	Tentative	9
-1	To be entered	0
-2	Not performed	0

All labs but one performed **amino acid** analysis: an increase of glycine was reported by 18 of them (secondary to valproate treatment: 13 labs).

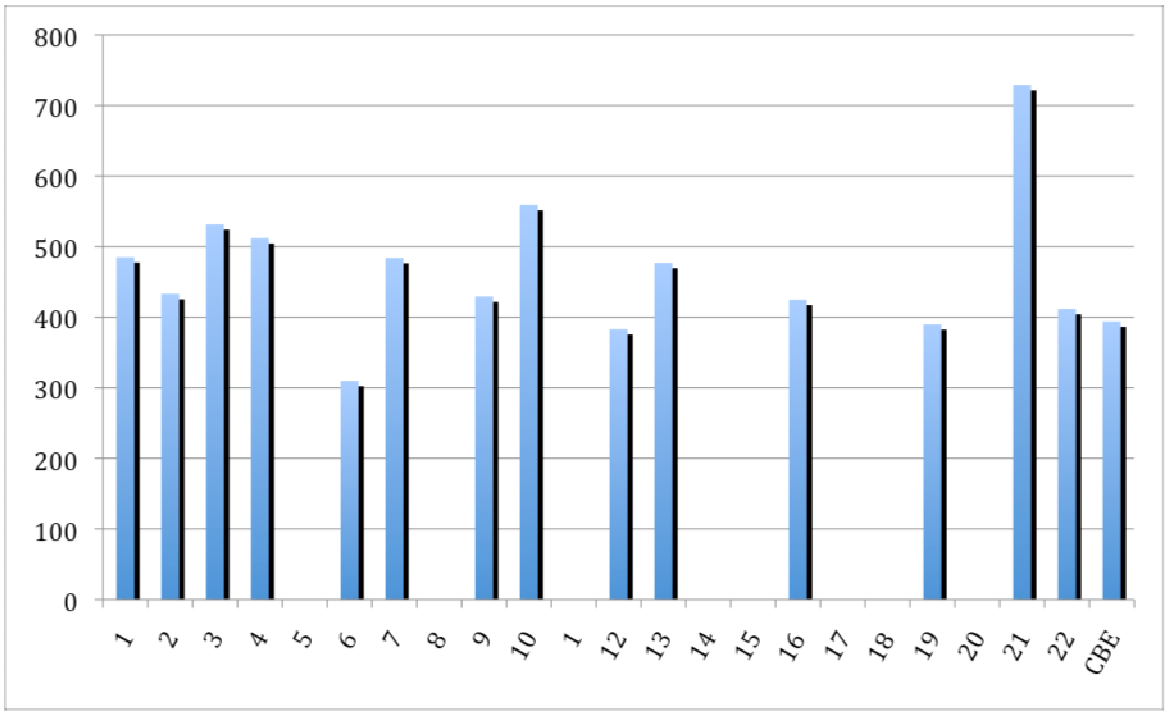
Glycine : median = 974 mmol/mol creatine – CV = 13 %



Among the 21 labs who performed **organic acids**, 19 reported metabolites of valproate.

Fourteen labs measured **creatine and guanidinoacetate:** all but one reported an increase of guanidinoacetate and 8 of them a decrease of creatine.

Guanidinoacetate : median = 433 mmol/mol creatinine – CV = 23%



Lab 21: creatinine = 2.3 mmol/L, median all labs = 3.4

Recommendations were OK for those who reached a correct diagnosis

Scoring

Creatine / guanidinoacetate analysis does not belong to the required tests. Therefore, this sample will not be scored but considered as an educational sample. **The scoring this year will be on 25 points**.

- **Patient C – methylmalonic semialdehyde dehydrogenase (MMSDH) deficiency**

This 12-year old boy is the second child of consanguineous parents. He has a non specific clinical presentation: slight psychomotor retardation, excessive weight, frequent vomiting, one kidney, and vitiligo. A repeatedly abnormal urinary organic and amino acid profile (three different urine samples) was observed. His 2 sisters are healthy, and have a normal organic acid and amino acid profile. Mutation analysis is pending (Pr Wanders, Amsterdam).

Diagnosis

Most likely diagnosis

Twelve labs concluded to methylmalonic semialdehyde deficiency, and 8 labs to 3-hydroxyisobutyric aciduria. Only 2 labs gave a wrong diagnosis.

Other possible diagnosis

Two labs gave 3-hydroxyisobutyrate dehydrogenase deficiency and one lab gave methylmalonic semialdehyde deficiency as an alternative diagnosis.

