ERNDiM

Quality Assurance in Laboratory Testing for IEM

HCL
LYON UNIVERSITY HOSPITAL

ERNDIM DIAGNOSTIC PROFICIENCY TESTING
FRANCE 2025
ANNUAL MEETING
Madrid, 9 October 2025

Christine Vianey-Saban, Cécile Acquaviva

Certificate of participation 2024

- Certificates have been sent to the labs who sent reports for at least one of the two surveys
- Critical errors in 2024
  - No critical errors 😊
- Performance support letters
  - No performance support letters have been sent 😊
- No answer to one survey means a score ≤ 50%.

Information from Executive Committee and Scientific Advisory Board - DPT

- **Scoring**
  - The scoring you received in the interim reports for 2025 is provisional : it will be discussed in November at the SAB meeting. The critical error(s) will be defined
  - Results from each centre are scored by another scheme organizer. In 2025, results of DPT France will be scored by Joanne Croft (DPT UK). It changes every year
  - The score for satisfactory performance is 17 points from the maximum of 24 (70%)

Website reporting (CSCQ)

- Selection of tests
  - **Don't select a test if you will not perform it nor enter results**
  - The evaluation program includes it in the report
- Results
  - **Give quantitative data as much as possible**
  - Enter the key metabolites with the evaluation **in the tables** even if you don't give quantitative data, and **even if the analysis has been performed by your cluster lab**
  - If the profile is normal : enter "Normal profile" in "Key metabolites"
  - If the analysis has been performed by a cluster lab, enter the result in the Results section, not in "Comments on diagnosis", your are responsible for the analyses performed by the cluster lab
  - **Don't enter results in the "comments" window**

→ **Otherwise your results will not be included in the evaluation program**

CSCQ website

Analyte	Method	Key Metabolite	Quant. result	Unit	Evaluation	Qual. result
Amino acid quantitative	LC-MS/MS	Please specify key metabolite	******	mmol/mol creat	To be entered	
Amino acid quantitative	LC-MS/MS	Please specify key metabolite	******	mmol/mol creat	To be entered	
Amino acid quantitative	LC-MS/MS	Please specify key metabolite	******	mmol/mol creat	To be entered	
Amino acid quantitative	LC-MS/MS	Please specify key metabolite	******	mmol/mol creat	To be entered	
Amino acid quantitative	LC-MS/MS	Please specify key metabolite	******	mmol/mol creat	To be entered	
Amino acid quantitative	LC-MS/MS	Please specify key metabolite	******	mmol/mol creat	To be entered	

Comments:

No qualitative or quantitative results in this Comments box
They are not included in the evaluation program

Website reporting (CSCQ)

- Recommendations = **advice for further investigation**
  - Scored together with the interpretative score
  - Advice for treatment are not scored
  - **Don’t give advice for further investigation in “Comments on diagnosis”** : not included in the evaluation program

Reporting

- Interim reports of Survey 1 and Survey 2
  - Personalized (one per lab)
  - Available on the CSCQ website as a pdf file: mail sent by CSCQ when it is available
  - The scoring you received is **provisional**
  - The scoring can be modified by the second reviewer or by the SAB
- Annual report
  - Personalized (one per lab)
  - Will be issued before end of December 2025

DPT France Logistics

In 2025, 20 labs participated to the Diagnostic Proficiency Testing France Scheme
(one participant canceled his registration)

Organizing Centre :
C. Vianey-Saban, C. Acquaviva
Maladies Héréditaires du Métabolisme
Centre de Biologie Est, CHU de Lyon
Bron, France

Participants

Country	Number of labs
France	8
Italy	5
Spain	4
Portugal	2
Netherlands	1
Total	**20**

Tests required

- Amino acids
- Organic acids
- Oligosaccharides
- Mucopolysaccharides
- Purines & Pyrimidines
- Possibility of cluster labs. The lab who receives the samples is responsible for the results

Shipment of samples

- 2 surveys
  - 2025-1 : patient A, B and C
  - 2025-2 : patient D, E and F
- Mailing
  - Samples were aliquoted and sent by CSCQ at room temperature. 1 mailing for the 2 surveys
  - Samples were sent together with qualitative organic acids in urine and acylcarnitines in DBS
- All labs received the samples in good conditions
  - Custom problems in Spain and Italy have been solved: samples were sent by MCA (quantitative schemes)
  - It seems that there is some problems with Portugal

Origin of samples

- Patient A : **Mucopolysaccharidosis type VI** – This sample has been sent to all labs participating to the DPT scheme in Europe
- Patient B : **Hawkinsinuria**
- Patient C : **MSUD**
- Patient D : **GM1 gangliosidosis**
- Patient E : **Hyperoxaluria type II**
- Patient F : **Glutaric aciduria type I, low excretor**

Samples have been provided by Dr Joachim Janda, QLOU Heidelberg scheme, Dr Cristiano Rizzo, Hospital Bambino Gesù, Rome, Dr Anne-Frédérique Dessein, CHU de Lille and the Scientific Advisors of DPT France

Timetable of the scheme

February 5	Shipment of samples of Survey 1 and Survey 2 by CSCQ
March 17	Clinical data available on CSCQ website and start analysis of samples A, B, C (Survey 1)
March 31	Reminder for website submission
April 7	Deadline for result submission (Survey 1)
July 1	Interim report of Survey 1 available on CSCQ website (**sent to CSCQ by SA on May 1**)
June 2	Clinical data available on the CSCQ website and start analysis of samples D, E, F (Survey 2)
June 16	Reminder for website submission
June 23	Deadline for result submission (Survey 2).
August **?**	Interim report of Survey 2 available on CSCQ website (sent to CSCQ by SA on July 31)
October 9	Meeting of participants in Madrid during the ERNDIM meeting
November 28	SAB meeting: definition of critical errors
December 2025	Annual Report with definitive scoring

Scoring of results

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

Recommendations are not scored separately : eventually with interpretation

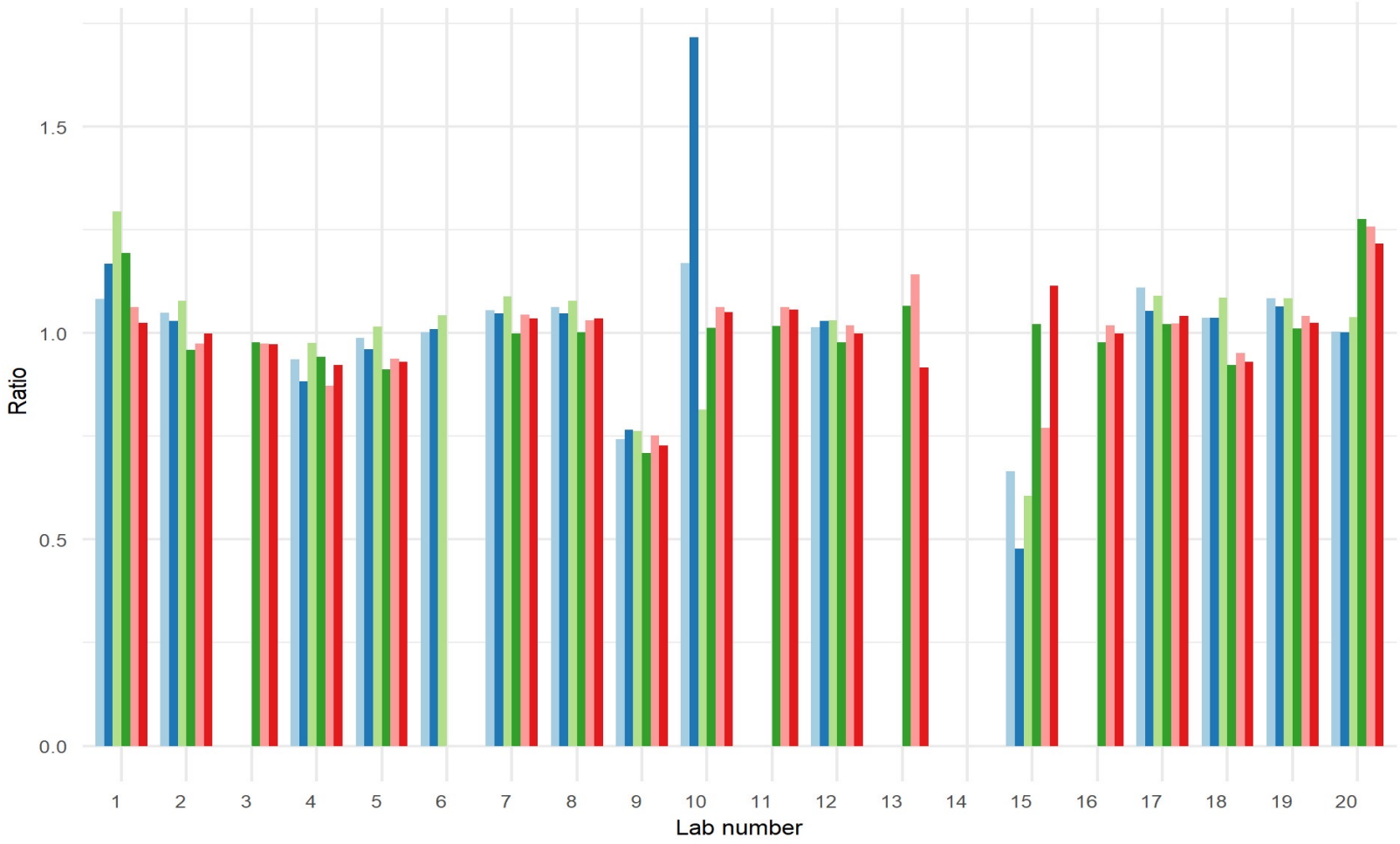
Participation to the scheme

- Survey 1 19 labs
- Survey 2 20 labs

20 registered labs

1 lab could not submit results for the first survey because of non-payment of the 2024 invoice

Creatinine : ratio to median



Sample	A	B	C	D	E	F
Median	5.90	3.00	4.38	5.53	2.30	3.85
SD	0.70	0.71	0.68	0.63	0.27	0.38

Creatinine determination

- Satisfying for most labs
- Lab 15 (same last year) and lab 10 had scattered results
- Lab 9 had low results
- Exclusion of 3 values for CV calculation
- Median values for creatinine
  - Patient A = 5.9 mmol/L (CV = 11.9 %)
  - Patient B = 3.0 mmol/L (CV = 11.7 %) exclusion of 2 wrong values
  - Patient C = 4.4 mmol/L (CV = 12.5 %) exclusion of 1 wrong value
  - Patient D = 5.5 mmol/L (CV = 11.2 %)
  - Patient E = 2.3 mmol/L (CV = 11.7 %)
  - Patient F = 3.9 mmol/L (CV = 9.9 %)
- All CV between 10% and 12.5%, but samples with relatively low creat
  - Interlab CV 2024 Special Assay urine = 5.5 % (n = 128)

Patient A – Mucolysaccharidosis type VI

Common sample distributed to all DPT centres. Will be discussed later this morning

- 15-year-old male patient
- Normal pregnancy and delivery
- From 2 months to 6 years of age : frequent upper airways infections
- 3 years: pectus carinatum
- 10 years
  - Scoliosis with platyspondyly
  - Dorsal kyphosis
  - Narrow cervical canal
  - Decrease in visual and hearing acuity

