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Lo Screening Neonatale in Italia, stato dell'arte

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ITALY

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STUDIORUM UNIVERSITAS FLORENTINA

Newborn Screening

Newborn screening (NBS) program is a complex and organized system consisting of family and personnel education, biochemical tests, confirmatory biochemical and genetic tests, diagnosis, therapy, and patient follow up.

Newborn Screening

It identifies biochemical or other inherited conditions that may produce mental retardation, other disabilities and/or death.

Babies are screened for these conditions during the newborn period.

These conditions are identified using tests on blood collected from a heel stick onto filter paper

SCREENING: DEFINIZIONE

Lo screening è **un'indagine a tappeto**, estensibile alla popolazione, **non costosa**.

Si basa su una ***"diagnosi biochimica"*** perché il neonato alla nascita è sano:

lo screening evidenzia una malattia PRIMA che compaiano segni/sintomi clinici.

Criteria of a screening programme

- The condition being screened for should be an important health problem
- The natural history of the condition should be well understood
- There should be a detectable early stage
- Treatment at an early stage should be of more benefit than at a later stage
- A suitable test should be devised for the early stage
- The test should be acceptable
- Intervals for repeating the test should be determined
- Adequate health service provision should be made for the extra clinical workload resulting from screening
- The risks, both physical and psychological, should be less than the benefits
- The costs should be balanced against the benefits

Wilson-Jungner criteria; World Health Organisation 1968

CRITERI DI AMMISSIBILITA' ALLO SCREENING

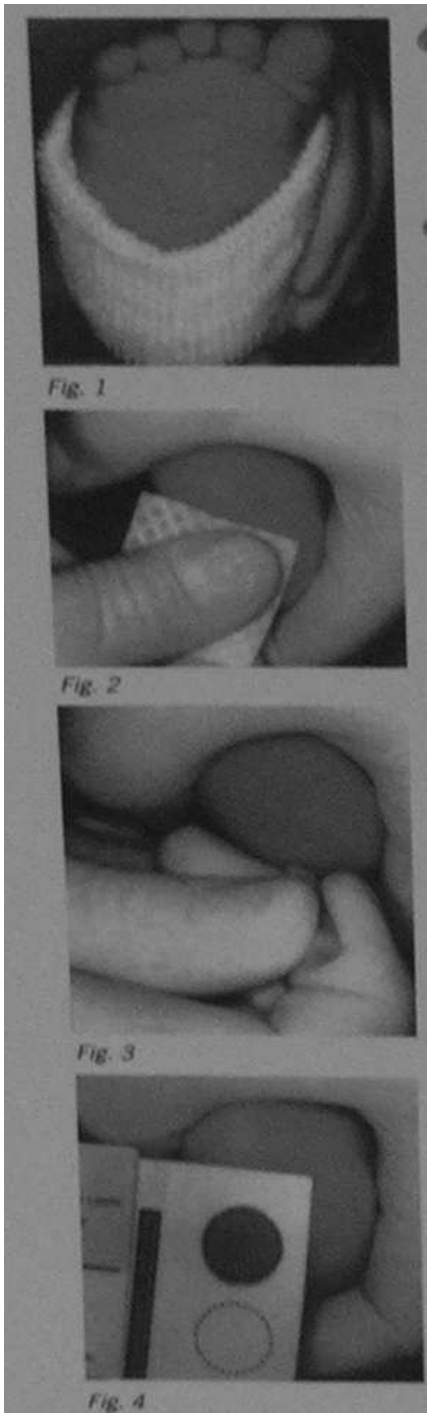
- PROBLEMA IMPORTANTE DI SALUTE PER L'INDIVIDUO E LA COMUNITA'
- ESISTENZA DI UN'ACCETTABILE FORMA DI TERAPIA CHE INFLUENZI POSITIVAMENTE IL SUCCESSIVO DECORSO
- ESISTENZA DI UN PERIODO DI LATENZA O DI SINTOMI PRODROMICI
- IL TEST DEVE ESSERE APPLICABILE IN TALE PERIODO ED ACCETTABILE DALLA POPOLAZIONE
- PROCEDIMENTI DIAGNOSTICI SUCCESSIVI FACILMENTE DISPONIBILI
- COSTO DIAGNOSTICO BILANCIATO DALLE SPESE MEDICHE O DI ALTRO TIPO IN CASO DI MANCATA DIAGNOSI

* AUMENTO ASPETTATIVA DI VITA

* MIGLIORAMENMTO QUALITA' DI VITA

* POSSIBILITA' DI CONSIGLIO GENETICO

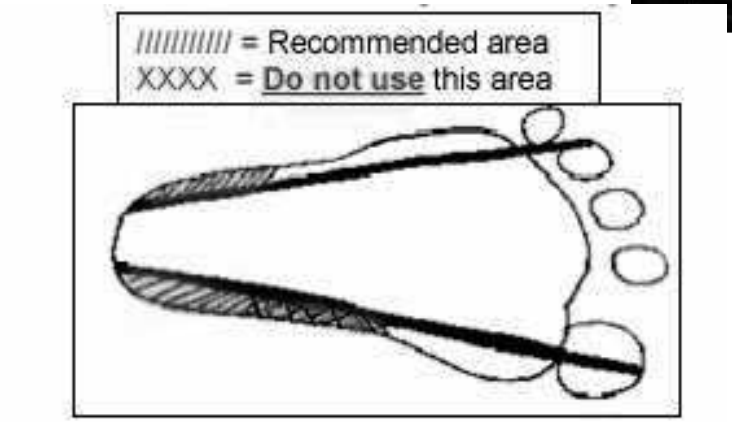
* DIAGNOSI PRENATALE



PRELIEVO DAL TALLONE

Riscaldare il tallone con un panno caldo (39-41°C) per 3-5 minuti

Disinfettare il punto del prelievo con alcool e rimuoverne l'eccesso con una garza sterile



Fare una nella zona laterale

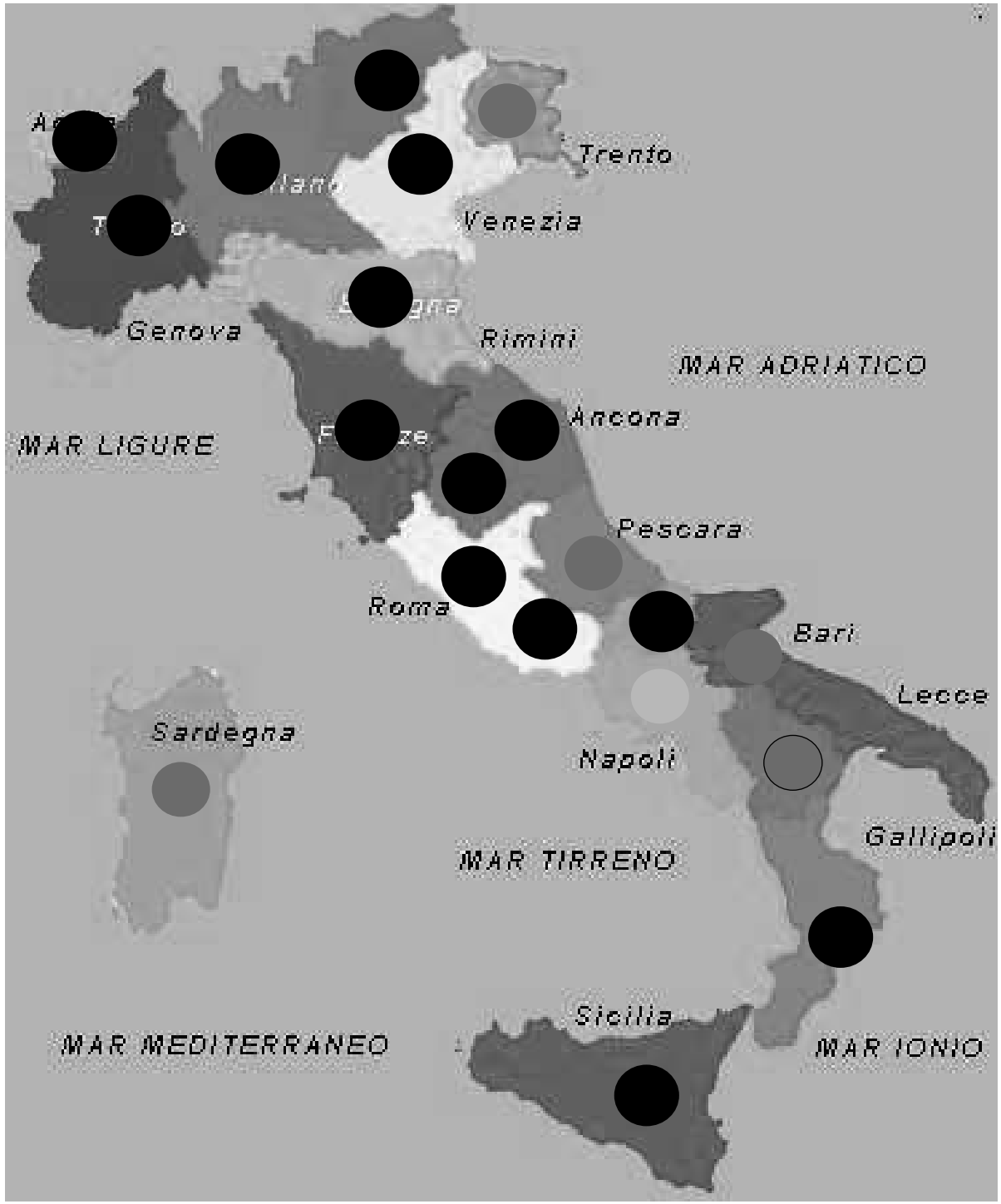
Rimuovere la prima goccia di sangue perché diluito da liquido interstiziale e aspettare che si formi una nuova goccia. Applicare leggermente la carta bibula sulla goccia lasciandola diffondere