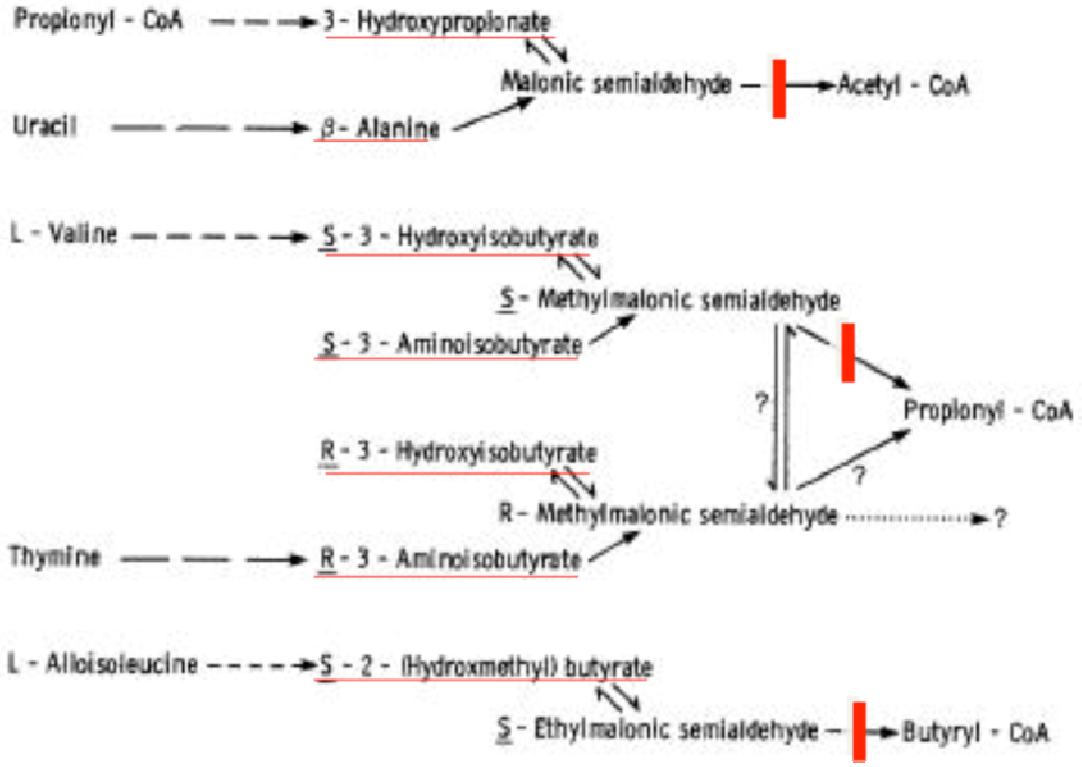
Diagnostic reliability

Score	Significance	Number of labs
1	Certain	13
2	Fairly certain	8
3	Tentative	1
-1	To be entered	0
-2	Not performed	0

Among the 20 labs who performed **amino acid** profile, 17 labs reported an increase of 3-aminoisobutyric acid (BAIBA), and 16 labs an increase of β-alanine.

All labs performed **organic acids** and reported an increase of 3-hydroxyisobutyric (20 labs), 3-hydroxypropionic (19 labs), or 2-ethyl-3-hydroxypropionic (2-ethylhydracrylic, 2-hydroxymethylbutyric) (16 labs).

Methylmalonate semialdehyde dehydrogenase (MMSDH) belongs to the aldehyde dehydrogenases family of proteins. This mitochondrial enzyme is coded by *ALDH6A1* gene, and plays a role in the valine and pyrimidine catabolic pathways. It catalyzes the irreversible oxidative decarboxylation of malonate and methylmalonate semialdehydes to acetyl-CoA and propionyl-CoA.



From Pollitt et al, J Inher Metab Dis 1985;8:75

Recommendations were mostly satisfying. The molecular characterization of methylmalonic semialdehyde dehydrogenase deficiency has been described by Chambliss et al (J Inher Metab Dis 2000; 23:497-504). The enzyme assay is under development by the group of Pr Ronald Wanders in Amsterdam.

Scoring

- Analytical performance: increase of BAIBA and/or β-alanine (score 1), increase of 3-hydroxyisobutyric and/or 2-ethyl-3-hydroxypropionic(2-hydroxymethylbutyric acid) (score 1).
- Interpretation of results: methylmalonic semialdehyde dehydrogenase deficiency (score 2), 3-hydroxyisobutyric aciduria (score 1)
- Recommendations: mutation analysis *ALDH6A1* or *HIBADH* gene, or enzyme assay of methylmalonic semialdehyde dehydrogenase, or enzyme assay of 3-hydroxyisobutyrate dehydrogenase (score 1)

- **Patient D – Mucopolysaccharidosis type IVA (Morquio disease type A)**

This 16-year old girl is the 2nd child of consanguineous parents. She was investigated at 2 years of age because of dorso-lumbar kyphosis, pectus carinatum, speech delay, and vertebral dysplasia. Mucopolysaccharides analysis revealed the presence of keratan sulfate, but quantification of GAG's was normal, as well as the oligosaccharides profile. N-acetylgalactosamine-6-sulfatase activity was severely decreased (<0.1 nmol/h/mg prot - controls: 1.1 – 4.5), whereas β-D-galactosidase activity was normal (202 µkat/kg - controls: 167-334). Mutation analysis of *GALNS* gene revealed homozygocity for the c.477G>A (p.Trp159X) mutation. Persistent speech delay was due to repeated otitis. From 7 years of age, she presented cardiac and respiratory insufficiency, and corneal opacity. Her weight is now 24.2 kg, and height 93 cm; she is severely handicapped.

Diagnosis

Most likely diagnosis

Eleven labs concluded to mucopolysaccharidosis (MPS) type IV, 3 labs to MPS type IVA, 3 labs to an unspecified mucopolysaccharidosis, and 1 lab to MPS IVB. Only 4 labs gave a wrong diagnosis.

Other possible diagnosis

MPS type IVB (1 lab), unspecified MPS type IV (1 lab), MPS type IX (1 lab).