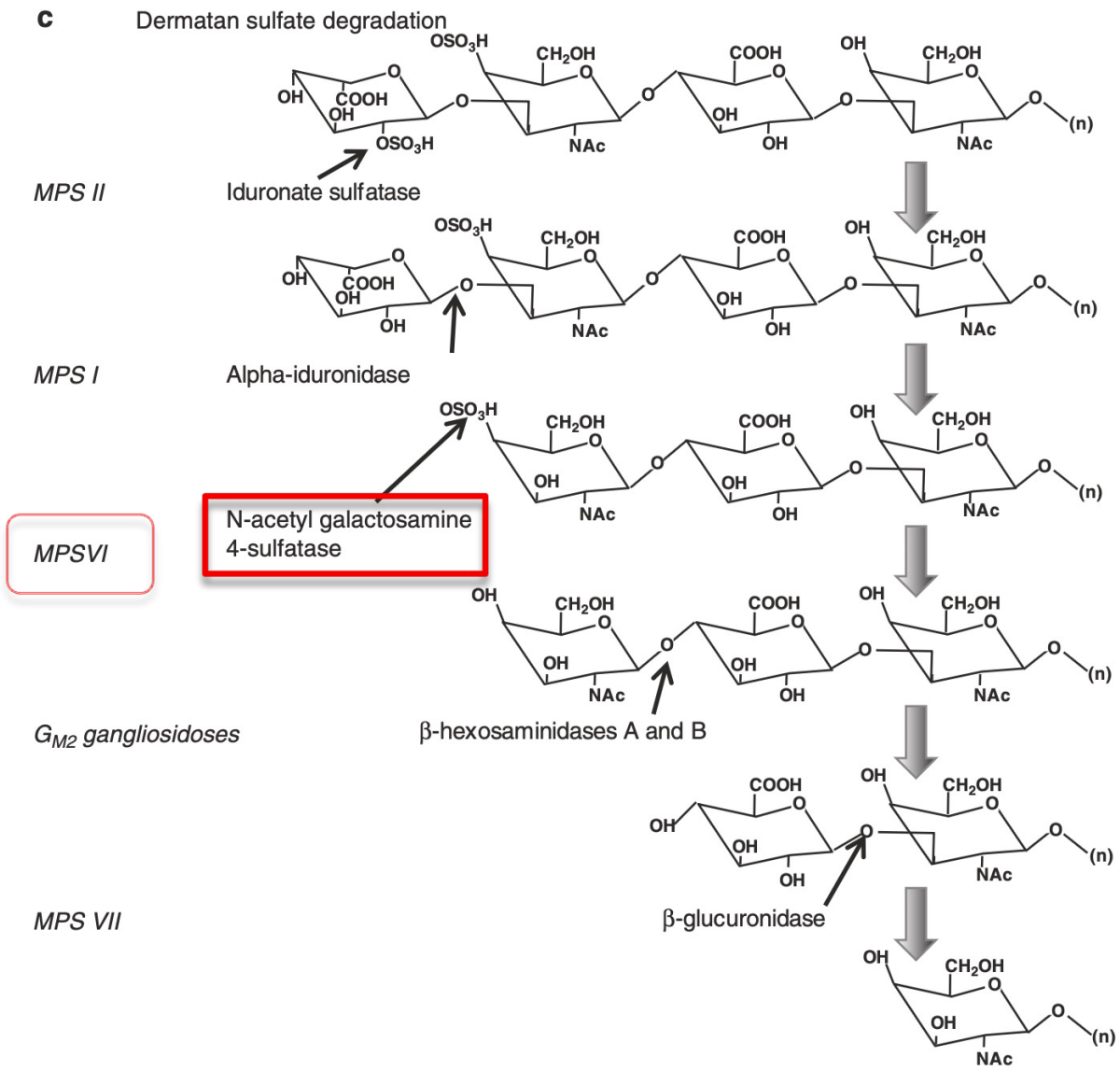
Patient A – Mucolysaccharidosis type VI

- 15 years
  - Normal intellectual development
  - Arthrodesis T10-T12
  - Height: +3 SD at 1 year of age, -1.5 SD at 15 years
  - Urinary MPS analysis because of spine abnormalities and dysmorphic features
  - Diagnosis of MPS VI confirmed by measurement of arylsulfatase B activity in leucocytes
- He is receiving enzyme replacement therapy every week

Mucopolysaccharidosis type VI

- Maroteaux-Lamy syndrome is a rare autosomal recessive IEM
- Due to arylsulphatase B deficiency (*ARSB* gene)
- Wide phenotypic spectrum (S Jones, F Wijburg, Inborn Metabolic Diseases – Diagnostic & Treatment, 2016)
  - Usual signs: short stature, dysostosis multiplex, degenerative joint disease
  - Frequent signs: cardiac valve disease, hearing loss, obstructive sleep apnoea, corneal, clouding, carpal tunnel disease , and inguinal or umbilical hernia
  - Possible signs: cervical cord compression, communicating hydrocephalus, optic nerve atrophy and blindness
- Arylsulphatase B (N-acetylgalactosamine 4-sulphatase): lysosomal enzyme, removes 4-sulfate groups from the non-reducing end of chondroitin 4-sulfate and dermatan sulphate, and thereby regulates their degradation

Mucopolysaccharidosis type VI



From Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases, 2022

Patient A – MPS VI

- **Most likely diagnosis**
  - **Mucopolysaccharidosis type VI** **8**
  - MPS I, MPS II or **MPS VI** **1**
  - Mucopolysaccharidosis type IV 6
  - MPS IVA 2
  - Mucopolysaccharidosis 2
- **Alternative diagnosis**
  - **MPS VI** or MPS VII **2**
  - MPS I, MPS II, **MPS VI** or MPS VII **2**
  - MPS I or MPS II 1
  - MPS IV 1
  - Oligosaccharidosis 1

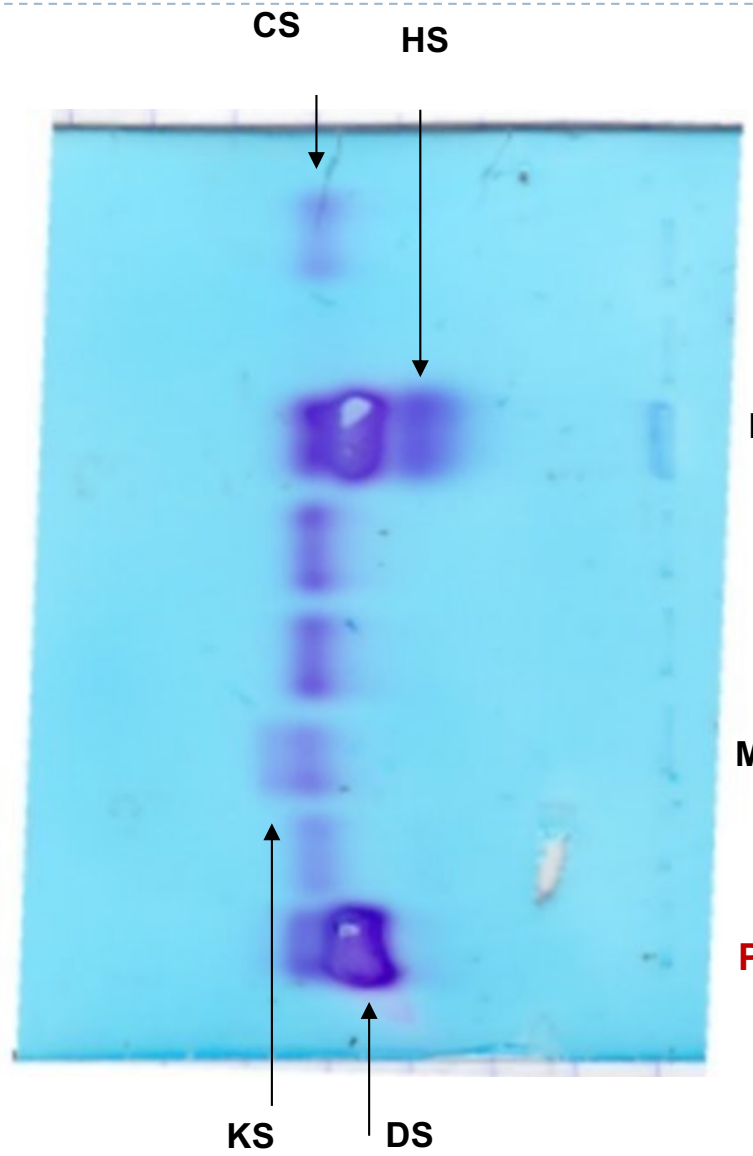
Patient A – MPS VI

- **GAGs quantification (17/19)**
  - **Elevated** **15**
  - No elevation 2
    (1 using DMB assay, 1 using harmine assay)

- **GAGs fractionation (17/19)**
  Increase in
  - **Dermatan sulphate** **13**
  - Chondroitin sulphate 9
  - Heparan sulphate 6
  - Keratan sulphate 1

- **Oligosaccharides (11/20)**
  - No significant abnormality 9
  - Slight increase of sialyl-oligosaccharides 2

Patient A – MPS VI



Hurler (MPS I)

Morquio (MPS IV)

Patient A (MPS VI)

KS: keratan sulphate
CS: chondroitin sulphate
DS: dermatan sulphate
HS: heparan sulphate

Patient A – MPS VI

- **GAGs quantification (17/19)**
  - **Elevated** **15**
  - No elevation 2
    (1 using DMB assay, 1 using harmine assay)

- **GAGs fractionation (17/19)**
  Increase in
  - **Dermatan sulphate** **13**
  - Chondroitin sulphate 9
  - Heparan sulphate 6
  - Keratan sulphate 1

- **Oligosaccharides (11/20)**
  - No significant abnormality 9
  - Slight increase of sialyl-oligosaccharides 2

Patient A : interim scoring

- **Analytical performance**
  - Increase in dermatan sulphate (score 2)
  - Increase in GAGs quantification (score 1)

- **Interpretation of results**
  - MPS VI as main diagnosis (score 2)
  - Other or wrong MPS type, diagnosis according to clinical signs (score 1)

Patient A : interim scoring

Similar urine samples have been distributed in 2006 and 2015: the overall performance was better the previous years

	2006	2015	2025
Analytical performance	84 %	87 %	79 %
Interpretative performance	82 %	89 %	74 %
Overall performance	84 %	88 %	76 %

Patient B : Hawkinsinuria

- 21-year-old female patient
- Feeding difficulties and failure to thrive in infancy
- Evaluation at the age of 12 months revealed mild developmental delay and metabolic acidosis
- Today well
- At the time of sample collection, the patient was pregnant