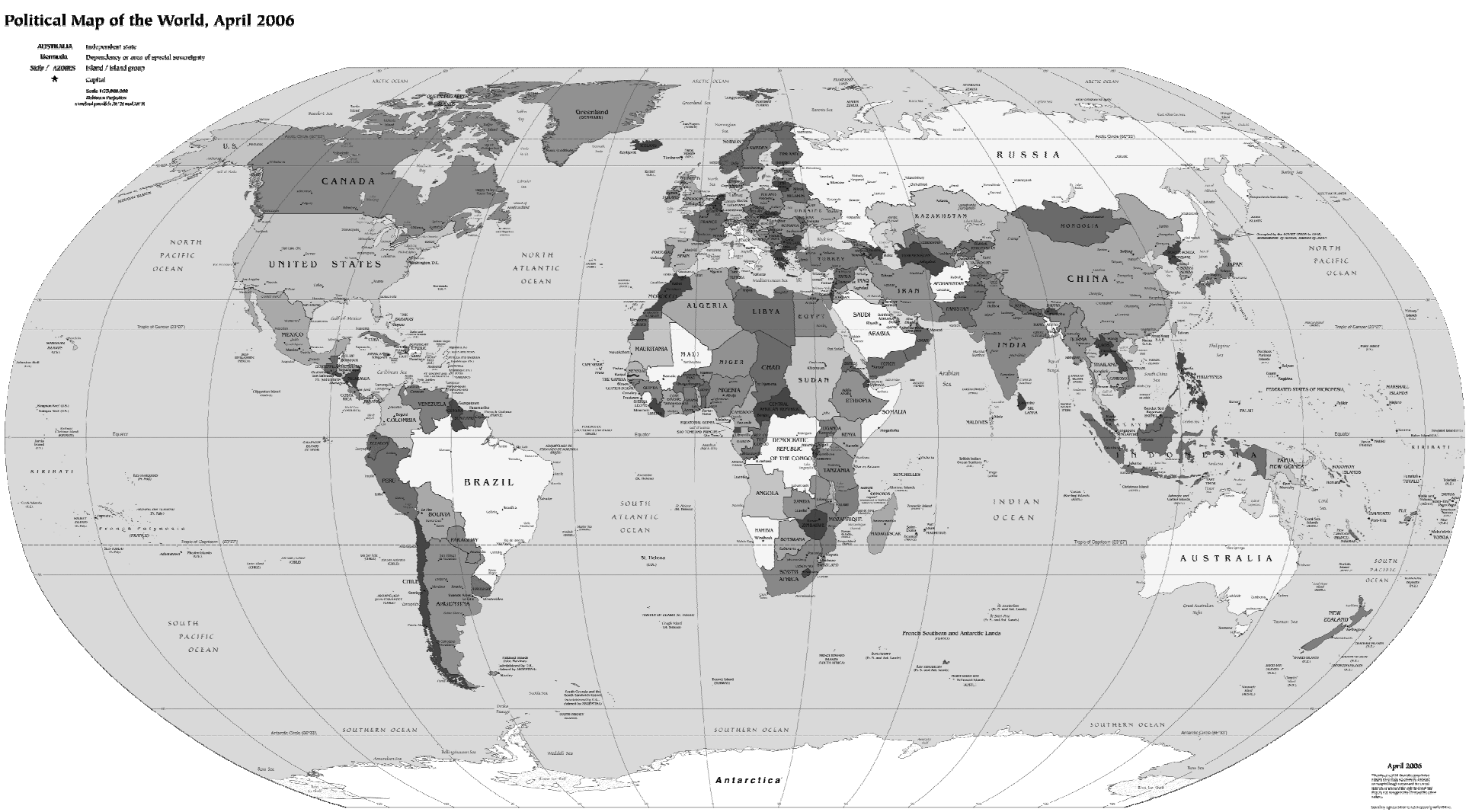
LEGGE ITALIANA N. 104/1992

…nei primi giorni di vita, ancora in ospedale, il bimbo viene sottoposto al cosiddetto "screening neonatale", una serie di esami che permettono di individuare precocemente alcune malattie congenite (cioè presenti alla nascita), ma che si manifestano in genere più tardivamente. Grazie a questo test, che deve essere eseguito dopo quarantotto ore di vita, è possibile individuare e curare precocemente queste malattie, che possono, altrimenti, avere gravi conseguenze sullo sviluppo psicomotorio e sull'accrescimento del bambino. Dal 1992 (legge-quadro n. 104 del 5-5-1992) questo esame deve essere eseguito su tutti i neonati italiani (la prima legge che ne ha sancito l'importanza e quella della regione Liguria del 17-8 -1973).

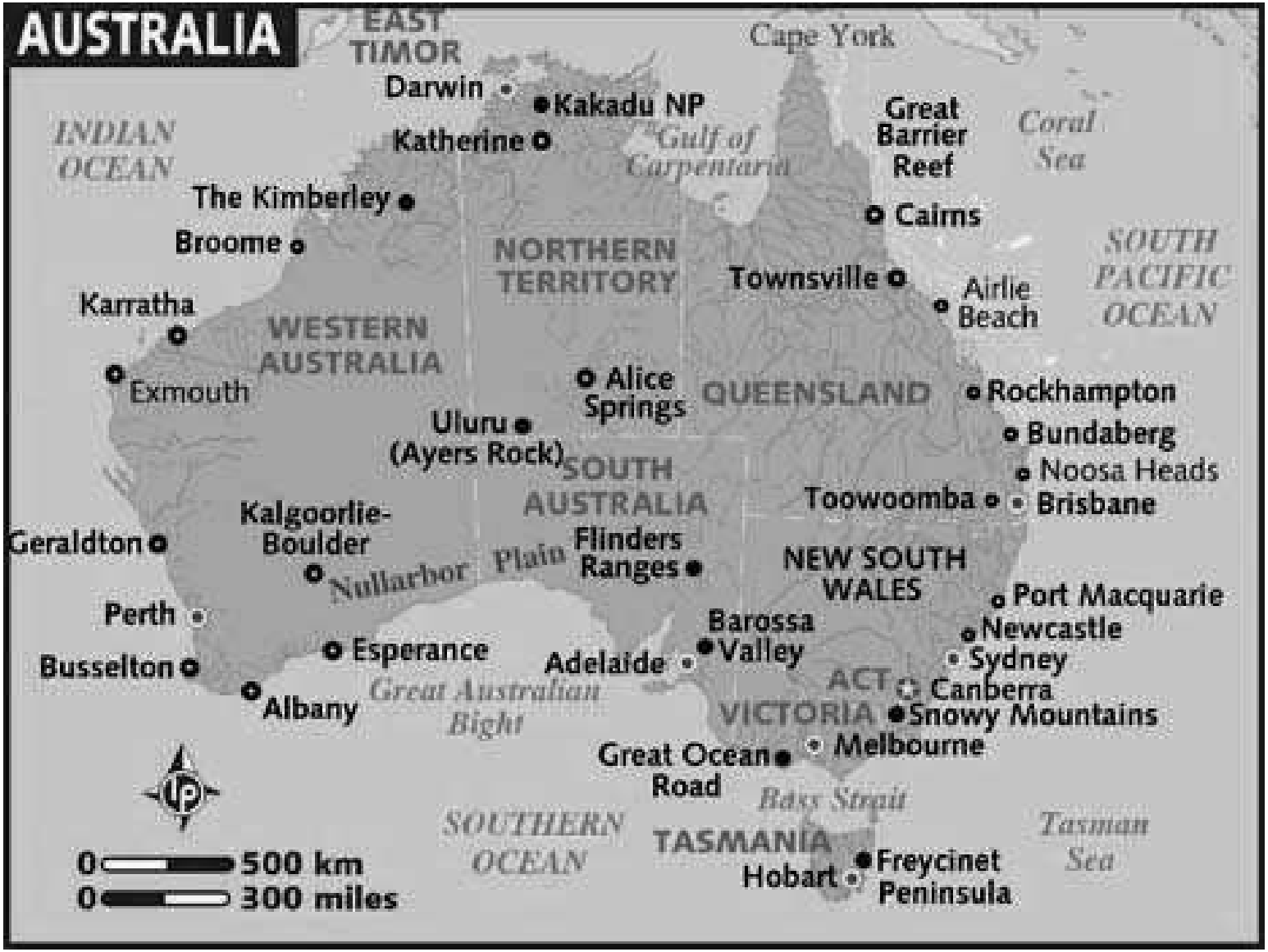
Lo "screening neonatale" viene effettuato per identificare alcuni disturbi molto seri, che se vengono individuati precocemente possono essere curati con ottimi risultati. Queste malattie sono congenite, presenti cioè già dalla nascita, ma nei primi giorni di vita non si manifestano e, se non viene eseguito il test, possono essere individuate solo più tardi. I disturbi individuabili con questo esame sono tre: la fenilchetonuria, una malattia ereditaria che provoca problemi nell'assimilazione di una sostanza, la fenilalanina (monitorando il dosaggio di quest'ultima); l' ipotiroidismo congenito, un problema della tiroide, le ghiandola che regola lo sviluppo e la crescita (in base al dosaggio del TSH o ormone tireotropo) e la fibrosi cistica, una malattia respiratoria molto seria (verificata tramite la concentrazione di un enzima la tripsina).

FC: copertura 82%

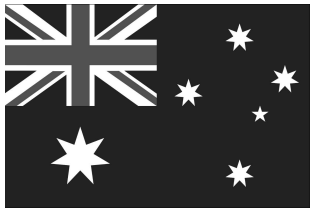




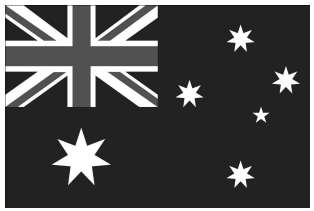
Lo screening neonatale esteso nel mondo


AUSTRALIA
EAST TIMOR
Cape York
Darwin
Kakadu NP
Katherine
INDIAN OCEAN
Gulf of Carpentaria
Great Barrier Reef
Coral Sea
The Kimberley
Broome
Cairns
NORTHERN TERRITORY
SOUTH PACIFIC OCEAN
Townsville
Airlie Beach
Karratha
WESTERN AUSTRALIA
Exmouth
Alice Springs
QUEENSLAND
Rockhampton
Uluru (Ayers Rock)
Bundaberg
Noosa Heads
SOUTH AUSTRALIA
Toowoomba
Brisbane
Kalgoorlie-Boulder
Geraldton
Flinders Ranges
Nullarbor Plain
NEW SOUTH WALES
Port Macquarie
Perth
Barossa Valley
Newcastle
Esperance
Adelaide
Sydney
Busselton
ACT
Canberra
Great Australian Bight
Albany
VICTORIA
Snowy Mountains
Melbourne
Great Ocean Road
Bass Strait
SOUTHERN OCEAN
TASMANIA
Tasman Sea
Hobart
Freycinet Peninsula
0 500 km
0 300 miles

AUSTRALIA



25 Disorders



Department of Health

health

Newborn screening policy and guidelines

2011

#	Disorder	Other names
1	Hypothyroidism	
2	Cystic fibrosis	
	Disorders detected by tandem mass spectrometry:	
3	3-hydroxy-3-methylglutaryl CoA lyase	HMG CoA lyase
4	3-methylglutaryl CoA hydratase	3-methylglutaconic aciduria type 1
5	Argininosuccinic aciduria	Argininosuccinate lyase
6	Citrullinaemia type 1	Argininosuccinate synthetase
7	Beta ketothiolase	T2 deficiency, 3-oxothiolase
8	Maple syrup urine disease	MSUD, branched chain keto acid dehydrogenase (mild/ intermittent forms may not be detected)
9	Carnitine palmitoyl transferase 1	CPT1
10	Carnitine palmitoyl transferase 2	CPT2
11	Carnitine uptake defect	CUD, systemic carnitine deficiency, carnitine transporter defect, OCTN2 defect
12	Carnitine-acyl carnitine translocase	CACT
13	Cobalamin disorders	cblC, cblD, cblF disease
14	Homocystinuria	Cystathionine betasynthase, CBS (vitamin responsive forms may not be detected)
15	Glutaric aciduria type 1	Glutaryl CoA dehydrogenase, GA1
16	Holocarboxylase synthase	HCS, multiple carboxylase deficiency, MCD
17	Isovaleryl CoA dehydrogenase	Isovaleric acidaemia, MA
18	Medium-chain acyl CoA dehydrogenase	MCAD
19	Methylmalonic acidaemia	Methylmalonyl CoA mutase, MMA, cblA, cblB disease
20	Mitochodrial trifunctional protein	Long-chain hydroxy acyl carnitine dehydrogenase, LCHAD, MTP
21	Multiple acyl CoA dehydrogenase	MADD, glutaric aciduria type 2, GA2, ETF deficiency
22	Phenylketonuria	PKU, phenylalanine hydroxylase, including tetrahydrobiopterin defects
23	Propionic acidaemia	Propionyl CoA carboxylase, PA, ketotic hyperglycinaemia
24	Tyrosinaemia 2	Tyrosine aminotransferase
25	Very long chain acyl CoA	VLCAD

