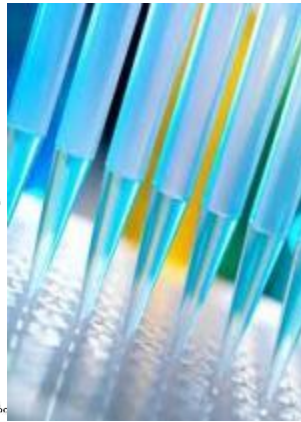
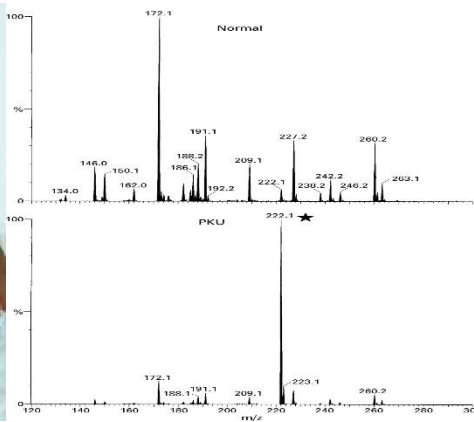
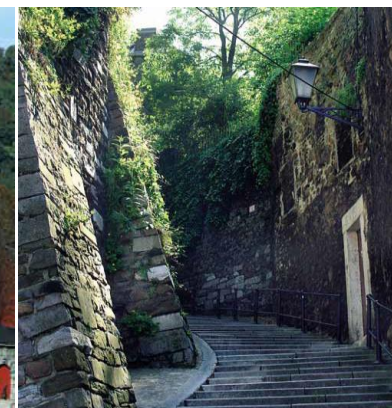




Biochemical Genetics Lab in IEM

François BOEMER

MANAMA Training, Clinical Genetics
Inborn Errors of Metabolism
09/12/2025



Biochemical Genetics: definition

- Inborn errors of metabolism include a broad spectrum of defects of various gene products that affect intermediary metabolism, 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.

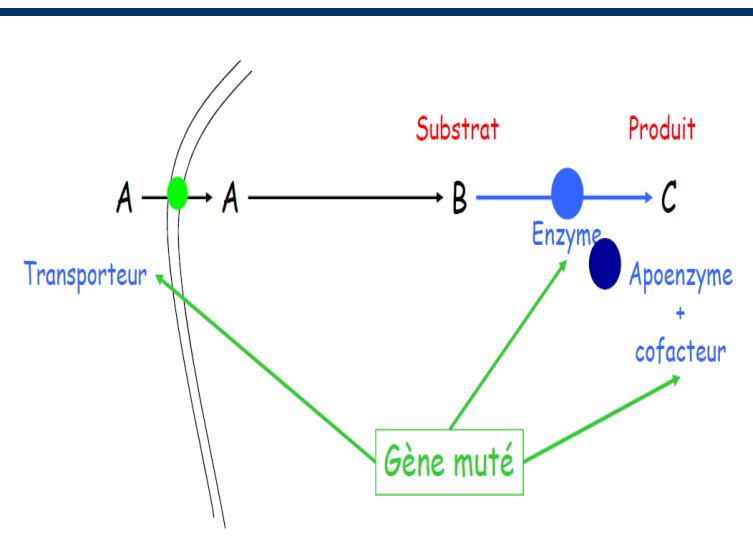
Inborn Errors of Metabolism (IEM)

➤ Anomaly of an enzyme or its cofactor

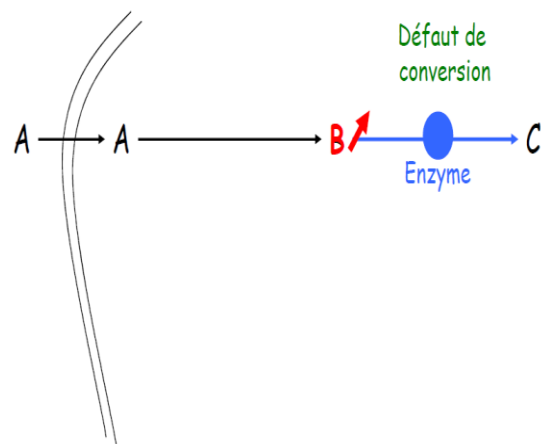
1 gene = 1 enzyme

→ **Metabolites' accumulation/depletion**

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

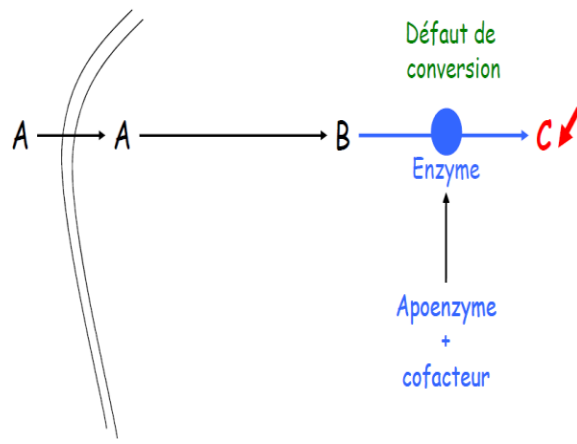


1. Accumulation du substrat



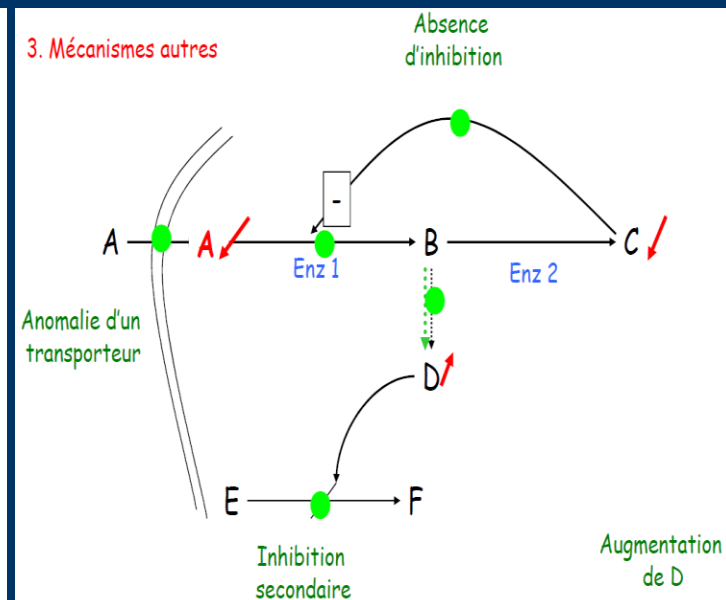
Maladie par intoxication

2. Déficit du produit en aval



Maladie par déficit

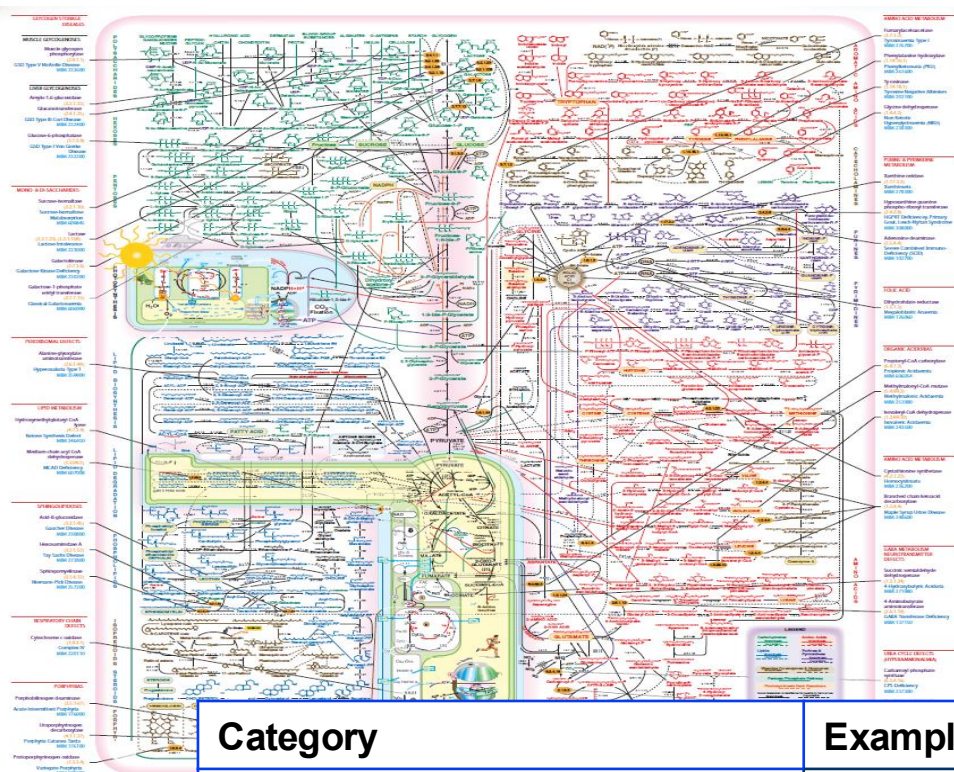
3. Mécanismes autres



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
 Porphyrrias
 Metal Metabolism disorders
 ...



