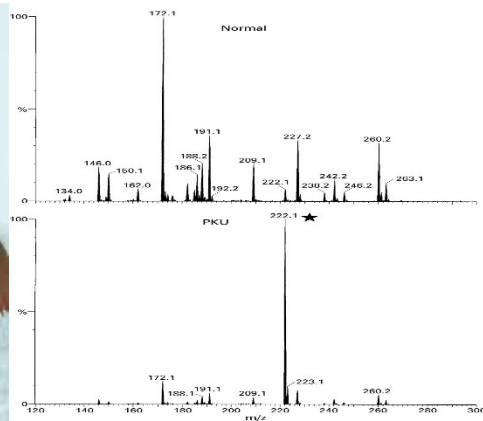
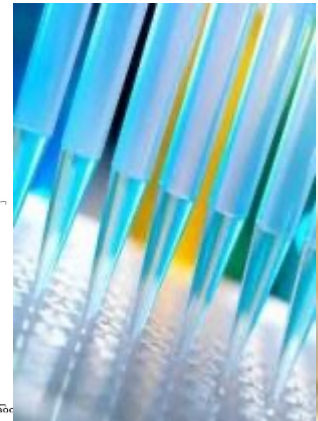
Biochemical Testing in IEM

François BOEMER

MANAMA Training, Clinical Genetics
Inborn Errors of Metabolism

06/12/2022





Biochemical Genetics: definition

- Inborn errors of metabolism include a broad spectrum of defects of various gene products that affect intermediary metabolism in the body, resulting in clinical disease.

- Biochemical Genetics aims
  - to study the **biochemical** and molecular mechanisms of these inherited disorders, systematically summarizing the disease phenotype and its natural history
  - to provide a diagnostic rationale, and to orientate treatment strategy.

- Biochemical Genetics is then a combination of biochemistry and genetics.

Screening vs 'Diagnostics'

- **1. Metabolic Workup / Follow-up**
  - Patients: mainly pediatric population, adults
  - Sample: Plasma/Serum, Urine, CSF…
  - Wide panel of disorders
  - Low-througput testing

- **2. Newborn Screening**
  - Patients: neonates
  - Sample: DBS
  - Specific program with limited number of diseases
  - Polpulation testing

1. Metabolic Workup

General testing

- Acid-Base imbalance, hyperammonemia, hypoglycemia
- Hematological disturbance (pancytopenia, anemia, …)
- Liver markers
- Kidney…

Specific biochemical genetics tests

- Amino acids (IEC, LCMS)
- Urinary organic acids (GC-MS)
- Acylcarnitines (LCMS)
- VLCFA (GC-MS)
- CDG (IEF, HPLC-UV)
- MPS (GAGs electrophoresis, quantification)…

Confirmation assays

- Enzymatic testing on cultured cells
- Molecular sequencing

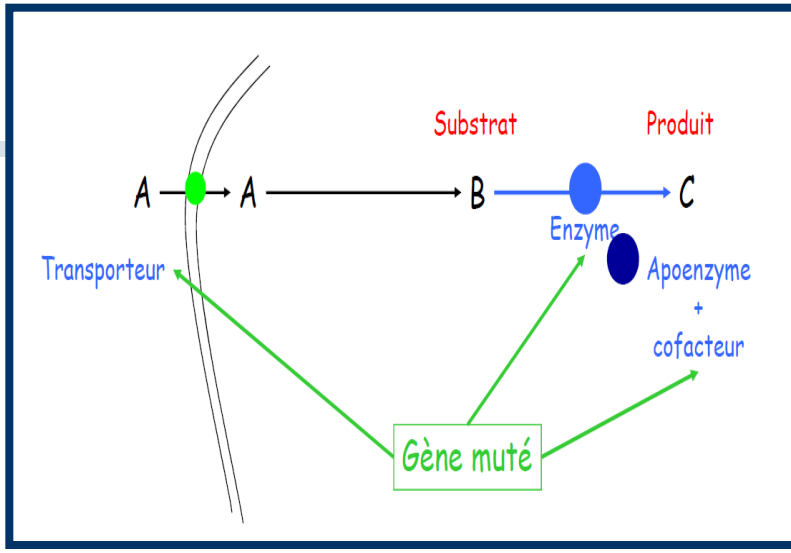
IEM

- **Anomaly of an enzyme or its cofactor**

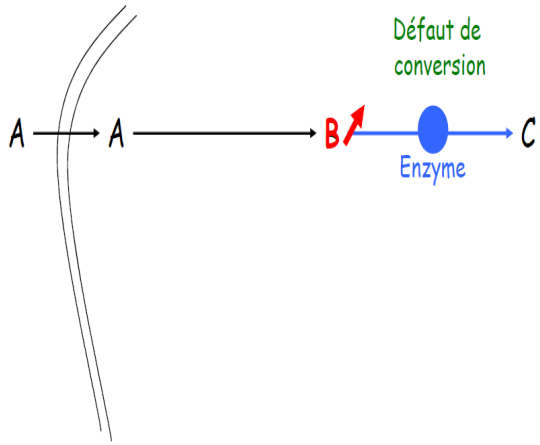
  1 gene = 1 enzyme

  → Metabolites' accumulation/depletion

  1. Substrate's accumulation
  2. Product's decrease
  3. Secondary biomarkers
  4. Lack of negative feedback
  5. Transporters' disorders