Diagnostic reliability

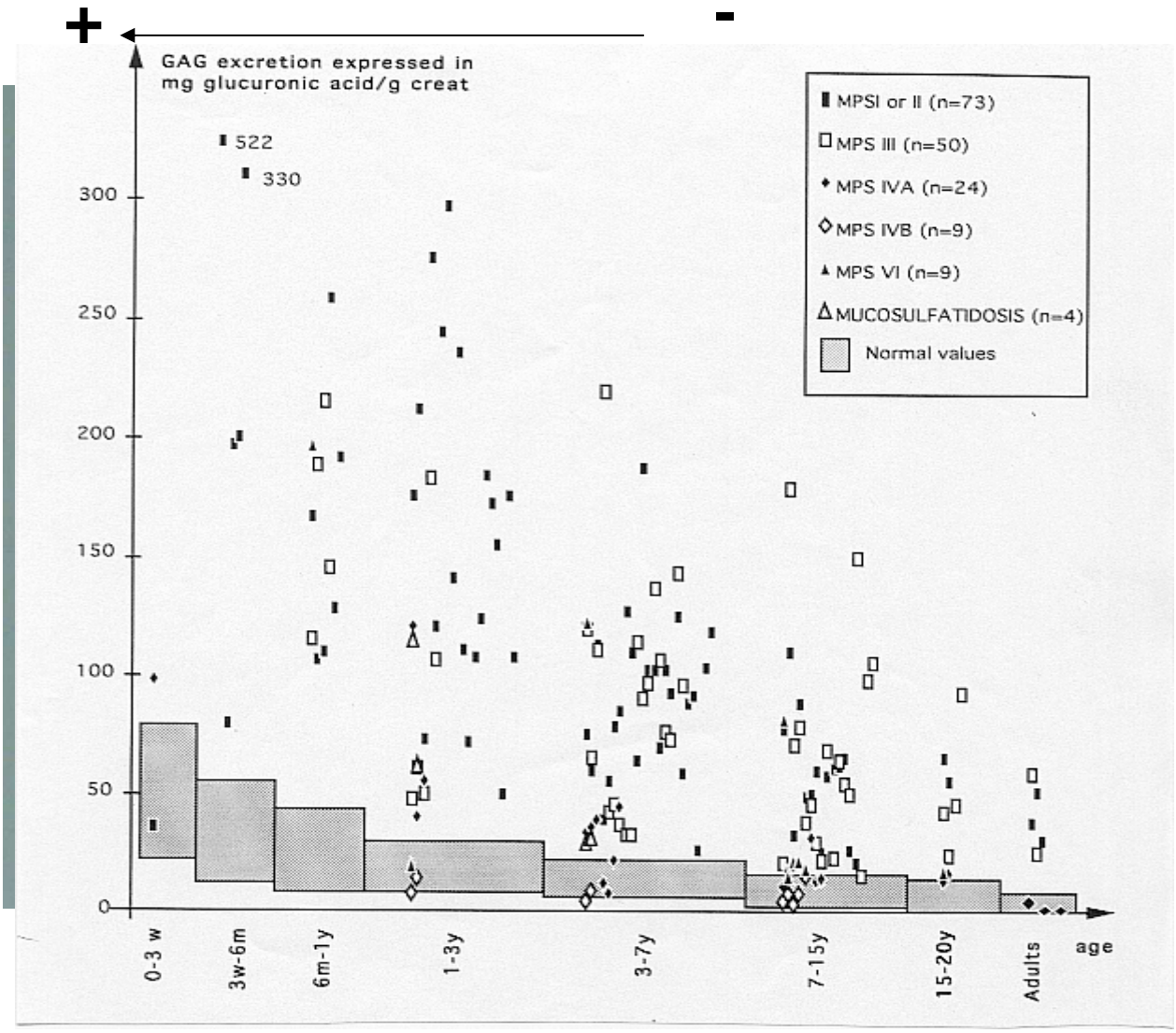
Score	Significance	Number of labs
1	Certain	9
2	Fairly certain	8
3	Tentative	4
-1	To be entered	1
-2	Not performed	0

Among the 17 labs who performed **mucopolysaccharides** quantification, 16 reported an increase of GAG's; and among the 15 labs who performed identification of GAG'S, 12 reported an increase of keratan sulfate. Only 3 labs performed a screening test, but only one was positive.

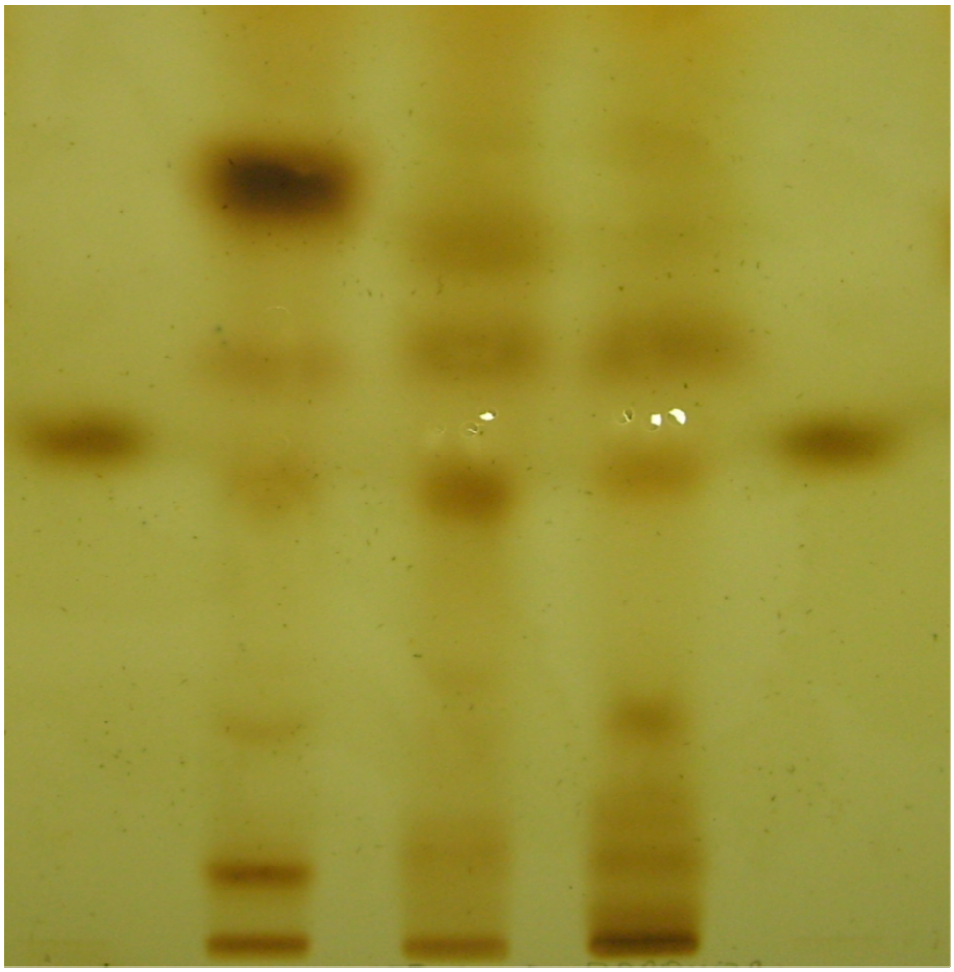
These results highlight the poor performance of screening tests, and the necessity to perform identification of GAG's, since a normal quantitative result does not allow excluding a mucopolysaccharidosis, and MPS IV in particular. This is illustrated by the following slide from Piraud et al. Clin Chim Acta 1993;221:171.