Category	Examples
1. Intoxication-type disorders (catabolic pathways)	<i>Examples:</i> Phenylketonuria, tyrosinemia, homocystinuria, MSUD, organic acidurias, hyperammonemia (urea cycle disorders), ...
2. Energy metabolism disorders	<i>Examples:</i> Glycogen storage diseases, pyruvate dehydrogenase deficiency, disorders of fatty-acid β -oxidation, ketogenesis and ketolysis defects, mitochondrial cytopathies, ...
3. Disorders of organelle metabolism and complex molecules	<i>Examples:</i> Lysosomal diseases (sphingolipidoses, mucopolysaccharidoses, oligosaccharidoses), peroxisomal disorders, CDG syndromes, ...

'Diagnostics' vs Screening

➤ 1. Metabolic Workup / Follow-up

- Patients: mainly pediatric population, adults
- Sample: Plasma/Serum, Urine, CSF...
- Wide panel of disorders
- Low-throughput testing

➤ 2. Newborn Screening

- Patients: neonates
- Sample: DBS
- Specific program with limited number of diseases
- Population-based testing, very high throughput

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)
- ...

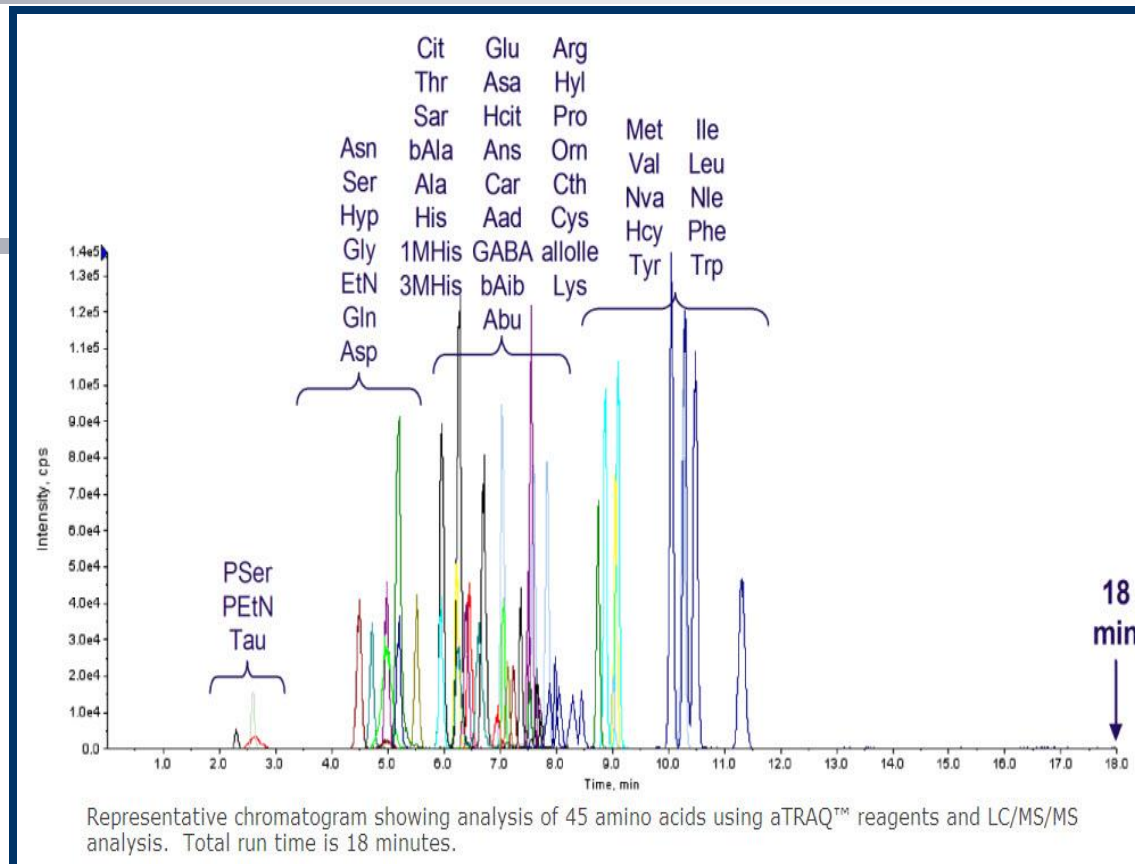
Confirmation assays

- Enzymatic testing on cultured cells
- Molecular sequencing

Amino Acids

➤ Technical aspects

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



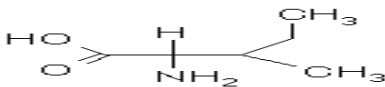
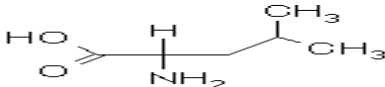
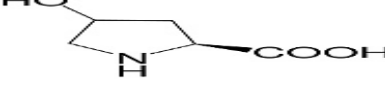
➤ Sample

- 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

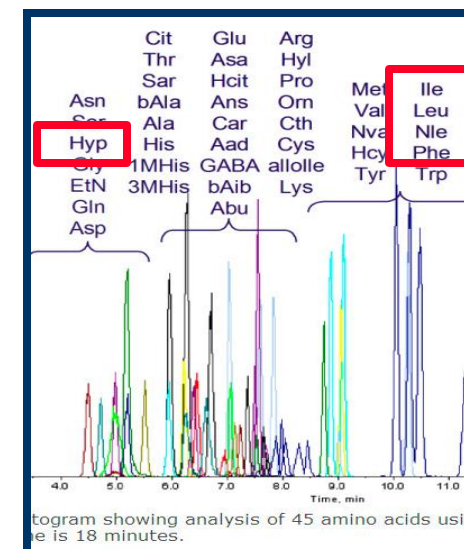
➤ Result interpretation

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

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

not specific

LC separation upfront of MS

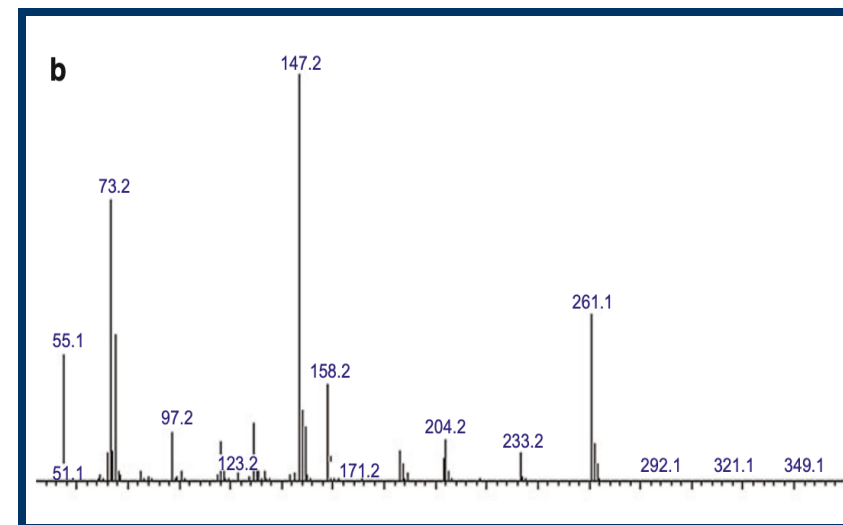
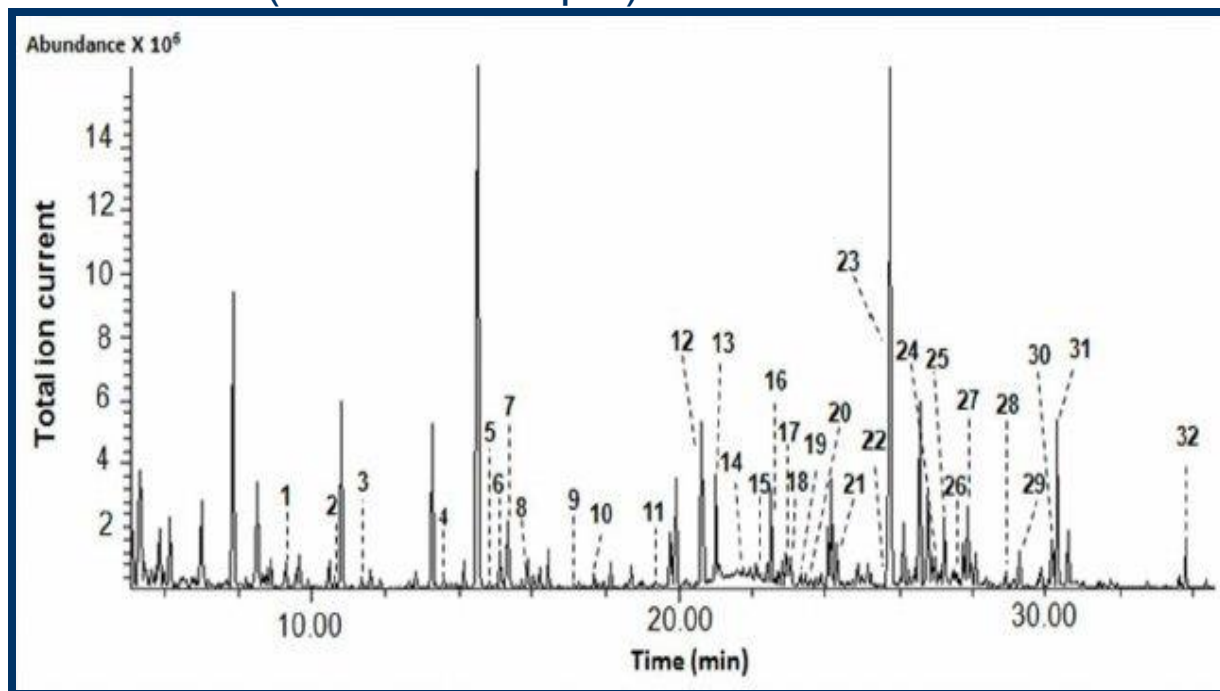


- Profile should be interpreted in the context of dietary history, nutritional status, and concurrent medication history.
- Report should include explanation of result, possible diagnoses, and recommendation for further testing if required.