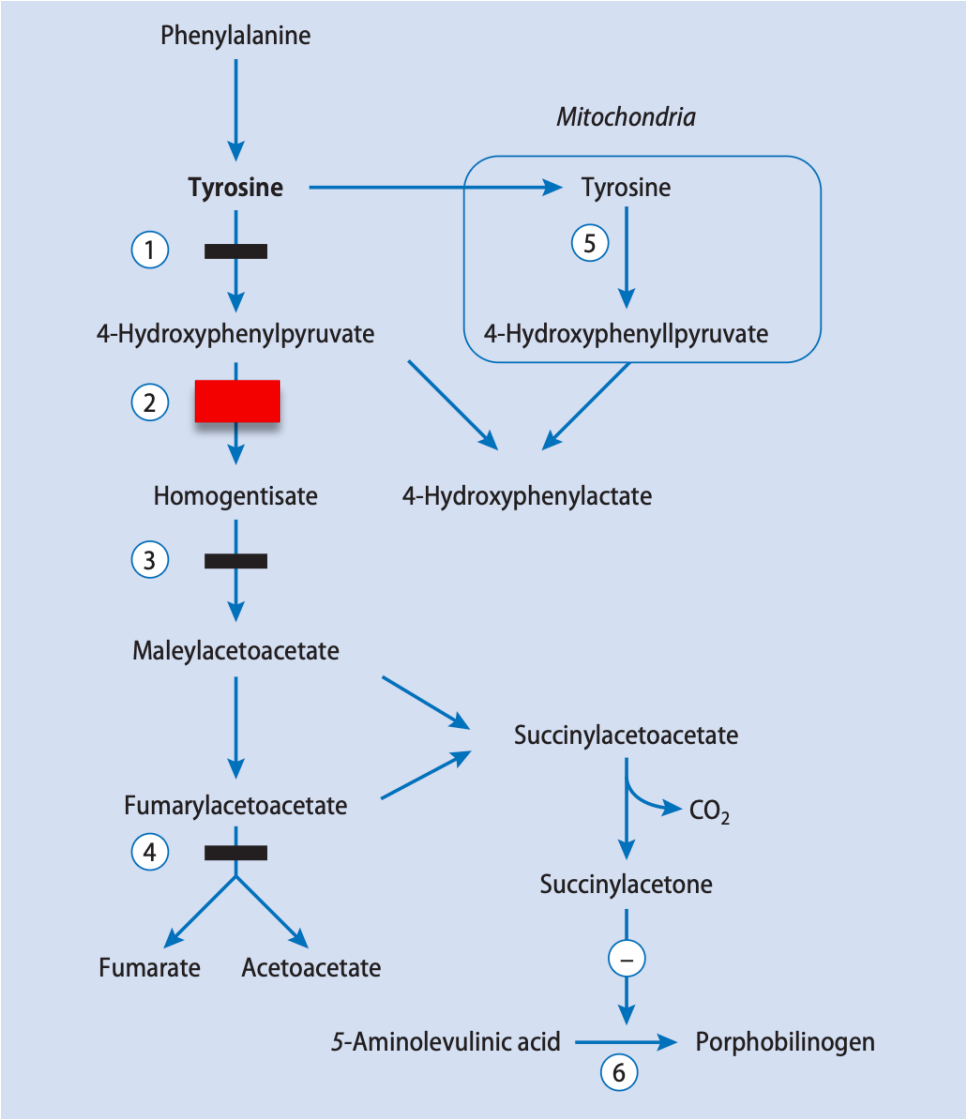
Hawkinsinuria

- Very rare autosomal dominant IEM, not completely understood
- Clinical presentation
  - Failure to thrive and acidosis, but not in all affected infants
  - No symptoms after the first year of life
- Biochemical diagnosis
  - Amino acids
    - Hawkinsin (IEC): eluted between urea and threonine
    - Slight increase of tyrosine (in infancy)
  - Organic acids, increase in
    - Hawkinsin (2-cystenyl-1, 4-dihydroxycyclohexenylacetate)
    - 4-hydroxycyclohexylacetate (appears after infancy)
    - 4-hydroxyphenylacetate, 4-hydroxyphenyllactate, 4-hydroxyphenylpyruvate (in infancy)
- Metabolic derangement
  - Mutations in the 4-hydroxyphenylpyruvate dioxygenase gene (*HPD*) result in an altered HPD enzyme. Complete deficiency of this enzyme leads to tyrosinemia type III
  - Hawkinsin and 4-hydroxycyclohexylacetate are thought to derive from incomplete conversion of 4-hydroxyphenylpyruvate to homogentisate

Hawkinsinuria

4-hydroxyphenylpyruvate dioxygenase deficiency

- Partial: Hawkinsinuria (AD)
- Complete: tyrosinemia type III (AR)



From Inborn Metabolic Diseases, Diagnosis & Treatment, 6th Edition

Patient B – Hawkinsinuria

- **Most likely diagnosis**
  - **Hawkinsinuria** **14**
  - Tyrosinemia type III 2
  - Iminoglycinuria 2
  - 3HMG-CoA lyase deficiency 1
- **Alternative diagnosis**
  - Hyperprolinemia type I 2
  - Serine biosynthesis disorder 1

Patient B – Hawkinsinuria

- **Organic acids (19/19)**

  Increase in

  - **4-hydroxycyclohexylacetic acid** (cis and/or trans) **16**

    (562 ; 660 mmol/mol creatinine ; n = 2)

  No increase in

  - 4-hydroxyphenylacetic acid 4
  - 4-hydroxyphenyllactic acid 3

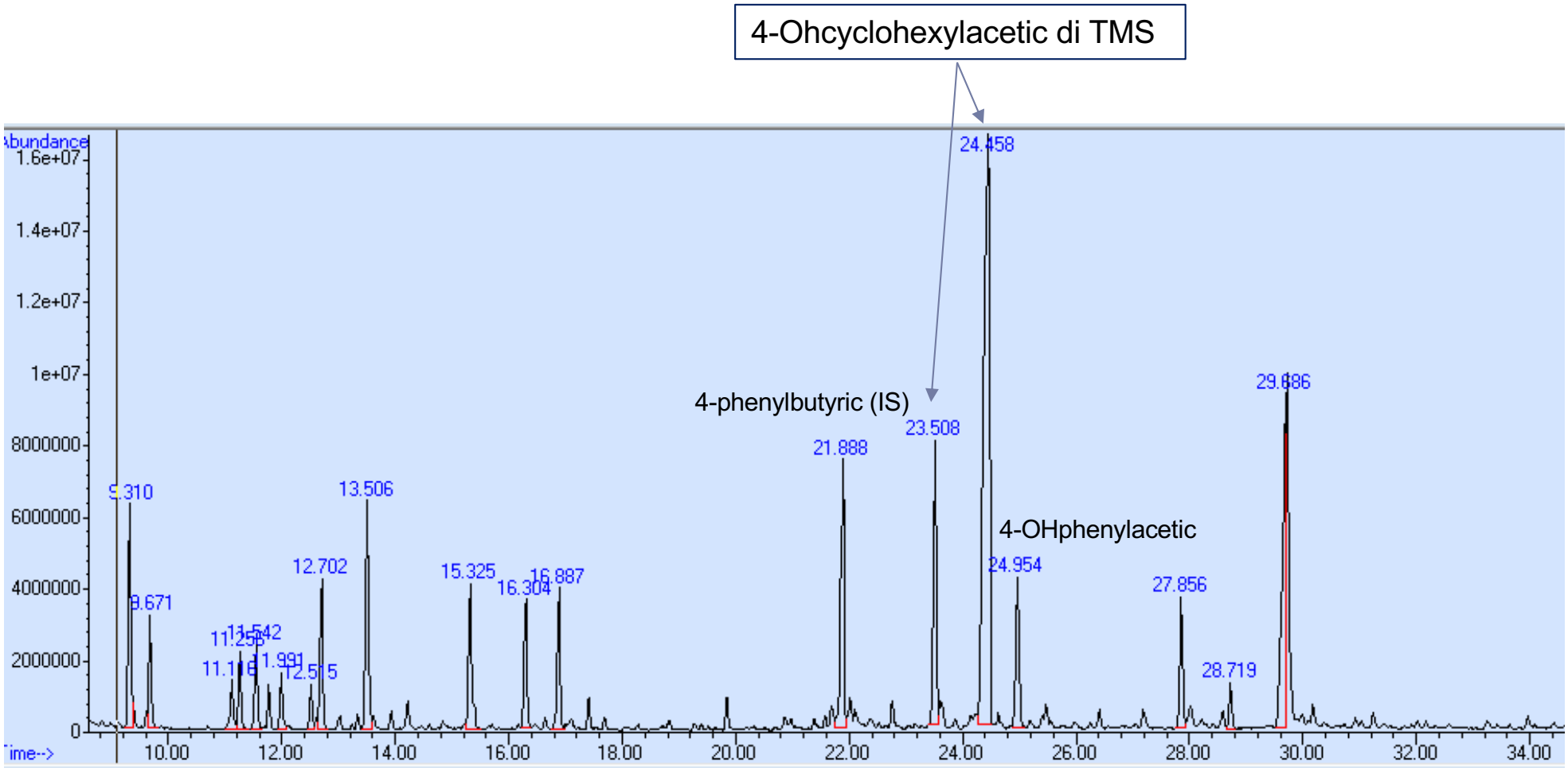
- **Amino acids (18/19)**

  Increase in

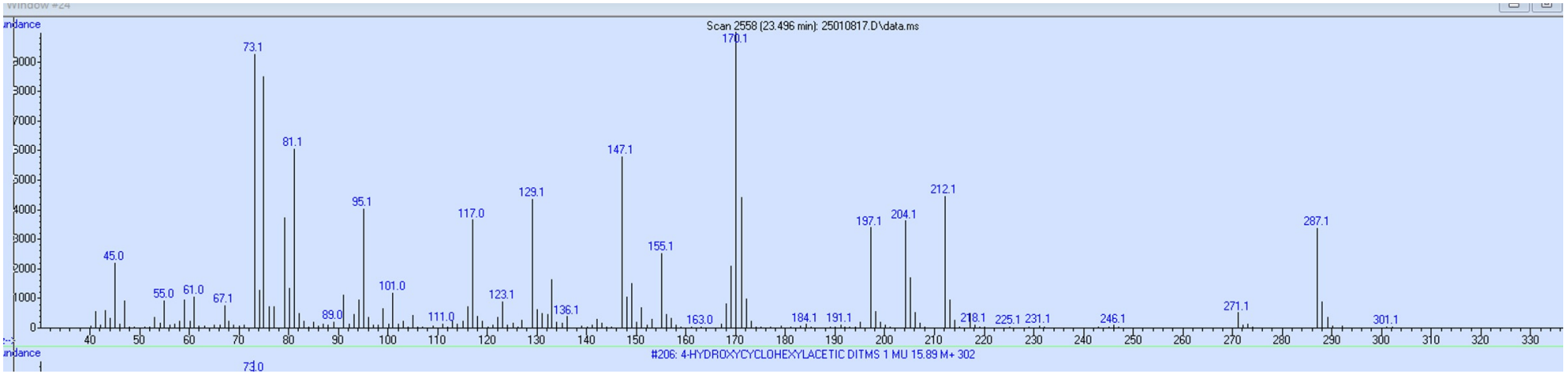
  - **Hawkinsin** **5**
  - Glycine 16
  - Proline 12

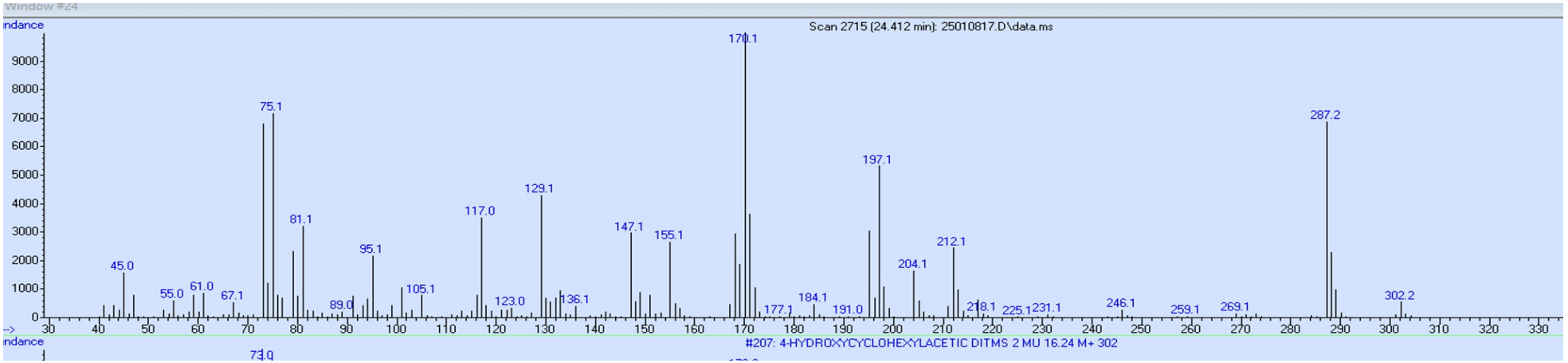
  No increase in tyrosine 3

4-hydroxycyclohexylacetic acid



4-hydroxycyclohexylacetic acid





Hawkinsin

2-cystenyl-1, 4-dihydroxycyclohexenylacetatic acid

We could not find its mass spectrum
and its elution time 😩

We need your help!