NB: other disorders are occasionally detected as part of the newborn screening testing, including disorders affecting the mother


North Pole
Norwegian Sea
Norway
Polar Ice
Greenland Sea
UK
Russia
Arctic Ocean
Ellesmere Island
Alert
Iceland
Bering Strait
North Magnetic Pole
Kalaallit Nunaat
(Grønland)
(Denmark)
Arctic Circle
Beaufort Sea
Banks I
Resolute
Baffin Bay
Alaska
(USA)
Inuvik
Victoria Island
Baffin Island
Davis Strait
Dawson
Great Bear Lake
Gjoa Haven
Yukon Territory
Mackenzie River
Whitehorse
Iqaluit
Labrador Sea
Atlantic Ocean
Northwest Territories
Nunavut
Baker Lake
Yellowknife
Ungava Bay
Newfoundland and Labrador
Fort Nelson
Great Slave Lake
CANADA
Nain
British Columbia
Fort McMurray
Churchill
Hudson Bay
Churchill Falls
Prince George
Pacific
Alberta
Saskatchewan
Manitoba
St John's
Edmonton
L Winnipeg
Saint-Pierre et Miquelon (France)
Vancouver
Fraser River
Kamloops
Sandy Lake
James Bay
Quebec
Prince Edward Island
Charlottetown
Calgary
Saskatoon
Victoria
Ocean
Winnipeg
New Brunswick
Nova Scotia
Regina
Thunder Bay
Ontario
Halifax
Fredericton
United States of America
Ottawa
Lake Superior
Toronto
Lake Michigan
Huron
Lake Ontario
Lake Erie
Atlantic Ocean

CANADA

A national screening program does not exist in Canada.
The federal government has no role in newborn screening beyond the licensing of some tests and other medical devices, and the regulation of foods, drugs and supplements for the treatment of rare and orphan diseases. ***Health care and screening programs fall under provincial and territorial jurisdiction.***

There is a wide spectrum in the number of disorders for which screening is offered, ranging from **5 disorders to 38**, depending on the jurisdiction.

SOURCE: Canadian Agency for Drugs and Technologies in Health

Unites States of America

Uniform Screening Panel

- 29 primary conditions
  - 20 detected by MS/MS (AA, FAO, OA)
  - 3 Hb-pathies (S/S, S/βThal, S/C)
  - 6 others (BIOT, CAH, CF, CH, GALT, HEAR)
- 25 secondary targets
  - 22 detected by MS/MS (AA, FAO, OA) *
  - 1 Hb-pathy (many variants counted as one)
  - 2 others (GAL-epimerase, GAL-kinase)

***At least 20 more conditions could be detected**

National Newborn Screening and Genetics Resource Center
NNSGRC

National Newborn Screening Status Report

Updated 01/06/13

The U.S. National Screening Status Report lists the status of newborn screening in the United States.

STATE	Core[1] Conditions											Additional Conditions Included in Screening Panel (universally required unless otherwise indicated)
	Hearing	Endocrine		Hemoglobin			Other					
	HEAR	CH	CAH	S/S	S/A	S/C	BIO	GALT	CF	CCHD	SCID	
Alabama	●	●	●	●	●	●	●	●	●			
Alaska	●	●	●	●	●	●	●	●	●			
Arizona	A	●	●	●	●	●	●	●	●		B	
Arkansas	●	●	●	●	●	●	●	●	●			
California	B	●	●	●	●	●	●	●	●		A	HHH; PRO; EMA ; [OTC, MTHFR] (D)
Colorado	A	●	●	●	●	●	●	●	●		●	
Connecticut	●	●	●	●	●	●	●	●	●	C	●	HHH; HIV[2]; NKH
D.C.	●	●	●	●	●	●	●	●	●			G6PD
Delaware	●	●	●	●	●	●	●	●	●	B	C	
Florida	●	●	●	●	●	●	●	●	●		●	
Georgia	A	●	●	●	●	●	●	●	●			
Hawaii	●	●	●	●	●	●	●	●	●			
Idaho	A	●	●	●	●	●	●	●	●			
Illinois	●	●	●	●	●	●	●	●	●		C	[Pompe, Krabbe, Niemann-Pick, MPS I, MPS II Gaucher, Fabry] (C) CPS (D), NKH, 5-OXO, HIV[2]
Indiana	●	●	●	●	●	●	●	●	●	●		
Iowa	●	●	●	●	●	●	●	●	●			
Kansas	●	●	●	●	●	●	●	●	●			
Kentucky	B	●	●	●	●	●	●	●	●			
Louisiana	●	●	●	●	●	●	●	●	●			
Maine	A	●	●	●	●	●	●	●	●			HHH; CPS (D)
Maryland	●	●	●	●	●	●	●	●	●	●		EMA
Massachusetts	●	●	●	●	●	●	●	●	●		A	TOXO; HHH(A), CPS
Michigan	●	●	●	●	●	●	●	●	●		●	
Minnesota	●	●	●	●	●	●	●	●	●		C	
Mississippi	●	●	●	●	●	●	●	●	●		C	5-OXO; CPS; HHH
Missouri	●	●	●	●	●	●	●	●	●			[Pompe, Krabbe, Niemann-Pick, Gaucher, Fabry (C in July 2012)]
Montana	●	●	●	●	●	●	●	●	●			
Nebraska	A	●	●	●	●	●	●	●	●			5-OXO; HHH; NKH (A)
Nevada	B	●	●	●	●	●	●	●	●			
New Hampshire	A	●	●	●	●	●	●	●	●	●		TOXO
New Jersey	●	●	●	●	●	●	●	●	●	●		
New Mexico	●	●	●	●	●	●	●	●	●			
New York	B	●	●	●	●	●	●	●	●		●	HIV; HHH; Krabbe Disease
North Carolina	●	●	●	●	●	●	●	●	●			
North Dakota	A	●	●	●	●	●	●	●	●			HHH; NKH
Ohio	●	●	●	●	●	●	●	●	●			
Oklahoma	●	●	●	●	●	●	●	●	●			
Oregon	B	●	●	●	●	●	●	●	●			
Pennsylvania	●	●	●	●	●	●	●	●	●		B	5-OXO; CPS; G6PD; HHH; NKH (B)
Rhode Island	●	●	●	●	●	●	●	●	●		C	
South Carolina	●	●	●	●	●	●	●	●	●			
South Dakota	A	●	●	●	●	●	●	●	●			
Tennessee	●	●	●	●	●	●	●	●	●	●		HHH; NKH
Texas	B	●	●	●	●	●	●	●	●		●	
Utah	●	●	●	●	●	●	●	●	●			
Vermont	●	●	●	●	●	●	●	●	●			
Virginia	●	●	●	●	●	●	●	●	●			
Washington	A	●	●	●	●	●	●	●	●		C	
West Virginia	●	●	●	●	●	●	●	●	●	●	C	
Wisconsin	●	●	●	●	●	●	●	●	●		●	
Wyoming	●	●	●	●	●	●	●	●	●			

STATE	Core[1] Conditions - Metabolic																			
	Fatty Acid Disorders					Organic Acid Disorders									Amino Acid Disorders					
	CUD	LCHAD	MCAD	TFP	VLCAD	GA-I	HMG	IVA	3-MCC	CbI-A,B	BKT	MUT	PROP	MCD	ASA	CIT	HCY	MSUD	PKU	TYR-I
Alabama	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Alaska	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Arizona	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Arkansas	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
California	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Colorado	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Connecticut	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
D. of Columbia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Delaware	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Florida	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Georgia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Hawaii	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Idaho	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Illinois	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Indiana	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Iowa	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Kansas	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Kentucky	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Louisiana	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Maine	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Maryland	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Massachusetts	●	●	●	D	●	●	●	●	D	●	●	●	●	D	●	●	●	●	●	●
Michigan	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Minnesota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Mississippi	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Missouri	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Montana	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Nebraska	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Nevada	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New Hampshire	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New Jersey	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New Mexico	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New York	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
North Carolina		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
North Dakota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Ohio	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Oklahoma	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Oregon	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Pennsylvania	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Rhode Island	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
South Carolina	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
South Dakota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Tennessee	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Texas	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Utah	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Vermont	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Virginia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Washington	●	●	●	●	●	●	●	●	D	●	●	●	●	●	●	●	●	●	●	●

29
Core
Conditions

STATE	Secondary Target[1] Conditions																									
	Fatty Acid Disorders								Organic Acid Disorders						Amino Acid Disorders								Other Metabolic		Hbg
	CACT	CPT-Ia	CPT-II	DE-RED.	GA-II	MCKAT	MSCHAD	SCAD	2MGHBA	2MBG	3MGA	C4-C,D	IBG	MAL	ARG	BIOPT-BS	BIOPT-RG	CIT-II	H-PHE	MET	TYR-II	TYR-III	GALE	GALE	Variant Hbg's
Alabama	●		●		●				●	●	●	●				●	●	●	●	●	●	●			●
Alaska	●	●	●		●			●	●	●	●	●	●	●	●	B	B	●	●	●	●	D	B	B	●
Arizona	D	D	D		D				D		D	D						D	D		D	D			D
Arkansas																									●
California	●	●	●		●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●				●
Colorado	●	●	●		●		●	●			●	●		●	●			●	●	●	●	●			●
Connecticut	●	●	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●
D. of Columbia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	A	A	●	●	●	●	●	●	●	●
Delaware	●		●		●	D		●	D	●	D	●	●		●	D	D	●	●	●	●	●	●	●	●
Florida	●	●	●		●			●	D	D	D	D	D	D		D		D	●	D	●	D			
Georgia	D	D	D		D	D	D	D	D	D	D	D	D	D	A			D	D	D	D	D	B	B	●
Hawaii	●	●	●		●			●	●	●	●	●	●	●	●	B	B	●	●	●	●		B	B	●
Idaho	●	●	●		●			●	●	●	●	●	●	●	●	B	B	●	●	●	●		B	B	●
Illinois	●	D	●	D	●	D	●	●	D	●	●	●	●	●	●	D	D	D	●	●	●	●			●
Indiana	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●
Iowa	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●
Kansas																			●						●
Kentucky	A	A	A		A			●	A	A	A	A	A	A	A	D	D	A	●	A	A	A			●
Louisiana																			●						●
Maine	D	D	●		●			●		D	D	●	D		●			●	●	D	●	D	●	●	●
Maryland	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	B	B	●	●	●	●	●	●	●	●
Massachusetts	D	D	A	A	D	D	A	D	D	D	D	●	D	A	●	D	D	A	D	D	D	D	D	D	D
Michigan	●	●	●	●	●	●	●	●	●	●	●	●	●	D	●	●	●	●	●	●	●	●			●
Minnesota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Mississippi	●	●	●	A	●	A	●	●	A	●	●	●	●	●	●	A	A	●	●	●	●	A	●	●	●
Missouri	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●
Montana	D		D	D	D	D	D	D	D	D	D	D	D			D	D	D	●	D	D	D			●
Nebraska	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	●	D	D	D	●	●	●
Nevada	●	●	●		●			●	●	●	●	●	●	●	●	B	B	●	●	●	●		B	B	A
New Hampshire	D	D	●		●					D	D	D			●	D	D	D	●	D			●	●	●
New Jersey	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New Mexico	A	D	A		A			A	D	D	A	A	D	D	D	B	B	A	A	A	A	D	B	B	●
New York	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●	●	●	●	●			●
North Carolina	●		●		●			●		●		●	●			●	●	●	●	●	●	●			●
North Dakota	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●
Ohio	●	●	●		●			●		●		●	●		●			●	●	●	●	●			●
Oklahoma	●	●	●		●	D		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●
Oregon	●	D	●		●			●	D	D	●	●	D	D	D	B	B	●	●	●	●	D	B	B	●
Pennsylvania	B	B	B	B	B		B	B		B	B	B	B	B	B	B	B	B	●	B	B	B	●	●	●
Rhode Island		D																	●				●	●	●
South Carolina	●	●	●	●	●	●	●	●	●	●	●	●	●	●		●	●	●	●	●	●	●	●	●	●
South Dakota	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●
Tennessee	●	●	●	●	●	D		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Texas	D	D	D	C	D	C	C	C	D	D	D	D	C	C	C	D	D	D	●	D	D	D			●
Utah	●	●	●		●	D		●	●	●	D	●	●	D	●	●	●	●	●	●	●	●			●
Vermont	D	D	D		D					D	D	●			D			●	●	D	D	D	●	●	●
Virginia	D	D	D		D	D			D	D	D	D				D	D	D	D	D	D	D	D	D	●
Washington																									

25 Secondary targets

E in Europa?