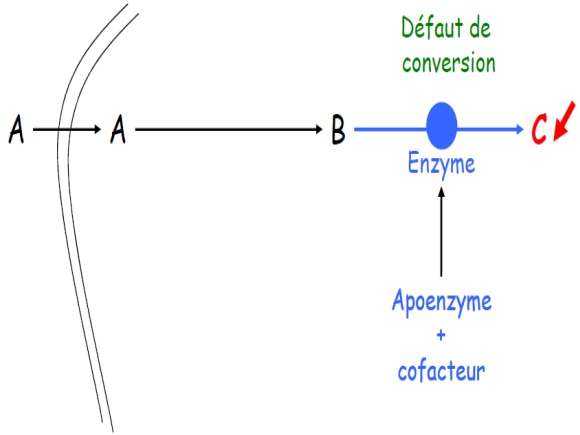


1. Accumulation du substrat



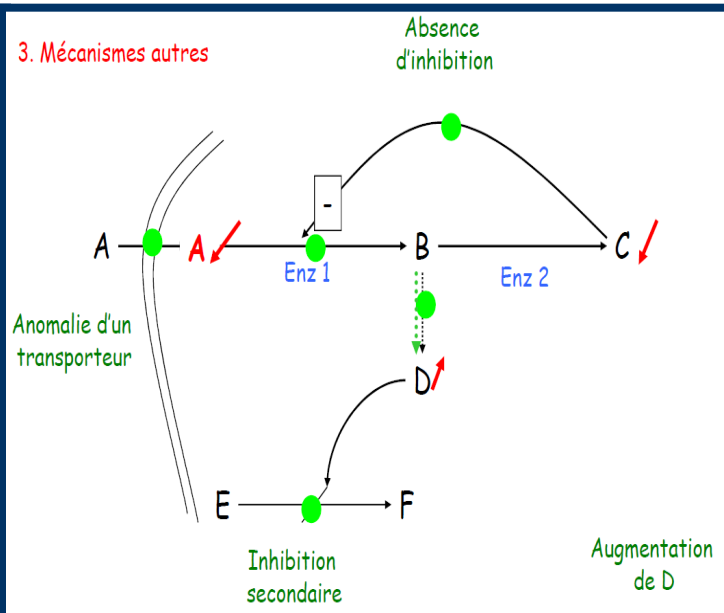
Maladie par intoxication

2. Déficit du produit en aval



Maladie par déficit

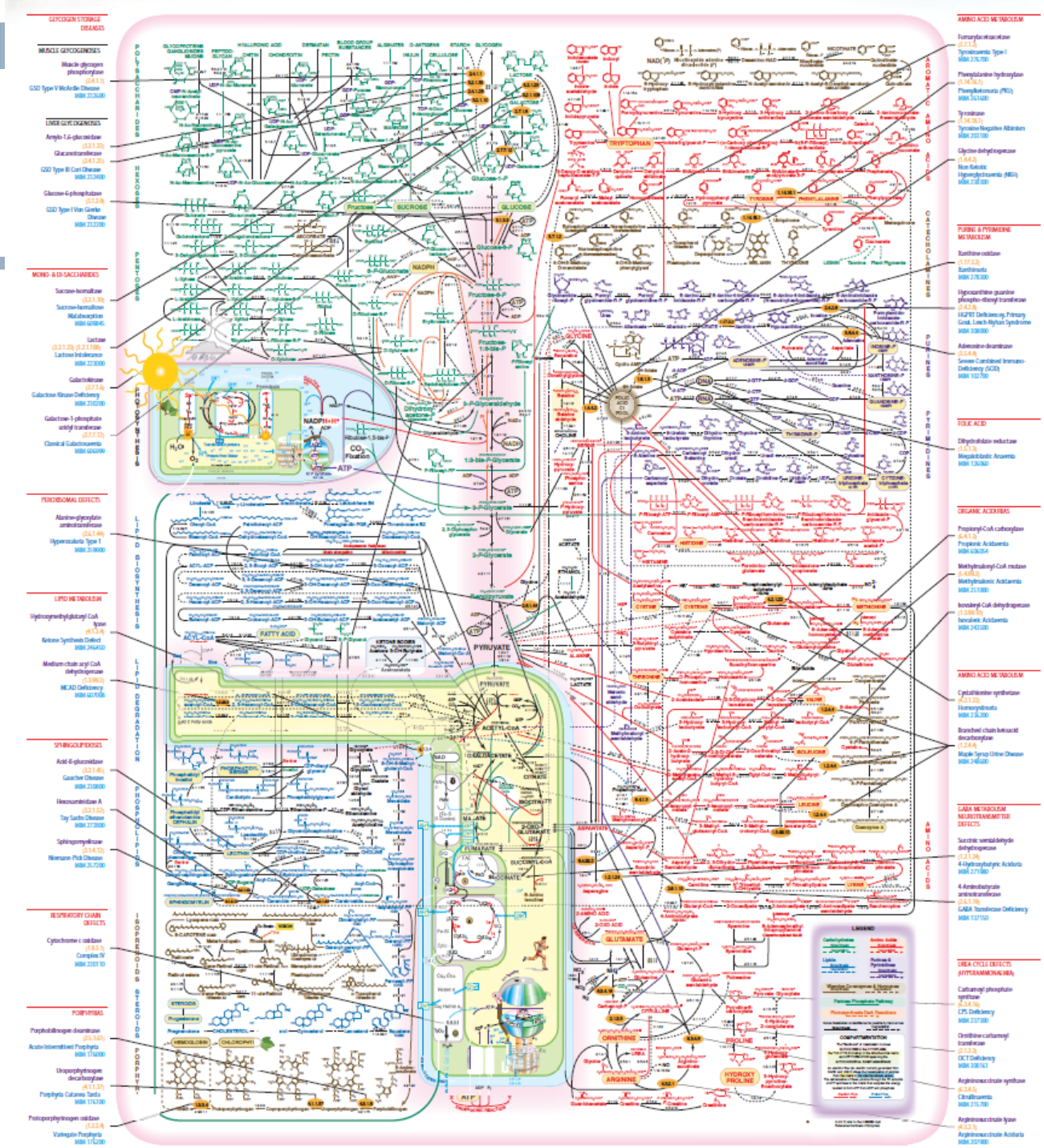
3. Mécanismes autres



IEM

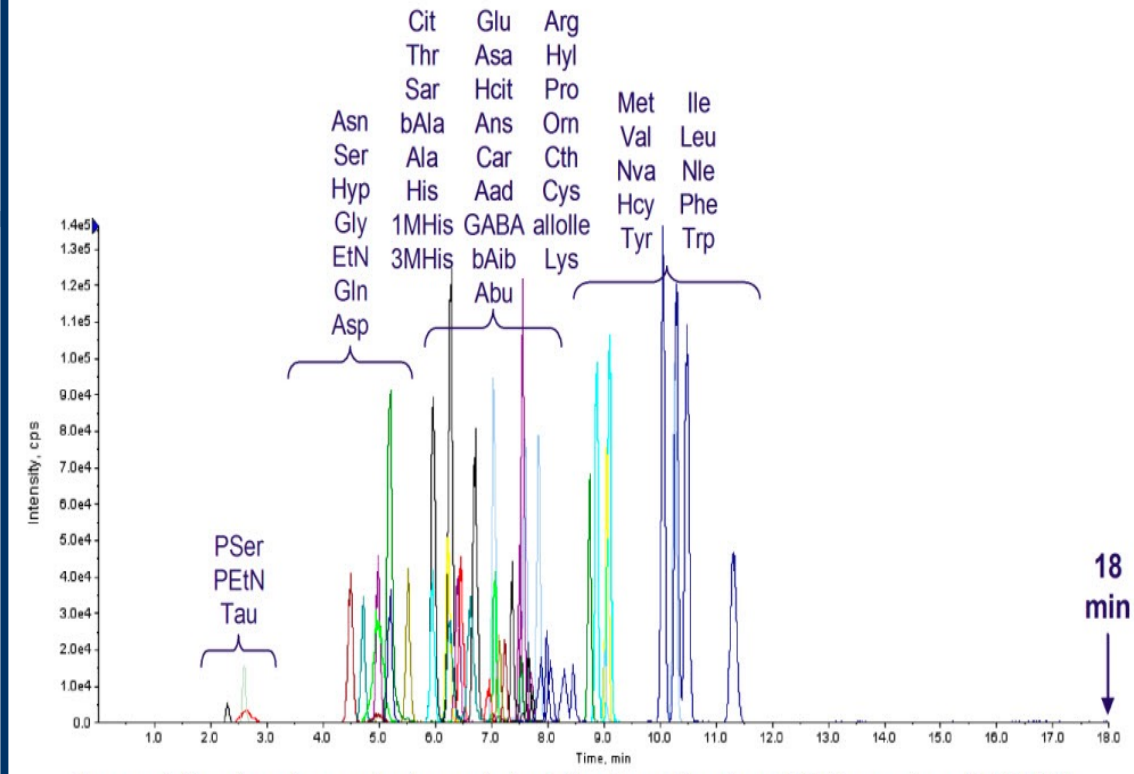
➢ Classification

Amino Acid disorders
Organic Acidemias
Urea Cycle disorders
Carbohydrate disorders
Fatty Acid Oxidation disorders
Mitochondrial disorders
Peroxisomal disorders
Purine and Pyrimidine disorders
Lysosomal Storage disorders
Creatine disorders
Porphyrias
Metal Metabolism disorders
…



Amino Acids

- **Technical aspects**
  - IEC + ninhydrin (> 3h / sample)
  - LC-MS-MS (20 min / sample)



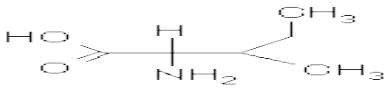
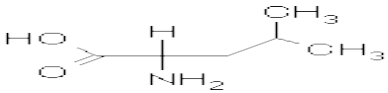
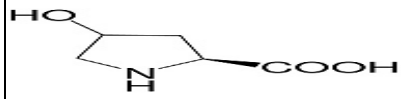
Representative chromatogram showing analysis of 45 amino acids using aTRAQ™ reagents and LC/MS/MS analysis. Total run time is 18 minutes.

- **Sample**
  - Plasma: the preferred specimen for diagnosis and monitoring of most AA disorders and some organic acidemias.
  - Urine: useful for evaluation of specific disorders of renal transport, such as cystinuria and lysinuric protein intolerance, as well as generalized renal tubular dysfunction.
  - CSF is needed with a concurrent plasma sample for the evaluation of glycine encephalopathy or serine deficiency disorders.

Amino Acids analysis

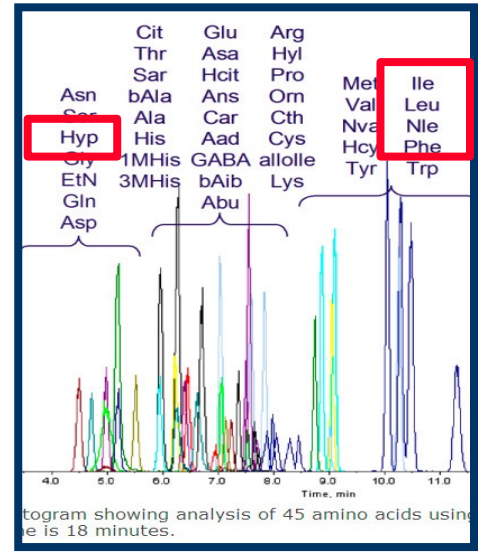
Result interpretation

- Reportable > 40 AA against age-matched reference ranges
- More specific than AA analysis performed for NBS
  - Ie. Leucine, Isoleucine, allo-Isoleucine, Hyroxyproline are isobars