Patient B : interim scoring

- **Analytical performance**
  - Identification of 4-hydroxycyclohexylacetic acid (cis or trans) or Hawkinsin (2-cysteinyl-1,4-dihydroxycyclohexenylacetic acid) (score 2)
- **Interpretation of results**
  - Hawkinsinuria as main or alternative diagnosis (score 2)
  - Tyrosinemia type III (score 1)

Patient B : interim scoring

- Analytical performance 84 %
- Interpretative performance 79 %
- Overall performance 82 %

Patient C : MSUD

- 25-year-old adult female
- Revelation by digestive and neurological signs leading to a coma with seizures at 9 days of life, treated by phenobarbital, phenytoin and peritoneal dialysis
- The management has always been difficult since the patient has never accepted the low protein diet, leading to feeding difficulties
- A gastrostomy was placed at the age of 3 years
- The course of the disease was marked by numerous episodes of decompensation and the subsequent development of slight mental retardation
- She is waiting for liver transplant

Patient C : MSUD

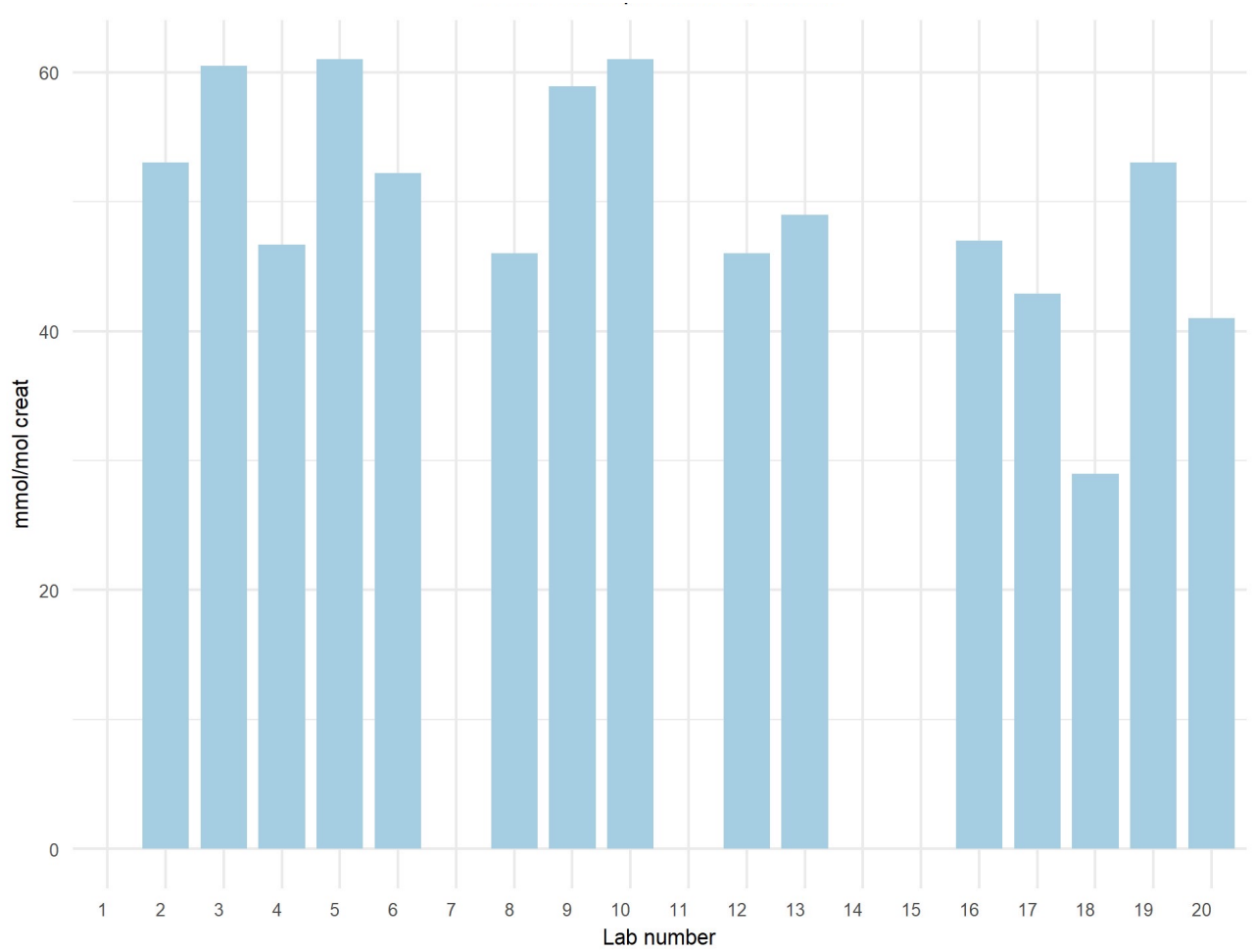
- **Most likely diagnosis**
  - **Maple Syrup Urine disease** **18**
    (leucinosis, branched-chain 2-ketoacid dehydrogenase complex def.)
  - Isovaleric aciduria 1
- **Alternative diagnosis**
  - E3 deficiency 2
    (dihydrolipoamide dehydrogenase deficiency)

Patient C – MSUD

- **Amino acids (18/19)**
  Increase in
  - **Leucine** **15**
    (median = 49 mmol/mol creatinine; range : 29.0 – 61.0 ; n = 15)
  - **Alloisoleucine** **14**
    (median = 7.2 mmol/mol creatinine; range : 6.0 – 11.0 ; n = 12)
  - **Isoleucine** **13**
    (median = 9 mmol/mol creatinine; range : 6.0 – 11.1 ; n = 15)
  - **Valine** **12**
    (median = 14.4 mmol/mol creatinine; range : 1.0 – 17.9 ; n = 12)

  Normal profile 2
  (1 IEC and 1 LC-MS/MS)