From: Piraud et al. Diagnosis of mucopolysaccharidoses in a clinically selected population by urinary glycosaminoglycan analysis: a study of 2,000 urine samples. Clin Chim Acta 1993;221:171.

The following slide illustrates the electrophoresis of GAG's.



Eleven labs performed **oligosaccharide** analysis: 4 labs reported an abnormal profile but the conclusion was wrong for two of them (MPS IVB and sialidosis).



Sialidosis **Patient D** **Morquio B**

Advice for further investigations was appropriate for those who reached a correct diagnosis.

Scoring

- Analytical: increase of GAG's (score 1), increase of keratan sulfate (score 1)
- Interpretation of results: mucopolysaccharidosis type IV (score 2), mucopolysaccharidosis or MPS type VII (score 1), sialidosis (score 0)
- Recommendations: N-acetylgalactosamine-6-sulfatase and/or β-D-galactosidase activity or mutation analysis *GALNS* and/or *GLB1* genes or oligosaccharides to exclude MPS IVB or control MPS on a new urine sample (score 1)

- **Patient E – Phenylketonuria (phenylalanine hydroxylase deficiency)**

This 26-year old young man was diagnosed through the neonatal screening. He is under treatment from the first week of life. His psychomotor development is almost normal but his compliance to treatment is not strict. He applied for a job in police force: a urinary test was found positive for amphetamines, but he assured that he never used drugs. We were asked to explain this positiveness.

Diagnosis

Most likely diagnosis

All labs concluded to phenylketonuria.

Other possible diagnosis

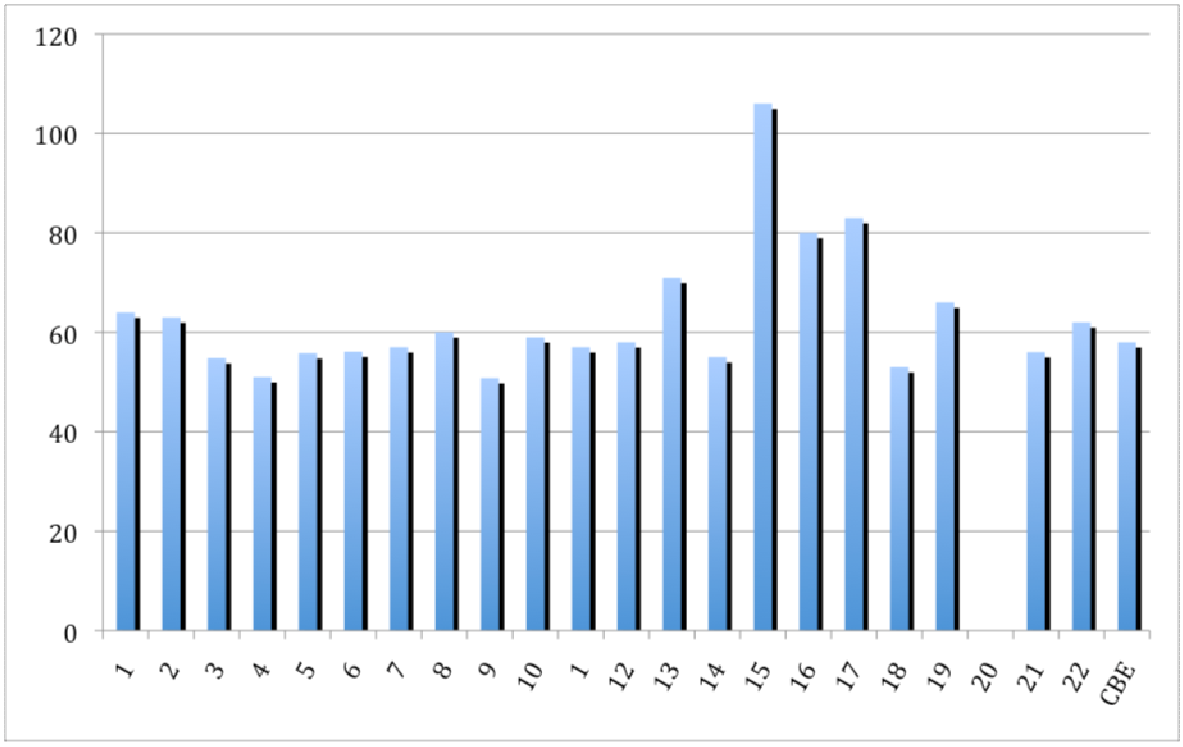
Four labs suggested hyperphenylalaninemia or biopterin disorder.