FORMULA	NAME	MW
	Isoleucine	131
	Leucine	131
	Proline	115
	OH-Proline	131

FIA-MS not specific

Need of LC separation upfront of MS

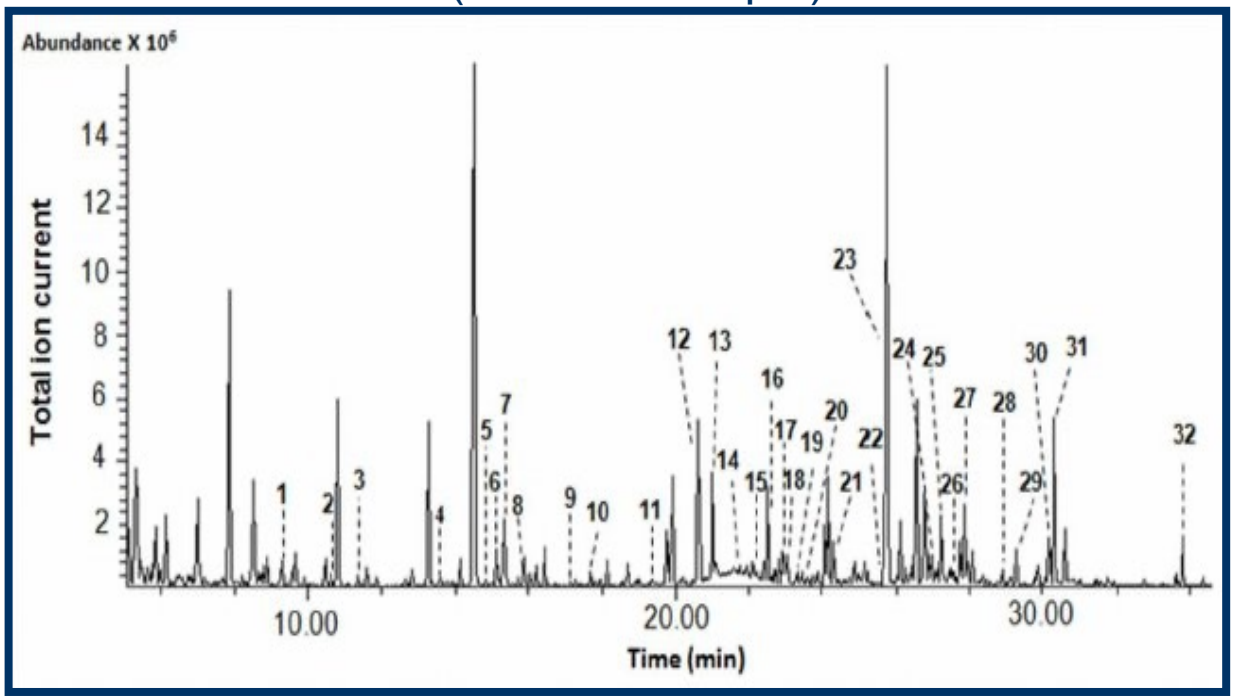


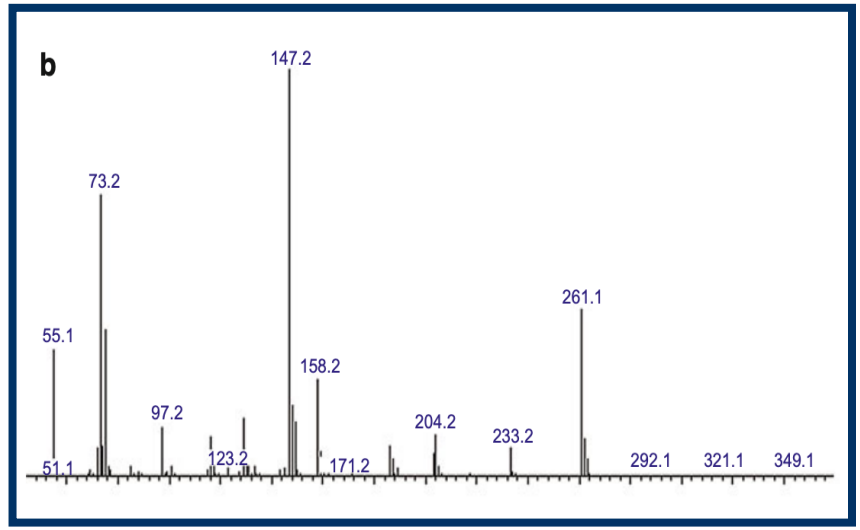
togram showing analysis of 45 amino acids usin
e is 18 minutes.

- Profile should be interpreted in the context of dietary history, nutritional status, and concurrent medication history.
- Report should include explanation of result, possible diagnoses, and recommendation for further testing if required.

Urinary Organic Acids

- **Technical aspects**
  - Time-consuming sample preparation
  - GC-MS (run: 1h / sample)





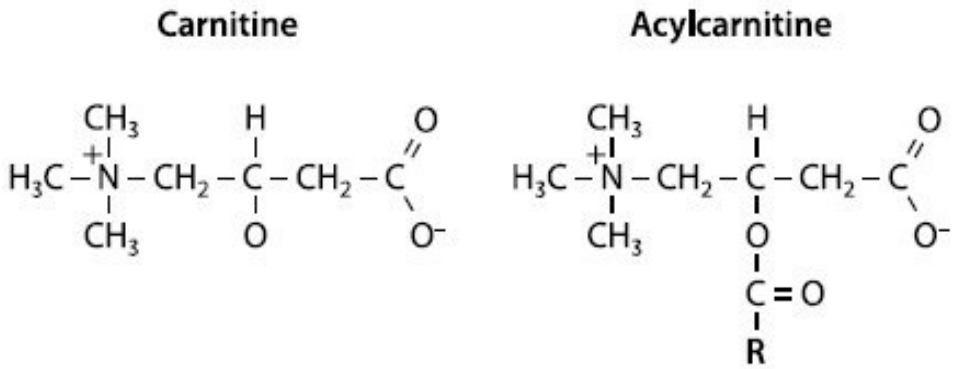
- **Sample**
  - Urine: best to collect urine when patient is acutely ill

Urinary Organic Acids

- **Interpretation of results**
  - Identification of primary disorders of intermediary metabolism (amino acids, fatty acids, nucleic acids…)
    - PKU, TYR, MSUD …
    - MMA / PA, GA 1/2, IVA …
    - MCAD …
  - Some coeluting organic acids are often critical for diagnosis of certain disorders
    - 4-Hydroxybutyric acid (m/z 204, 233) vs urea peak (m/z 171, 189)
    - 3-Hydroxyglutaric acid (m/z 185, 259) vs 2-hydroxyglutaric acid (m/z 157, 203)
  - Profile should be interpreted in the context of dietary history, nutritional status, and medical information including medication

Acylcarnitines

- **Technical aspects**
  - LC-MS-MS
- **Sample**
  - Plasma / serum: sample should be kept frozen until analysis
  - DBS: 1–2 circles, fully saturated
  - Urine: useful for primary carnitine deficiency (CUD) – *SLC22A5*
- **AC profile**
  - Acylcarnitine analysis measures concentrations of acylcarnitine species from chain length C0 to C18 including some dicarboxylic and hydroxylated species



Acylcarnitines

- **Interpretation of results**
  - AC profile can be influenced by nutritional and medical status.
    - B12 deficiency can result in mild C3 elevation
    - Some medications can cause artifacts (ie. pivalic acid-based antibiotic leads to C5 elevation)
  - Profile best interpreted in the context of urine organic acid and plasma amino acid findings
  - In some diseases, profile can be normal when patients are stable under good metabolic control

Acylcarnitines

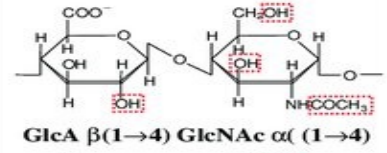
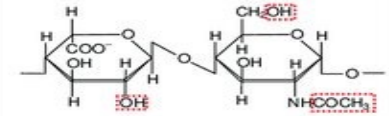
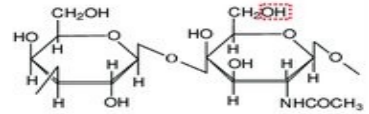
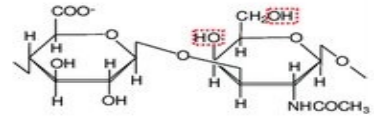
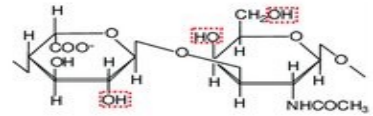
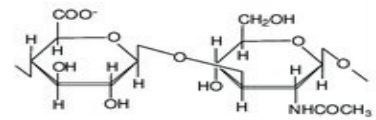
- Patient 3 - 36 years: Presented an acute episode of rhabdomyolysis at 18 years, evolving to a chronic form of lipid storage myopathy.
- Patient 4 - 50 years: Patient 3's sister, with similar clinical presentation. Patients 3 and 4 were from consanguineous parents.
- Patient 5 - 16 years: Endured an acute episode of rhabdomyolysis at 5 years, without any recurrence. Complained of chronic fatigue and asthenia.