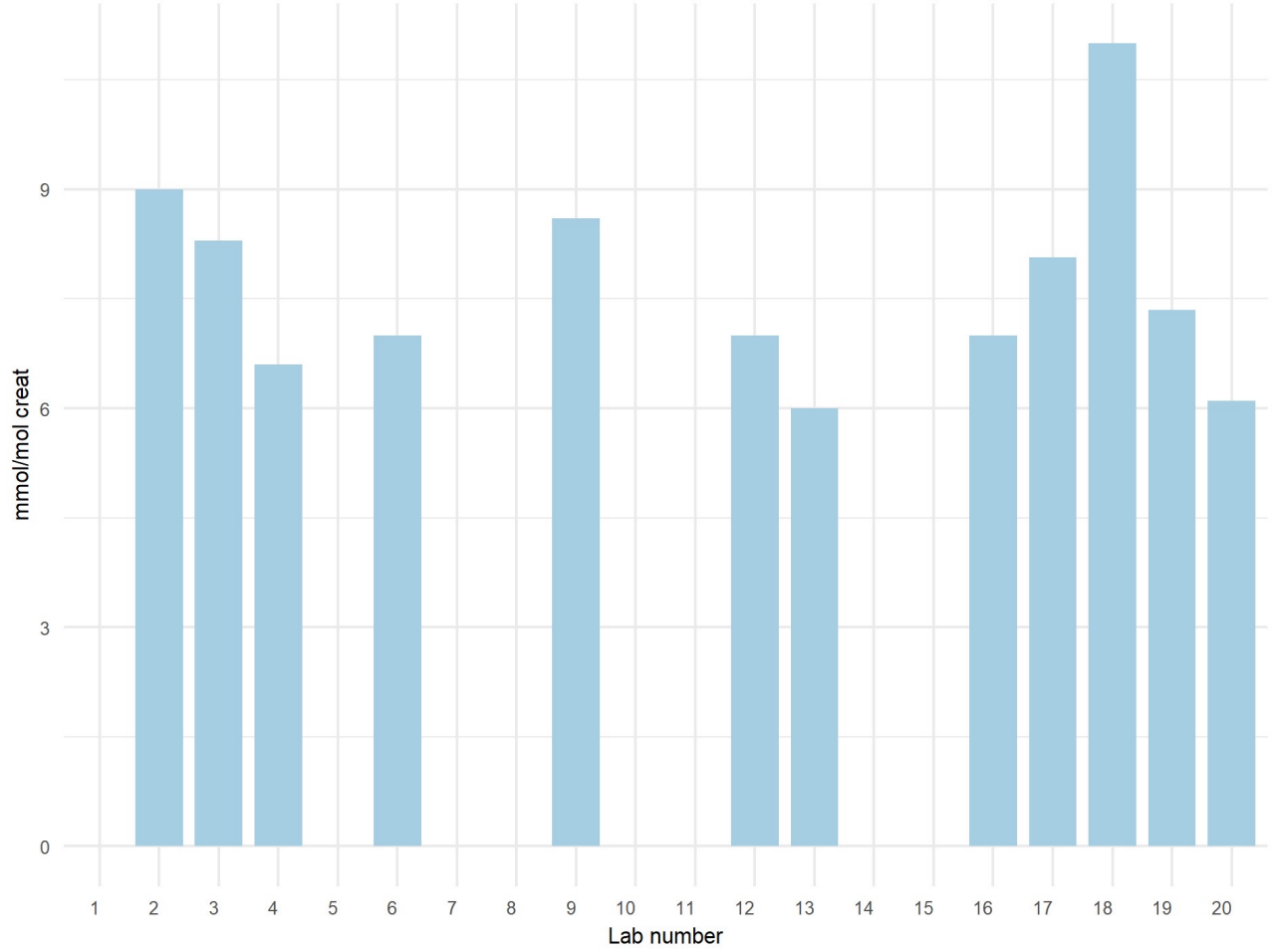
Patient C – Leucine mmol/mol creat



Sample C

Sample	C
Median	49
SD	8.48
CV = 17 %	

Patient C – Alloisoleucine mmol/mol creat

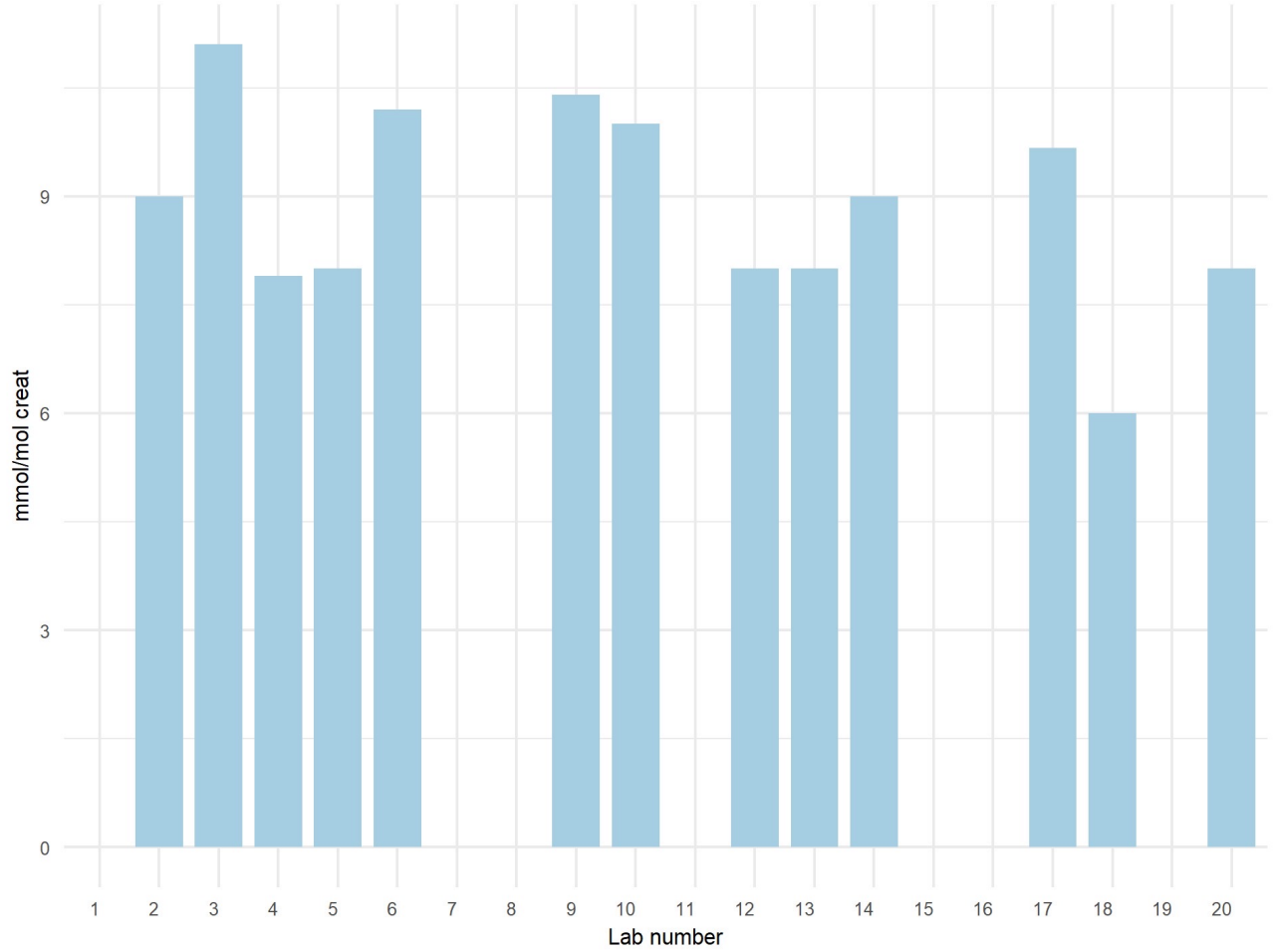


Sample C

Sample	C
Median	7.17
SD	1.36

CV = 19 %

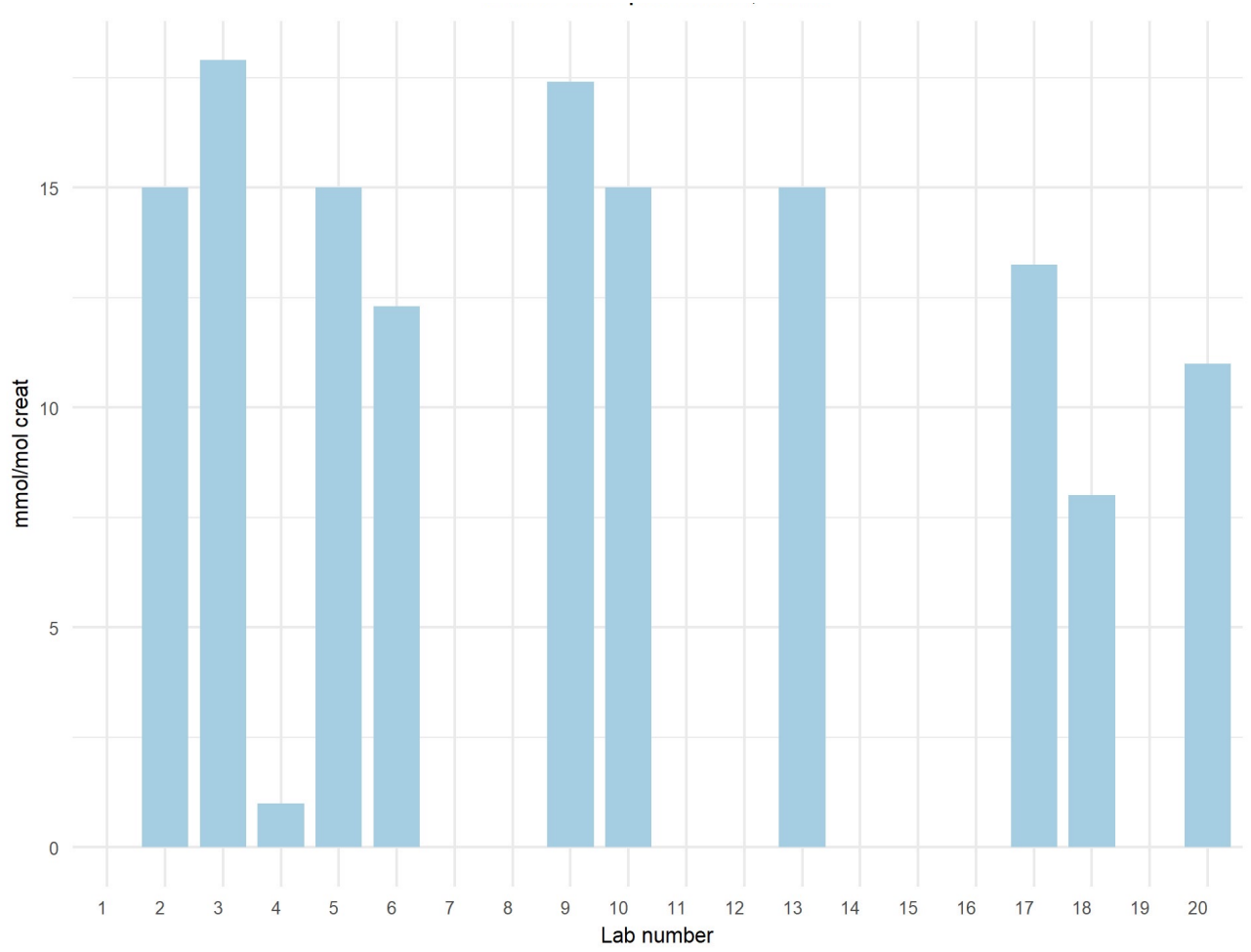
Patient C – Isoleucine mmol/mol creat



Sample C

Sample	C
Median	9
SD	1.34
CV = 15 %	

Patient C – Valine mmol/mol creat



Sample	C
Median	14.35
SD	4.41
CV = 31 %	

Patient C – MSUD

- **Organic acids (19/19)**

  Increase in

  - **2-ketoisocaproic acid** **13**

    (12 ; 38 ; 120 mmol/mol creatinine ; n = 3)
  - **2-keto-3-methylvaleric** **9**

    (28 ; 90 mmol/mol creatinine ; n = 2)
  - **2-ketoisovaleric acid** **6**

    (35 mmol/mol creatinine ; n = 1)
  - **2-hydroxyisovaleric acid** **16**

    (median = 96 mmol/mol creatinine; range : 76 – 140 ; n = 4)
  - **2-hydroxyisocaproic acid** **9**

    (4 ; 40 mmol/mol creatinine ; n = 2)
  - **2-hydroxy-3-methylvaleric acid** **9**
  - 3-hydroxyisovaleric acid (isolated) 1

Patient C : interim scoring

- **Analytical performance**
  - Elevation of at least one branched-chain amino acid (alloisoleucine, leucine, isoleucine, valine) (score 1)
  - Elevation of at least two branched-chain 2-keto or 2-hydroxyacids (2-ketoisocaproic, 2-ketoisovaleric, 2-keto-3-methylvaleric, 2-hydroxyisocaproic, 2-hydroxyisovaleric, 2-hydroxy-3-methylvaleric acids (score 1)

- **Interpretation of results**
  - MSUD as main diagnosis (score 2)

Patient C : interim scoring

Similar urine samples have been distributed in 2003 : the overall performance was slightly better the previous year

	2003	2025
Analytical performance	87 %	87 %
Interpretative performance	100 %	95 %
Overall performance	95 %	91 %

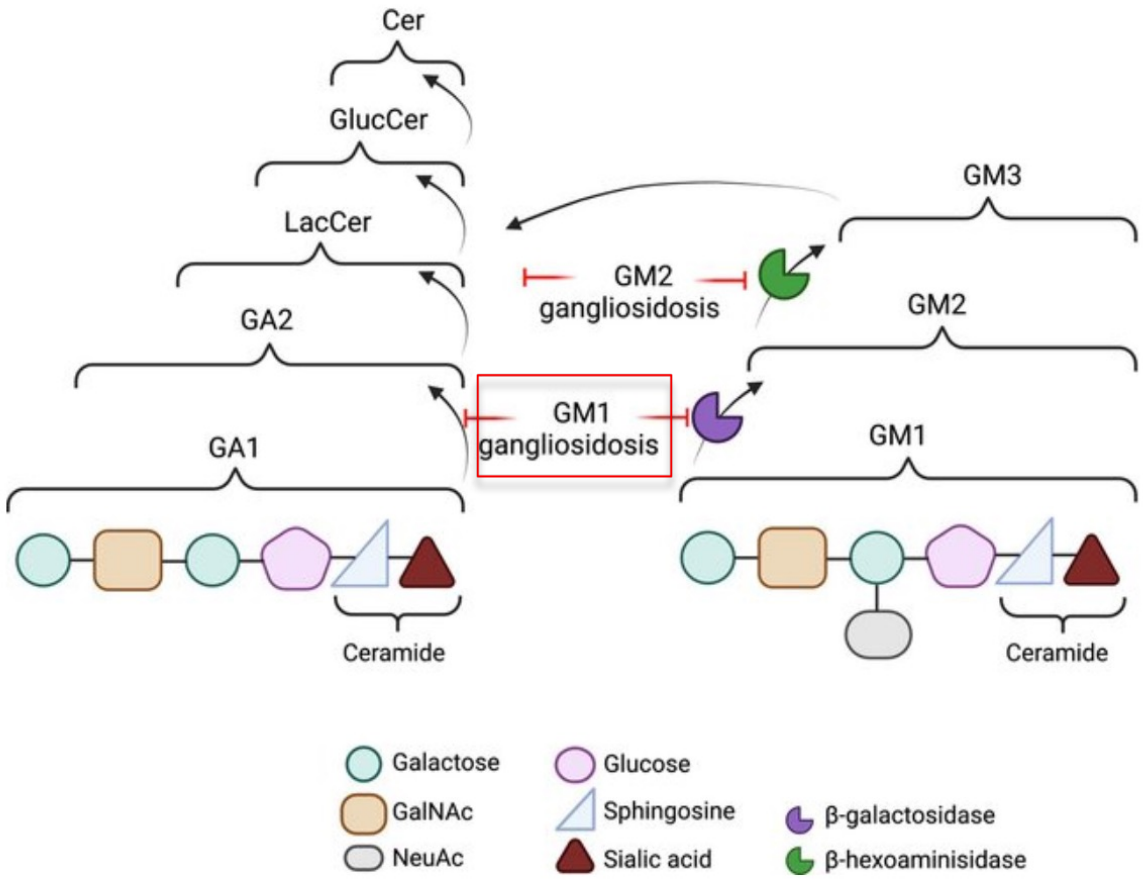
Patient D : GM1 gangliosidosis

- 9-year-old girl, born from unrelated parents
- She presented with mild intellectual disability, language disorder, hypotonia, facial dysmorphia, minor limb anomalies and walking difficulties
- The diagnosis was confirmed enzymatically and genetically at 9 years of age
  - Clinical exome: compound heterozygosity for 2 missense variants in *GLB1* gene
  - Beta-galactosidase activity in leukocytes: reduced by 99%
- Results compatible with the pathological phenotype of the patient and the diagnosis of GM1 gangliosidosis type II (late infantile/juvenile)

GM1 gangliosidosis

- Different clinical presentations
  - Severe **neonatal form**, with cardiomyopathy. Also a cause of *hydrops fetalis*
  - **Early infantile form** (type I) : the more frequent. Early developmental delay, and neurological disease, hepatosplenomegaly, coarse features, Hurler-like bone changes. Death by 1-2 years of age
  - **Late infantile variant** (type II) : slower course with loss of developmental milestones
  - **Adult form** (type III) : very rare, cerebellar dysfunction
- Due to a deficient activity of acid β-galactosidase (*GLB1* gene) : cleaves glycoconjugates containing a terminal β-galactosidic linkage and is necessary for the degradation of GM1 ganglioside, other galactose-containing glycosphingolipids or oligosaccharides, as well as keratan sulphate. Consequently, the more severe forms of the disease combine features of a neuronal lipidosis, a mucopolysaccharidosis and an oligosaccharidosis
- *GLB1* gene is also mutated in Morquio type B (MPS IV B), with a completely different phenotype, indicating different substrate binding sites, protein folding-relevant sites, or subdomains in the enzyme

GM1 gangliosidosis



Caption

Catabolism of GM1 and GM2 gangliosides and other sphingolipids. GM1 ganglioside is metabolized to GM2 ganglioside by β-galactosidase and, subsequently, GM2 is converted to GM3 by β-hexosaminidase and/or GM2 activator protein (not pictured). Deficiencies in these enzymes lead to accumulation in these sphingolipids leading to GM1 or GM2 based on enzyme defect. Abbreviations: GalNAc, N-acetylgalactosamine; NeuAc, N-acetylneuraminic acid; GM1, GM1 ganglioside; GM2, GM2 ganglioside; GM3, GM3 ganglioside; GA1, GA1 ganglioside; GA2, GA2 ganglioside; LacCer, lactosylceramide; GlucCer, glucosylceramide; Cer, ceramide.

