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**ERNDIM**  
**Diagnostic proficiency testing**  
**2004**  
**Southern Europe**

## **ANNUAL REPORT 2004**

In 2004, 20 labs participated to the Proficiency Testing Scheme Southern Europe.  
Organizing Centre: Dr Christine Vianey-Saban, Service de Biochimie Pédiatrique, Hôpital Debrousse, Lyon, in collaboration with Pr Claude Bachmann, CHUV, Lausanne, Switzerland.

### **Geographical distribution of participants**

<b>Country</b>	<b>Number of participants</b>
France	7
Italy	5
Spain	4
Portugal	2
Switzerland	1
Czech Republic	1
<b>TOTAL</b>	<b>20</b>

### **Logistic of the scheme**

- 2 surveys 2004-1 : patient P1, P2 and P3  
2004-2 : patient P4, P5 and P6
  
- Origin of patients : 3 out the 6 urine samples have been kindly provided by participants
- Patient P1: Tyrosinemia type I - Dr Encarnació Riudor, Dr José Antonio Arranz, Vall d'Hebron, Barcelona
- Patient P2: Propionic acidemia - Dr Encarnació Riudor, Dr José Antonio Arranz, Vall d'Hebron, Barcelona
- Patient P3: Non metabolic disease : septic shock - Hôpital Debrousse
- Patient P4: Mevalonic aciduria – Pr Willems, Nijmegen. *This sample has been sent to all labs participating to the DPT scheme in Europe*
- Patient P5: Fucosidosis - Hôpital Debrousse
- Patient P6: Alkaptonuria - Hôpital Debrousse

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

### Timetable of the schemes

- May 5<sup>th</sup> shipment of samples of Survey 1 and Survey 2 by DHL and of the forms by e-mail
- May 28<sup>th</sup> deadline for results submission (Survey 1)
- June 21<sup>st</sup> analysis of samples of the second survey
- July 12<sup>th</sup> deadline for results submission (Survey 2)
- August 10<sup>th</sup> report of Survey 1 by e-mail
- August 13<sup>th</sup> report of Survey 2 by e-mail
- August 31<sup>st</sup> meeting in Amsterdam
- February 3<sup>rd</sup> annual report sent by e-mail

### Date of receipt of samples

DHL has been more efficient than EMS Chronopost who performed shipment of samples in the previous years.

	<b>Survey 1 + 2</b>
+ 24 hours	17
+ 48 hours	2
+ 7 days	1

### Date of reporting

Most labs (80%) sent the forms in time and the number of labs who did not send their answer is low this year.

	<b>Survey 1</b>	<b>Survey 2</b>
	(3 weeks)	(3 weeks)
Receipt of results :		
Before deadline	16 / 20	16 / 20
+ 1 day		1 / 20
+ 4 to 12 days	3 / 20	2 / 20
No answer	1 / 20 ( 5 % )	1 / 20 ( 5 % )

## Scoring of results

The scoring system established by the International Scientific Advisory Board of ERNDIM is still the same. Three criteria are evaluated :

<b>A</b>	Analytical performance	Correct results of the appropriate tests	2
		Partially correct or non-standard methods	1
		Unsatisfactory or misleading	0
<b>I</b>	Interpretation of results	Good, diagnosis is established	2
		Helpful but incomplete	1
		Misleading / wrong diagnosis	0
<b>R</b>	Recommendations for further investigations	Complete	1
		Unsatisfactory or misleading	0

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

No answer to one survey is scored as 0 for the 3 samples.

## Meeting of participants

It took place in Amsterdam on August 31<sup>st</sup> from 9H30 to 11h00, during the SSIEM 41<sup>st</sup> Annual Meeting.

### ❖ Participants

Representatives from at least 10 labs were present, but the presence form has not been filled by all participants.

### ❖ Informations from the Executive Board and the Scientific Advisory Board for next year

- In 2004, there were 4 centres in Europe for the DPT-scheme. This will be the same in 2005. A fifth centre will be created in Basel in 2006
- The scoring system will be used in all centres in 2005
- Certificate of participation for 2004 will be issued for participation and it will be additionally notified whether the participant has received a warning letter. This warning letter is sent out if the performance is less than 50%.
- Fee for 2005 : 2% increase
- 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 a "normal" urine, together with a short clinical report. 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. 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 44 tubes), add stoppers and freeze. Send the aliquots on dry ice by rapid mail or express transport to: Christine Vianey-Saban, Service de Biochimie Pédiatrique, Bâtiment D, Hôpital Debrousse, 29 Rue Sœur Bouvier, 69322 Lyon cedex 05, France. Please send me an e-mail on the day you send the samples.