Sample Type	Serum	Serum	Serum	Serum	Dried Blood Spot
Sampling Date	17/05/2013	11/04/2013	13/12/2011	05/10/2011	16/07/2008
Free Carnitine	33.8	42.20	35.20	32.43	31.81
C3-Carnitine	0.66	0.32	0.39	0.48	2.18
C4-Carnitine	0.15	0.72	0.39	0.19	0.23
C5-Carnitine	0.13	0.24	0.18	0.13	0.15
C5-DC-Carnitine	0.22	0.79	0.13	0.15	0.09
C6-Carnitine	0.06	0.88	0.32	0.20	0.20
C8-Carnitine	0.07	0.84	0.24	0.56	0.22
C10-Carnitine	0.12	1.12	0.20	0.50	0.23
C10:1-Carnitine	0.05	0.86	0.16	0.45	0.12
C12-Carnitine	0.06	0.15	0.11	0.06	0.10
C14-Carnitine	0.07	0.07	0.05	0.04	0.12
C16-Carnitine	0.06	0.42	0.19	0.40	1.53
C18-Carnitine	0.08	0.22	0.08	0.14	1.00
C8 / C2	0.00	0.08	0.04	0.04	0.01
C8 / C10	0.50	0.75	1.20	1.12	0.96

	Patient 3	Patient 4 P3's Sister
Free Carnitine	68.90	44.08
C3-Carnitine	0.71	1.29
C4-Carnitine	3.3 (0.07-0.58)	0.16
C5-Carnitine	0.45	0.28
C5-DC-Carnitine	0.9 (0.09-0.64)	0.12
C6-Carnitine	6.38 (0.03-0.24)	0.04
C8-Carnitine	3.35 (0.04-0.43)	0.09
C10-Carnitine	4.54 (0.05-0.67)	0.16
C12-Carnitine	0.88 (0.03-0.49)	0.06
C14-Carnitine	0.36	0.26
C16-Carnitine	0.35	0.84
C18-Carnitine	0.15	0.52
C8 / C2	0.19 (0-0.01)	0.00
C8 / C10	0.74	0.57
ETF-DH Analysis	p.Ile98Asn homozygote	p.Ile98Asn homozygote
Comment	Not described mut. Potentially altered protein function	Not described mut. Potentially altered protein function

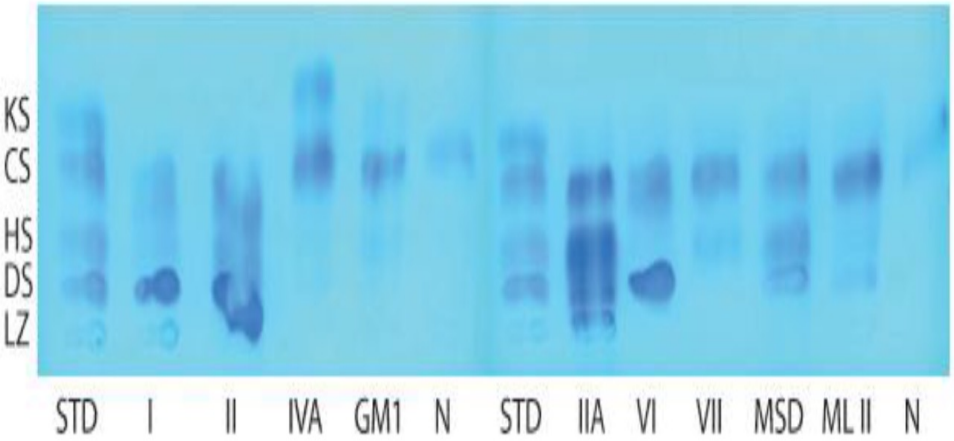
Lysosomal storage diseases

- **Mucoploysaccharidosis**
  - Biomarker: GAGs
  - GAGs are negatively-charged polysaccharide compounds. They are composed of repeating disaccharide units, present in every mammalian tissue
- **Role**
  - Cell hydration and structural scaffolding
  - Cell signaling

GAG	Hexuronic or Iduronic acid	Galactose	Hexosamine	Disaccharide composition
Heparan sulphate/ Heparin	D-glucuronic acid **(GlcA)** L-iduronic acid **(IdoA)**	-	D-glucosamine **(GlcNAc)**	 **GlcA β(1→4) GlcNAc α((1→4)**  **IdoA α(1→4) GlcNAc α(1→4)**
Keratan sulphate	-	Galactose **(Gal)**	D-glucosamine **(GlcNAc)**	 **Gal β(1→4) GlcNAc β(1→3)**
Chondroitin sulphate	D-glucuronic acid **(GlcA)**	-	D-galactosamine **(GalNAc)**	 **GlcA β(1→3) GalNAc β(1→4)**
Dermatan sulphate	D-glucuronic acid **(GlcA)** L-iduronic acid **(IdoA)**	-	D-galactosamine **(GalNAc)**	 **IdoA β(1→3) GalNAc β(1→4)**
Hyaluronic acid	D-glucuronic acid **(GlcA)**	-	D-glucosamine **(GlcNAc)**	 **GlcA β(1→3) GlcNAc β(1→4)**

Lysosomal storage diseases

- **MPS analysis**
  - Quantitative assay (MB coloration)
  - Electrophoresis (MB coloration)

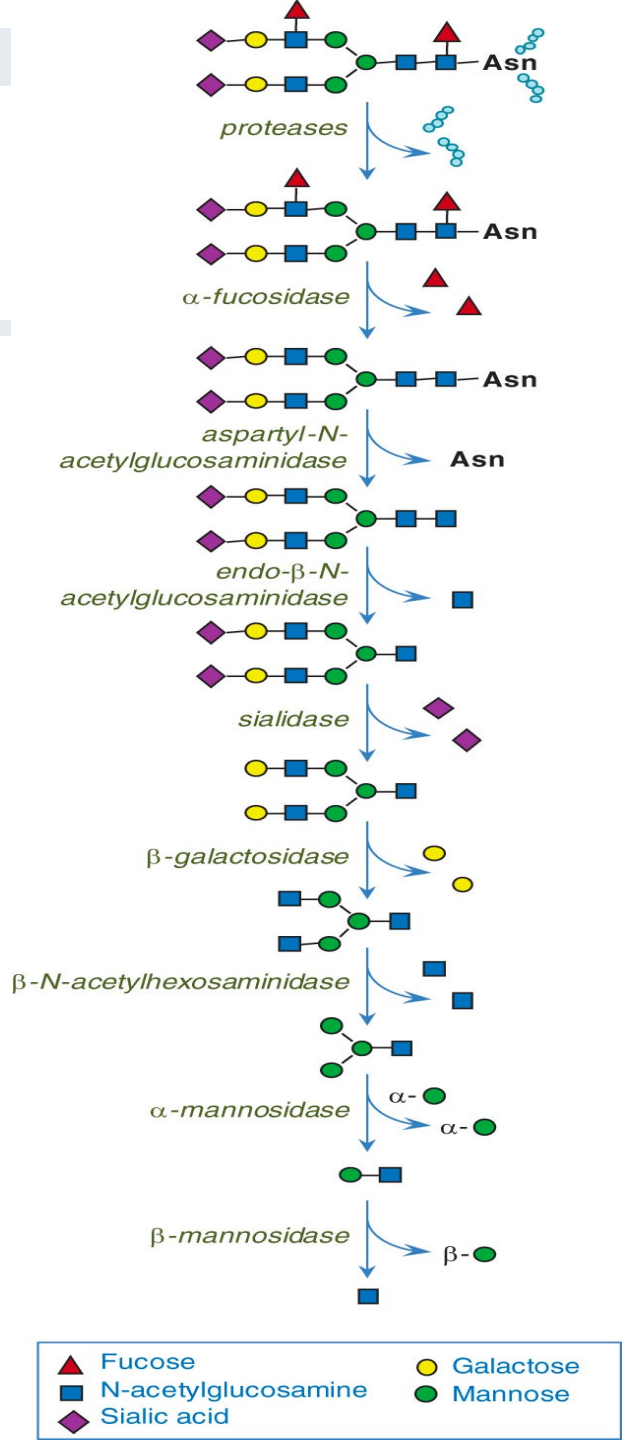


MPS	Name	Increased GAGs
I	Hurler, Hurler-Scheie or Scheie	HS + DS
II	Hunter	HS + DS
III A	Sanfilippo A	HS
III B	Sanfilippo B	HS
III C	Sanfilippo C	HS
III D	Sanfilippo D	HS
IV A	Morquio A	KS
IV B	Morquio B	KS
(V)	Scheie syndrome, initially proposed as type V,	
VI	Maroteaus-Lamy	DS
VII	Sly	HS + DS

  - Specific enzymatic assay (on DBS or WBC / fibroblasts) using fluorimetric methods or LC-MS-MS

Lysosomal storage diseases

- **Oligosaccharidoses (glycoproteinoses)**
  - Saccharide polymers containing a small number (typically 2-10) of monosaccharides
  - Result from deficient activity of one of the lysosomal enzymes involved in the degradation of oligosaccharide components of glycoproteins.