Patient D : GM1 gangliosidosis

- **Most likely diagnosis**
  - **GM1 gangliosidosis** **13**
    (GM1 type I, II or III, beta-galactosidase deficiency)
  - Aspartylglucosaminuria 2
  - Hyperphenylalaninaemia 2
  - Mucopolysaccharidosis type I, II or VI 1
  - Creatine transporter deficiency 1
  - No abnormality detected 1
- **Alternative diagnosis**
  - MPS IVB (Morquio B) 4
  - Galactosialidosis 2
  - Another oligosaccharidosis 1
  - Hyperphenylalaninaemia 2
  - GAMT deficiency 1
  - Creatine transporter deficiency 1

Patient D : GM1 gangliosidosis

- **Oligosaccharides (18/20)**
  - **Profile evocative of GM1 gangliosidosis** **13**
  - Profile evocative of aspartylglucosaminuria 2
  - Normal profile 3
    (2 labs: TLC-1D-orcinol, 1 lab: MS/MS no separation)
- **GAGs fractionation (10/20)**
  - Normal profile 7
  - Slight increase in keratan sulphate 2
  - Increase in dermatan sulphate, traces heparan sulphate 1
- **GAGs quantification (14/20)**
  - Normal quantification 14

Patient D : interim scoring

- **Analytical performance**
  - Oligosaccharide profile evocative of GM1 gangliosidosis (score 2)
  - Oligosaccharide profile evocative of aspartylglucosaminuria (score 1)

- **Interpretation of results**
  - GM1 gangliosidosis as main diagnosis (score 2)
  - Aspartylglucosaminuria or other lysosomal storage disorder(s) (score 1)

Patient D : interim scoring

Similar urine samples have been distributed in 2015 and 2017: the overall performance was better the previous years

	2015	2017	2025
Analytical performance	78 %	84 %	70 %
Interpretative performance	80 %	92 %	72 %
Overall performance	79 %	88 %	71 %

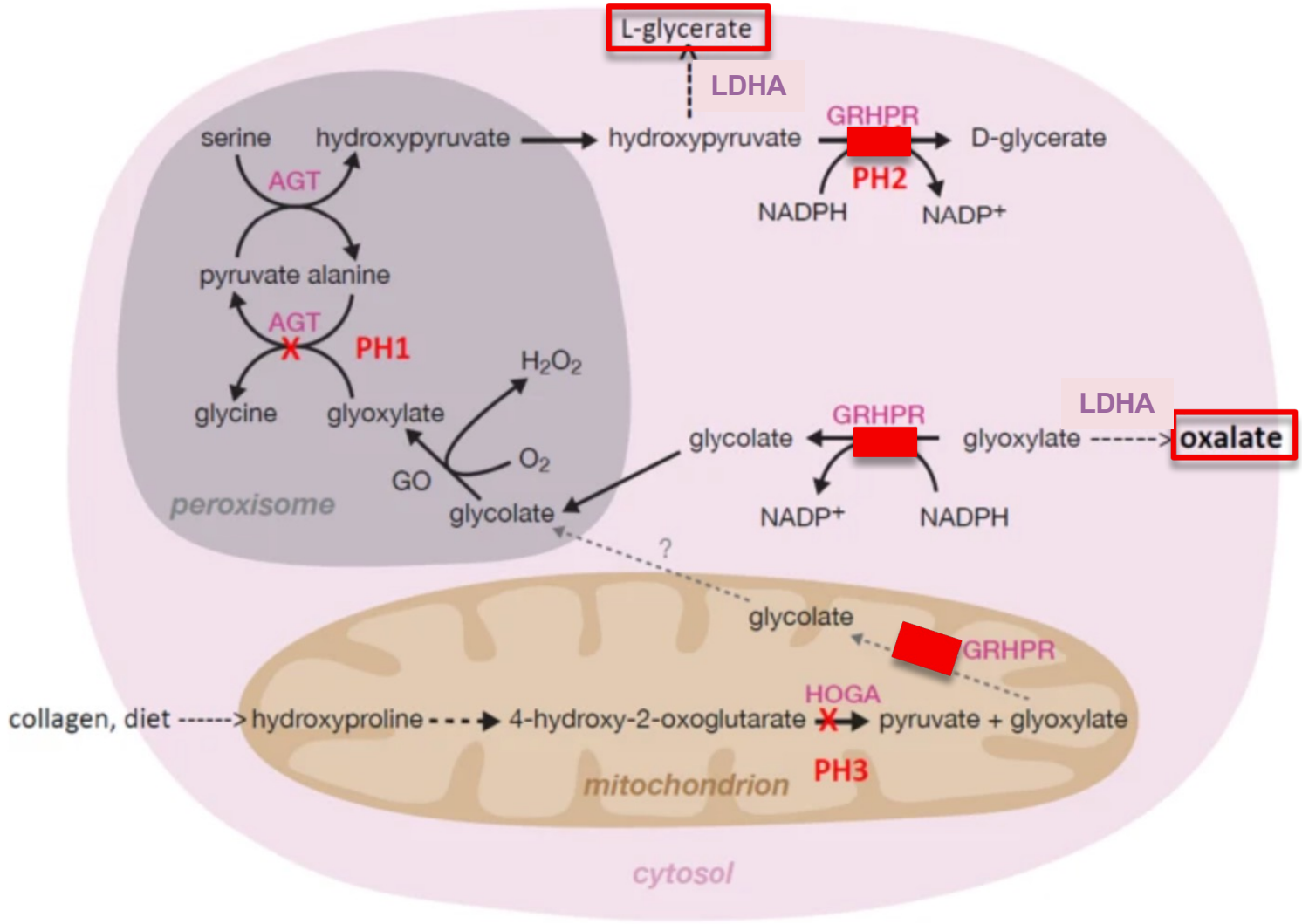
Patient E : Hyperoxaluria type II

- 6-year-old boy
- Antenatal bilateral pyelectasis
- At birth: hyperechogenic kidneys and nephrocalcinosis
- 8 months: first episode of haematuria
- 13 months: Oxalic acid = 445 mmol/mol creat (controls: <120), normal excretion of glycolic acid
- 15 months:
  - Gene panel: compound heterozygosity for 2 variants in *GRHPR* gene
  - Organic acids: high increase in glyceric acid
  - Start treatment: potassium citrate and hyperhydration
- 4 years: introduction of stiripentol, an antiepileptic drug which has been shown to inhibit neuronal lactate dehydrogenase and to reduce hepatic oxalate production
- Today well under treatment

Hyperoxaluria type II

- Primary hyperoxaluria type II: rare autosomal recessive disorder
- Clinical course comparable but generally less severe as compared to primary hyperoxaluria type I
  - Nephrocalcinosis, nephrolithiasis, renal colic
  - Chronic kidney disease (CKD) and end stage renal failure (ESRF) occur less frequently, have not been reported in childhood but affects about 50% of adult patients
- Due to a defect in the glyoxylate reductase / hydroxypyruvate reductase (GR/HPR) activity (*GRHPR* gene)
- A single nucleotide deletion, c.103delG, accounts for 31–35% of mutant alleles in hyperoxaluria type II, mainly restricted to those of Caucasian descent
- Lack of GR/HPR leads to an accumulation of glyoxylate and hydroxypyruvate, which are both metabolized by lactate dehydrogenase A to oxalate and L-glycerate, respectively

Hyperoxaluria type II



From PMID: 35695965

Patient E : Hyperoxaluria type II

- **Most likely diagnosis**
  - **Hyperoxaluria type II** **19**
    (L-glyceric aciduria, glyoxalate/hydroxypyruvate reductase def.)
  - Hyperoxaluria type I 1

- Alternative diagnosis
  - D-glyceric aciduria 4
  - Double compound hyperoxaluria type II & III 1

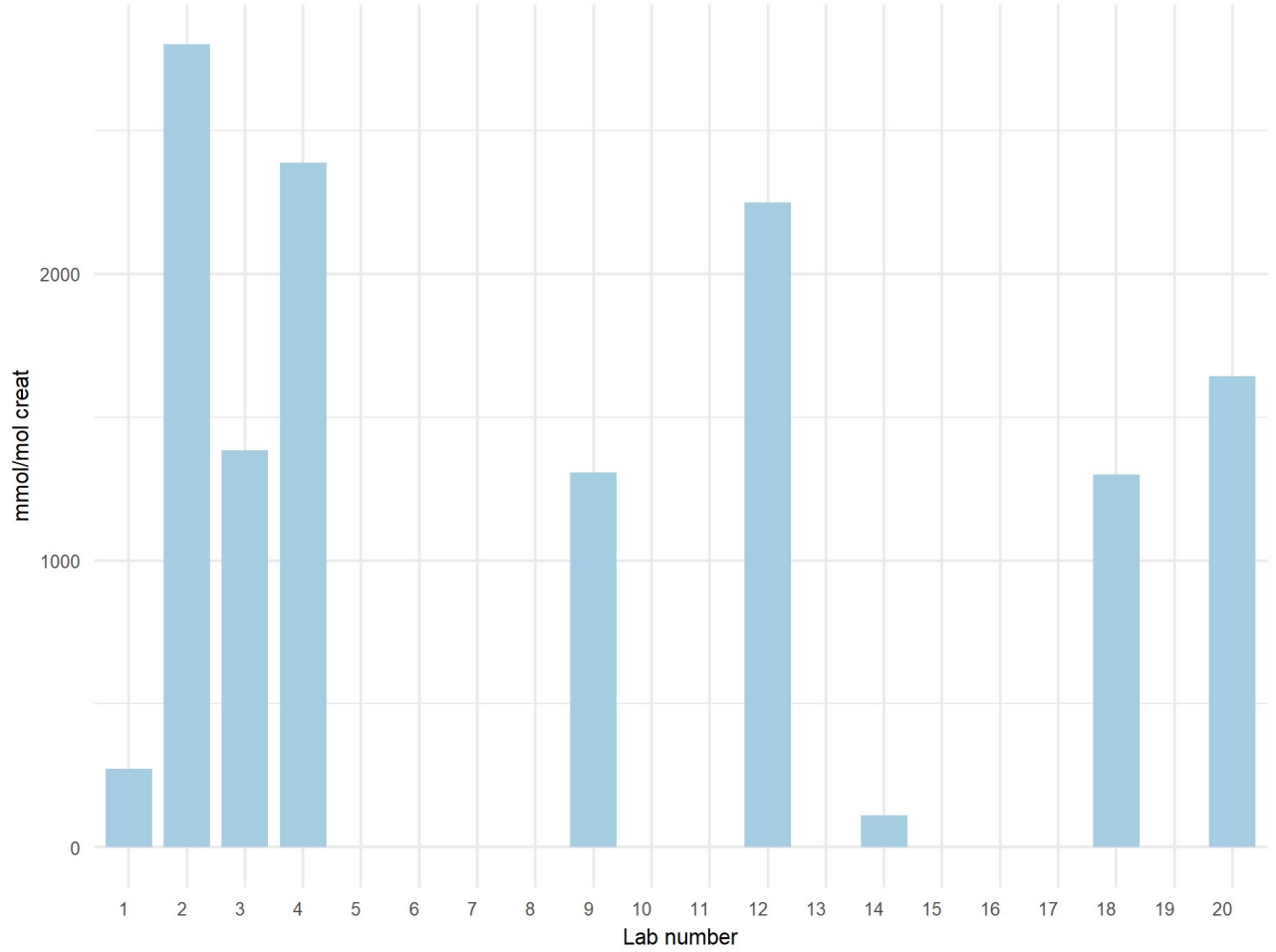
Patient E : Hyperoxaluria type II

- **Organic acids (20/20)**
  Increase in
  - **Glyceric acid** **20**
    (median = 1383 mmol/mol creatinine; range : 110 – 2800 ; n = 9)
  - **Oxalic acid** **9**
    (99 ; 105 ; 109.5; 156 ; 800 mmol/mol creatinine : n = 5)

  No increase in
  - Glycolic acid 9
    (median = 42.5 mmol/mol creatinine; range : 28 – 169 ; n = 4)
  - Oxalic acid 4

- Specific measurement of oxalic acid by Scientific Advisors
  - By GC/MC SID = 277 mmol/mol creat, controls: 17 – 100