### ❖ Discussion of results

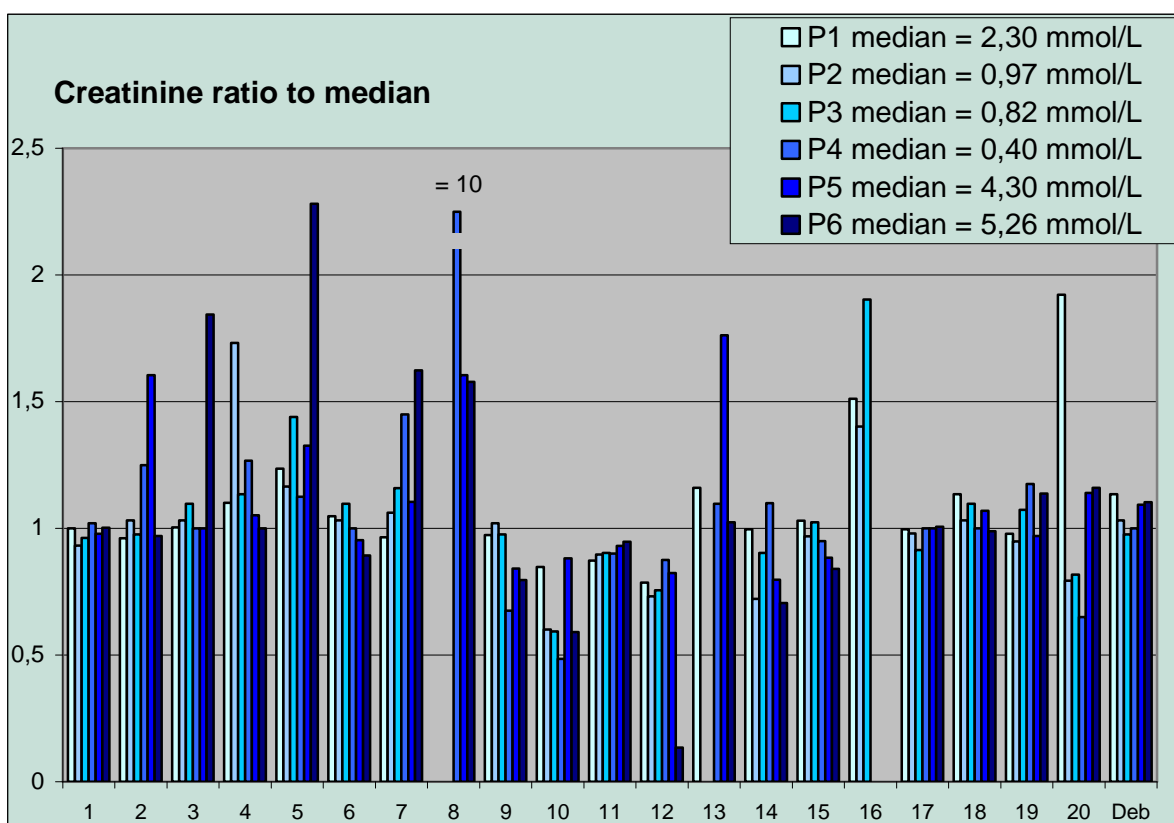
#### • Creatinine measurement

Results worsened compared to last year.

Creatinine determination is included in 2 ERNDIM QAP: Quantitative Organic Acids and Special Assays in Urine. Please check for your results in these QAP, since a wrong measurement has important consequences on quantitative data.

Lab 3, 4 and 13 had 1 wrong measurement (likely errors of dilution). In addition to imprecision, lab 10 and 12 seem to have systematically low values, while lab 2, 5, 7, 8 and 16 have systematically high values. For Lab 20, high imprecision seems to be the predominant problem.