J Inherit Metab Dis (2007) 30:423–429
DOI 10.1007/s10545-007-0647-2

NEWBORN SCREENING

Introducing new screens: Why are we all doing different things?

R. J. Pollitt

Instituto_Nacional de Saúde
Doutor Ricardo Jorge

Estados Unidos

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Secretary's Advisory Committee on Heritable
Disorders in Newborns and Children
5600 Fishers Lane, Room 18A39
Rockville, Maryland 20857
(301) 443-1080 – Phone
(301) 480-1312 – Fax
www.hrsa.gov/heritabledisorderscommittee

February 25, 2010

The Honorable Kathleen Sebelius
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

- The addition of SCID to the uniform panel, and related T-cell lymphocyte deficiencies to the list of secondary targets as a comprehensive entity, with the understanding that the following activities will also take place in a timely manner.

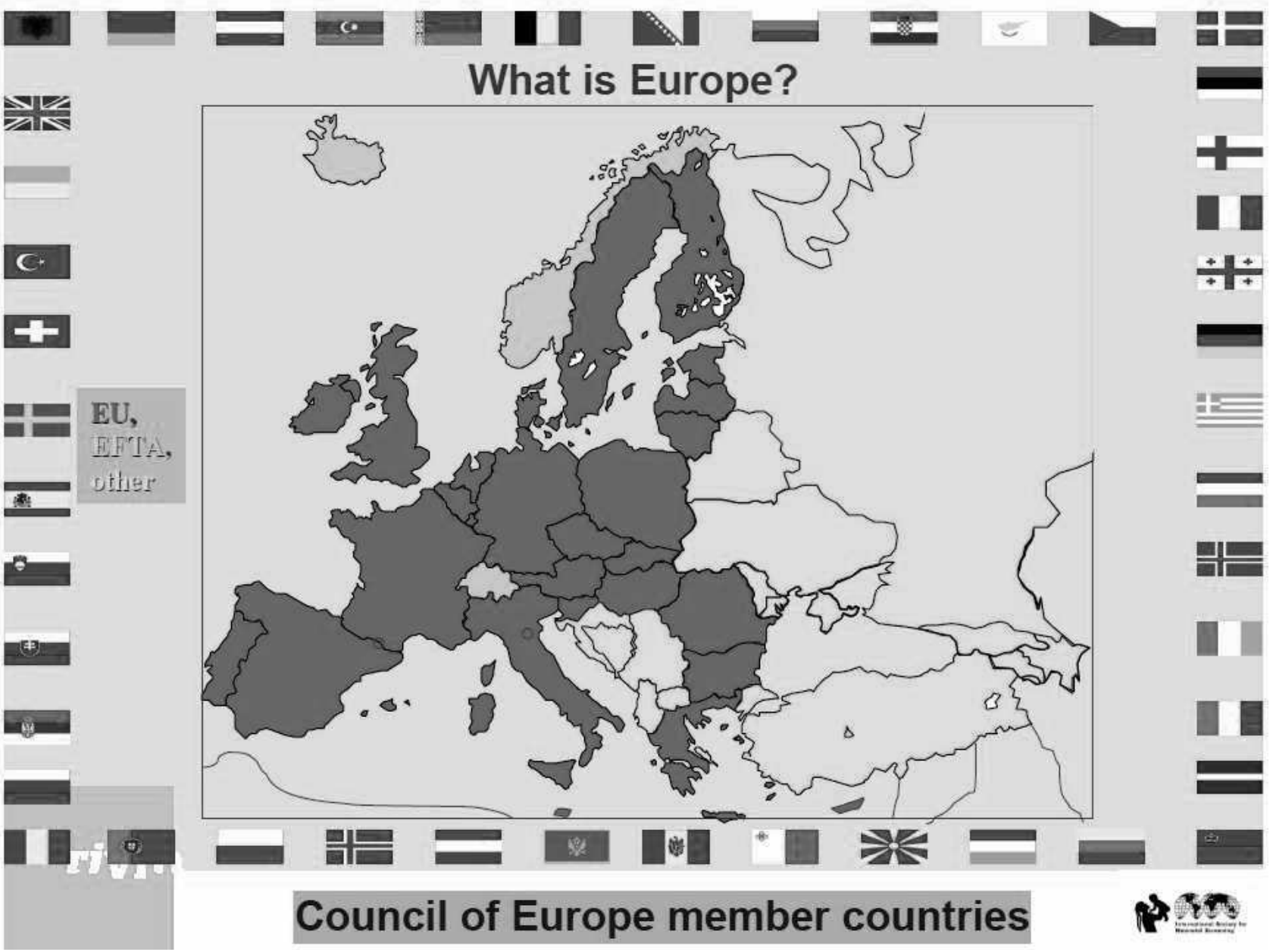
Europa

FINAL 28/08/2011

EU Tender

"Evaluation of population newborn screening practices for rare disorders in Member States of the European Union"

dehydrogenase deficiency, lysosomal storage disorders, 3-methylcrotonyl-CoA carboxylase deficiency, SCIDD,[40] tyrosinemia type I and II, very-long-chain acyl-CoA dehydrogenase deficiency and vitamin B12 deficiency.[41] For these disorders HTA at EU level could inform the decision-making in individual EU countries. Due to fast technological changes in high



http://www.aecne.es/

European languages

English
German
Dutch
French
Spanish
Portuguese
Italian
Icelandic
Norwegian
Swedish
Danish
Finnish
Estonian
Latvian
Lithuanian
Polish
Czech
Slovak
Hungarian
Slovenian
Croatian
Serbian
Macedonian
Albanian
Romanian
Bulgarian
Greek
Russian
Belarusian
Ukranian
Armenian
Turkish
Azerbaijani
Georgian

Castillian

Catalan

Galician

Euskarian

Aranès

and many more …

http://www.ielanguages.com/eurolang.html

No consensus …

UK

Rest of Europe

No consensus …

Red → Green

NL

Red → Orange →Green

Rest of Europe

No consensus …

Left hand traffic

UK, Ireland, Malta, Cyprus

Right hand traffic

Rest of Europe

Currency	Region	¤	ISO	Euro peg	Year	Notes
Euro	Eurozone (show)	€	EUR	See below	1999/2002	Used by the institutions
Bulgarian lev	Bulgaria	лв	BGN	Currency board	2007	cannot be before 2016 for euro target
British pound sterling Gibraltar pound	United Kingdom Gibraltar	£	GBP GIP	Floating Currency board	1973	Formal opt-out
Croatian kuna	Croatia	kn	HRK	Floating	2013	no current target date
Czech koruna	Czech Republic	Kč	CZK	Floating	2004	no current target date
Danish krone	Denmark	kr	DKK	ERM	1973	Formal opt-out
Hungarian forint	Hungary	Ft	HUF	Floating	2004	No current target for euro
Latvian lats	Latvia	Ls	LVL	ERM	2004	1-1-2014 official target date [1]
Lithuanian litas	Lithuania	Lt	LTL	ERM	2004	1-1-2015 official target date [2]
Polish złoty	Poland	zł	PLN	Floating	2004	No current target for euro
Romanian leu	Romania	Leu	RON	Floating	2007	cannot be before 2016 for euro target
Swedish krona	Sweden	kr	SEK	Floating	1995	*De facto* opt-out
Swiss franc	Campione d'Italia (Italy)[3]	Fr.	CHF	Floating[4]	1957	Also unofficially used in Büsingen am Hochrhein, Germany [5] Swiss Franc is issued by Switzerland

So what are we doing in Europe?

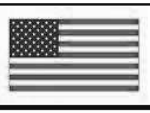
Country	Screened infants	Number of labs	Country	Screened infants	Number of labs
Austria	83649	1	Latvia	21655	1
Belgium	121999	6	Lithuiania	34456	1
Bulgaria	74510	2	Luxembourg	6159	1
Cyprus	9749	1	Malta	4100	2
Czechia	118348	6	Netherlands	185743	5
Denmark	65000	1	Poland	421000	8
Estonia	15730	1	Portugal	99809	1
Finland	60794	18	Romania	226000	4
France	841931	22	Slovakia	56475	1
Germany	675000	11	Slovenia	20269	1
Greece	120852	1	Spain	498711	20
Hungary	95000	2	Sweden	110523	1
Ireland	74278	1	UK	797214	16
Italy	576000	40			

Source: http://www.erndim.org/store/docs/JBonhamERNDIM

So what are we doing in Europe?

Country	Birth interval	Storage of spots (yrs)	Country	Birth interval	Storage of spots (yrs)
Austria	36-72h	10	Latvia	72-120h	7
Belgium	72-120h	5	Lithuiania	48-96h	25
Bulgaria	72-120h	20	Luxembourg	96-168h	8
Cyprus	96-168h	5	Malta	Cord blood	n/a
Czechia	48-96h	5	Netherlands	72-168h	5
Denmark	48-72h	1000	Poland	48-96h	1
Estonia	48-72h	100	Portugal	48-96h	12
Finland	Cord blood	n/a	Romania	48-96h	2-5
France	48-96h	1	Slovakia	72-96h	20
Germany	48-96h	0.25	Slovenia	72-120h	10
Greece	96-168h	3	Spain	48-96h	1-1000
Hungary	48-72h	1	Sweden	48-96h	1000
Ireland	72-120h	26	UK	797214	5
Italy	48-96h	1-10			

Table 2 Disorders recommended for newborn screening using MS/MS

Disorder					
Phenylketonuria	P	+	+	+	+
Maple syrup urine disease	P	+	+	+	
Homocystinuria	P			+	
Tyrosinaemia type I	P			+	
Citrullinaemia	P	+			
Argininosuccinic aciduria	P	+			
Argininaemia	S	+			
HHH syndrome		+			
Very long-chain acyl-CoA dehydrogenase deficiency	P	+	+	+	
Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency[b]	P	+	+	+	
Medium-chain acyl-CoA dehydrogenase deficiency	P	+	+	+	+
Short-chain acyl-CoA dehydrogenase deficiency	S	+			
Multiple acyl-CoA DD (glutaric aciduria type II)	S	+			
Carnitine palmitoyltransferase deficiency type I	S	+	+		
Carnitine palmitoyltransferase deficiency type II	S	+	+		
Carnitine-acylcarnitine translocase deficiency	S	+	+		
Carnitine uptake (OCTN2) deficiency	P				
Propionic acidaemia	P	+			
Methylmalonic acidaemia	P[c]	+			
Isovaleric acidaemia	P		+	+	
Glutaryl-CoA dehydrogenase deficiency	P	+	+	+	
Multiple carboxylase (holocarboxylase synthase) deficiency	P			+	
3-Hydroxy-3-methylglutaryl-CoA lyase deficiency	P	+		+	
Beta-ketothiolase (T2) deficiency	P	+			
3-Methylcrotonyl-CoA carboxylase deficiency	P	+		+	
Plus 17 other conditions	S				
	54 (2013)	**18** (2012)	**12** (2011)	**18** (2012)	**8** (2013)

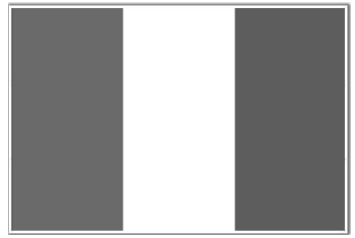
Data sources as for Table 1.