Lysosomal storage diseases

- **Oligosaccharides analysis**
  - Thin layer chromatography
  - (Mass spectrometry)
- **Interpretation of results**
  - Disorders
    - α and β Mannosidosis (*MAN2B1, MANBA*)
    - Gangliosidosis (GM1: *GLB1*, GM2: *HEXA*, *HEXB, GM2A*)
    - Pompe (*GAA*)
    - Sialidosis (*NEU1*)
    - Fucosidosis (*FUCA1*)
    - Mucolipidosis II and III (*GNPTAB*)
    - Schindler disease (*NAGA*)
    - Aspartylglucosaminuria (*AGA*)
  - False positive: parenteral nutrition, glue
  - Specific enzymatic assay (on DBS or WBC / fibroblasts)

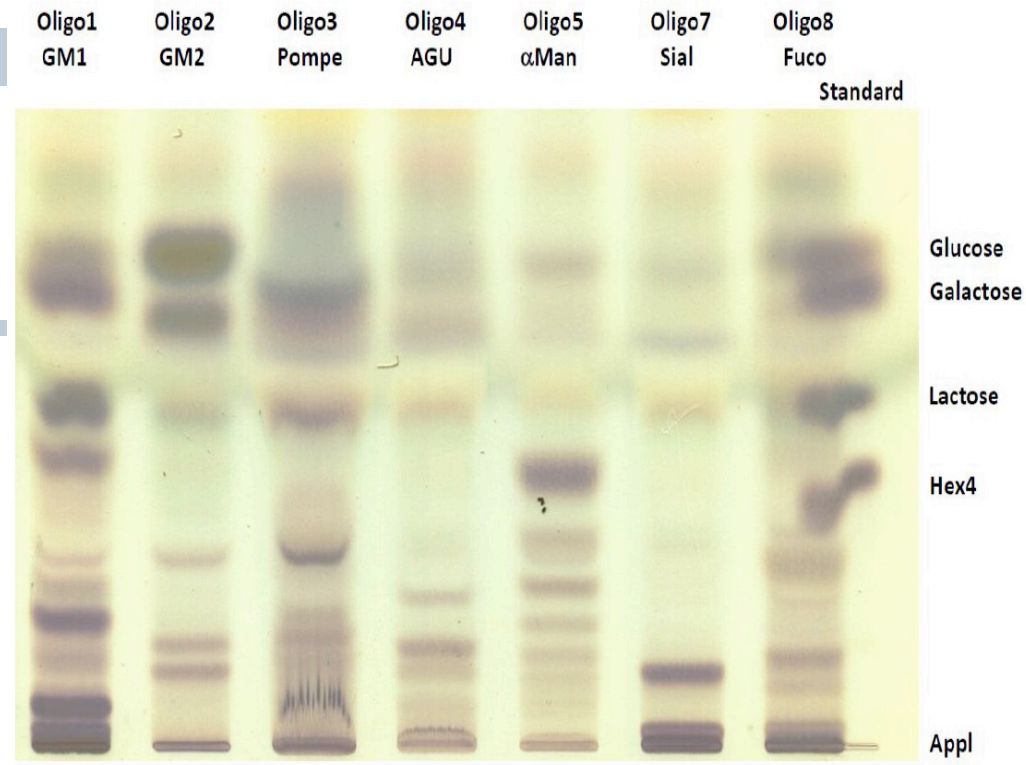


Table 1. Seven selected FOSs and the IS, with SRM transitions, retention times (RT), and corresponding disorders listed for each.

FOS ID	FOS composition	SRM transition	RT, min	Disorder
FOS 1	Hex[a]1HexNAc[b]1Asn[c]	498.2 > 133.03	2.5	Aspartylglucosaminuria
FOS 2	Hex3HexNAc2Fuc[d]1	1234.45 > 399.25	1.7	α-Fucosidosis
FOS 3	Hex3HexNAc1	885.4 > 399.25	1.0	α-Mannosidosis
FOS 4	Hex1HexNAc1	561.25 > 399.25	0.4	β-Mannosidosis
FOS 5	Hex3HexNAc2	1088.45 > 399.25	1.5	β-Galactosidase deficiency
FOS 6	Hex2HexNAc3	1129.45 > 399.25	1.3	GM2 (Sandhoff disease)
FOS 7	Neu5Ac[e]1Hex3HexNAc2	1379.55 > 399.25	2.0 and 2.1	Sialidosis/galactosialidosis
IS	ΔHexA[f]GlcNAc	557.28 > 399.25	0.5	NA[g]

[a] Hexose.
[b] *N*-acetyl hexose.
[c] Asparagines.
[d] Fucose.
[e] Sialic acid.
[f] Unsaturated hexuronic acid.
[g] Not applicable.

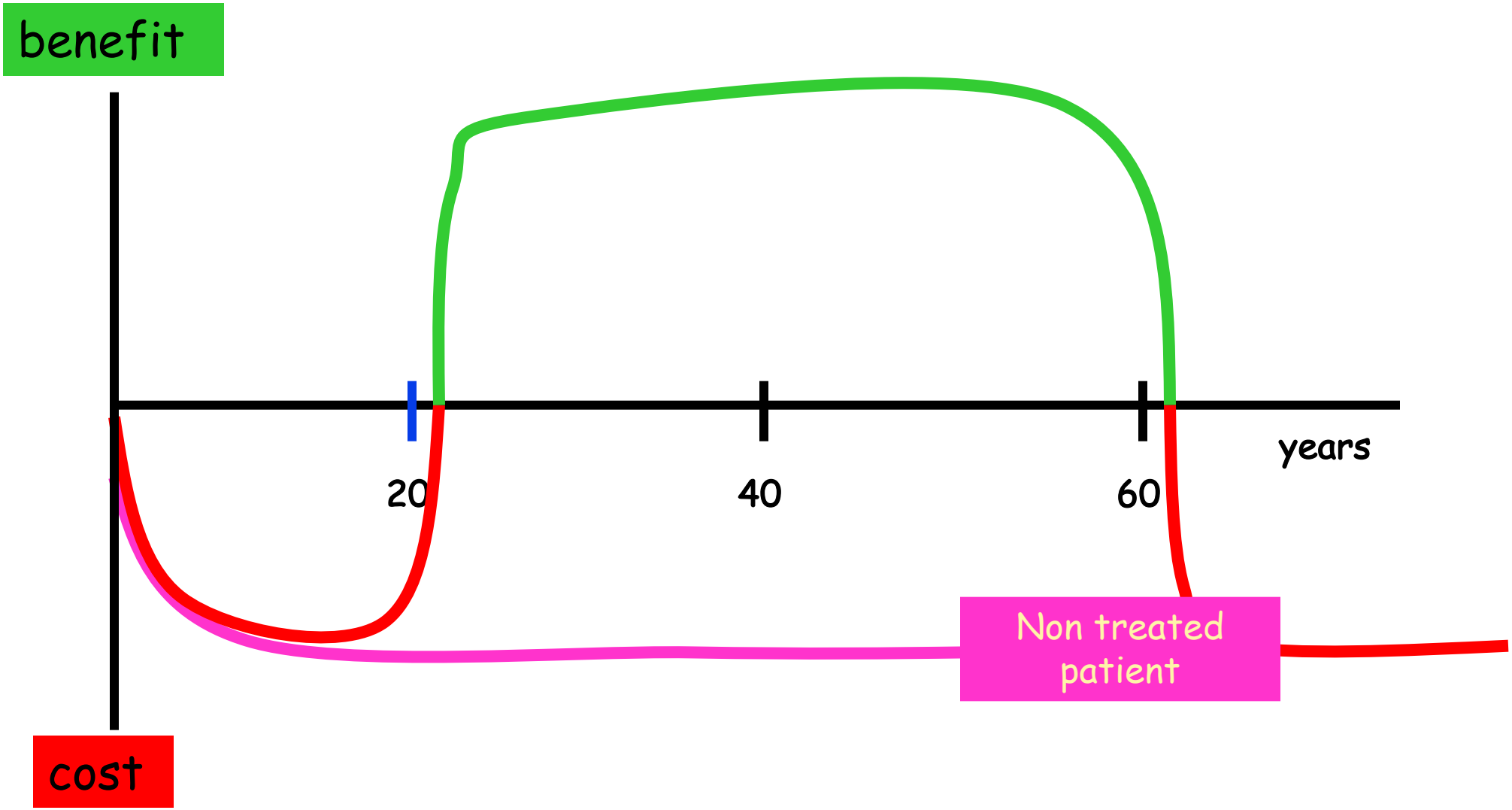
2. Newborn screening

- **Definition**
  - Public health program aimed to identify and treat, at birth, severe congenital disorders in a whole population
  - NBS facilitates timely delivery of live-saving treatments that improve quality of life

- **History**
  - Guthrie test > Phenylketonuria

- **Criteria**
  - 10 WHO criteria defined by Wilson & Jungner in 1968
    - Public health problem
    - Accepted by population
    - Disease physiopathology well understood
    - Pre-symptomatic
    - Therapeutic protocol
    - Efficient treatment
    - Reliable method
    - Validated tests
    - Cost-effective
    - Sustainable

Socio-economical aspects



Organisation in Belgium

- **~ 120.000 births / year**

- **5 NBS centres – 4 screening labs**
  - Liège – ULiege
  - Bruxelles – UCL
  - Bruxelles – ULB
  - Bruxelles – VUB