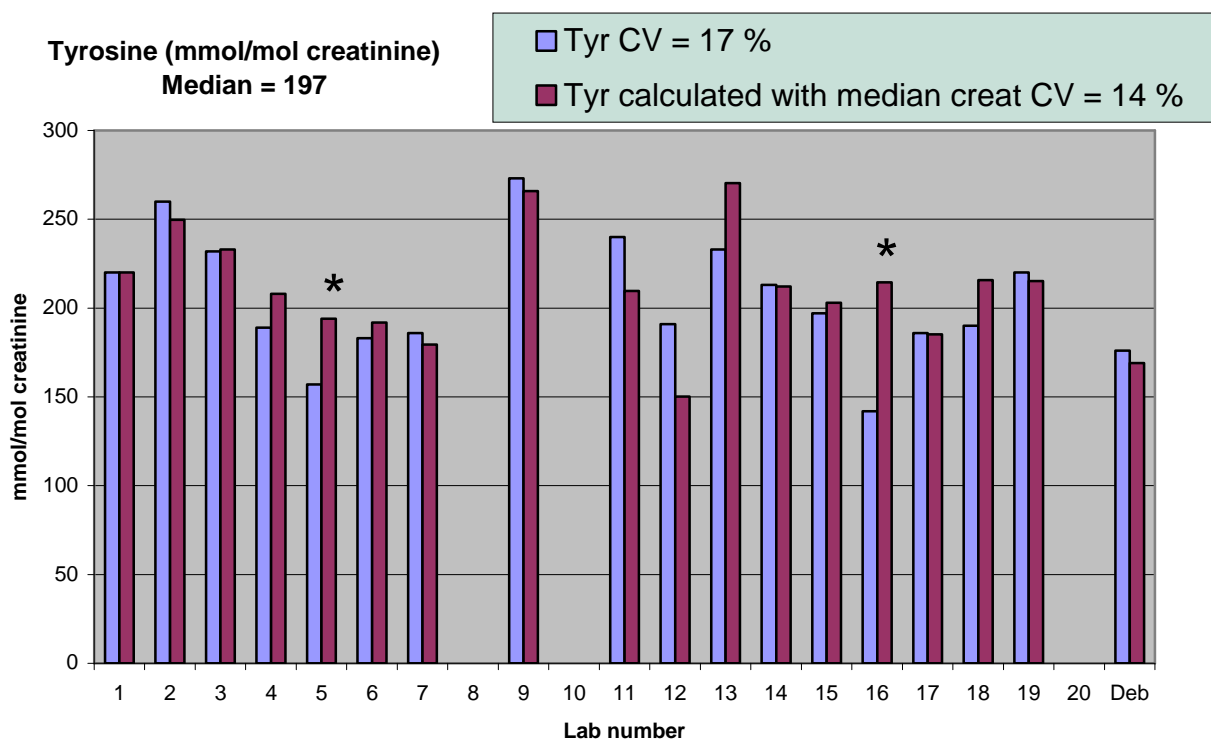
*Pro memoria:* Systematic errors lead to decision errors when comparing own results (expressed per creatinine) to those of the literature (including reference values), while high imprecision disallows result dependent follow-up of patients and adaptation therapy.