Patient E : Glyceric acid



Sample E

Sample	E
Median	1383
SD	855.53

Patient E : Hyperoxaluria type II

- **Organic acids (20/20)**

  Increase in

  - **Glyceric acid** **20**

    (median = 1383 mmol/mol creatinine; range : 110 – 2800 ; n = 9)
  - **Oxalic acid** **9**

    (99 ; 105 ; 109.5; 156 ; 800 mmol/mol creatinine : n = 5)

  No increase in

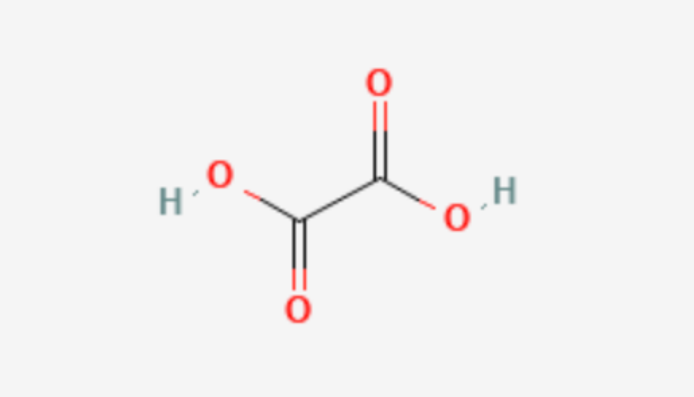
  - Glycolic acid 9

    (median = 42.5 mmol/mol creatinine; range : 28 – 169 ; n = 4)
  - Oxalic acid 4

- Specific measurement of oxalic acid by Scientific Advisors
  - By GC/MC SID = 277 mmol/mol creat, controls: 17 – 100

Patient E : Oxalic acid

- Oxalic acid is a polar compound that is poorly extracted by organic solvents such as ethylacetate
- In urine, it occurs mainly as calcium oxalate and precipitates at alkaline pH
- For an accurate measurement of oxalic acid
  - Urines must be acidified prior to extraction to solubilize oxalic acid
  - A stable isotope of oxalic acid must be added as internal standard, to normalize experimental variables such as extraction
- This probably explains why lot of labs did not report an increase in oxalic using a standard organic acid analysis



Patient E : interim scoring

- **Analytical performance**
  - Increase in glyceric acid (score 1)
  - Increase in oxalic acid (score 1)

- **Interpretation of results**
  - Hyperoxaluria type II (score 2)
  - Primary hyperoxaluria type I (score 1)

Patient E : interim scoring

- Analytical performance 72 %
- Interpretative performance 98 %
- Overall performance 85 %

Patient F : Glutaric aciduria type I

- 57-year-old woman, born from consanguineous parents
- Has been complaining for many years of fatigue, dyspnea, balance problems
- And recently of reduced walking perimeter, and cognitive problems
- Abnormal brain MRI and electroneuromyogram (no details provided)
- DBS acylcarnitine profile, performed as part of a broader etiological assessment, revealed an increase in glutarylcarnitine
- Urinary organic acids: isolated increase in 3-hydroxyglutaric acid
- Diagnosis of glutaric aciduria type I, low excretor, confirmed by mutation analysis *GCDH* gene (homozygosity for a deleterious variant)

Patient F : glutaric aciduria type I

- **Most likely diagnosis**
  - **Glutaric aciduria type I** **18**
    (GAI low excretor, glutaryl-CoA dehydrogenase def.)
  - Pompe disease 2

- **Alternative diagnosis**
  - **Glutaric aciduria type I, late onset** **1**
  - Glutaric aciduria type II 2
  - CPT I, SCHAD def. 1

Patient F : Glutaric aciduria type I

- **Organic acids (20/20)**

  Increase in

  - **3-hydroxyglutaric acid** **20**

    (median = 24.2 mmol/mol creatinine; range : 7.06 – 41 ; n=14)

  - Glutaric acid **1**

    (no quantification)

  No increase in

  - Glutaric acid 13

    (median = 2.3 mmol/mol creatinine; range : 0.5 – 14.0 ; n=11)

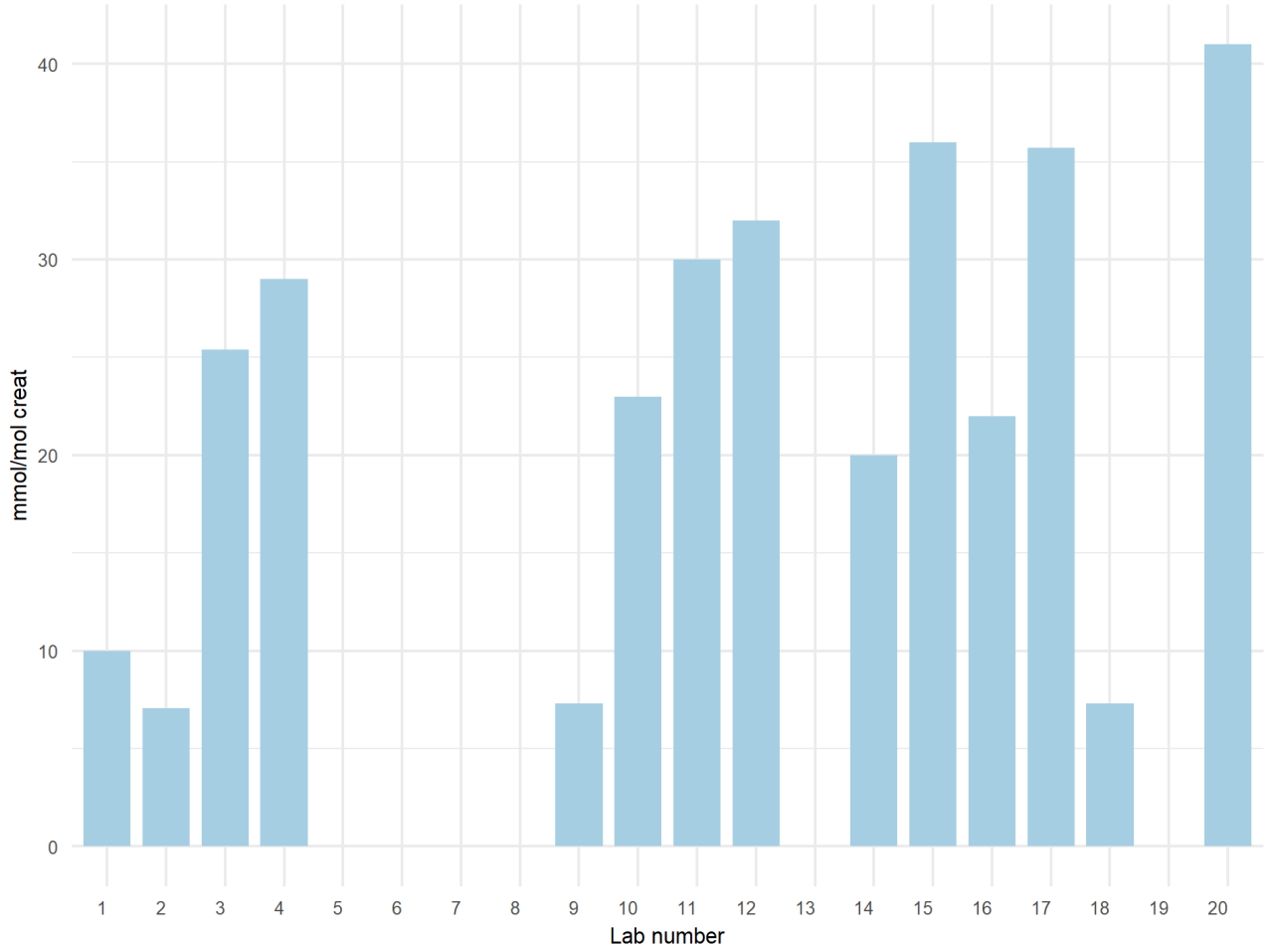
- **Acylcarnitines (11/20)**

  Increase in

  - **Glutarylcarnitine** **11**

    (median = 9 mmol/mol creatinine; range : 1.7 – 32 ; n=9)

Patient F : 3-hydroxyglutaric acid

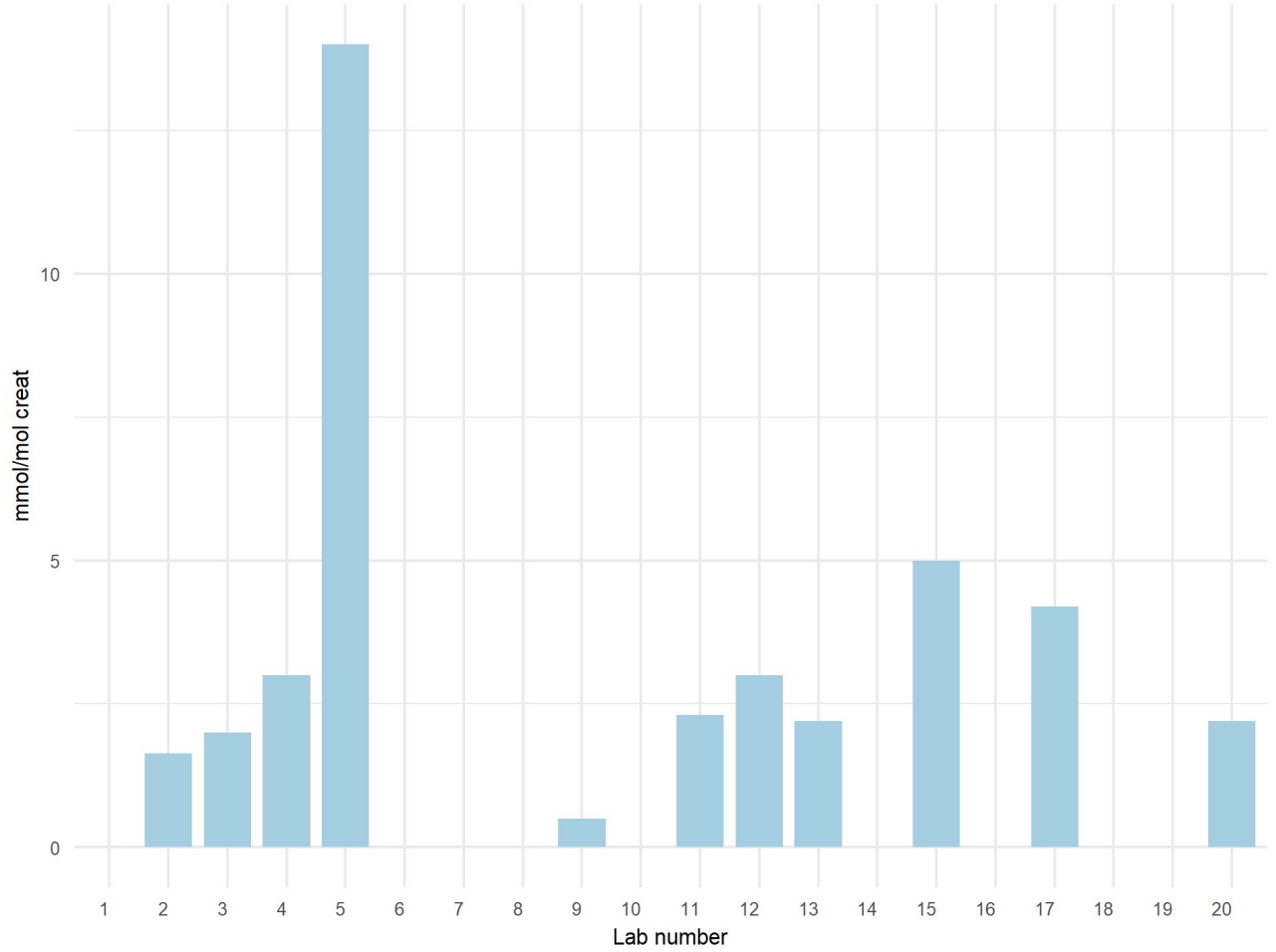


Sample F

Sample	F
Median	24.2
SD	11.18

CV = 46 %

Patient F : glutaric acid



Sample	F
Median	2.3
SD	3.48

3-hydroxyglutarate excretion

- **Glutaric aciduria type I, low excretors of glutaric acid** (Busquets, Merinero et al, Pediatric Research 2000;48: 315–322): results from 17 patients

mmol/mol creat	Range	Median	Mean	Controls
3-hydroxyglutaric acid	18 - 571	**101**	160	2 – 14
Glutaric acid	2 - 84	10	21	2 – 10