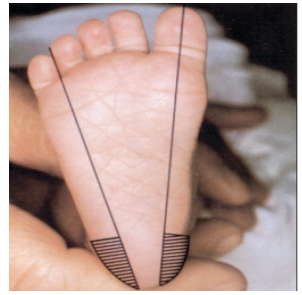
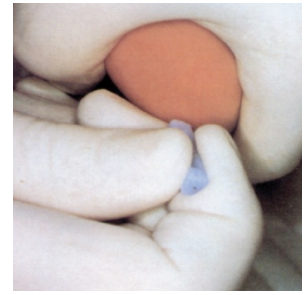
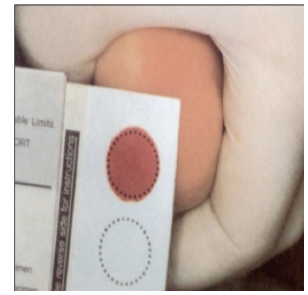
  } 1 lab

  - Anvers – UA

Sampling

Day 0 : birth

Day 2-5 : Sampling – filter paper

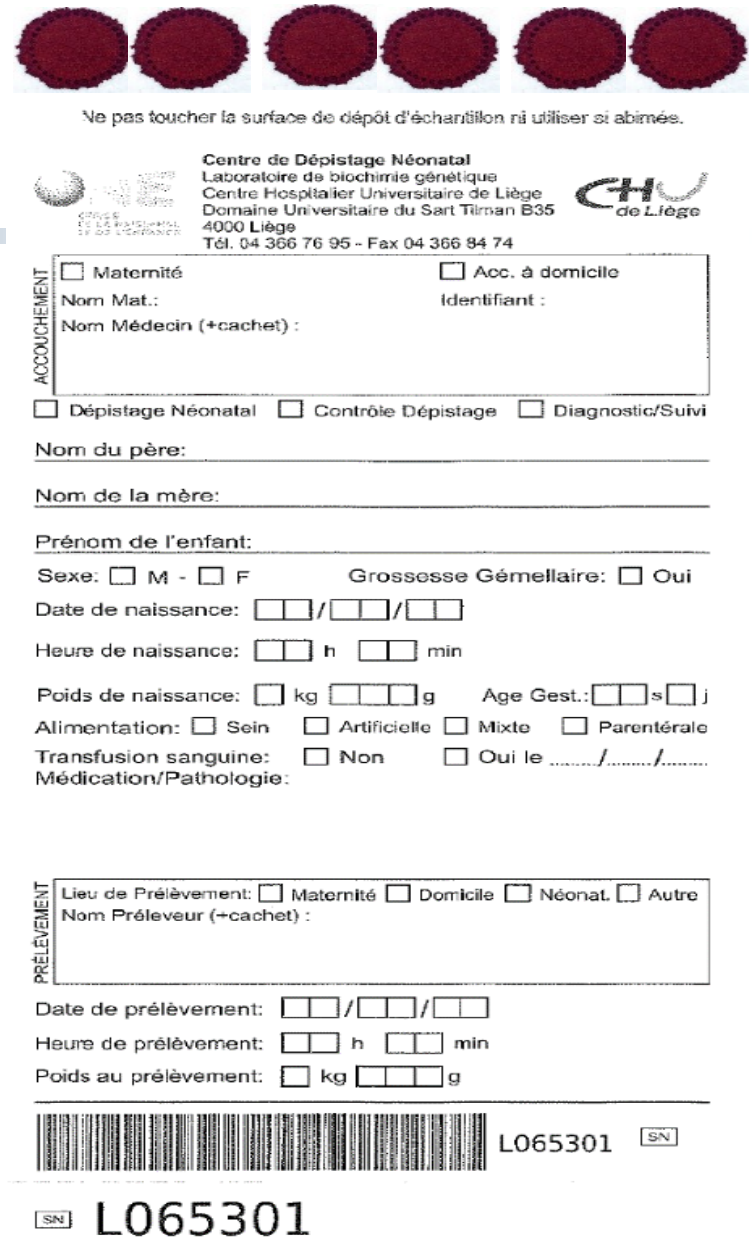




Day 3-10 : Mail

Day 6-15 : Lab analysis

NBS Sample

- **Filter paper**
  - Standardized and regulated (CDRH FDA - « CE » label)
  - Logistical ease
  - Conservation
  - International standard international for collection, transport, analysis and archiving of biological fluids



Ne pas toucher la surface de dépôt d'échantillon ni utiliser si abimée.

Centre de Dépistage Néonatal
Laboratoire de biochimie génétique
Centre Hospitalier Universitaire de Liège
Domaine Universitaire du Sart Tilman B35
4000 Liège
Tél. 04 366 76 95 - Fax 04 366 84 74

ACCOUCHEMENT
☐ Maternité ☐ Acc. à domicile
Nom Mat.: Identifiant :
Nom Médecin (+cachet) :

☐ Dépistage Néonatal ☐ Contrôle Dépistage ☐ Diagnostic/Suivi

Nom du père:

Nom de la mère:

Prénom de l'enfant:

Sexe: ☐ M - ☐ F Grossesse Gémellaire: ☐ Oui

Date de naissance: ☐☐/☐☐/☐☐

Heure de naissance: ☐☐ h ☐☐ min

Poids de naissance: ☐ kg ☐☐☐ g Age Gest.: ☐☐ s ☐ j

Alimentation: ☐ Sein ☐ Artificielle ☐ Mixte ☐ Parentérale

Transfusion sanguine: ☐ Non ☐ Oui le ...../...../.....

Médication/Pathologie:

PRÉLÈVEMENT
Lieu de Prélèvement: ☐ Maternité ☐ Domicile ☐ Néonat. ☐ Autre
Nom Préleveur (+cachet) :

Date de prélèvement: ☐☐/☐☐/☐☐

Heure de prélèvement: ☐☐ h ☐☐ min

Poids au prélèvement: ☐ kg ☐☐☐ g

L065301 SN

SN L065301

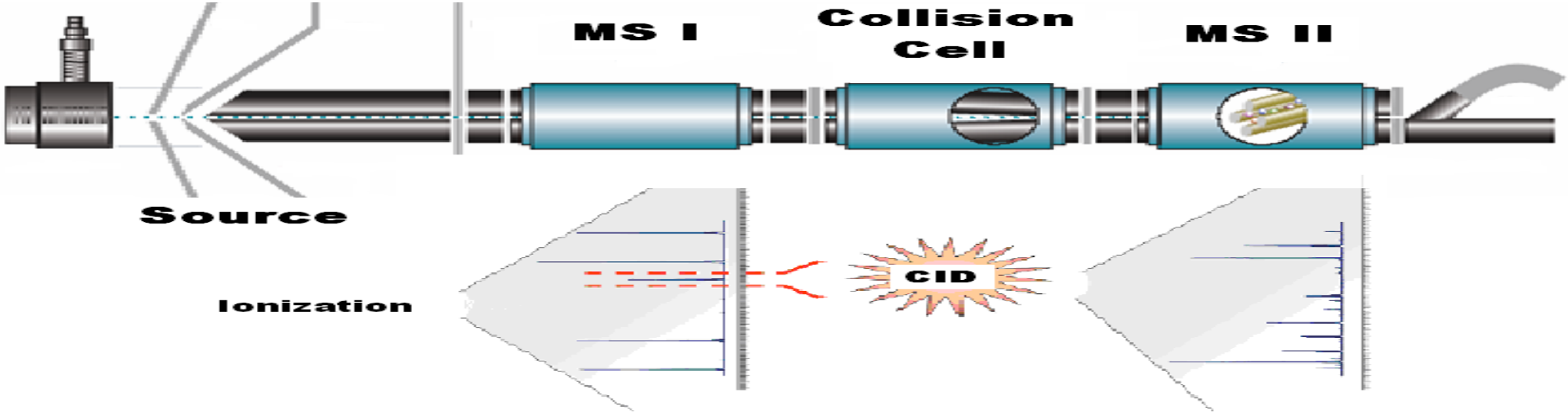
Official NBS programs in Belgium

Disorders	Wallonia	Flanders
Inborn Errors of Metabolism		
Phenylketonuria	X	X
Leucinosis - Maple Syrup Urine Disease (MSUD)	X	X
Homocystinuria	X	
Tyrosinemia	X	
Propionic Acidemia	X	X
Methylmalonic Acidemia	X	X
Glutaric Acidemia type 1	X	X
Isovaleric Acidemia	X	X
Medium Chain Acyl-CoA DH deficiency (MCAD)	X	X
Multiple Acyl-CoA DH deficiency (MADD)	X	X
Very-Long Chain Acyl-CoA DH deficiency (VLCAD)	X	
Long-Chain 3-Hydroxyacyl-CoA DH deficiency (LCHAD)	X	
Carnitine uptake defect (CUD)	X	
Galactosemia	X	X
Biotinidase deficiency	X	X
Endocrinal / Other disorders		
Congenital Hypothyroidism	X	X
Cystic Fibrosis	X	X
Congenital Adrenal Hyperplasia	X	
SMA	X	X