• **Patient P1 – tyrosinemia type I : fumarylacetoacetase deficiency**

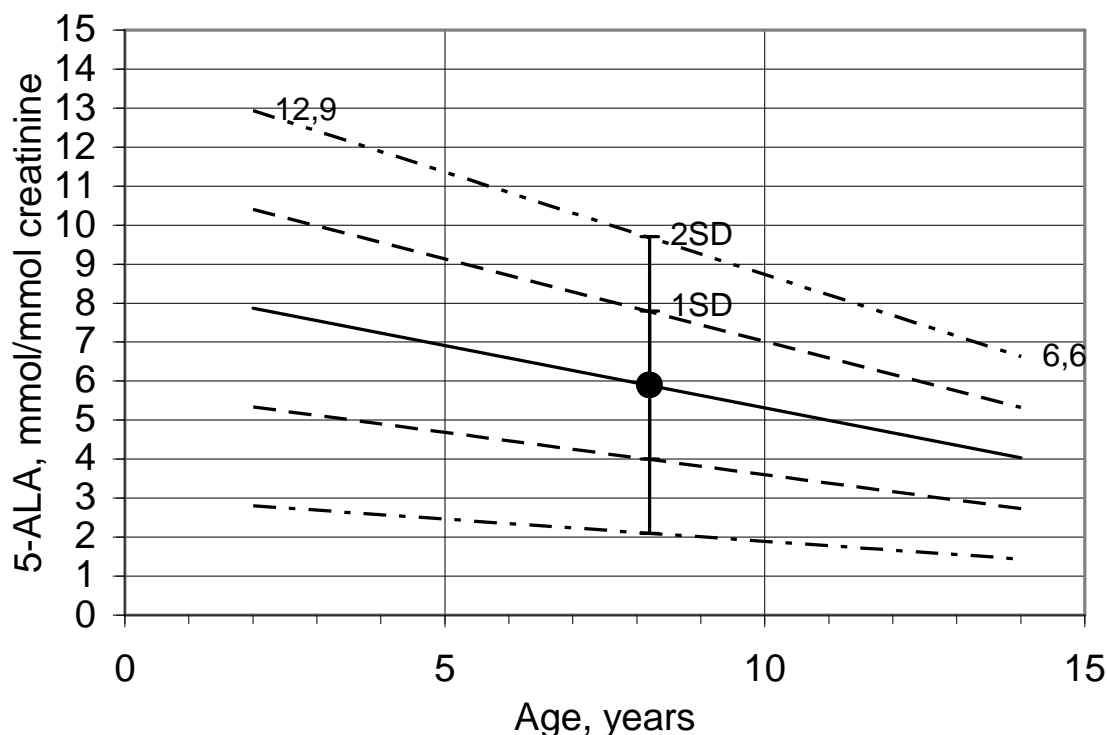
19 reports

- The urine sample was collected from a 7 year-old boy. His brother died from liver failure. From 6 months of age, he had repeated respiratory infections, pain crises, marked hypotonia, hepatomegaly and malnutrition. At diagnosis, succinylacetone was 997 mmol/mol creatinine. He was treated with NTBC and diet and has a good clinical evolution.
- 18 labs performed amino acid analysis: all labs reported an increase of tyrosine. Quantification of tyrosine, when performed, was correct (median = 197 mmol/mol creatinine, CV = 17%). We re-calculated tyrosine excretion using the median creatinine value obtained by all labs (see figure below): the CV improved to 14%, emphasizing again the need of an accurate measurement of creatinine.



- All labs performed organic acids. There was a very high variability in quantitative results for 4-hydroxyderivatives: is it due to a problem of oximation ? 16 labs reported that succinylacetone was undetectable, even with the inhibition assay.
- Delta-aminolevulinic acid (5-ALA): some labs reported normal values for this metabolite, while other labs indicated an increased value (aminoacid analysis or HPLC). Using our new method for aminoacids by LC/MS/MS we found a value of 12 mmol/mol creat, whereas in all the other urine tested (n= 500) we found values < 5.

We asked Elizabeth Holme for advice. According to her data, the reference range for 5-ALA for the patient examined here is 2 - 10 mmol/mol creat (see graph)



In her experience, there is no increase in 5-ALA excretion in infants with liver failure of other causes than tyrosinemia type I. Conversely, in liver failure of other causes, a slight increase of succinylacetone (up to 0.5  $\mu\text{mol/L}$  in plasma) can be observed.

- Interpretation of results and recommendations were correct, except that some labs advised to perform measurement of fumarylacetoacetase activity in a liver biopsy (?).
- Scoring
  - o Analytical : increase of 4-hydroxyderivatives without succinylacetone and increase of Tyr (score 2), wrong creatinine, amino acid analysis not performed (score 1)
  - o Interpretation : tyrosinemia type I as first diagnosis (score 2), tyrosinemia type I as second diagnosis, tyrosinemia type II or III (score 1)
  - o Recommendations : plasma AA, fumarylacetoacetase activity or mutation analysis (score 1)

- **Patient P2 : propionic acidemia, propionyl-CoA carboxylase deficiency**

#### 19 reports

- This male newborn, from unrelated parents, was born with an appropriate weight. Few days later, he presented metabolic acidosis, respiratory distress and weight loss. Ammonia was 280  $\mu\text{mol/L}$ . He clinically improved with a standard treatment for acidosis. Shortly after, diagnosis of propionic acidemia was established and he received an appropriate diet together with biotin and carnitine. He had a satisfactory evolution.