Diagnostic reliability

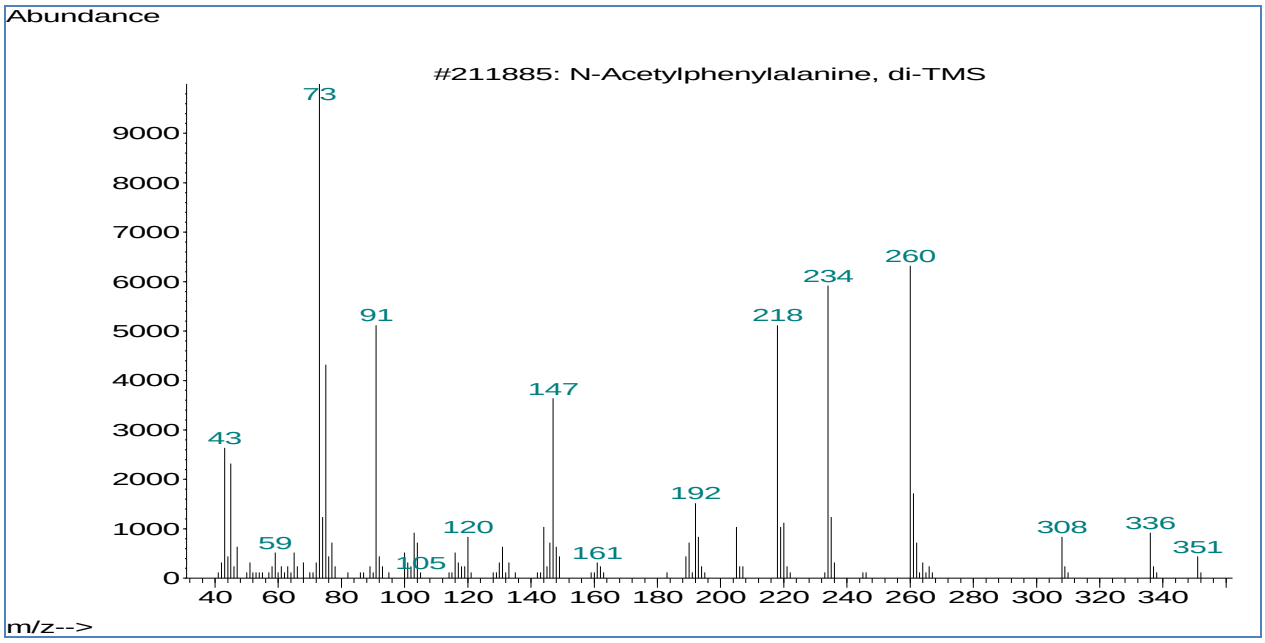
Score	Significance	Number of labs
1	Certain	16
2	Fairly certain	5
3	Tentative	1
-1	To be entered	0
-2	Not performed	0

All labs performed **amino acids** and all, but one, reported an increase of phenylalanine.

Phenylalanine : median = 57 mmol/mol creatinine – CV = 15% (lab 15 excluded)

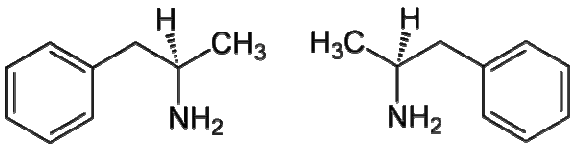


All labs also performed **organic acids** and reported an increase of phenylpyruvic acid (21 labs), phenyllactic acid (21 labs), 2-hydroxyphenylacetic acid (14 labs), mandelic acid (12 labs), and N-acetylphenylalanine (3 labs). N-acetylphenylalanine is eluted just after azelaic acid, and has the following spectra (thanks to Dr Merinero and Dr Ferrer from Madrid).

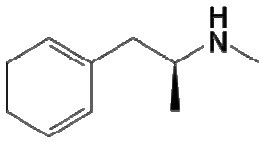


One lab performed analysis of pterins (HPLC fluorescence), and obtained normal levels for neopterins and biopterins and normal ratio, excluding a defect in biosynthesis or regeneration of BH4.

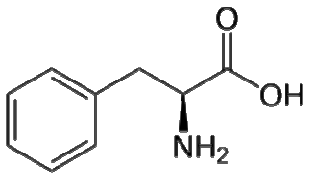
Recommendations: Surprisingly, only 10 labs discussed the positiveness of amphetamines, although this problem compromises the patient's professional future. Screening for amphetamines is a one step immunoassay. Molecular structure for amphetamines and its derivative, metamphetamine, is very close to phenylalanine and its metabolites phenylethylamine and phenolic acids.



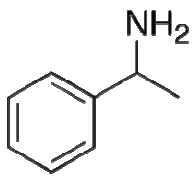
L- et D-amphetamine



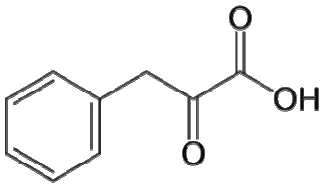
Metamphetamine



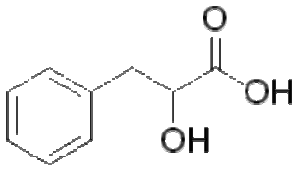
Phenylalanine



Phenylethylamine



Phenylpyruvic acid



Phenyllactic acid

Screening for amphetamines can also be falsely positive test with drugs such as Largactil®, Tercian®, Survector®, Nivaquine®. In this patient, another test for amphetamines by GC/MS was performed and found negative, confirming the false positiveness of the screening test. Otherwise, recommendations for the confirmation of phenylketonuria were appropriate.

Scoring

- Analytical: increase of phenylalanine (score 1), increase of phenylpyruvic, and phenyllactic acids (score 1)
- Interpretation of results: phenylketonuria (score 2)
- Recommendations: screening test for amphetamines was positive because the molecular structure of Phe and its metabolites is close to amphetamines (score 1)

- **Patient F – Citrullinemia type I (argininosuccinate synthetase deficiency)**

The patient is the second child of consanguineous Turkish parents. He presented in the neonatal period with lethargy, poor feeding, hyperventilation, leading to coma with alkalosis (pH = 7.50). Ammonemia was 1576 µmol/L (controls: 37-63). Plasma amino acids, performed at 6 days of life, revealed a huge increase of citrulline (2990 µmol/L; controls: 11 – 19) and glutamine (2669 µmol/L; controls: 40 – 760), contrasting with low level for arginine (23 µmol/l ; controls: 23 – 101). Orotic acid excretion was highly elevated (3937 mmol/mol creatinine; controls: 0.3 – 4.1). He is now 8-year old and has a normal psychomotor development.

Diagnosis

Most likely diagnosis

All labs, except one, concluded to citrullinemia type I.