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

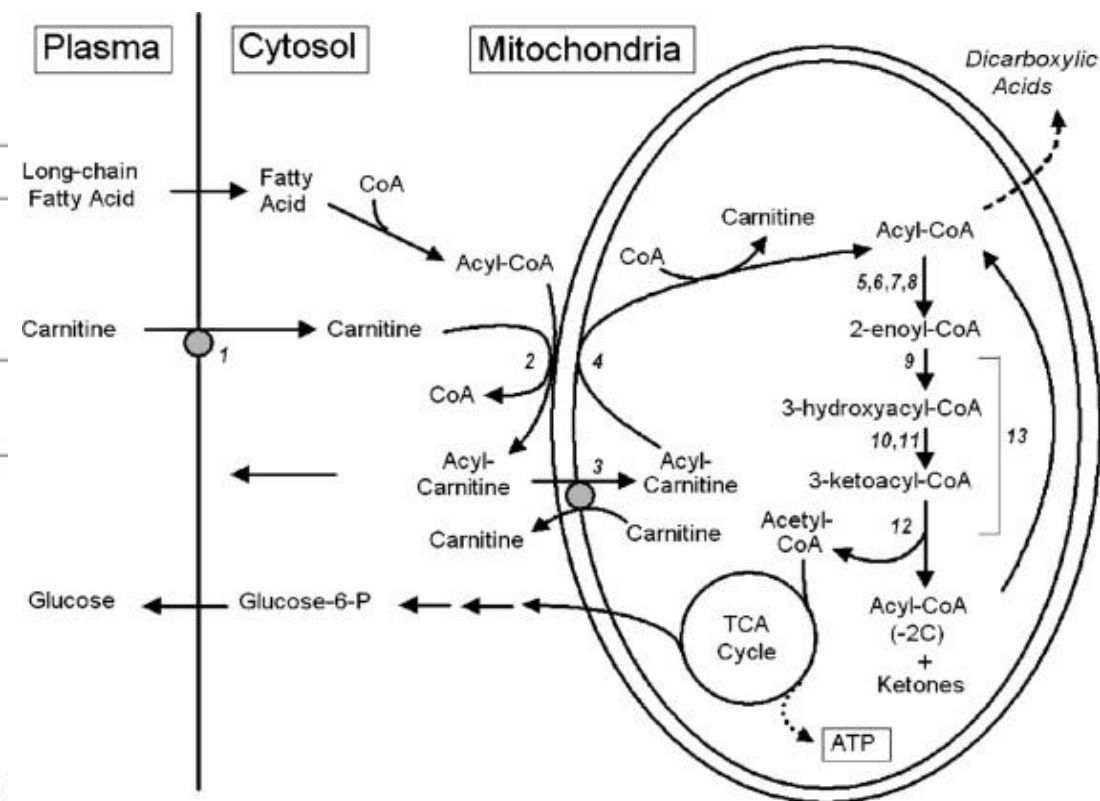
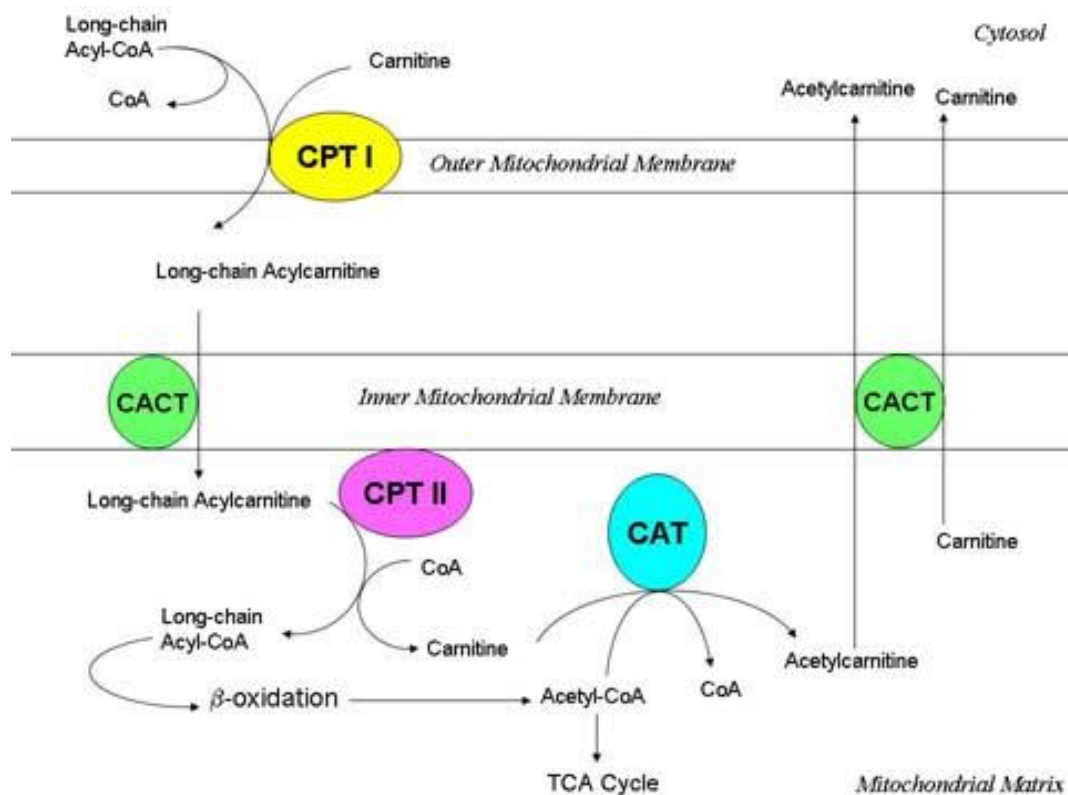
➤ Interpretation of results

- 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

➤ Role of Carnitine

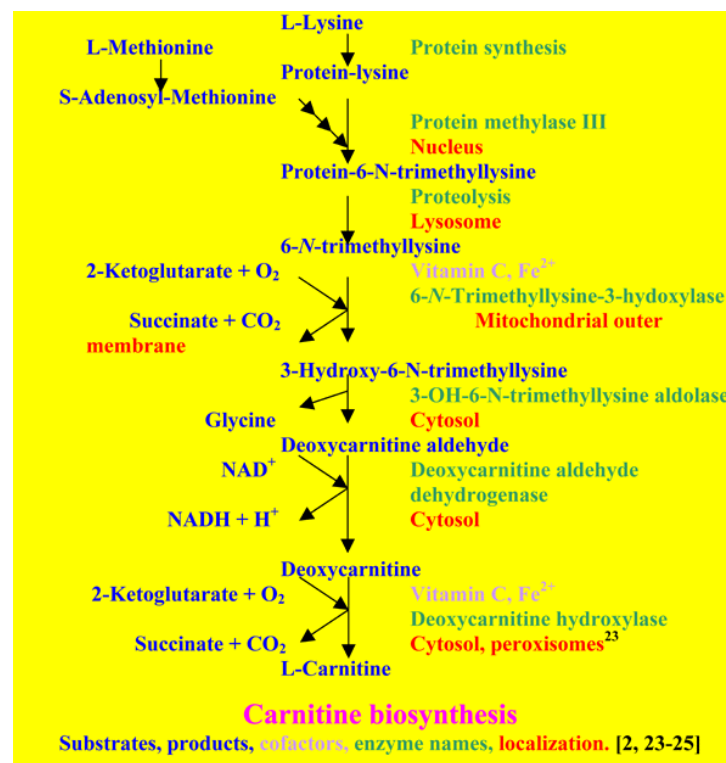
- Transport of long-chain fatty acids across mitochondrial membranes
- Detoxification of mitochondria in cases of acyl-CoA accumulation associated with enzyme deficiency (in the form of acylcarnitines)



Acylcarnitines

➤ Carnitine origine

- Alimentation (75%)
- Biosynthesis, mainly in liver and kidney



Acylcarnitines

➤ Technical aspects

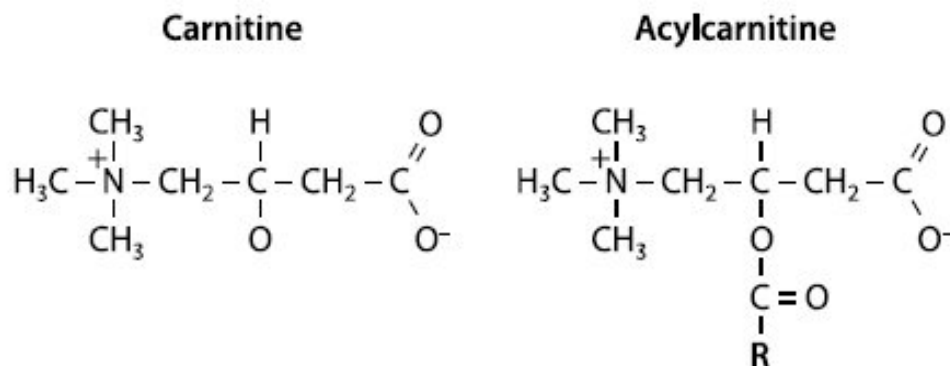
- LC-MS-MS

 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-carnitine 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