- All labs gave a correct diagnosis.
- 16 labs performed aminoacid analysis and reported an increase of glycine (CV = 19 %).
- All labs performed organic acids and identified abnormal metabolites. There was a great variability in the quantification of metabolites and, in particular, for methylcitrate measurement. A standard for methylcitrate and its stable isotope are available (Interchim, [www.interchim.com](http://www.interchim.com), ref X-4176 and D-4162) and we recommend their use for an accurate follow-up of treated patients.
- Advice for further investigations was OK
- Scoring
  - o Analytical : increase of 3-hydroxypropionic, methylcitric acids, tiglyglycine, propionylglycine and other propionate metabolites with ketosis, increase of glycine (score 2), increase of propionate metabolites, aminoacids not performed, wrong creatinine (score 1)
  - o Interpretation : propionic acidemia (score 2)
  - o Recommendations : blood acylcarnitines, propionyl-CoA carboxylase activity, propionate incorporation and/or mutation analysis (score 1)

- **Patient P3 : septic shock**

19 reports

- This 9-month-old boy had a normal development, except 2 episodes of bronchiolitis. In the course of an acute gastroenteritis with fever, vomiting and weight loss, he had an acute circulatory failure. Six hours later, he had again haemodynamic problems and received dopamine. Haemodynamic condition worsened, and despite symptomatic treatment, he developed multivisceral failure and cerebral oedema, and finally died. Infectious agent could be not identified but antibiotic therapy was started before samples were collected.
- Fifteen labs performed aminoacid analysis : no specific abnormalities were observed, except for unidentified peaks or an increase of ethanolamine. One lab reported an increase of Phe : due to an interference ?
- Organic acids: all labs identified correctly compounds : increase of lactic acid and, to a lesser extent, of pyruvic acid, due to circulatory failure; increase of homovanillic acid due to dopamine treatment.
- Interpretation was more problematic: some labs evoked congenital lactic acidosis, although there was no significant increase of malate, fumarate, EMA, 3-methylglutaconate, 4-hydroxyphenyllactate or 4-hydroxyphenylpyruvate. Moreover, this child was completely healthy before this episode. Others considered neuroblastoma although there was no significant increase of vanilmandelic acid.
- Recommendations depended of the interpretation of results.
- Scoring
  - o Analytical: increase of lactic, pyruvic, homovanillic (3,4-dihydroxyphenylacetic) acids in organic acid profile, no specific abnormality for other tests (score 2), wrong creatinine, increase of lactic acid not reported, increase of homovanillic acid not reported (score 1)

- Interpretation: lactic acidosis probably due to septic shock/circulatory failure, metabolites of dopamine treatment (score 2), lactic aciduria of unknown origin, metabolites of dopamine treatment (score 1), profile consistent with congenital lactic acidosis or suspected neuroblastoma (score 0)
- Recommendations: exclude infection, plasma investigations (AA , acylcarnitines, lactate and pyruvate) (score 1), respiratory chain in tissue or search for neuroblastoma as first investigation (score 0).

- **Patient P4 : mevalonic aciduria due to mevalonate kinase deficiency**

19 reports

- This urine sample was collected from a girl who admitted to the hospital at 4 weeks with failure to thrive, dysmaturity, infections, hepatomegaly. Her age was unknown.
- 16 labs identified an increase of mevalonic acid and/or mevalonolactone on organic acid analysis, but 3 labs failed to detect it. Another urine sample with increased mevalonic acid excretion had already been sent in 2001 (patient P1). Two out of these 3 labs already missed or did not identify mevalonic acid (???) at that time whereas the third one identified it properly (this lab told us that he did not look at the profile which had been interpreted by the technician). The CV for quantification of mevalonic acid was 67%. Stable isotopes for mevalonolactone are available from CDN isotopes ([www.cdniso.com](http://www.cdniso.com)).
- Interpretation and recommendations were satisfying for those who identified properly mevalonic acid.
- Scoring
  - Analytical : increase of mevalonic acid and/or mevalonolactone (score 2), wrong creatinine (score 1)
  - Interpretation : mevalonic aciduria (score 2)
  - Recommendations : measurement of mevalonate kinase activity or mutation analysis (score 1)