Other possible diagnosis

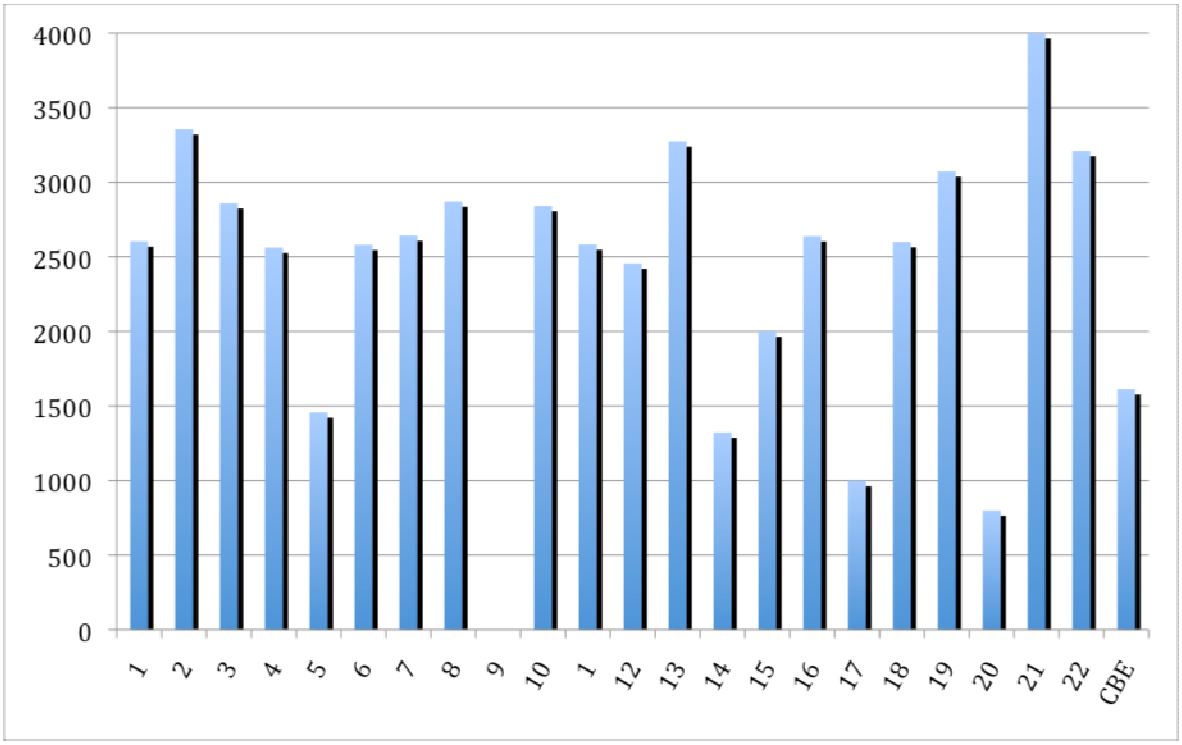
Citrullinemia type I variant (type 3) (1 lab), discard OTC deficiency with considerable citrulline supplementation (1 lab), and citrullinemia type II, galactosemia (1 lab) were proposed as other possible diagnoses.

Diagnostic reliability

Score	Significance	Number of labs
1	Certain	16
2	Fairly certain	5
3	Tentative	0
-1	To be entered	1
-2	Not performed	0

All labs performed **amino acid analysis**, and all, except one who used TLC analysis, reported an increase of citrulline.

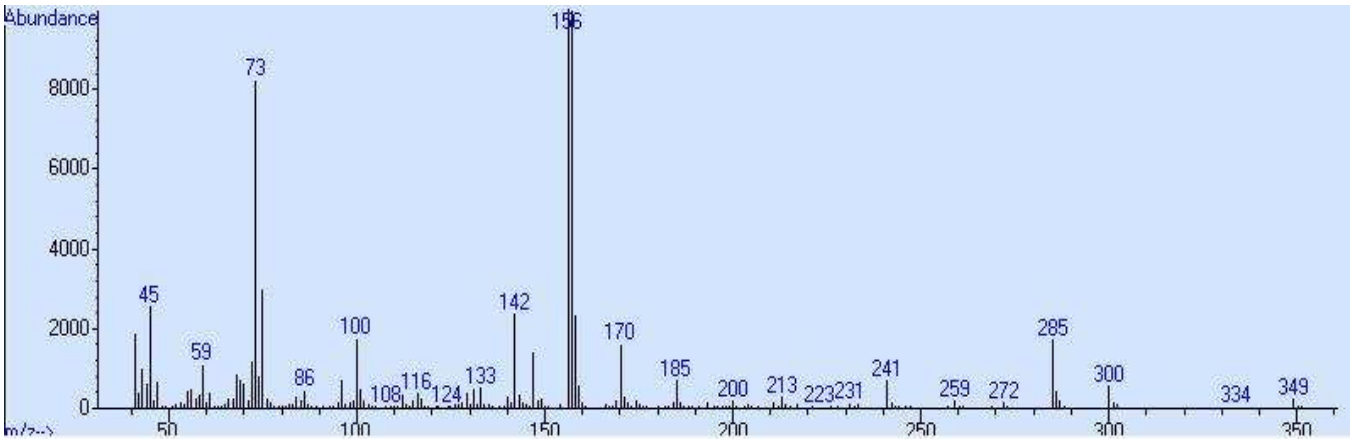
Citrulline : median = 2 600 mmol/mol creat – CV = 28% (lab 21 excluded: value 16 780)