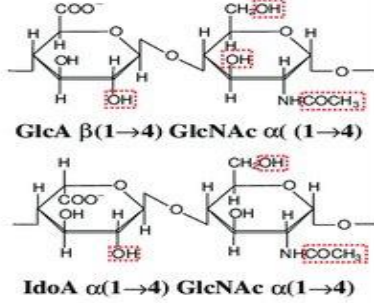
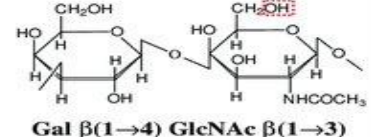
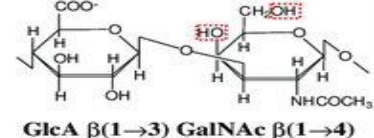
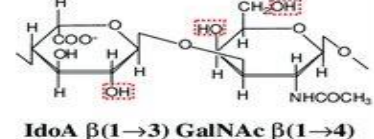
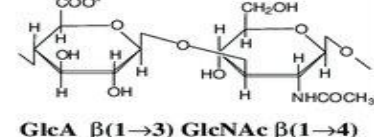
Lysosomal storage diseases

➤ Mucopolysaccharidosis

- Biomarker: Urinary GAGs
- GAGs are negatively-charged polysaccharide compounds. They are composed of repeating disaccharide units, present in every mammalian tissue

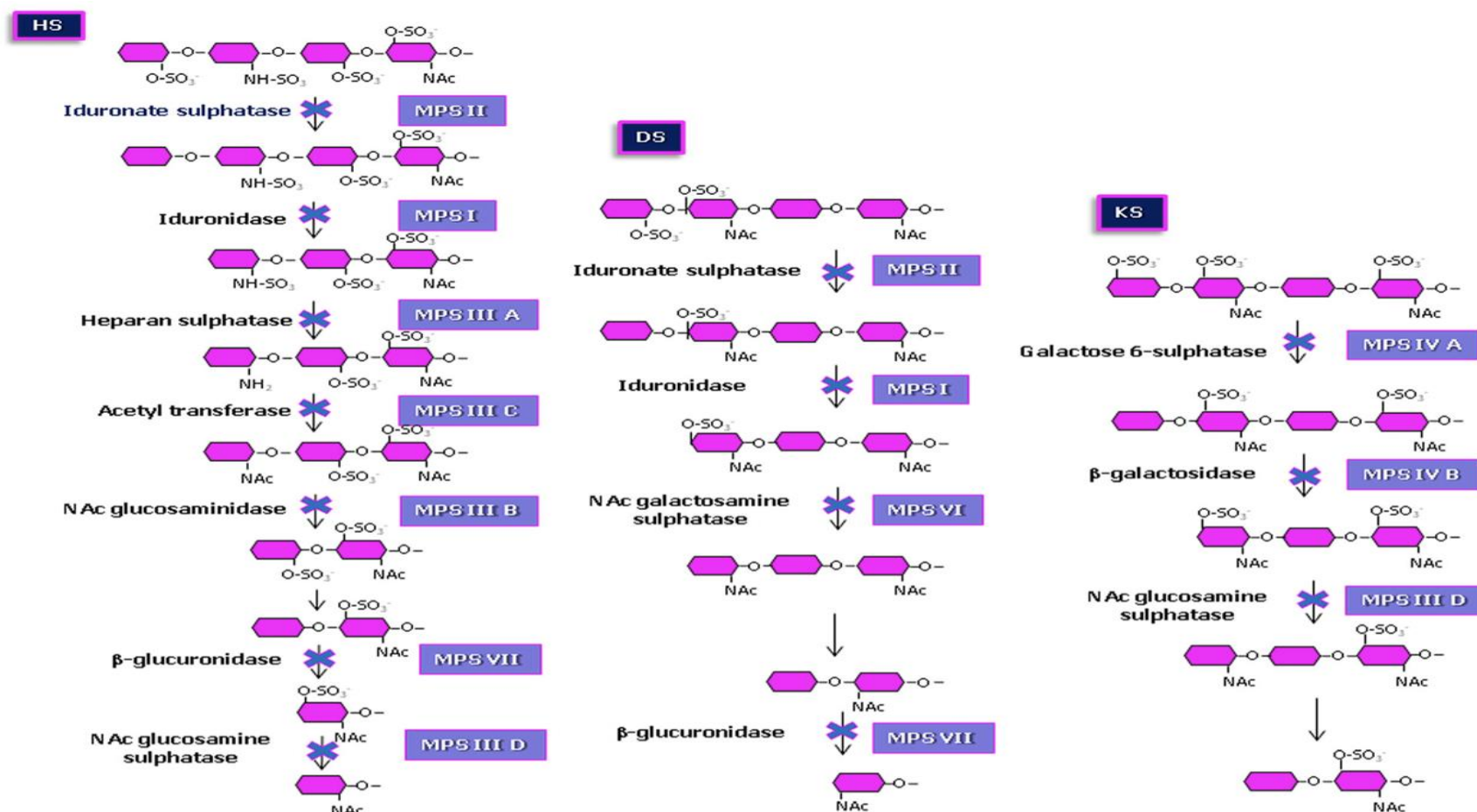
➤ Role

- 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

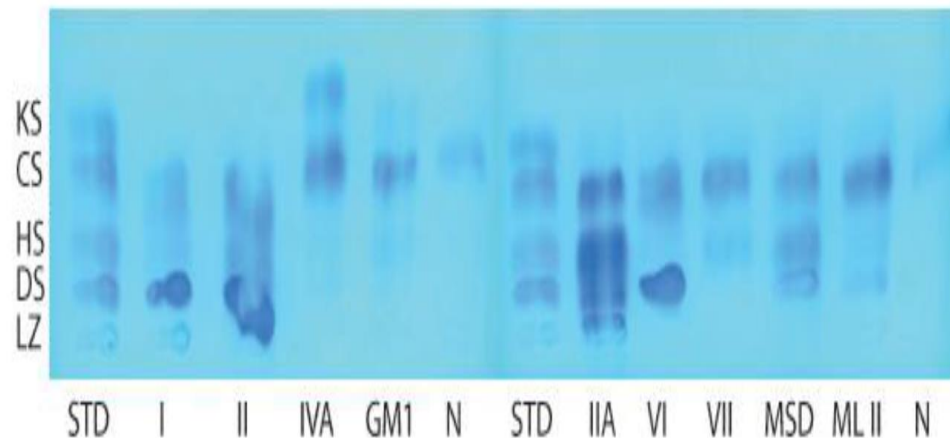
➤ Mucopolysaccharidosis



Lysosomal storage diseases

➤ MPS analysis

- Quantitative assay (MB coloration)
- Electrophoresis (MB coloration)



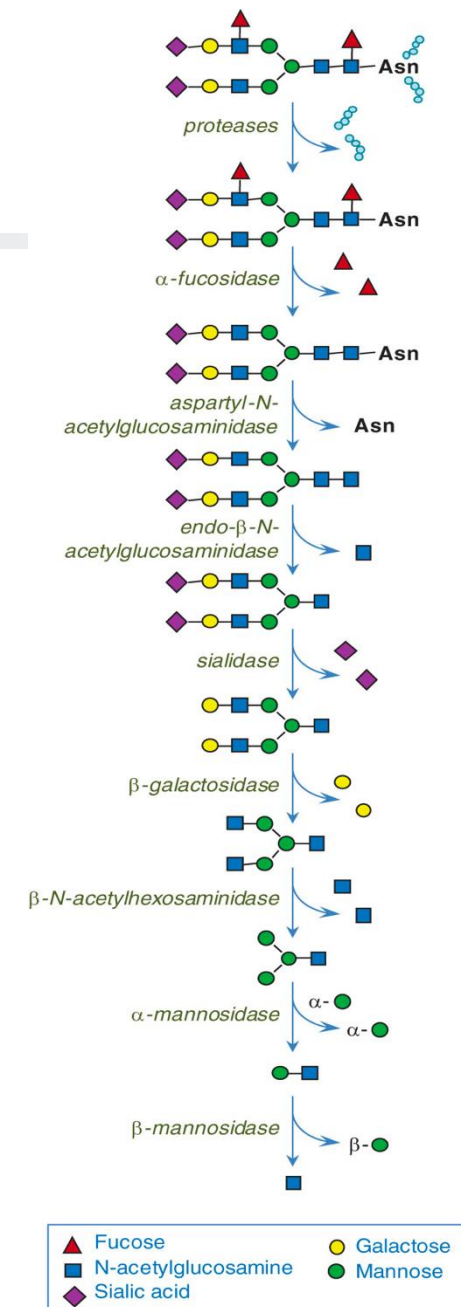
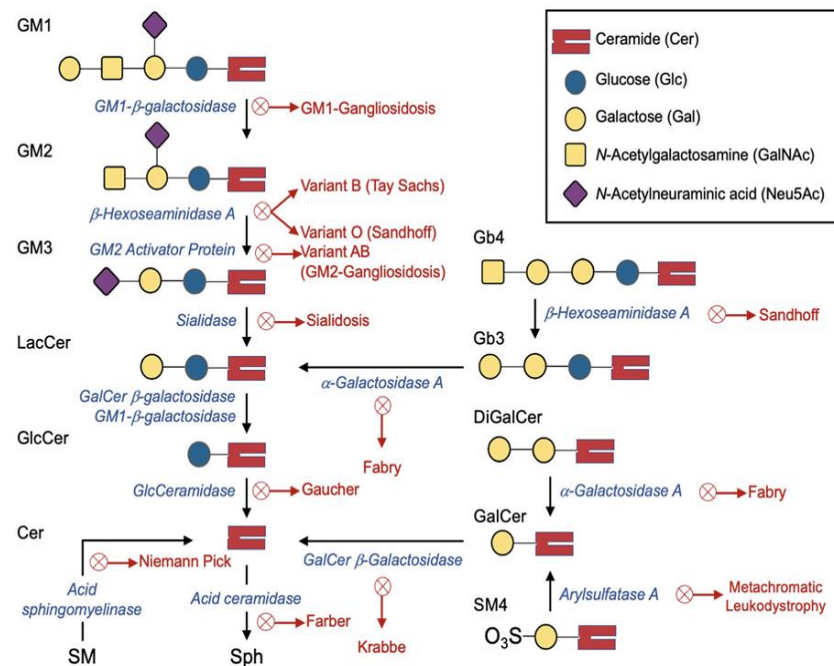
MPS	Name	Increased GAGs
I	Hurler, Hurler-Scheie or Scheie	HS + DS
II	Hunter	HS + DS
III A	Sanfilippo A	HS
III B	Sanfilippo B	HS
III C	Sanfilippo C	HS
III D	Sanfilippo D	HS
IV A	Morquio A	KS
IV B	Morquio B	KS
(V)	Scheie syndrome, initially proposed as type V,	
VI	Maroteaux-Lamy	DS
VII	Sly	HS + DS