[a] P denotes a primary target, S a secondary target.

[b] Includes trifunctional protein deficiency.

[c] Mut^0, CblA and CblB. CblC and CblD were secondary targets.

National Law N. 104/1992



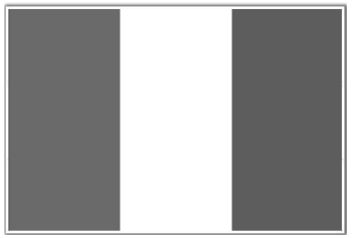
…nei primi giorni di vita, ancora in ospedale, il bimbo viene sottoposto al cosiddetto "screening neonatale", una serie di esami che permettono di individuare precocemente alcune malattie congenite (cioè presenti alla nascita), ma che si manifestano in genere più tardivamente. Grazie a questo test, che deve essere eseguito dopo quarantotto ore di vita, è possibile individuare e curare precocemente queste malattie, che possono, altrimenti, avere gravi conseguenze sullo sviluppo psicomotorio e sull'accrescimento del bambino. Dal 1992 (legge-quadro n. 104 del 5-5-1992) questo esame deve essere eseguito su tutti i neonati italiani (la prima legge che ne ha sancito l'importanza e quella della regione Liguria del 17-8 -1973).

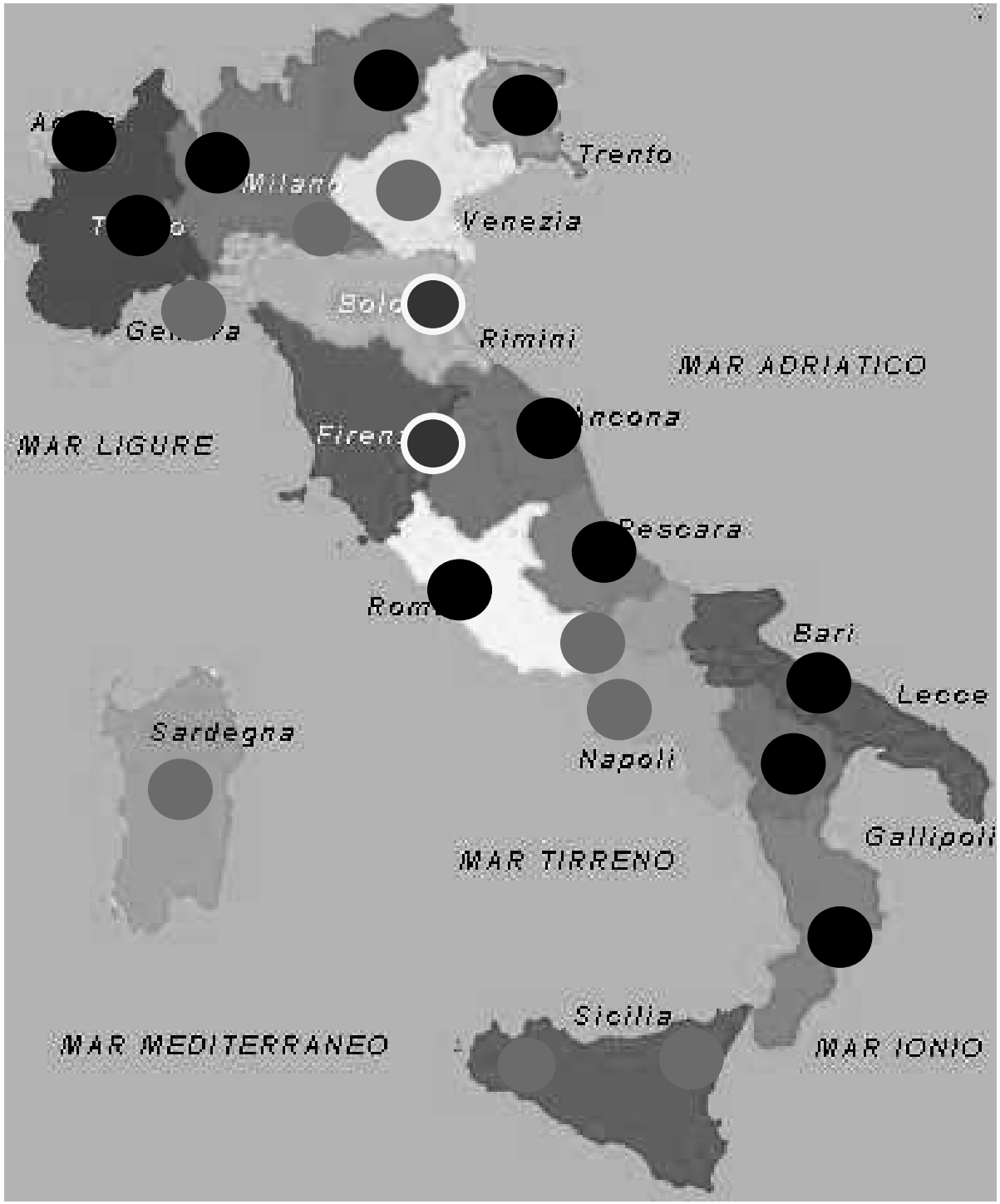
Lo "screening neonatale" viene effettuato per identificare alcuni disturbi molto seri, che se vengono individuati precocemente possono essere curati con ottimi risultati. Queste malattie sono congenite, presenti cioè già dalla nascita, ma nei primi giorni di vita non si manifestano e, se non viene eseguito il test, possono essere individuate solo più tardi. I disturbi individuabili con questo esame sono tre: la fenilchetonuria, una malattia ereditaria che provoca problemi nell'assimilazione di una sostanza, la fenilalanina (monitorando il dosaggio di quest'ultima); l' ipotiroidismo congenito, un problema della tiroide, le ghiandola che regola lo sviluppo e la crescita (in base al dosaggio del TSH o ormone tireotropo) e la fibrosi cistica, una malattia respiratoria molto seria (verificata tramite la concentrazione di un enzima la tripsina).

We have 32 newborn screening centers

Florence

Bologna





Padua/ Verona

Milan

Genova

Rome

Neaples

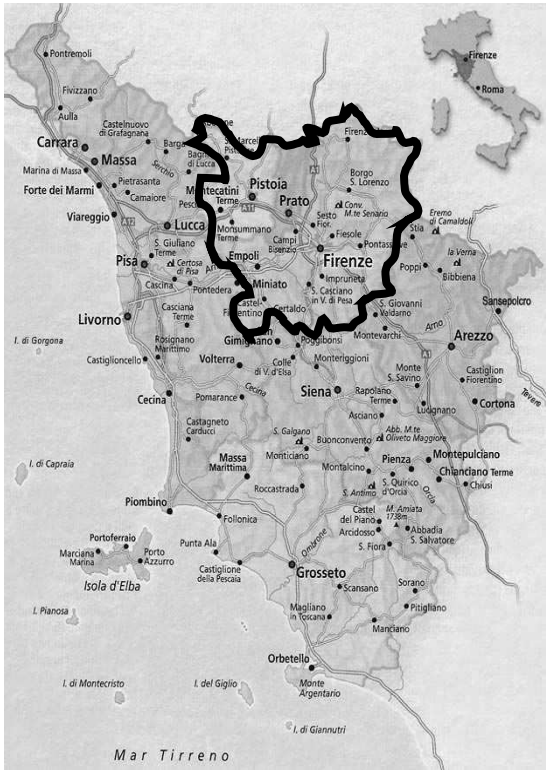
Cagliari

Catania/ Palermo

Su 514000 (2014) nati vivi

Copertura screening esteso circa 30%

PILOT PROJECT



01/11/2001-31/10/2004

in

Firenze, Prato and Pistoia areas

42371 screened

Regional Legislative Action no. 800 (3/8/2004):

since 01/11/2004

"…..tutti i neonati toscani dovranno essere sottoposti a screening allargato mediante spettrometria di massa tandem…"

35000 newborns/year

since 01/01/2010

Florence has performed the expanded newborn screening also for Umbria

MEYER

8500 newborns/year

Progress in expanded newborn screening for metabolic conditions by LC-MS/MS in Tuscany: Update on methods to reduce false tests

G. la Marca · S. Malvagia · B. Casetta · E. Pasquini · M. A. Donati · E. Zammarchi

Received: 22 May 2008 / Submitted in revised form: 22 August 2008 / Accepted: 28 August 2008 / Published online: 27 October 2008

Summary We report on our 6-year experience of expanded newborn screening by tandem mass spectrometry in Tuscany (Italy), the first Italian Region to screen all newborns for more than 40 inborn errors of metabolism: organization, diseases observed and updates on methods to reduce false-positive and false-negative tests are described. Blood collection is recommended between 48 and 72 h of life. Blood spots are sent daily by courier to laboratory. When a positive result occurs, two subsequent procedures are followed: for disorders with possible acute metabolic decompensation, the baby is immediately recalled and clinical examinations and confirmatory tests are performed; for the other disorders, the nursery provides for a second blood spot. If the test is positive, clinical examinations and confirmatory tests are performed. In both cases, if confirmatory tests are positive, a treatment and a follow-up programme are started. Up to now, spots from 160 000 infants have been analysed and 80 affected patients have been identified (disorders of amino acids, organic acids and fatty acids metabolism). We describe adjustments to cut-off values, the introduction of a second-tier test for propionic acidaemia and for methylmalonic aciduria, the inclusion of succinylacetone in the panel of metabolites, and protocols for premature infants and for newborns on parenteral nutrition or

Communicating editor: Bridget Wilcken

Our panel contained 20 primary targets and 22 secondary targets

J Inherit Metab Dis. 2008 Oct 27

2013: Tuscany NBS panel contains 46 disorders

PILOT PROJECT

01/01/2002-31/10/2004

3 provinces of Tuscany = 13,500/year

42,371 newborns

REGIONAL LEGISLATIVE ACTION No. 800 (3/8/2004)

… the program must screen all babies born in Tuscany starting from **November 2004** (approximately 40000/year) for selected acylcarnitines and amino acids....