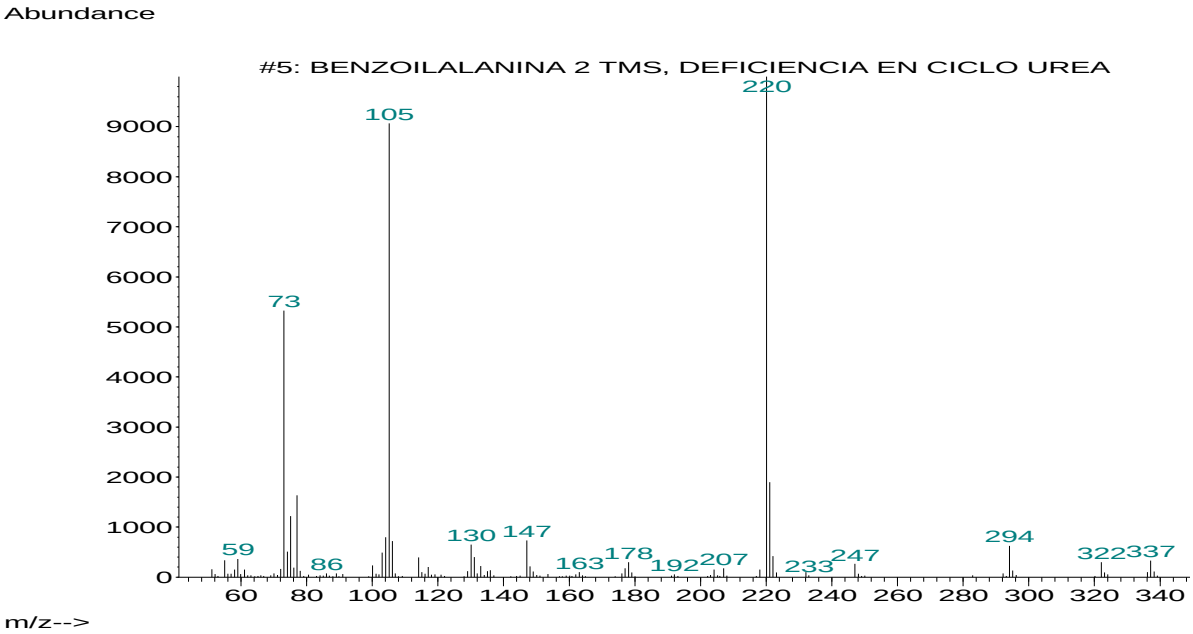
An increase of glycine (13 labs), glutamic acid (11 labs), and alanine (6 labs), a decrease of arginine (4 labs) were also reported. Three labs specified that argininosuccinic acid was undetectable.

All labs but one performed urinary **organic acids:** an increase of orotic acid (16 labs), and hippuric acid (13 labs) was reported. Interestingly, five labs reported the presence of **cyclic citrulline metabolite**, and 3 labs the presence of benzoylalanine, a metabolite secondary to benzoate treatment, accumulated in addition to hippuric acid. Thanks to Dr Corne from Grenoble and to Dr Merinero from Madrid, here are their spectra.

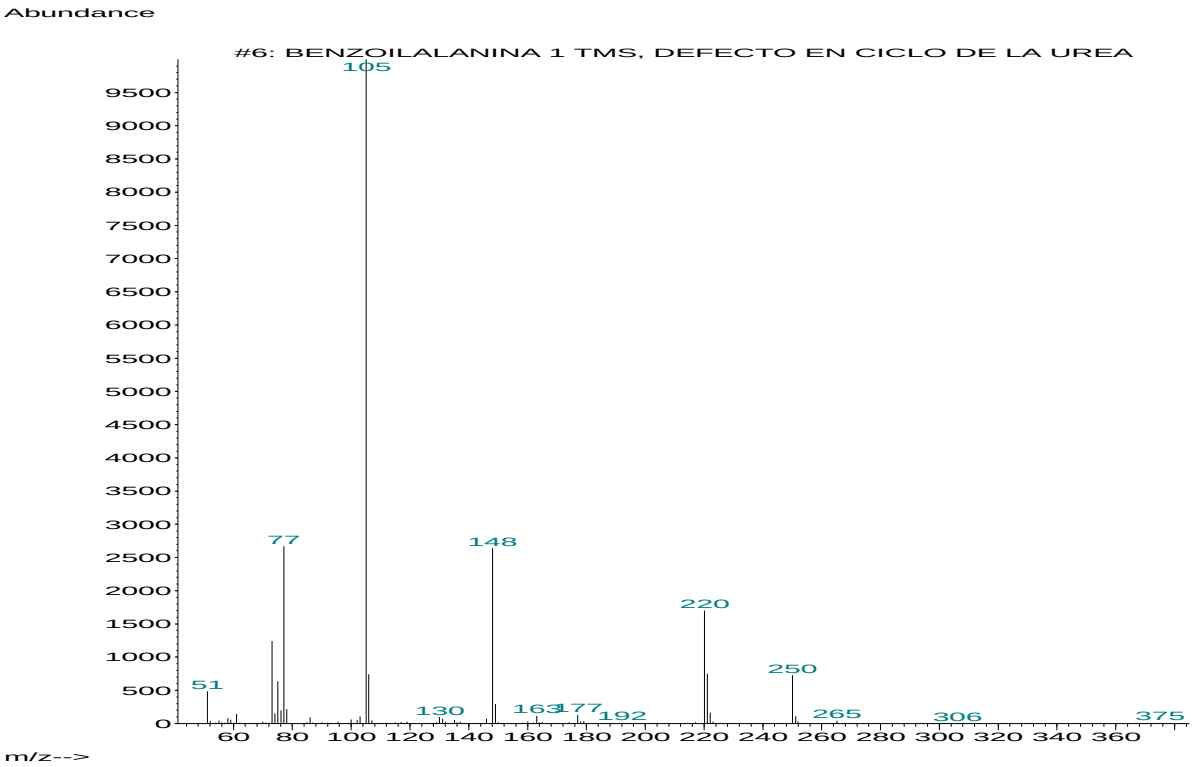
Cyclic citrulline metabolite is eluted few seconds later than 2-hydroxyglutaric.



Benzoylalanine di TMS is eluted between suberic acid and aconitic acid



whereas **benzoylalanine mono TMS** is eluted between homovanillic acid and hippuric acid.