- **Ketosis**: 3-hydroxyglutarate < 10 mmol/mol creat

3-hydroxyglutarate excretion

- **SCHAD deficiency** (*Vilarinho et al Mol Genet Metab 2012;106:277, **Martins et al, JIMD 2011;34:835, ***CBPE)

mmol/mol creat	1*	2**	3**	4**	5**	6***
C4OH µmol/L	1.22			0.5-0.6	0.7	0.7-1.6
3OHGlutaric	113	12 - 45	22 - 45	33 - 114	55	13 - 31

- **CPT I deficiency** (Korman et al, Mol Genet Metab 2005;86:337)

mmol/mol creat	Patient 1	Patient 2	Patient 3	Controls
Age	14 months	3 years	23 months	
3-hydroxyglutarate	9.8	24.7	14.7	0.88 – 4.5
Glutarate	3.4	1.2	2.3	0.5 – 10.8
Dicarboxylic acids	C6 – C12	C6 – C12	C6 – C12	

Patient F : Glutaric aciduria type I

- **Organic acids (20/20)**

  Increase in

  - **3-hydroxyglutaric acid** **18**

    (median = 24.2 mmol/mol creatinine; range : 7.06 – 41 ; n=14)
  - Glutaric acid 1

    (no quantification)

  No increase in

  - Glutaric acid 13

    (median = 2.3 mmol/mol creatinine; range : 0.5 – 14.0 ; n=11)

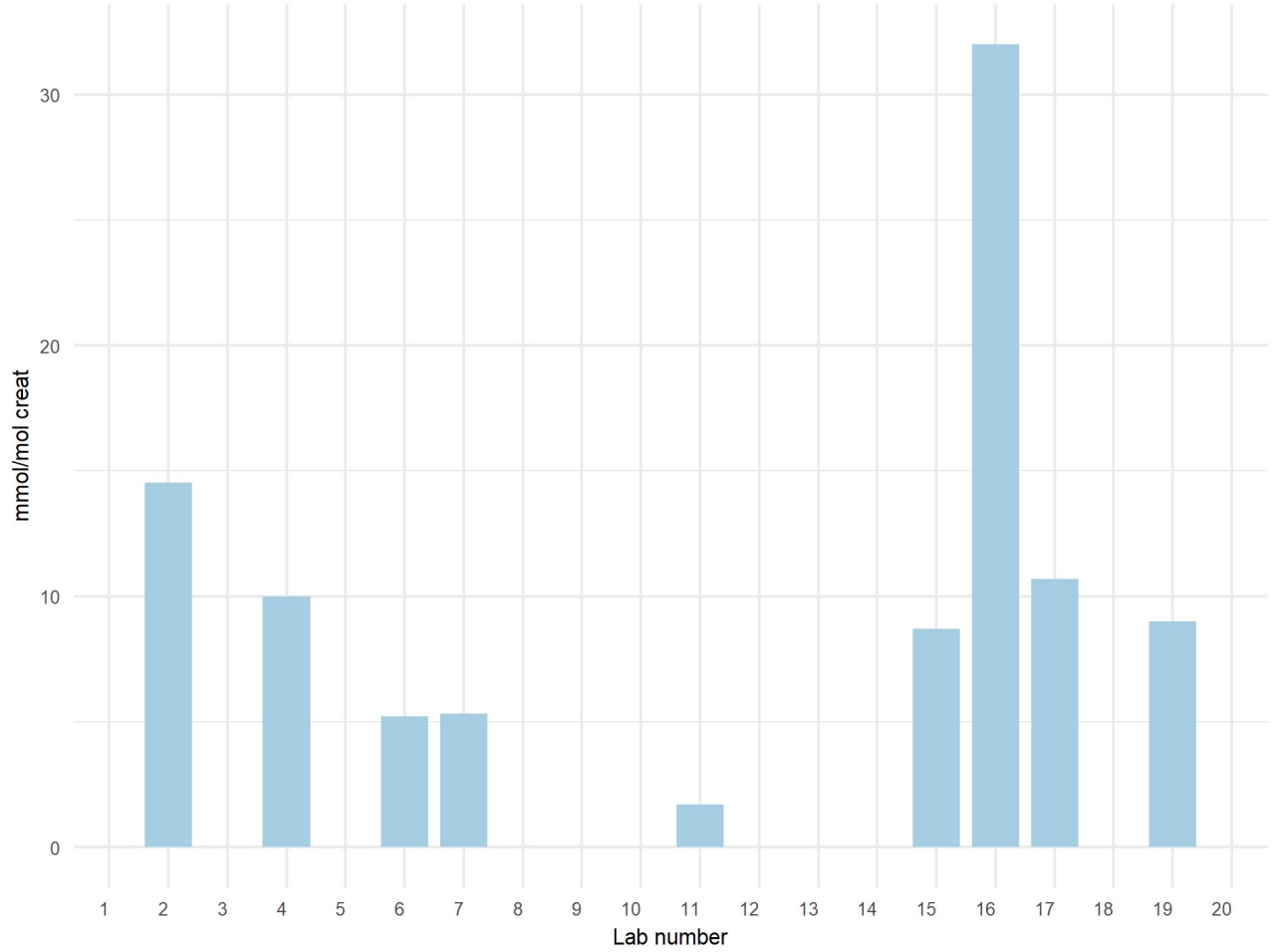
- **Acylcarnitines (11/20)**

  Increase in

  - **Glutarylcarnitine** **11**

    (median = 9 mmol/mol creatinine; range : 1.7 – 32 ; n=9)

Patient F : glutarylcarnitine



Sample F

Sample	F
Median	9
SD	8.27

Urinary glutarylcarnitine

- It may seem unusual to perform urinary acylcarnitines
- In 2005, Tortorelli et al. investigated
  - 14 GA-I patients: 5 of them had a normal glutaric acid excretion and 9 a normal plasma acylcarnitine profile
  - 54 subjects with glutaric aciduria secondary to other causes (16-7509 mmol/mol creatinine; reference range: <15) but a normal excretion of 3-hydroxyglutaric acid
- They demonstrated that the excretion of glutarylcarnitine was
  - Significantly elevated in the 14 GA-1 patients: 14-522 mmol/mol creatinine; reference range: <5.2
  - Normal in the 54 "control" subjects with glutaric aciduria Ilary to other causes
- They concluded: "Urinary excretion of **glutarylcarnitine is a specific biochemical marker of glutaric aciduria type I** which could be particularly useful in the work up of patients with suggestive clinical manifestations but without glutaric aciduria and with normal plasma acylcarnitine profiles"

Tortorelli S, Hahn SH, Cowan TM, Brewster TG, Rinaldo P, Matern D. The urinary excretion of glutarylcarnitine is an informative tool in the biochemical diagnosis of glutaric acidemia type I. Mol Genet Metab. 2005;84(2):137-43

Patient F : interim scoring

- Analytical performance
  - Increase in 3-hydroxyglutaric acid (score 1)
  - Increase in glutarylcarnitine (score 1)

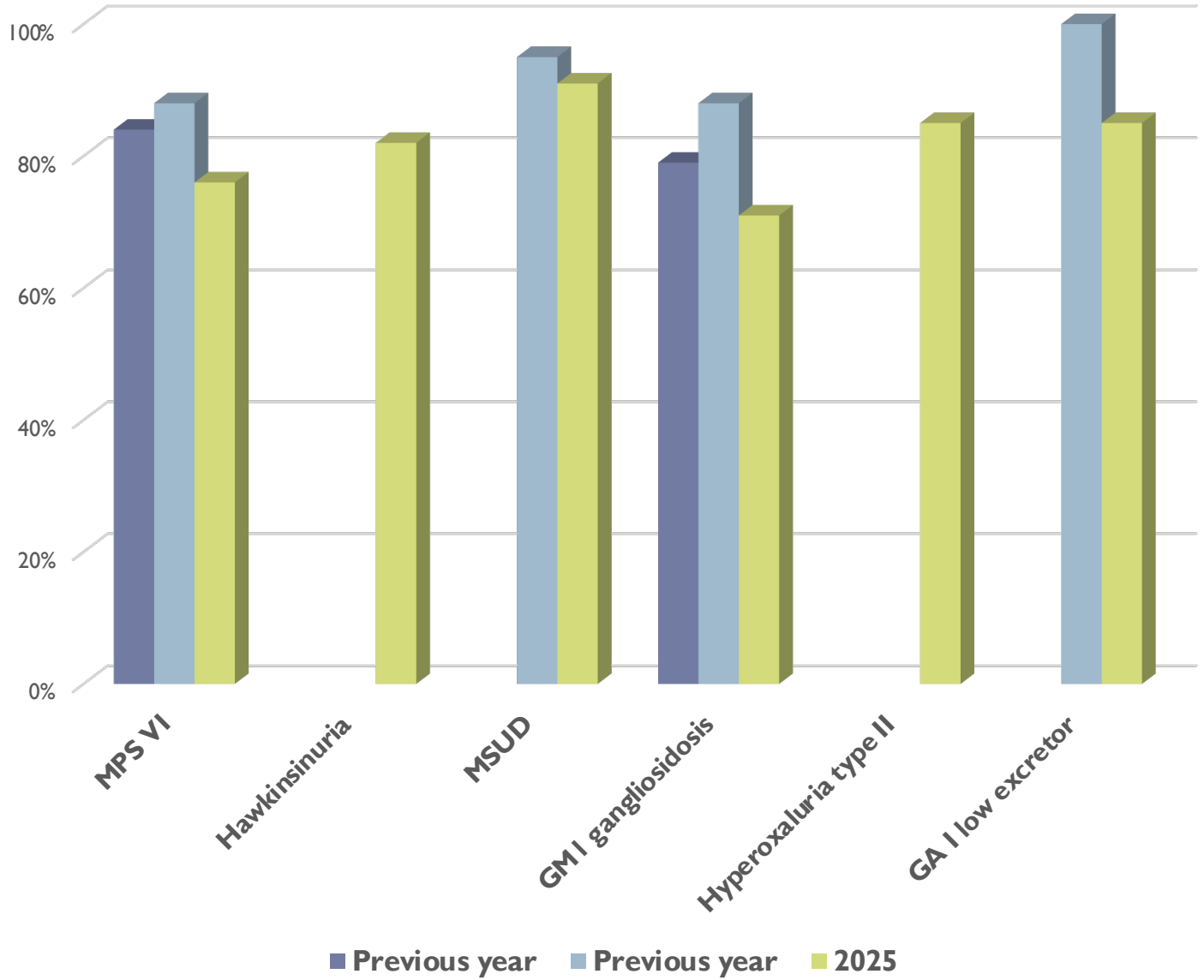
- Interpretation of results
  - Glutaric aciduria type I as main diagnosis (score 2)

Patient F : interim scoring

A similar urine sample (low excretor) has been distributed in 2018: the overall performance was better the previous year

	2018	2025
Analytical performance	100 %	78 %
Interpretative performance	100 %	92 %
Overall performance	100 %	85 %

Improvement DPT France



DPT France 2026

- Same "rules" than in 2025
  - 2 surveys of 3 urines, including "normal" patients
  - Samples distributed by CSCQ or MCA February 4th
  - Start of first survey March 17th and second survey June 1st (to be confirmed)
  - Results sent within 3 weeks
  - Reporting on CSCQ website
  - Scoring by 2 scheme organizers
- Satisfactory performance
  - Score >70% (score ≥17 / 24)
  - No critical error

DPT France meeting in 2026

- During SSIEM meeting in Helsinki
- Tuesday August 25th
- 9:00 – 10:30
- Further details will follow

Conclusion

- Questions
- Remarks
- Other …

We still need urine samples

Minimum : 200 ml

If possible : 1000 ml (common sample)

You will get a 20% discount the following year !

Thank you in advance !