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

Lysosomal storage diseases

➤ Oligosaccharidoses

- 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 or glycolipids.



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*)
 - Mucopolidosis II and III (*GNPTAB*)
 - Schindler disease (*NAGA*)
 - Aspartylglucosaminuria (*AGA*)
- False positive: parenteral nutrition, glue
- Specific enzymatic assay (on DBS or WBC / fibroblasts)

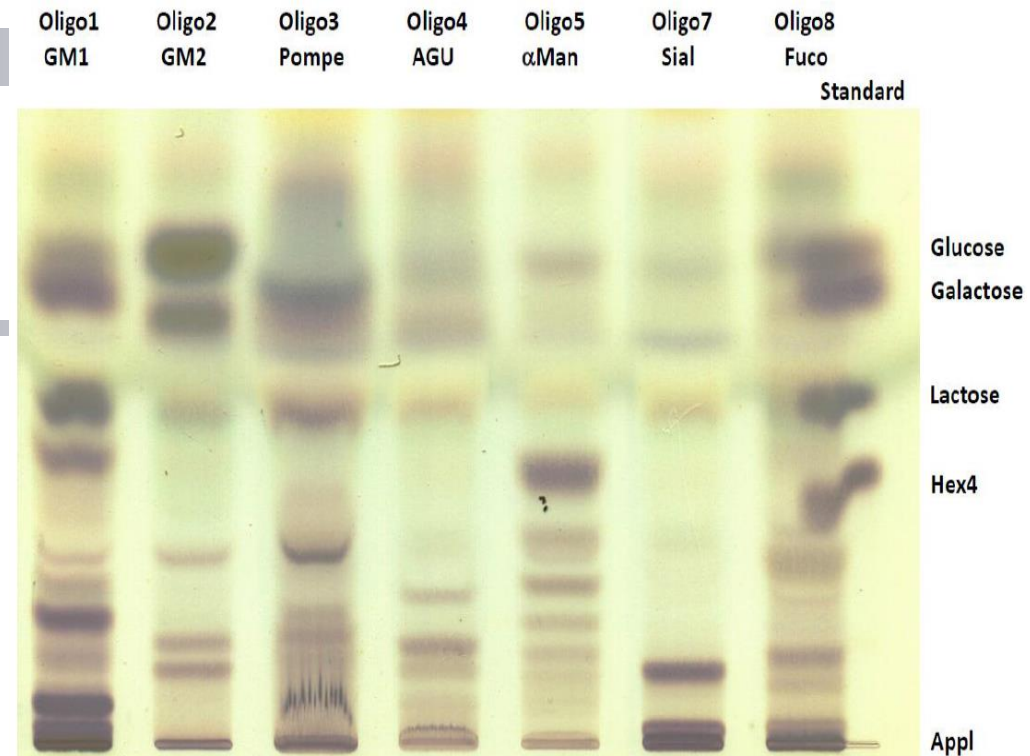


Table 1. Seven selected FOSs and the IS, with SRM transitions, retention times (RT), and corresponding disorders listed for each.

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	Δ HexA ^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.

CDG

➤ Sialotransferrin profiling

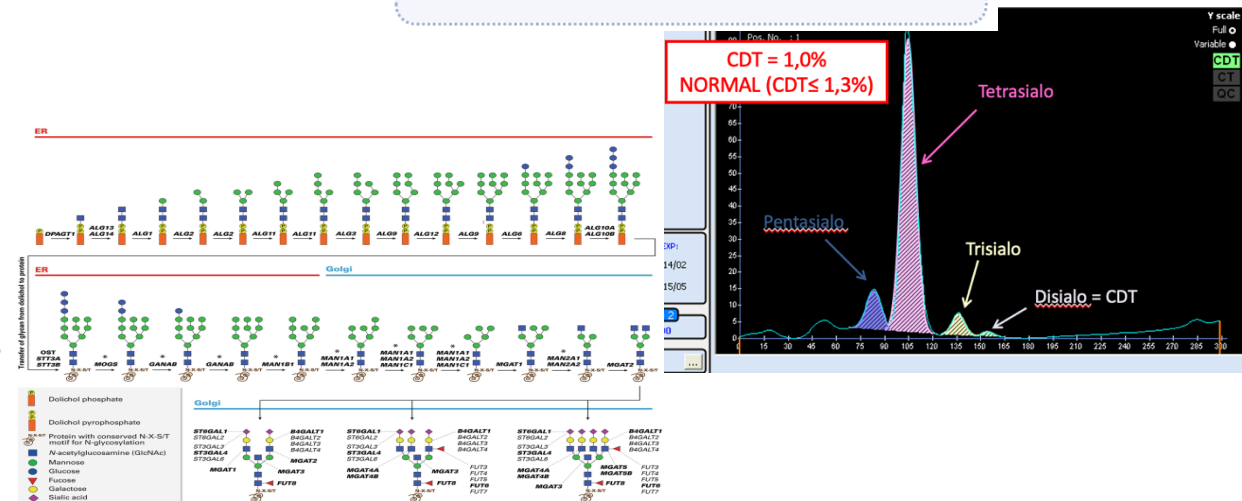
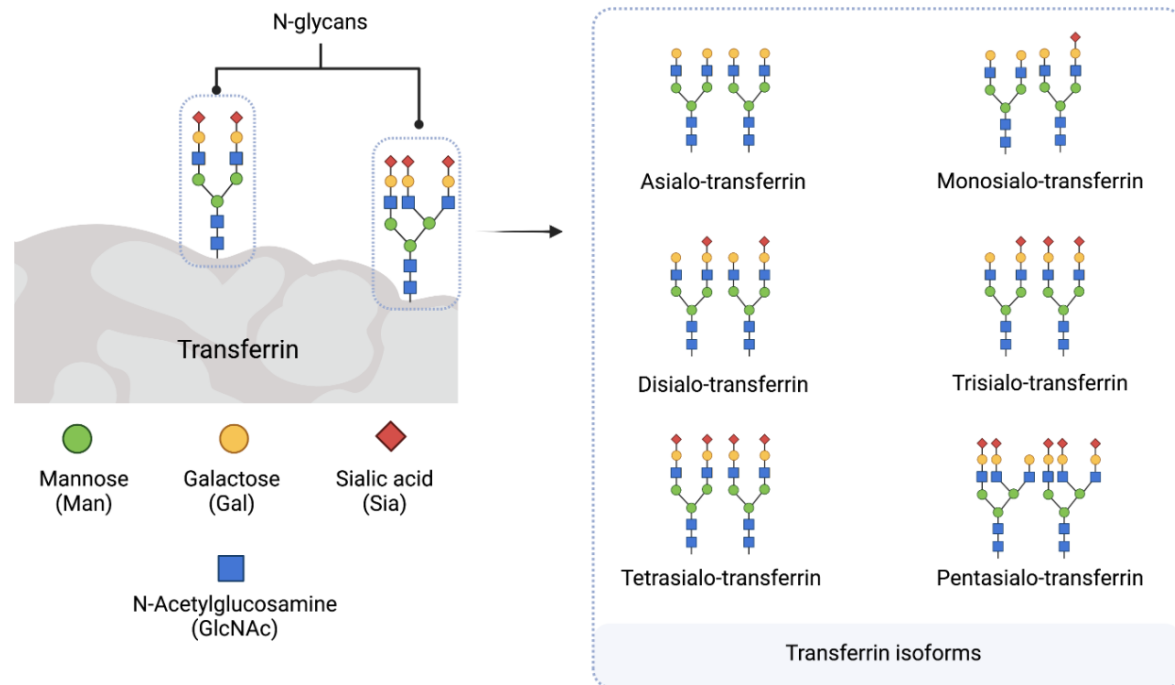
- IEF
- CZE

➤ Sample

- Serum !