Twenty one labs measured orotic acid excretion by GC/MS, tandem MS or other methods. The median value was 22.0 mmol/mol creat (range: 6.6 – 155).

Recommendations were OK.

Scoring

- Analytical: increase of citrulline (score 1), increase of orotic or cyclic citrulline metabolite (score 1)
- Interpretation: Citrullinemia type I (score 2)
- Recommendations: amino acids in plasma or mutation analysis *ASS1* gene or measurement of argininosuccinate synthetase activity (score 1)

Scores of participants

- **Survey 2011-1**

Lab n°	Patient A Molybdenum cofactor def.				Patient B GAMT deficiency (common sample)				Patient C MMSDH deficiency			
	A	I	R	Total	A	I	R	Total	A	I	R	Total
1	2	2	1	5	Not scored Educational sample				2	2	1	5
2	2	2	1	5					2	1	1	4
3	1	2	1	4					2	2	1	5
4	2	2	1	5					2	2	1	5
5	2	2	1	5					2	2	1	5
6	2	2	1	5					1	0	0	1
7	0	0	0	0					2	1	0	3
8	2	2	1	5					2	2	1	5
9	0	0	0	0					1	0	0	1
10	2	2	1	5					2	2	1	5
11	0	0	0	0					2	2	0	4
12	2	2	1	5					2	2	1	5
13	2	2	1	5					1	1	1	3
14	2	2	1	5					1	1	1	3
15	2	2	1	5					2	2	1	5
16	0	1	0	1					2	1	1	4
17	2	2	1	5					2	2	1	5
18	2	2	1	5					2	2	1	5
19	0	0	0	0					2	2	1	5
20	2	2	1	5					1	1	1	3
21	2	2	1	5					2	2	1	5
22	2	2	1	5					2	1	0	3

❖ **Survey 2011-2**

Lab n°	Patient D Morquio A (MPSIVA)				Patient E Phenylketonuria				Patient F Citrullinemia type I			
	A	I	R	Total	A	I	R	Total	A	I	R	Total
1	2	2	1	5	2	2	1	5	2	2	1	5
2	2	2	1	5	2	2	1	5	2	2	1	5
3	2	2	1	5	2	2	0	4	2	2	1	5
4	2	2	1	5	2	2	0	4	2	2	1	5
5	1	1	1	3	2	2	1	5	2	2	1	5
6	1	1	1	3	1	2	0	3	2	2	1	5
7	2	2	1	5	2	2	1	5	2	2	1	5
8	0	0	1	1	2	2	1	5	2	2	1	5
9	0	0	0	0	2	2	0	4	0	0	0	0
10	0	1	1	2	2	2	0	4	2	2	1	5
11	2	2	1	5	2	2	1	5	2	2	1	5
12	2	2	1	5	2	2	0	4	2	2	1	5
13	2	2	1	5	2	2	0	4	2	2	1	5
14	0	1	1	2	2	2	0	4	2	2	1	5
15	1	2	1	4	2	2	0	4	2	2	1	5
16	1	2	1	4	2	2	1	5	2	2	1	5
17	0	0	0	0	2	2	0	4	2	2	1	5
18	2	2	1	5	2	2	1	5	2	2	1	5
19	2	2	1	5	2	2	0	4	2	2	1	5
20	2	2	1	5	1	2	0	3	2	2	1	5
21	1	1	0	2	2	2	1	5	2	2	0	4
22	1	2	1	4	2	2	1	5	2	2	0	4

❖ **Total scores**

Lab number	Survey 2011-1	Survey 2011-2	Cumulative score (max = 25)	Cumulative score (%)
1	10	15	25	100%
2	9	15	24	96%
3	9	14	23	92%
4	10	14	24	96%
5	10	13	23	92%
6	6	11	17	68%
7	3	15	18	72%
8	10	11	21	84%
9	1	4	5	20%
10	10	11	21	84%
11	4	15	19	76%
12	10	14	24	96%
13	8	14	22	88%
14	8	11	19	76%
15	10	13	23	92%
16	5	14	19	76%
17	10	9	19	76%
18	10	15	25	100%
19	5	14	19	76%
20	8	13	21	84%
21	10	11	21	84 %
22	8	13	21	84%

Performance

	Number of labs	% total labs
Excellent performers (100 % of good responses)	2	9 %
Poor performers (< 60 % good responses)	1	4 %

❖ **Summary of scores**

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Recommen-dations (%)	Total (%)
Patient A	CoMo deficiency	**75 %**	**80 %**	**77 %**	**77 %**
Patient B	GAMT def.	**Not scored**			
Patient C	MMSDH def.	**89 %**	**75 %**	**77 %**	**81 %**
Patient D	MPS IVA	**64 %**	**75 %**	**86 %**	**73 %**
Patient E	Phenylketonuria	**95 %**	**100 %**	**45 %**	**87 %**
Patient F	Citrullinemia type I	**95 %**	**95 %**	**86 %**	**94 %**

DPT-scheme in 2012

- Two surveys of 3 urines, including “normal” patients
- Results have to be sent within 3 weeks
- **Reporting** on CSCQ (Centre Suisse de Contrôle de Qualité) website is compulsory, before the deadline.
- **Poor performers**: any laboratory with a score of below 18 (<60%) is deemed unsatisfactory.
- **Scoring**: performed by two different scheme organizers. For the Lyon centre, this is also done by Viktor Kozich from Prague.

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, 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 2012

It will take place during the SSIEM meeting in Birmingham **Tuesday 4 September 2011**, at 9.00 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.

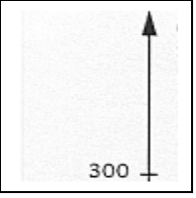
Service Maladies héréditaires du Métabolisme et Dépistage Néonatal
Centre de Biologie et de Pathologie Est
59, Bd Pinel
69677 Bron cedex
Tel 33 4 72 12 96 94
Fax 33 4 72 12 97 20

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**