~400,000 newborns

PREVALENCE 1:1500

~ 300 DIAGNOSES

Acylcarnitines

β-oxidation of fatty acids defects

-Short Chain Acyl-CoA Dehydrogenase Deficiency (SCAD)
-Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)
-Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)
-Very Long Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)
-Long Chain 3-OH-Acyl-CoA Dehydrogenase Deficiency (LCHAD)/ Mithocondrial Trifunctional Protein Defect
-Carnitine Transporter Defect
-Carnitine-Acylcarnitine Translocase Deficiency
-Carnitine Palmitoil Trasferase Deficiency (CPT I and II)

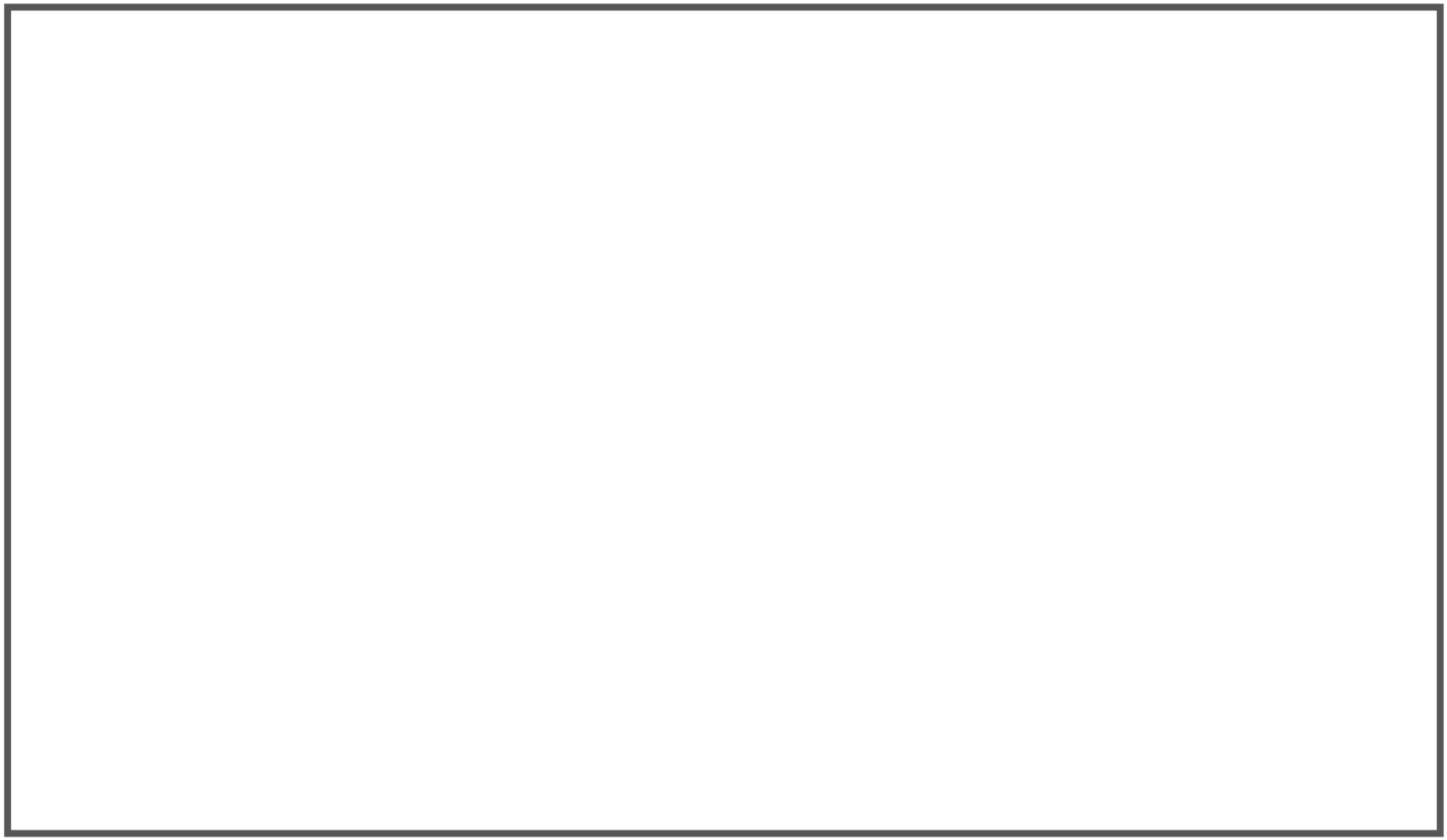
Organic acidurias

-Propionic Aciduria
-Methylmalonic Acidurias
-Isovaleric Aciduria
-Methylcrotonil-CoA Carboxilase Deficiency
-Holocarboxylase Synthetase Deficiency
-Glutaric Acidurias type I
-3-OH-3-Methylglutaryl-CoA Liase Deficiency
-β-Ketotiolasi Deficiency

Aminoacids

Aminoacidopathies

-HyperPhenylalaninaemias
-Tyrosinaemia type I and II
-Leucinosis
-Non ketotic Hyperglycinaemia
-Citrullinaemia type I and II
-Argininsuccinic aciduria
-Argininaemia
-Homocistinuria
-HyperOrnithinemias



Aminoacidopathies

PHENYLKETONURIA

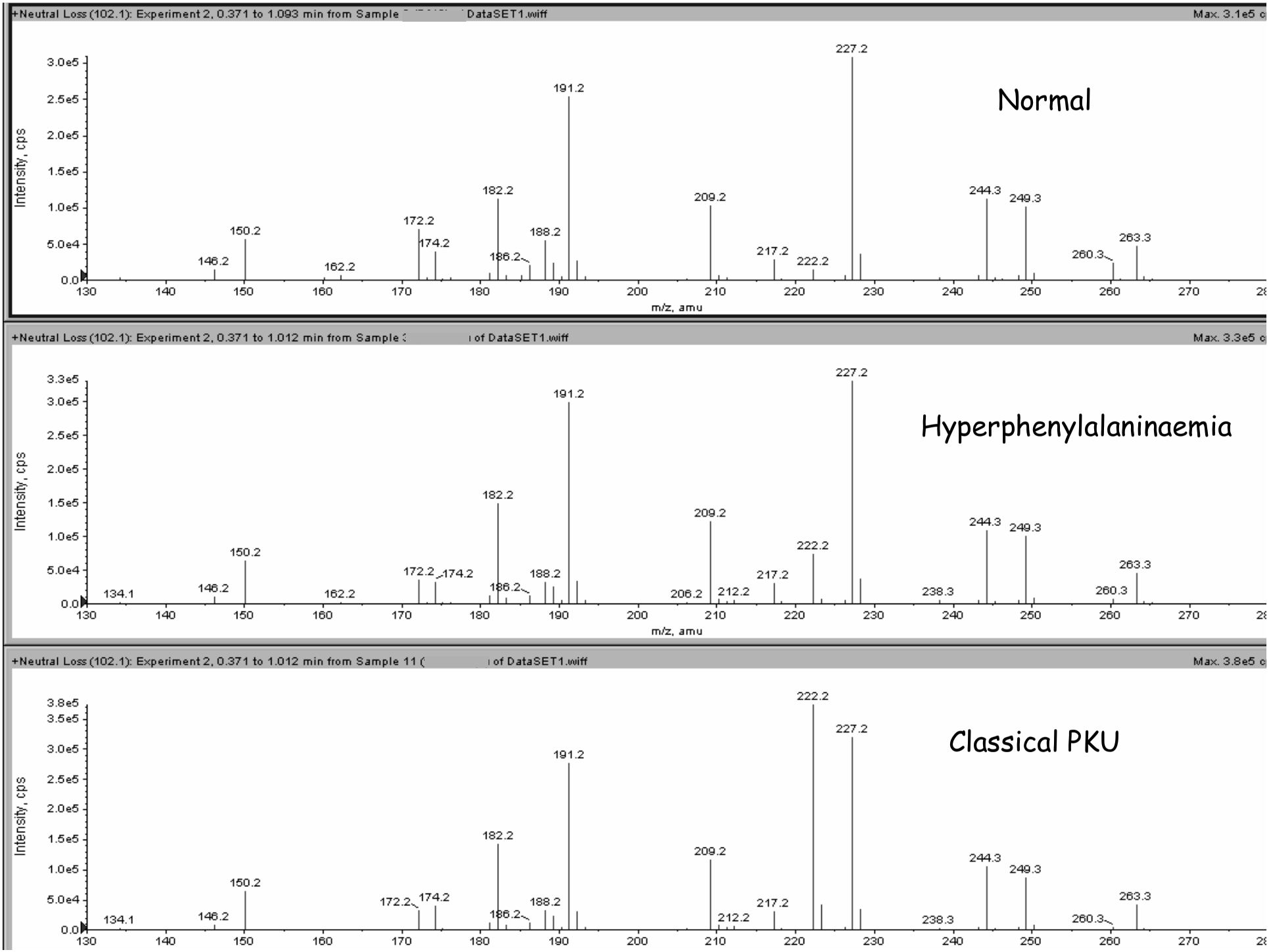
(Occurrence 1:15000)

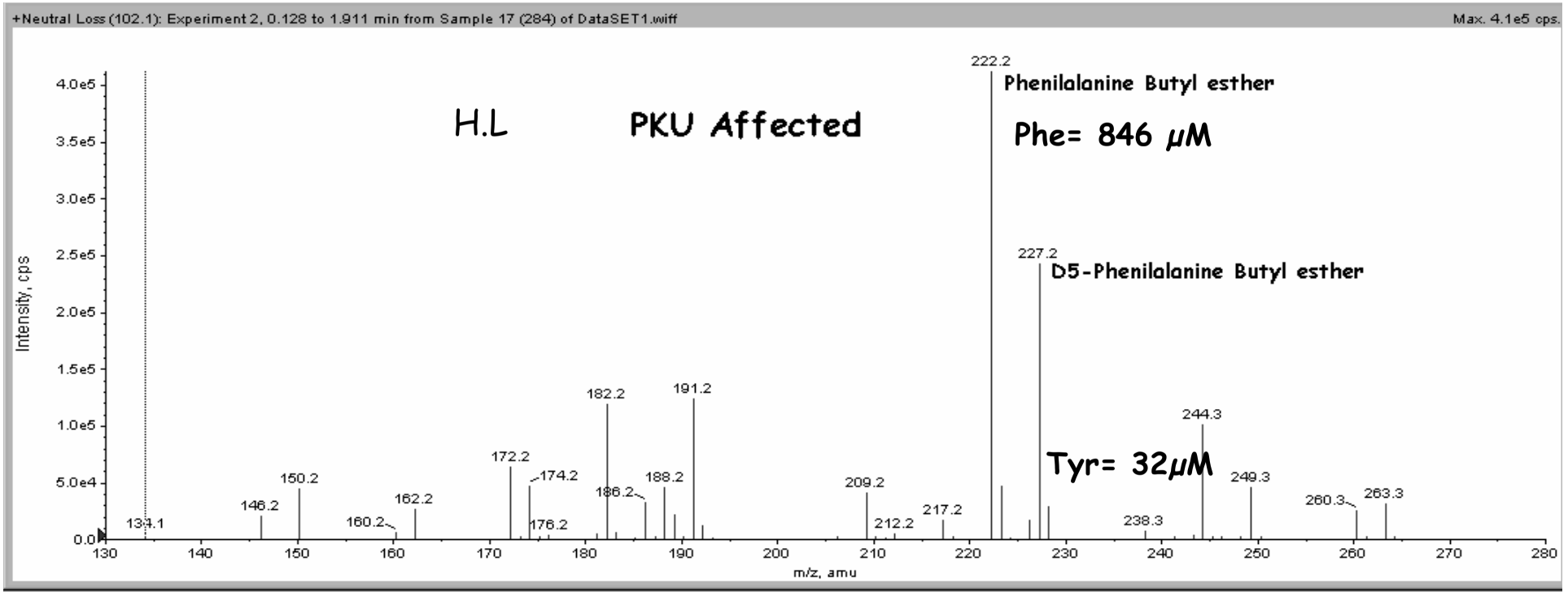
Phenylalanine Hydroxilase (PKU)