- **Patient P5 : fucosidosis due to  $\alpha$ - fucosidase deficiency**

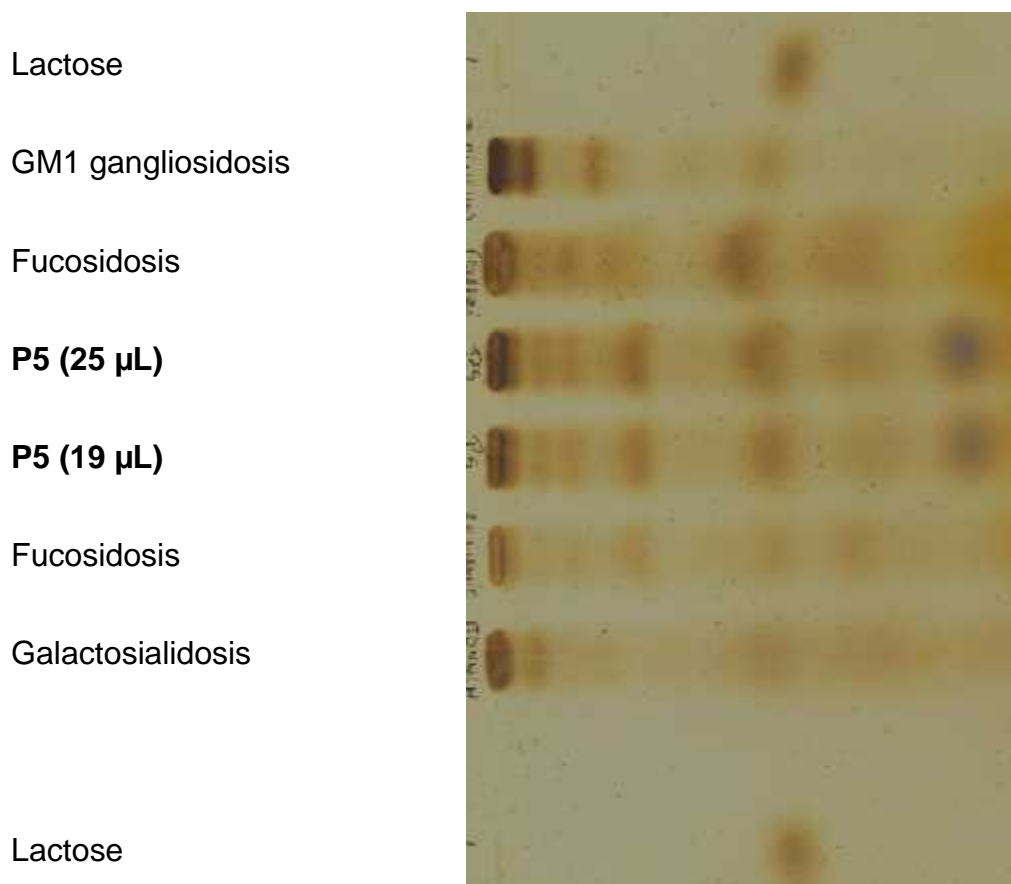
19 reports

- This 10 year-old girl is born in Turkey, from consanguineous parents. At 2 years of age, she could walk with help, could say a few words. She subsequently lost all skills. At 10 years of age, she has a coarse facies, dwarfism, angiokeratoma, amyotrophy, tetraparesis and recurrent lung infections.





- Fifteen labs performed oligosaccharides. All except one reported an abnormal profile but only 10 of them concluded to fucosidosis. One lab reported a normal profile. The next picture illustrates the TLC profile we obtained in urine from patient P5 compared to other oligosaccharidoses.



- Fifteen labs performed mucopolysaccharide analysis. Twelve reported a normal or a not specific increase. Three labs reported an abnormal profile suggestive of mucopolysaccharidosis (among them, one lab did not perform oligosaccharides). We also found a slight increase of GAG, with trace amounts of dermatane and heparane sulphate.
- Interpretation: 11 labs concluded to fucosidosis, as only diagnosis or together with (an)other diagnos(i)es. Six labs concluded to a lysosomal storage disorder, two of them concluding to a mucopolysaccharidosis. Two labs could not reach a diagnosis but did not perform oligosaccharides.
- Recommendations were correct for those who reached a correct diagnosis.
- Scoring
  - o Analytical: oligosaccharide pattern characteristic for fucosidosis (score 2), abnormal profile (score 1), normal oligosaccharide profile (score 0)
  - o Interpretation: fucosidosis (score 2), oligosaccharidosis (score 1), mucopolysaccharidosis (score 0)
  - o Recommendations:  $\alpha$ -fucosidase activity, or oligosaccharides must be performed by a specialized lab, or enzymes of oligosaccharidoses (score 1)