Technologies

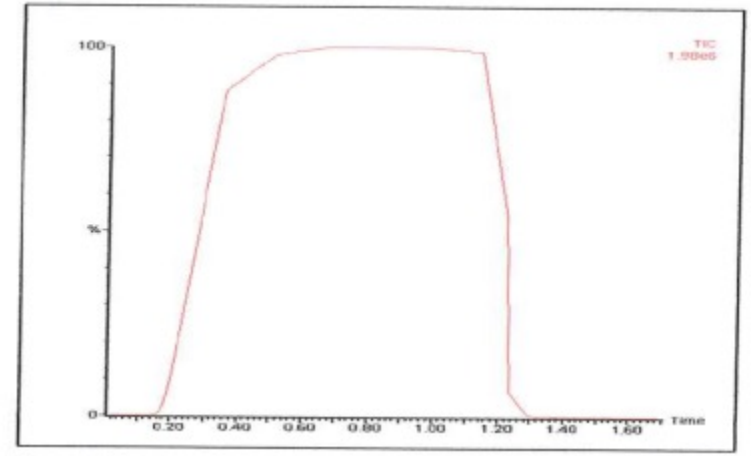
Disorders	Wallonia	Flanders	Technology
Inborn Errors of Metabolism			
Phenylketonuria	X	X	LC-MS-MS
Leucinosis - Maple Syrup Urine Disease (MSUD)	X	X	LC-MS-MS
Homocystinuria	X		LC-MS-MS
Tyrosinemia	X		LC-MS-MS
Propionic Acidemia	X	X	LC-MS-MS
Methylmalonic Acidemia	X	X	LC-MS-MS
Glutaric Acidemia type 1	X	X	LC-MS-MS
Isovaleric Acidemia	X	X	LC-MS-MS
Medium Chain Acyl-CoA DH deficiency (MCAD)	X	X	LC-MS-MS
Multiple Acyl-CoA DH deficiency (MADD)	X	X	LC-MS-MS
Very-Long Chain Acyl-CoA DH deficiency (VLCAD)	X		LC-MS-MS
Long-Chain 3-Hydroxyacyl-CoA DH deficiency (LCHAD)	X		LC-MS-MS
Carnitine uptake defect (CUD)	X		LC-MS-MS
Galactosemia	X	X	Enzymatic assay
Biotinidase deficiency	X	X	Enzymatic assay
Endocrinal / Other disorders			
Congenital Hypothyroidism	X	X	Immunoassay
Cystic Fibrosis	X	X	Immunoassay
Congenital Adrenal Hyperplasia	X		Immunoassay
SMA	X	X	qPCR

Mass Spectrometry - QQQ



- Ionisation des composés de l'échantillon.
- Sélection des ions précurseurs selon leurs masses dans le premier spectromètre.
- Fragmentation des ions « précurseurs » par collision avec un gaz neutre dans la cellule de collision afin d'obtenir des ions « produits » - Processus appelé COLLISION INDUCED DISSOCIATION (CID).
- Analyse des ions « produits » selon leurs masses dans le second spectromètre.

Analytical aspects

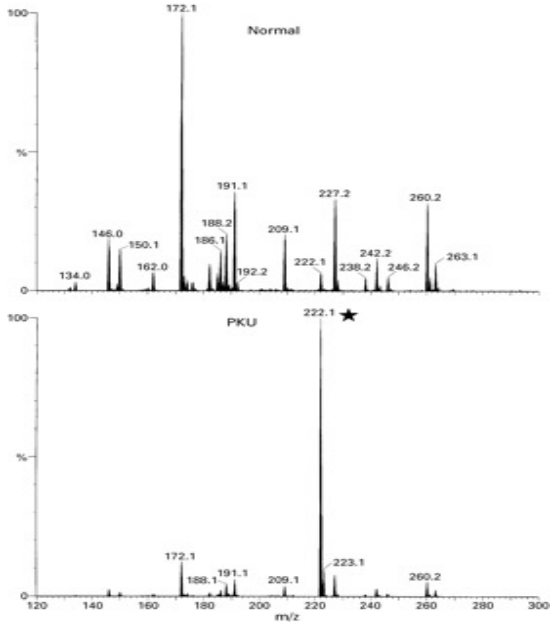


➢ Flow injection

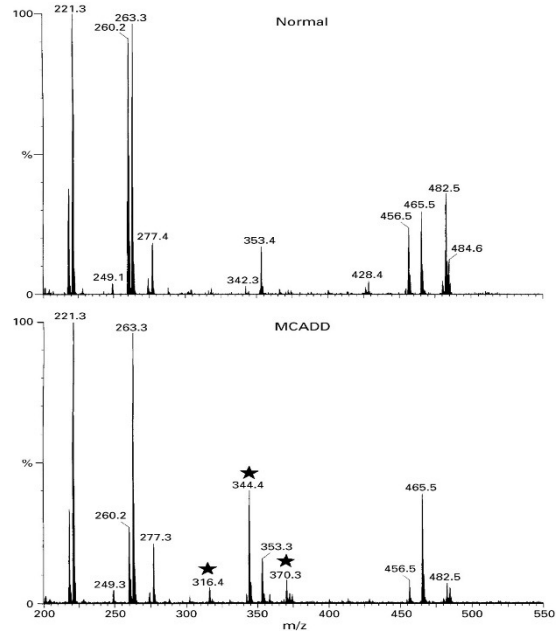
No chromatographic separation

➢ Quantitation based on MS spectrum

PKU

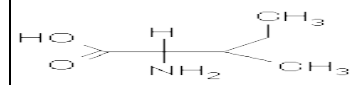
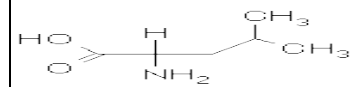
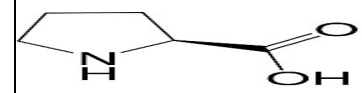
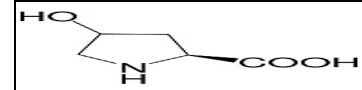


MCAD

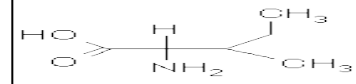
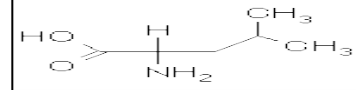
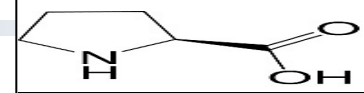
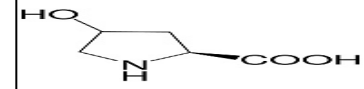


$$\frac{\text{Hauteur du Pic d'Intérêt}}{\text{Hauteur du Std Interne}} \times [\text{Std Interne}]$$

Lack of specificity for some compounds

FORMULA	NAME	MW
	Isoleucine	131
	Leucine	131
	Proline	115
	OH-Proline	131

Analytical aspects

FORMULA	NAME	MW
	Isoleucine	131
	Leucine	131
	Proline	115
	OH-Proline	131

- **Xle: 745 µM/L (cutoff: 475 µM/L)**

Figure1.A. MRM profile of patient with Hyper Leu/Ile
Leu/Ile: m/z=188.1 — Leu-D_3: m/z=191.1

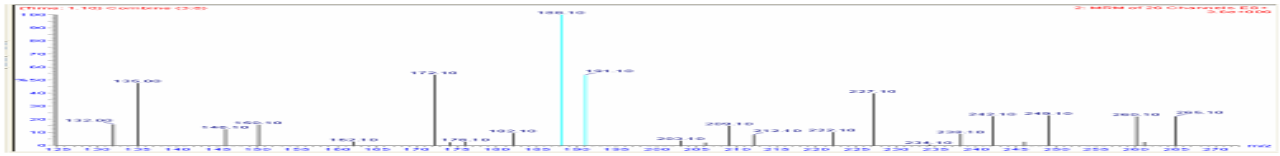
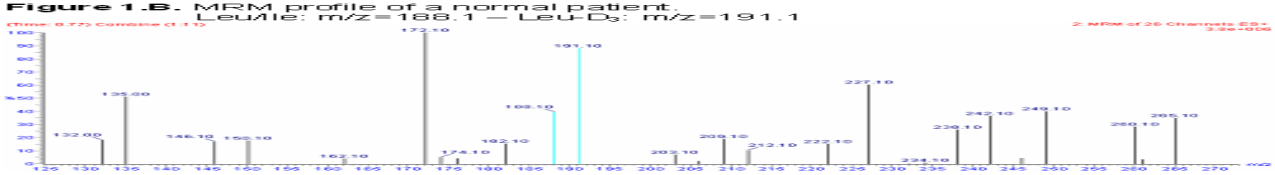