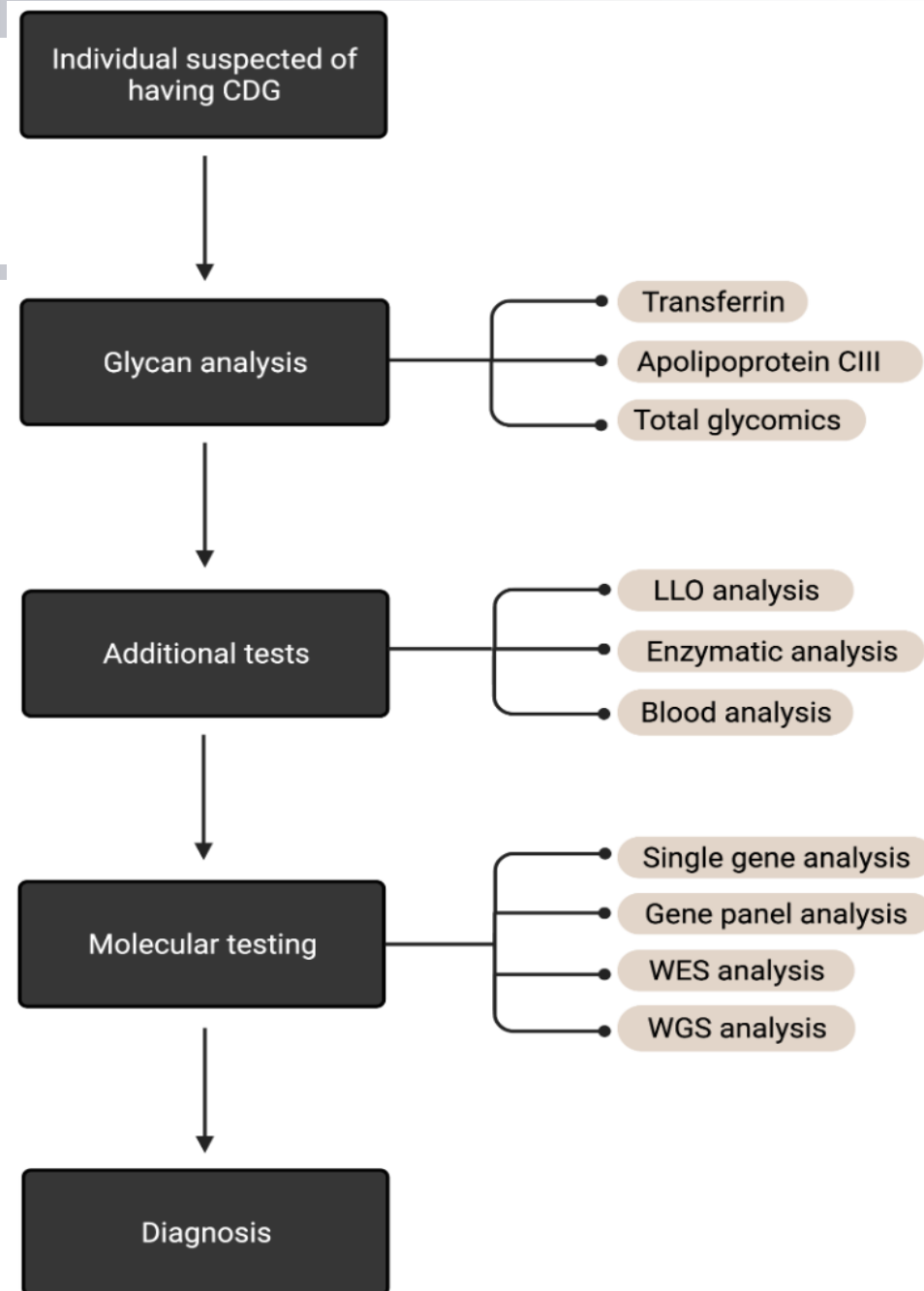
➤ Interpretation of results

- Disorders
 - CDG I: caused by defects in the assembly and transfer of oligosaccharides to an asparagine residue on a protein
 - CDG II: caused by defects in the processing of the N-glycans attached to proteins
- False positive: chronic alcohol consumption, severe hepatic def, transferrin variants



CDG

- **Growth problems** – feeding difficulties, failure to thrive
- **Development delays** – intellectual disability, delay in reaching developmental milestones
- **Neurological problems** – decreased muscle tone (hypotonia), seizures, poor balance and coordination (ataxia), cerebellar abnormalities, stroke-like episodes
- **Ophthalmological problems** – misaligned or crossed eyes (strabismus), eye abnormalities, retinal degeneration (retinitis pigmentosa)
- **Liver problems** – liver disease with elevated liver enzymes
- **Heart problems** – fluid accumulation around the heart, thickening and stiffening of the heart muscle (cardiomyopathy)
- **Hematologic problems** – abnormal bleeding or blot clotting
- **Endocrine problems** – low blood sugar due to high insulin levels (hypoglycemia), decreased thyroid hormone (hypothyroidism), growth hormone deficiency
- **Skeletal problems** – curving of the spine
- **Immunologic problems** – severe or long-lasting infections
- **Gastrointestinal symptoms** - chronic diarrhea, vomiting
- **Skin problems** - loose skin; rash, scaly skin, peeling of skin



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

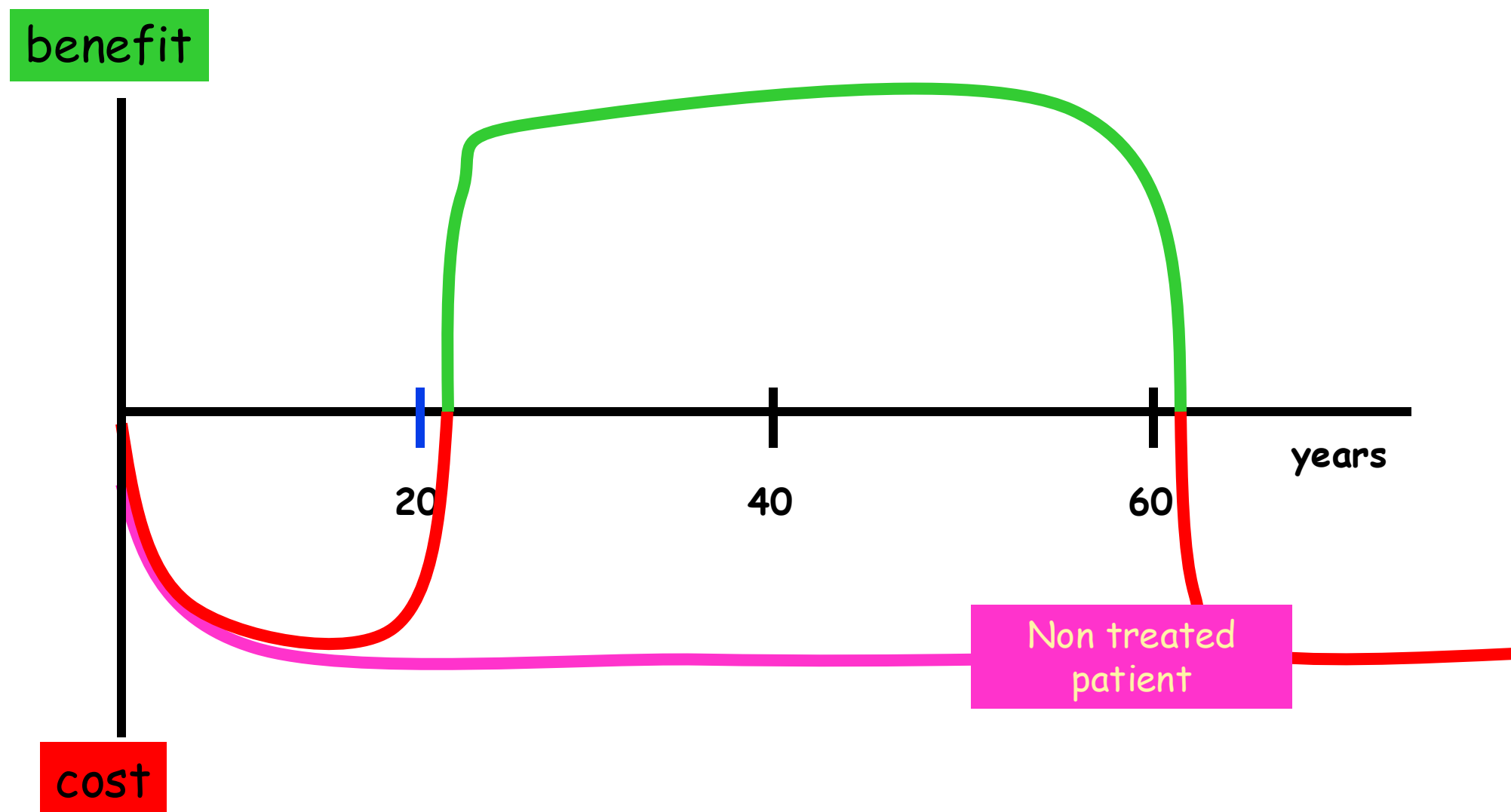
➤ History

- 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

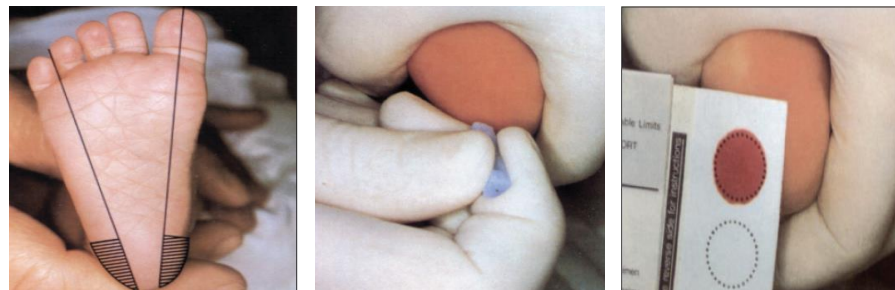
 - 5 NBS centres – 4 screening labs
 - Liège – ULiege
 - Bruxelles – UCL
 - Bruxelles – ULB
 - Bruxelles – VUB
 - Anvers – UA
- } 1 lab

Sampling

Day 0 : birth



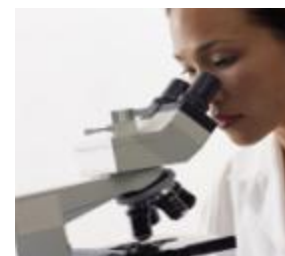
Day 2-5 : Sampling - filter paper



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 abimées.