- **Patient P6 : alkaptonuria due to homogentisate 1,2 dioxygenase, or ochronosis**

19 reports

- This 66 year-old woman had nephrectomy because of nephrocalcinosis. She subsequently had surgery for total knee replacement and the surgeon noticed black cartilage.
- Ten labs reported a dark color of urine.
- The 14 labs who performed aminoacid analysis reported no specific abnormality, except one who reported a generalized hyperaminoaciduria but this was due to a wrong creatinine determination.
- Organic acids: 19 labs, except one who reported a normal profile, demonstrated an increase of homogentisic acid excretion. The CV of quantification was 256%, probably due to a problem of storage. Homogentisate auto-oxidizes rapidly in hydrogen peroxide, superoxide (responsible for arthritis ?) and benzoquinoneacetate.
- Advice further investigations: correct, although some labs advised to measure homogentisate 1,2 dioxygenase activity in liver.
- Scoring
  - Analytical: increase of homogentisic acid excretion (score 2), increase of homogentisic acid excretion, hyperaminoaciduria due to a wrong creatinine measurement (score 1), normal organic acid profile (score 0)
  - Interpretation: alkaptonuria (score 2)
  - Recommendations: enzymatic diagnosis not required or mutation analysis of homogentisate 1,2 dioxygenase gene (score 1), homogentisate 1,2 dioxygenase activity in liver (score 0)

## Scores of participants

### ❖ Survey 2004-1

Lab n°	Patient P1 Tyrosinemia type I				Patient P2 Propionic acidemia				Patient P3 Septic shock			
	A	I	R	Total	A	I	R	Total	A	I	R	Total
<b>1</b>	2	2	0	<b>4</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>
<b>2</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>
<b>3</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>	2	0	0	<b>2</b>
<b>4</b>	2	2	1	<b>5</b>	1	2	1	<b>4</b>	2	1	0	<b>3</b>
<b>5</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>
<b>6</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>	2	1	1	<b>4</b>
<b>7</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>	1	1	0	<b>2</b>
<b>8</b>	0	0	0	<b>0</b>	0	0	0	<b>0</b>	0	0	0	<b>0</b>
<b>9</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>	2	2	0	<b>4</b>
<b>10</b>	1	2	1	<b>4</b>	1	2	1	<b>4</b>	1	0	1	<b>2</b>
<b>11</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>	1	2	0	<b>3</b>
<b>12</b>	1	2	1	<b>4</b>	2	2	1	<b>5</b>	2	1	0	<b>3</b>
<b>13</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>	2	1	0	<b>3</b>
<b>14</b>	1	1	1	<b>3</b>	2	2	1	<b>5</b>	1	2	1	<b>4</b>
<b>15</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>	2	0	1	<b>3</b>
<b>16</b>	1	2	1	<b>4</b>	1	2	1	<b>4</b>	1	2	0	<b>3</b>
<b>17</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>	2	2	0	<b>4</b>
<b>18</b>	2	1	1	<b>4</b>	2	2	1	<b>5</b>	2	1	0	<b>3</b>
<b>19</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>	2	2	1	<b>5</b>
<b>20</b>	1	2	1	<b>4</b>	2	2	1	<b>5</b>	1	0	0	<b>1</b>