Figure 1.B. MRM profile of a normal patient.
Leu/Ile: m/z=188.1 — Leu-D_3: m/z=191.1



- **Bi-allelic pathogenic mutations identified in PRODH1 (non-disease)**

PLASMA AMINO ACIDS

Hydroxyproline sg	323.9 µmol/L	0.0-63.0
Proline sg	297.5 µmol/L	52.0-298.0

PLASMA AMINO ACIDS

Hydroxyproline sg	346.2 µmol/L	0.0-63.0
Proline sg	422.1 µmol/L	52.0-298.0

URINE AMINO ACIDS

Hydroxyproline ur	3343.6 µmol/L	0.0-187.0
OH-proline (mM/Mcr)	2202.8 mM/M créat	0.0-106.0
Proline ur	87.8 µmol/L	0.0-172.0
Proline (mM/Mcr)	57.8 mM/M créat	0.0-86.0

Markers

Acides Aminés	Aminoacidopathie Anomalie du Cycle de l'Urée
Phenylalanine	Phénylcétonurie
Tyrosine (+SUAC)	Tyrosinémie
Leucine-Isoleucine	Leucinose (Maladie du Sirop d'Erable)
Methionine	Homocystinurie
Arginine	Déficit en Argininase (Cycle de l'Urée)
Citrulline	Déficit en ASA Synthase (Cycle de l'Urée)
Ornithine	Hyper-Ornithinémie (Cycle de l'Urée)
Argininosuccinic (ASA)	Déficit en ASA Lyase (Cycle de l'Urée)
Glycine	Hyper-Glycinémie non Cétogène

Markers

Acylcarnitines		Acidurie Organique, Anomalie de la β-Oxydation, …
Primaire	**Secondaire**	
Free Carnitine		Déficit en Transporteur de Carnitine, CPT I
C3-Carnitine		Acidurie Propionique et Méthylmalonique
C3-DC-Carnitine		Déficit en Malonyl-CoA Decarboxylase
C4-Carnitine		MAD et SCAD
C5-DC-Carnitine		Acidurie Glutarique
C5:1-Carnitine		Deficit en Beta-Ketothiolase
C5-Carnitine		Acidurie Isovalérique
C5-OH-Carnitine		Déficit en 3-Methylcrotonyl-CoA Carboxylase, Beta-Ketothiolase, 3-Hydroxy-3-Methylglutaryl-CoA Lyase, 3-Methylglutaconyl-CoA Hydratase
C8-Carnitine	C6-Carnitine C10:1- Carnitine	MCAD
C14:1-Carnitine	C12:1-Carnitine, C12-Carnitine, C14:2-Carnitine, C14-Carnitine	VLCAD
C16-OH-Carnitine	C18:2-OH-Carnitine, C18:1-OH-Carnitine, C18-OH-Carnitine, C14-OH-Carnitine	LCHAD
C18-Carnitine	C18:2-Carnitine, C18:1-Carnitine, 16:1-Carnitine, C16-Carnitine	CPT II

> 30 disorders identified simultaneously

Quantitation of ~60 markers (AA & AC) in less than 2 minutes / sample

- Amino acids
  - Phenylketonuria
  - Tyrosinemia : Type I, II, III
  - Maple syrup urine disease
  - Nonketotic hyperglycinemia
  - Cystathionine-ß-synthase deficiency (homocystinuria)
- Organic acids
  - Propionyl-CoA carboxylase deficiency
  - Methylmalonyl-CoA mutase deficiency plus cobalamin A and B defects
  - Cobalamin C defect
  - Isovalericacidemia
  - Glutaryl-CoA dehydrogenase deficiency
  - Holocarboxylase synthase deficiency
  - Biotinidase deficiency
  - Hydroxymethylglutaryl-CoA lyase deficiency
  - Methylglutaconicaciduria
  - 3-Methylcrotonyl CoA carboxylase deficiency
  - 3-Ketothiolase deficiency
- Urea cycle
  - Carbamyl phosphate synthetase deficiency
  - Ornithine transcarbamylase deficiency
  - Argininosuccinate synthase deficiency
  - Argininosuccinate lyase deficiency
  - Arginase deficiency
  - Citrullinemia, type II (citrin deficiency)
- Fatty acids
  - Short-chain acyl-CoA dehydrogenase deficiency
  - Medium-chain acyl-CoA dehydrogenase deficiency
  - Very-long-chain acyl-CoA dehydrogenase deficiency
  - Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
  - Multiple acyl-CoA dehydrogenase deficiency
  - Carnitine transporter defect
  - Carnitine palmitoyl transferase deficiency : Type I - Type II
  - Carnitine acylcarnitine translocase deficiency

Why NBS can make the différence

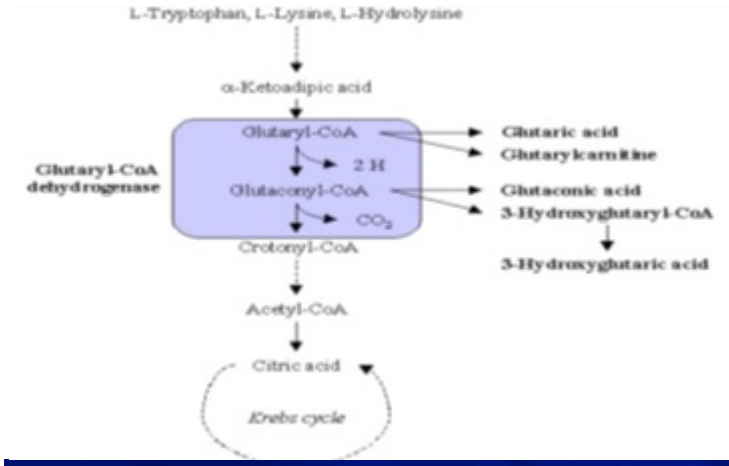
➢ Ex: Glutaric Aciduria I

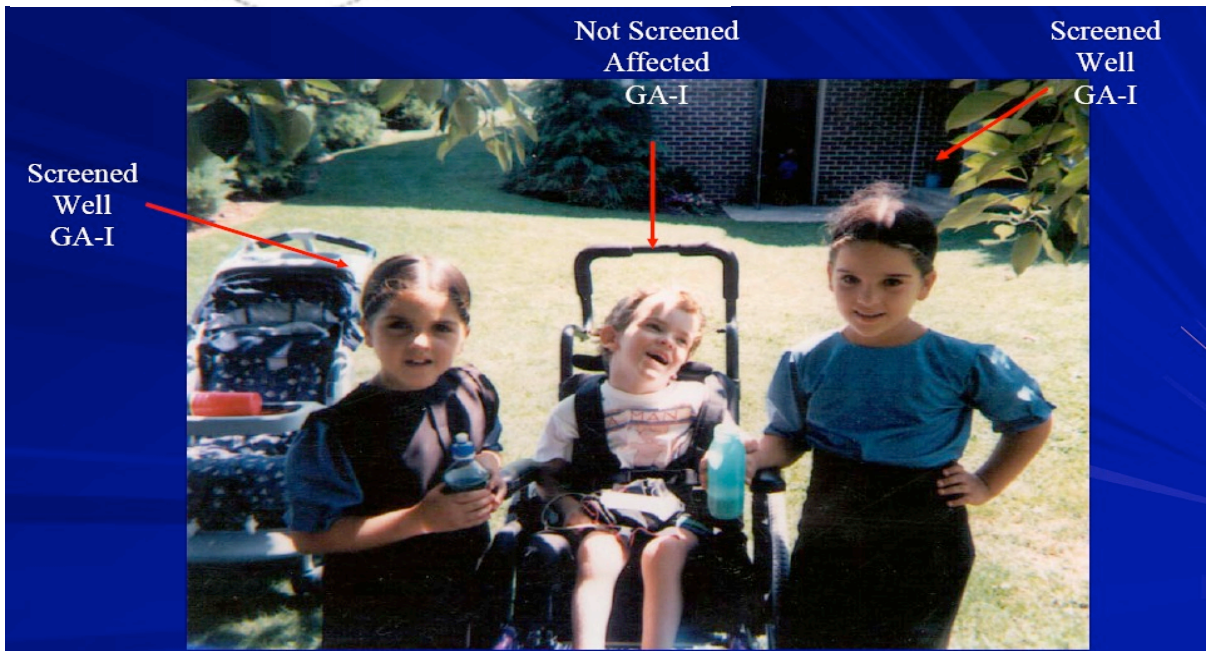
- **Prevalence : 1 / 30.000**

- **Untreated**
  - Metabolic decompensation, ketoacidosis, hyperammoniemia, hypoglycemia
  - Severe psychomoteur delay, cerebral atrophy
  - Sometimes subdural hemorrhage (can be mistaken with child abuse)

- **Treated from birth**
  - Carnitine + Riboflavine (Vit. B2) + Hypoproteic diet (depletion in Trp et Lys)

    → **Normal thrive**





SMA Treatment
Post >< Pre Symtpoms

- VIDEO

Thank you