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

ACCOCHEMENT

☐ 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: ____/____/____

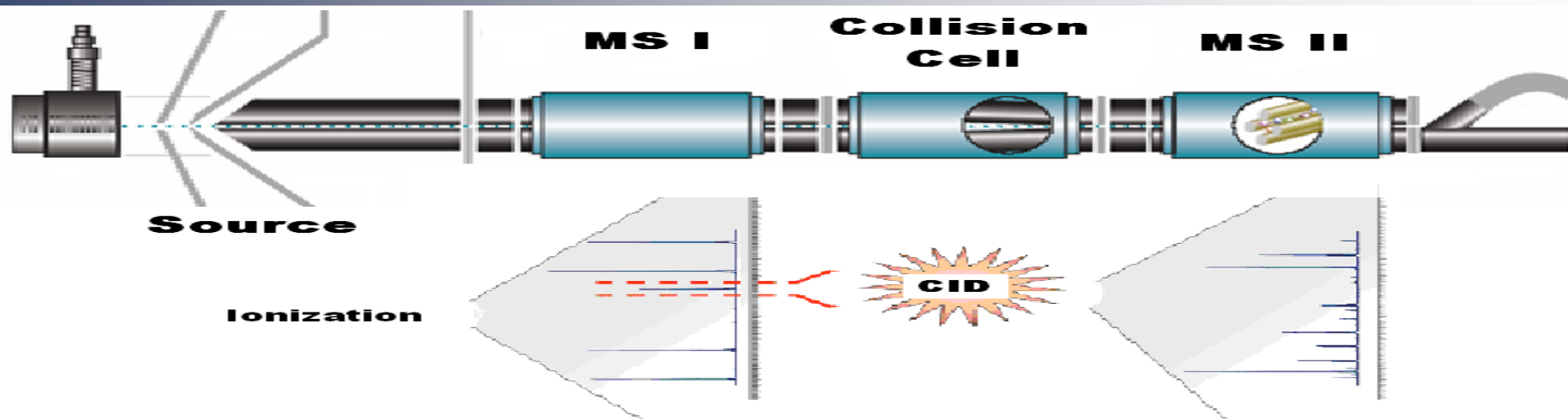
Heure de prélèvement: ____ h ____ min

Poids au prélèvement: ____ kg ____ g



SN L065301

Mass Spectrometry - QQQ



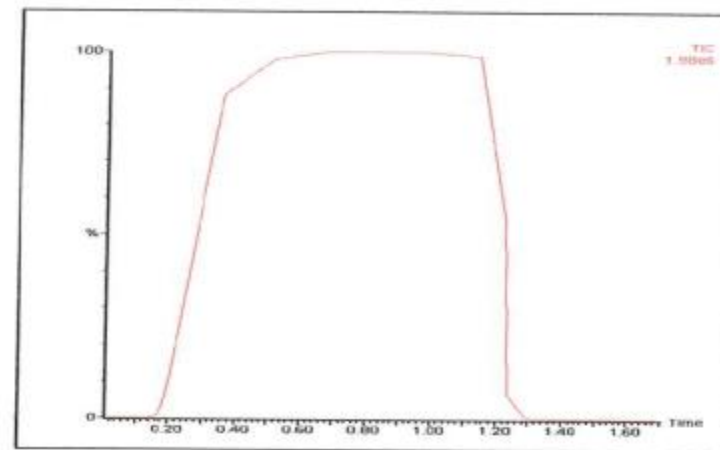
- Ionisation des composés de l'échantillon.
- Sélection des ions précurseurs selon leurs masses dans le premier spectromètre.
- Fragmentation des ions « précurseurs » par collision avec un gaz neutre dans la cellule de collision afin d'obtenir des ions « produits » - Processus appelé COLLISION INDUCED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

Analytical aspects

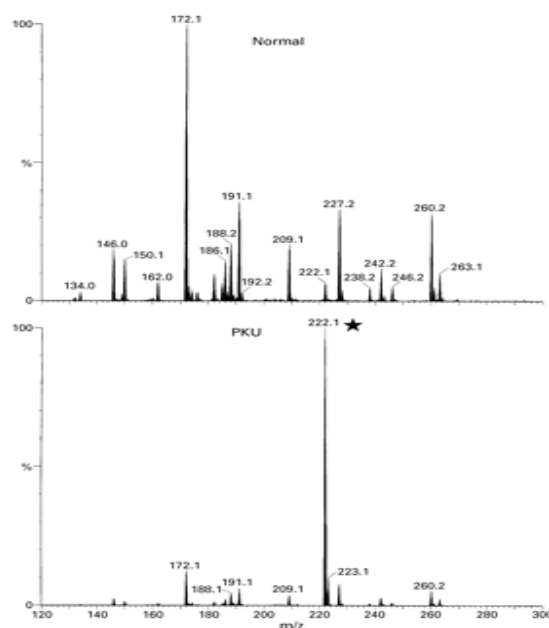
➤ FIA-MS

No chromatographic separation

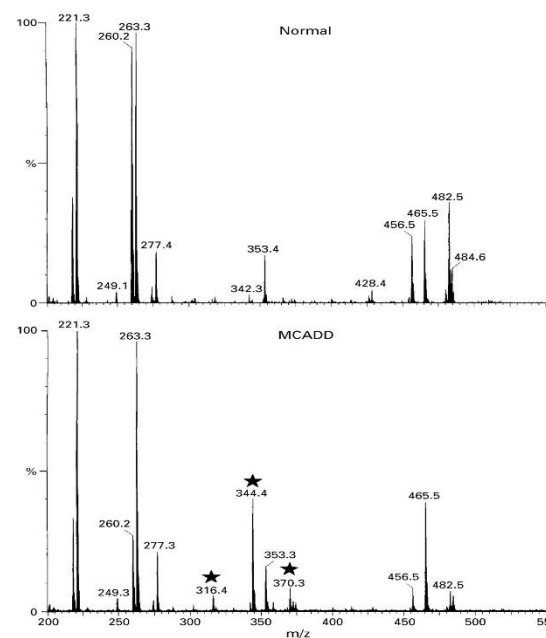
➤ Quantitation based on MS spectrum



PKU



MCAD



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

specificity for some compounds

FORMULA	NAME	MW
<chem>CC(C)C[C@@H](C(=O)O)N</chem>	Isoleucine	131
<chem>CC(C)C[C@H](C(=O)O)N</chem>	Leucine	131
<chem>C1CC[C@H](C(=O)O)N1</chem>	Proline	115
<chem>C1CC[C@H](C(=O)O)N1O</chem>	OH-Proline	131

Markers

Acides Aminés	Aminoacidopathie Anomalie du Cycle de l'Urée
Phénylalanine	Phénylcétonurie
Tyrosine (+SUAC)	Tyrosinémie
Leucine-Isoleucine	Leucinose (Maladie du Sirop d'Erable)
Méthionine	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	Déficit en ASA Lyase (Cycle de l'Urée)
Glycine	Hyper-Glycinémie non Cétogène

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		Déficit 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- β -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

Analytical aspects

➤ Xle: 745 $\mu\text{M/L}$ (cutoff: 475 $\mu\text{M/L}$)

Figure 1.A. MRM profile of patient with Hyper Leu/Ile
Leu/Ile: $m/z=188.1$ – Leu-D₃: $m/z=191.1$

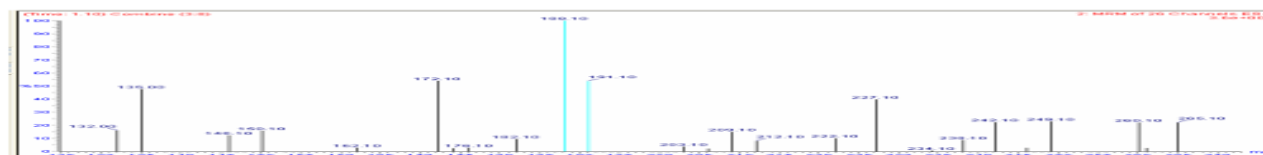


Figure 1.B. MRM profile of a normal patient.
Leu/Ile: $m/z=188.1$ – Leu-D₃: $m/z=191.1$



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

PLASMA AMINO ACIDS

Hydroxyproline sg

323.9 $\mu\text{mol/L}$

0.0-63.0

Proline sg

297.5 $\mu\text{mol/L}$

52.0-298.0

PLASMA AMINO ACIDS

Hydroxyproline sg

346.2 $\mu\text{mol/L}$

0.0-63.0

Proline sg

422.1 $\mu\text{mol/L}$

52.0-298.0

URINE AMINO ACIDS

Hydroxyproline ur

3343.6 $\mu\text{mol/L}$

0.0-187.0

OH-proline (mM/Mcr)

2202.8 mM/M créat

0.0-106.0

Proline ur

87.8 $\mu\text{mol/L}$

0.0-172.0

Proline (mM/Mcr)