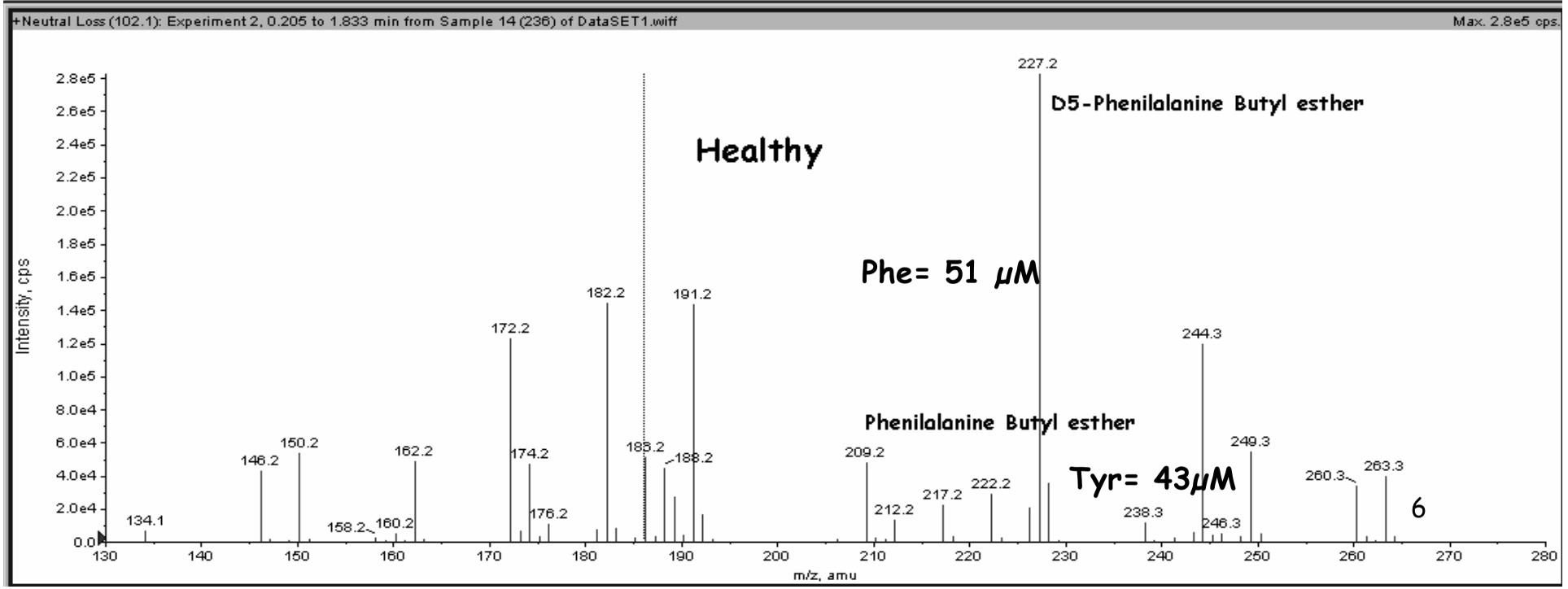
or co-factor BH_4 Deficit

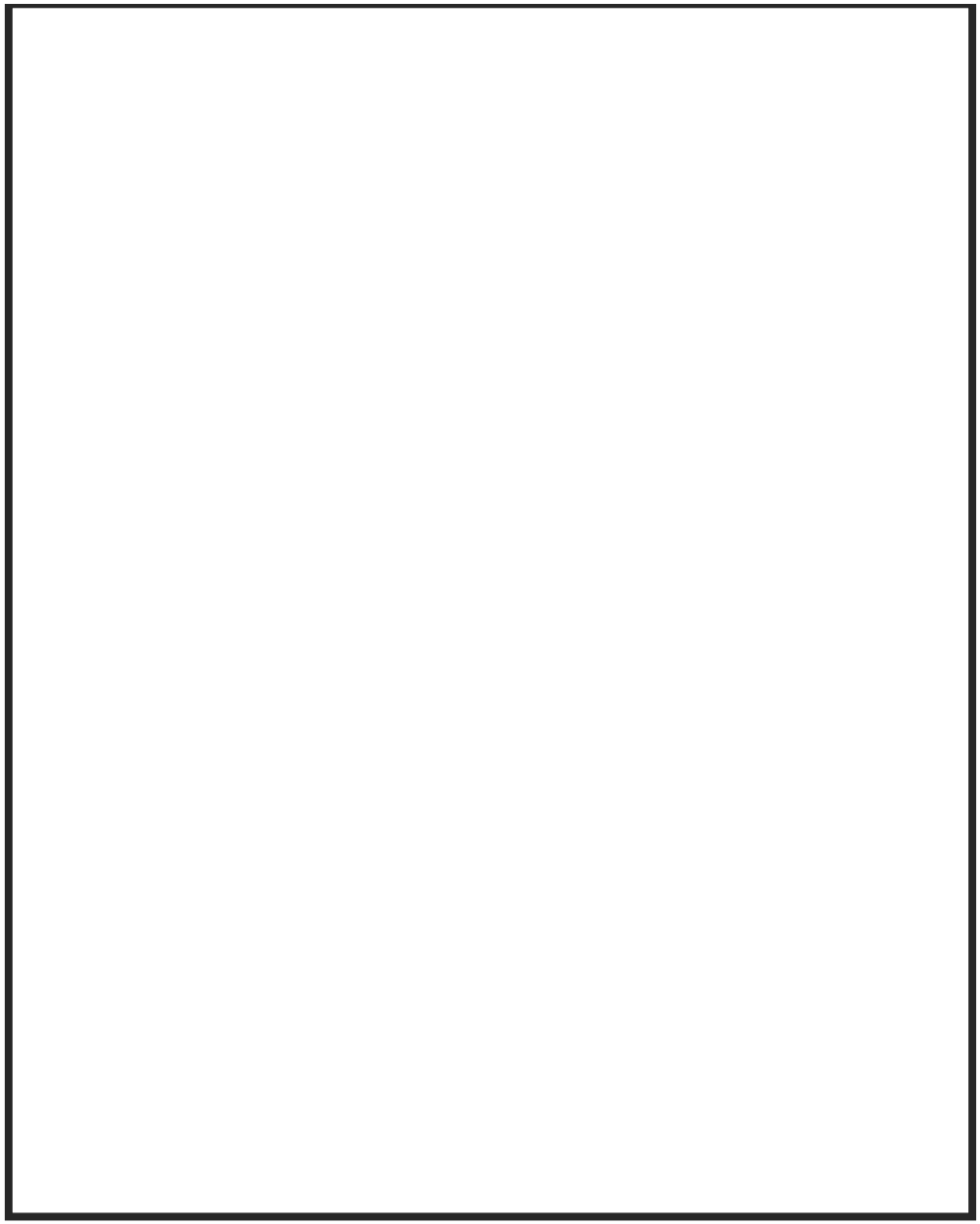
Toxic accumulation of Phenylalanine (SNC)

Mental retardation, epilepsy, depigmentation


+Neutral Loss (102.1): Experiment 2, 0.371 to 1.093 min from Sample DataSET1.wiff
Max. 3.1e5
Intensity, cps
m/z, amu
227.2
191.2
182.2
209.2
244.3
249.3
150.2
172.2
174.2
188.2
263.3
146.2
162.2
186.2
217.2
222.2
260.3
Normal
+Neutral Loss (102.1): Experiment 2, 0.371 to 1.012 min from Sample of DataSET1.wiff
Max. 3.3e5
Intensity, cps
m/z, amu
227.2
191.2
182.2
209.2
244.3
249.3
150.2
222.2
263.3
172.2
174.2
188.2
217.2
134.1
146.2
162.2
186.2
206.2
212.2
238.3
260.3
Hyperphenylalaninaemia
+Neutral Loss (102.1): Experiment 2, 0.371 to 1.012 min from Sample 11 (of DataSET1.wiff
Max. 3.8e5
Intensity, cps
m/z, amu
222.2
227.2
191.2
182.2
209.2
244.3
249.3
150.2
263.3
172.2
174.2
188.2
217.2
134.1
146.2
186.2
212.2
238.3
260.3
Classical PKU

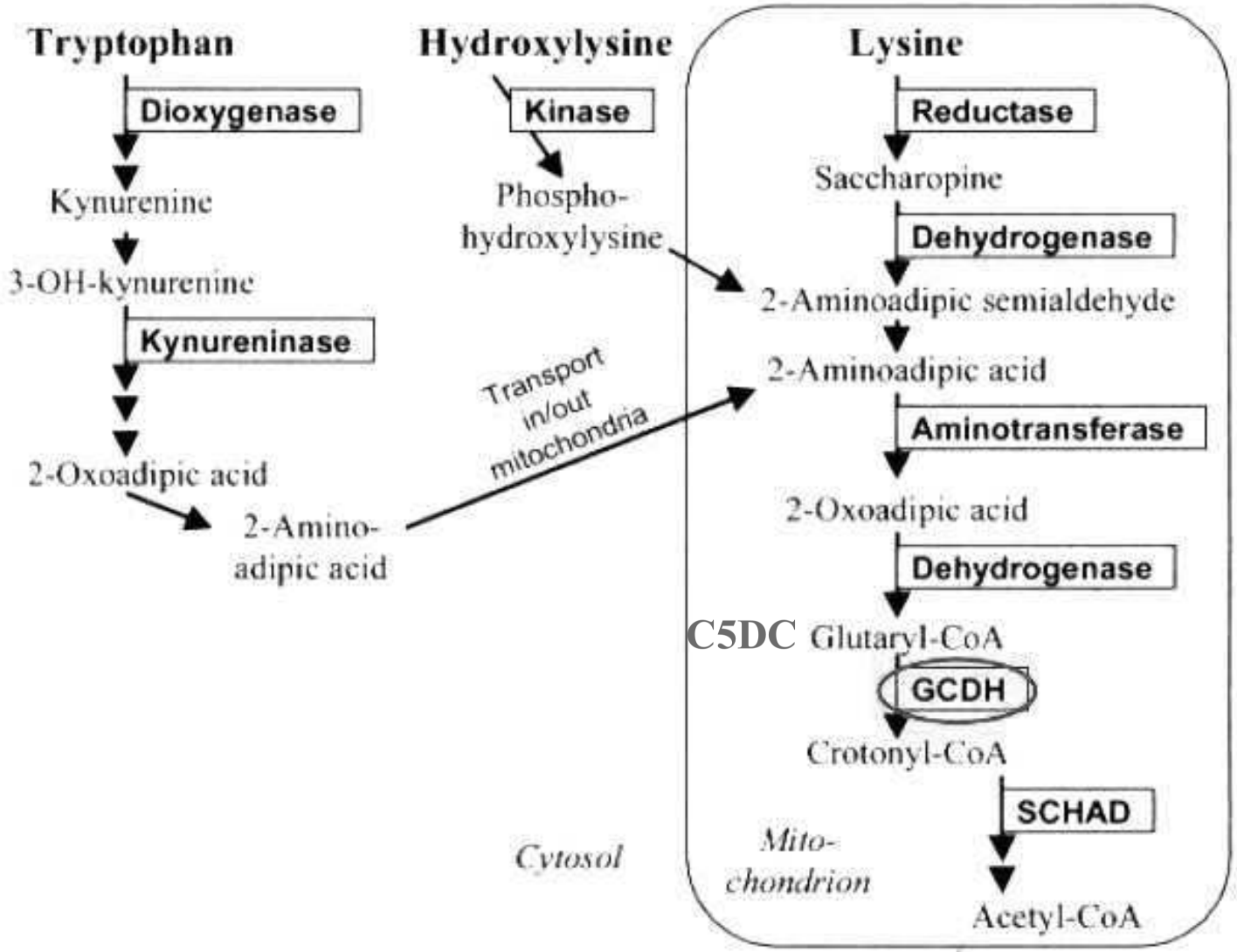

+Neutral Loss (102.1): Experiment 2, 0.128 to 1.911 min from Sample 17 (284) of DataSET1.wiff
Max. 4.1e5 cps.
H.L
PKU Affected
222.2
Phenilalanine Butyl esther
Phe= 846 µM
227.2
D5-Phenilalanine Butyl esther
Tyr= 32µM
Intensity, cps
m/z, amu