## ❖ Survey 2004-2

Lab n°	Patient P4 Mevalonic aciduria				Patient P5 Fucosidosis				Patient P6 Alkaptonuria			
	A	I	R	Total	A	I	R	Total	A	I	R	Total
1	2	2	1	5	1	2	1	4	2	2	1	5
2	2	2	1	5	2	2	1	5	2	2	1	5
3	2	2	1	5	1	0	1	2	1	2	1	4
4	2	2	1	5	0	2	1	3	0	0	0	0
5	2	2	1	5	1	1	1	3	1	2	1	4
6	2	2	1	5	2	2	1	5	2	2	1	5
7	0	0	0	0	0	0	0	0	1	2	1	4
8	1	2	1	4	2	2	1	5	2	2	0	4
9	2	2	1	5	1	1	1	3	2	2	1	5
10	0	0	0	0	2	2	1	5	2	2	1	5
11	2	2	1	5	0	0	1	1	2	2	0	4
12	2	2	1	5	0	0	0	0	1	2	1	4
13	2	2	1	5	2	2	1	5	2	2	0	4
14	2	2	1	5	1	0	0	1	2	2	1	5
15	2	2	1	5	2	2	1	5	2	2	1	5
16	0	0	0	0	0	0	0	0	0	0	0	0
17	2	2	1	5	2	2	1	5	2	2	1	5
18	2	2	1	5	2	2	1	5	2	2	1	5
19	2	2	1	5	2	1	1	4	2	2	1	5
20	0	0	0	0	2	2	1	5	2	2	1	5

## ❖ Total scores

<b>Lab number</b>	<b>Survey 2004-1</b>	<b>Survey 2004-2</b>	<b>Cumulative score</b>	<b>Cumulative score ( % )</b>
<b>1</b>	14	14	<b>28</b>	<b>93 %</b>
<b>2</b>	15	15	<b>30</b>	<b>100 %</b>
<b>3</b>	12	11	<b>23</b>	<b>77 %</b>
<b>4</b>	12	8	<b>20</b>	<b>67 %</b>
<b>5</b>	15	12	<b>27</b>	<b>90 %</b>
<b>6</b>	14	15	<b>29</b>	<b>97 %</b>
<b>7</b>	12	4	<b>16</b>	<b>53 %</b>
<b>8</b>	0	13	<b>13</b>	<b>43 %</b>
<b>9</b>	14	13	<b>27</b>	<b>90 %</b>
<b>10</b>	10	10	<b>20</b>	<b>67 %</b>
<b>11</b>	13	10	<b>23</b>	<b>77 %</b>
<b>12</b>	12	9	<b>21</b>	<b>70 %</b>
<b>13</b>	13	14	<b>27</b>	<b>90 %</b>
<b>14</b>	12	11	<b>23</b>	<b>77 %</b>
<b>15</b>	13	15	<b>28</b>	<b>93 %</b>
<b>16</b>	11	0	<b>11</b>	<b>37 %</b>
<b>17</b>	14	15	<b>29</b>	<b>97 %</b>
<b>18</b>	12	15	<b>27</b>	<b>90 %</b>
<b>19</b>	15	14	<b>29</b>	<b>97 %</b>
<b>20</b>	10	10	<b>20</b>	<b>67 %</b>

## ❖ Summary of scores

We excluded from this table, the labs who did not send results. The percentages given are the scores obtained from labs who sent a report.

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Recommendations (%)	Total (%)
Patient P1	Tyr. Type I	87	95	86	92
Patient P2	Propionic ac.	92	100	100	97
Patient P3	Septic shock	84	63	42	67
Patient P4	Mevalonic ac.	82	84	84	83
Patient P5	Fucosidosis	66	66	84	69
Patient P6	Alkaptonuria	84	95	79	87

### DPT-scheme in 2005

Same “rules” as in 2004 :

- Two surveys of 3 urines, including “normal” patients
- Results have to be sent within 3 weeks
- Scoring will be analyzed for all centres

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, if possible, for organic acids.

### Meeting in 2005

The next meeting for the DPT-scheme Southern Europe will take place during the 42<sup>nd</sup> Symposium of SSIEM in La Maison de la Chimie, Paris 7<sup>ième</sup>, on Tuesday September 6<sup>th</sup> from 9H30 to 11H.

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 URINE SAMPLES ALREADY SENT

- **1998 : 1**
  - A** **OCT**
  - B** **Propionic**
  
- **1999 : 1**
  - C** **MPS I or II**
  - E** **Cystinuria** SKZL
  
- **1999 : 2**
  - D** **CbIC**
  - 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 academia**
  - P3**            **Non metabolic disease, septic shock**
  
- **2004:2**
  - P4**            **Mevalonic aciduria (common sample)**
  - P5**            **Fucosidosis**
  - P6**            **Alkaptonuria**