57.8 mM/M créat

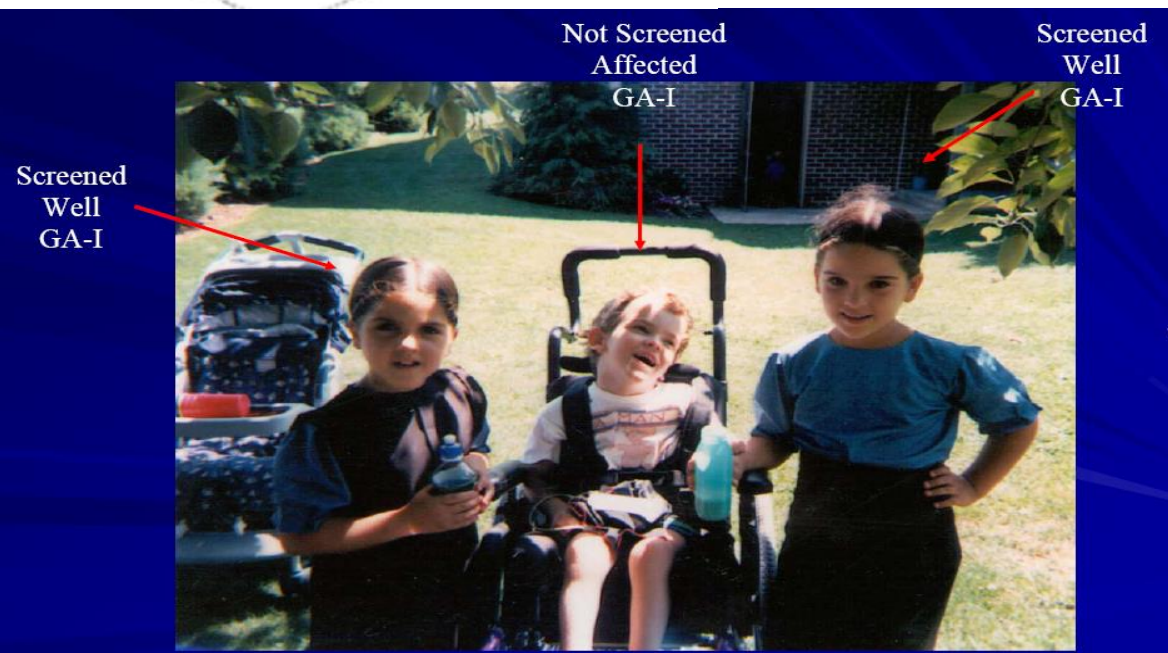
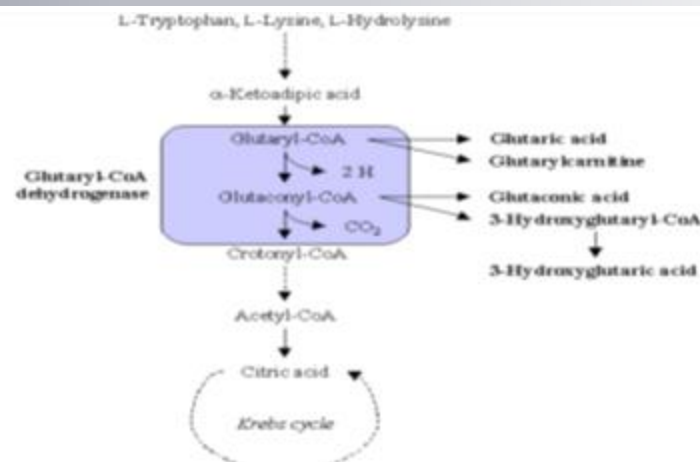
0.0-86.0

FORMULA	NAME	MW
<chem>CC(C)C[C@@H](C(=O)O)N</chem>	Isoleucine	131
<chem>CC(C)C[C@H](C(=O)O)N</chem>	Leucine	131
<chem>C1CC[C@H](C(=O)O)N1</chem>	Proline	115
<chem>C1CC[C@@H](C(=O)O)N1O</chem>	OH-Proline	131

Why NBS can make the difference

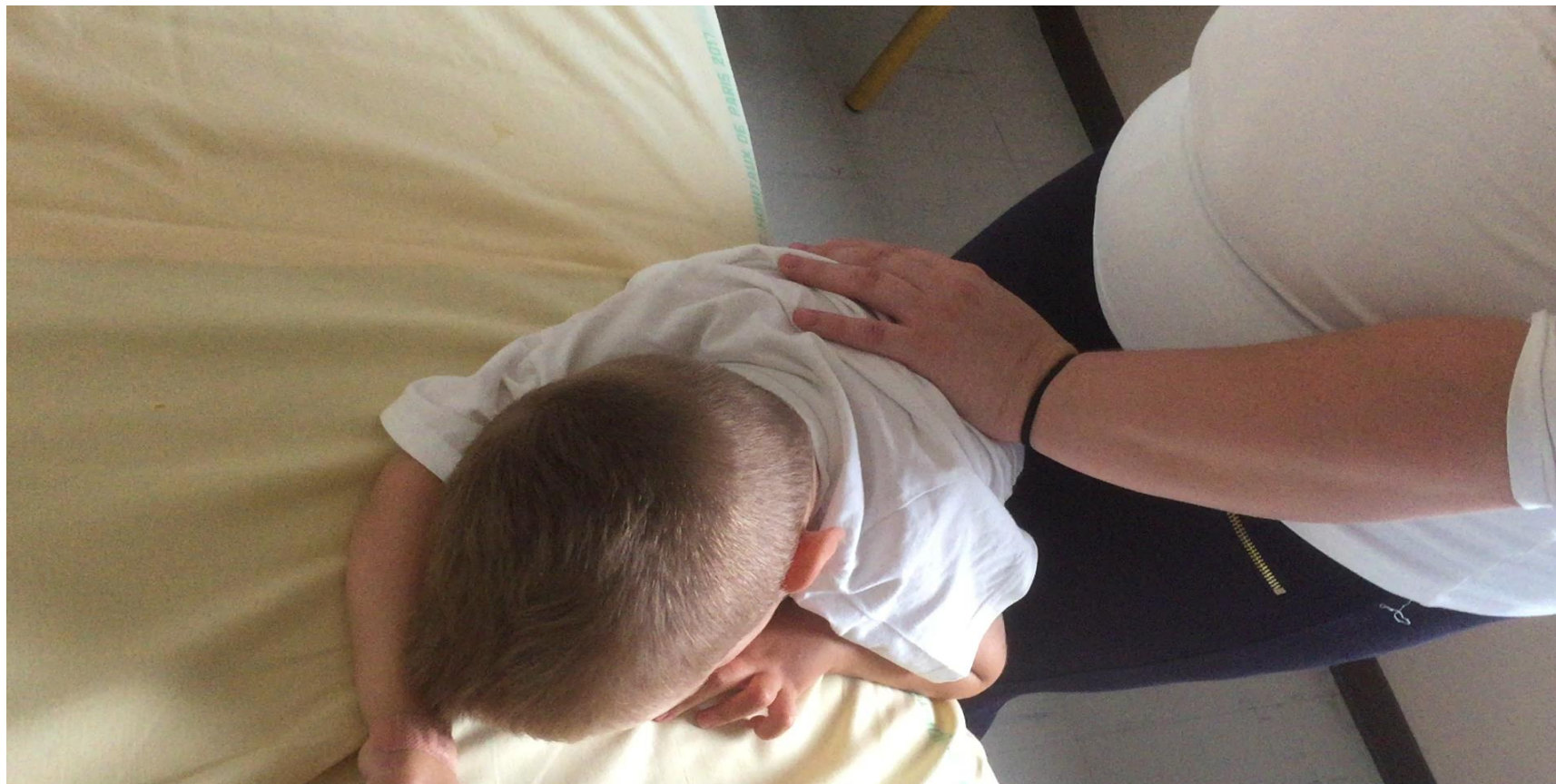
➤ Ex: Glutaric Aciduria I

- **Prevalence : 1 / 30.000**
- **Untreated**
 - Metabolic decompensation, ketoacidosis, hyperammonemia, hypoglycemia
 - Severe psychomotor 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**



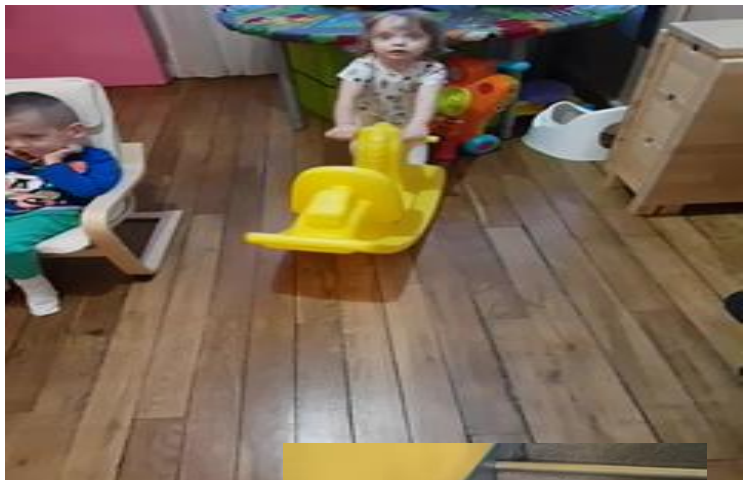
SMA Treatment

Post >< Pre Symtpoms



SMA Treatment

Post >< Pre Symtpoms



Thank you