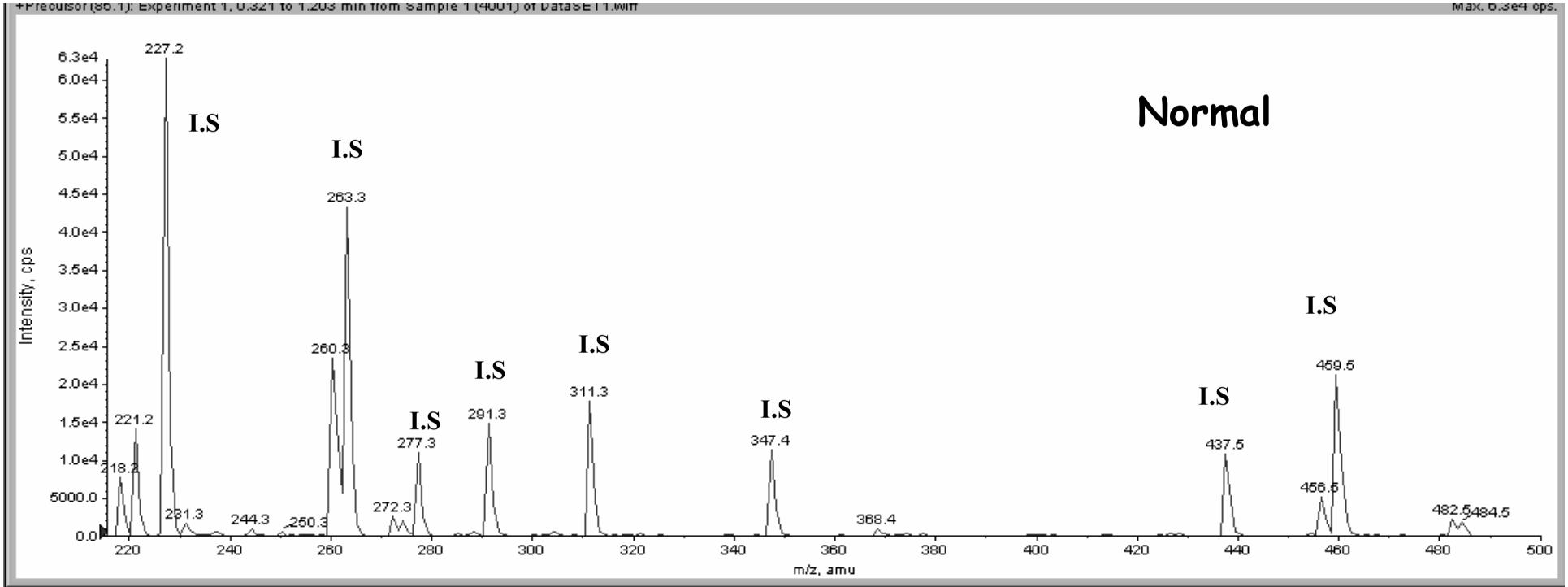

+Neutral Loss (102.1): Experiment 2, 0.205 to 1.833 min from Sample 14 (236) of DataSET1.wiff
Max. 2.8e5 cps.
227.2
D5-Phenilalanine Butyl esther
Healthy
Phe= 51 µM
Phenilalanine Butyl esther
Tyr= 43µM
Intensity, cps
m/z, amu

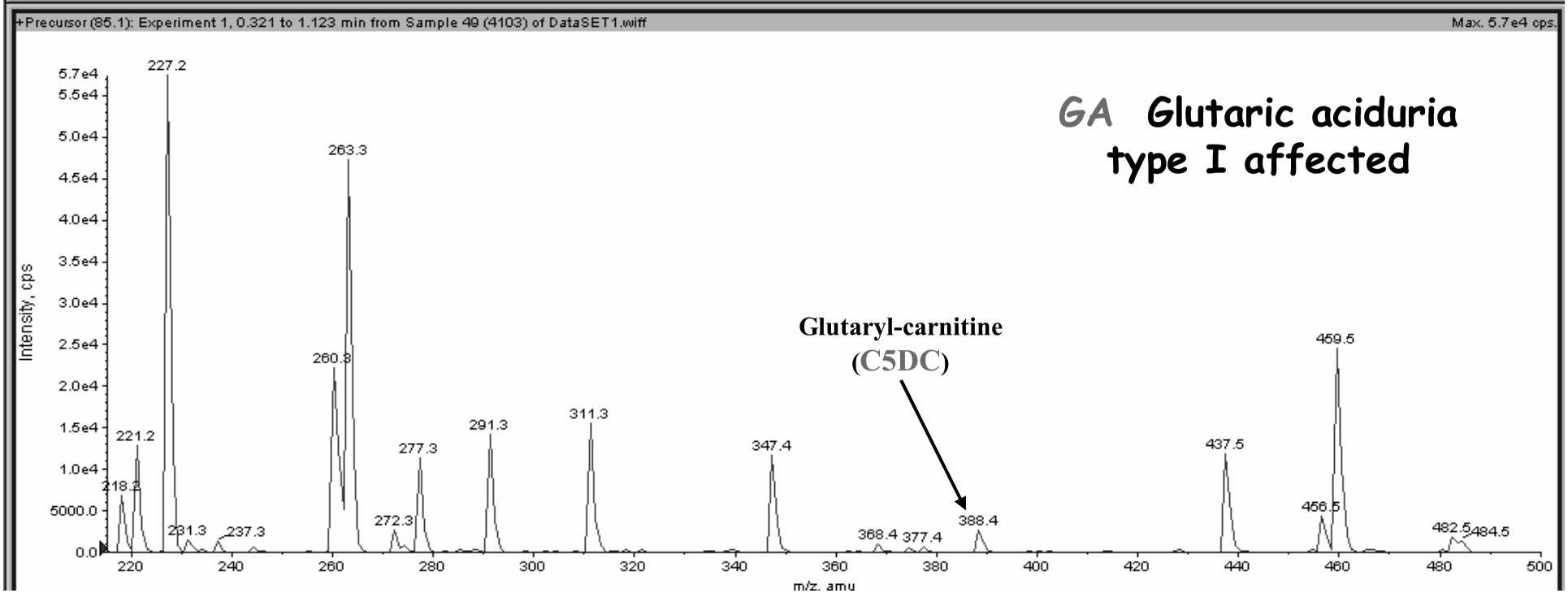


Organic Acidurias

GA GLUTARIC ACIDURIA TYPE I
Glutaryl-CoA Dehydrogenase

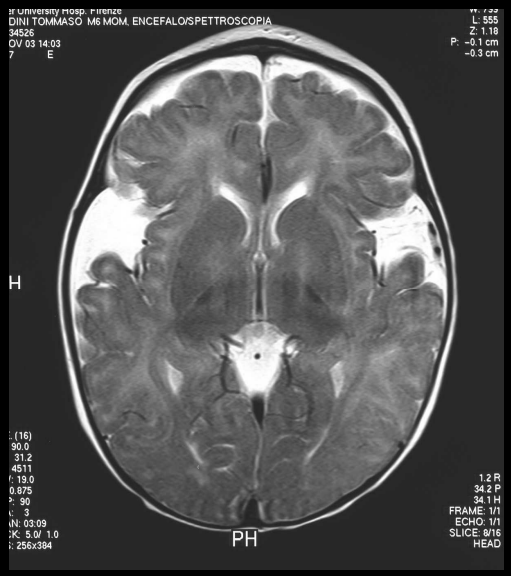



Normal
I.S
I.S
I.S
I.S
I.S
I.S
227.2
263.3
260.3
221.2
218.2
277.3
291.3
311.3
347.4
437.5
459.5
456.5
Intensity, cps
m/z, amu


+Precursor (85.1): Experiment 1, 0.321 to 1.123 min from Sample 49 (4103) of DataSET1.wiff
Max. 5.7e4 cps.
GA Glutaric aciduria
type I affected
Glutaryl-carnitine
(C5DC)
227.2
263.3
260.3
221.2
218.2
277.3
291.3
311.3
347.4
437.5
459.5
456.5
388.4
Intensity, cps
m/z, amu

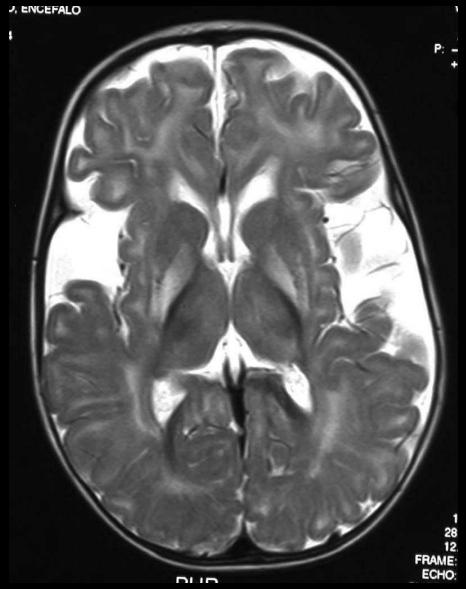
GLUTARIC ACIDURIA TYPE I

A)



RM pat diagnosed at screening test

C)

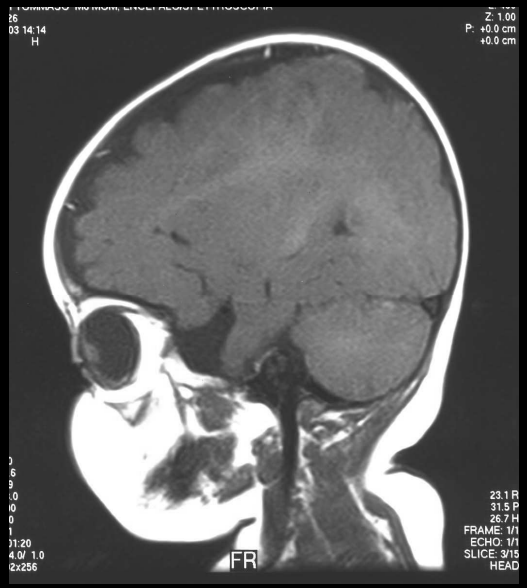


RM pt diagnosed at 8 months of age

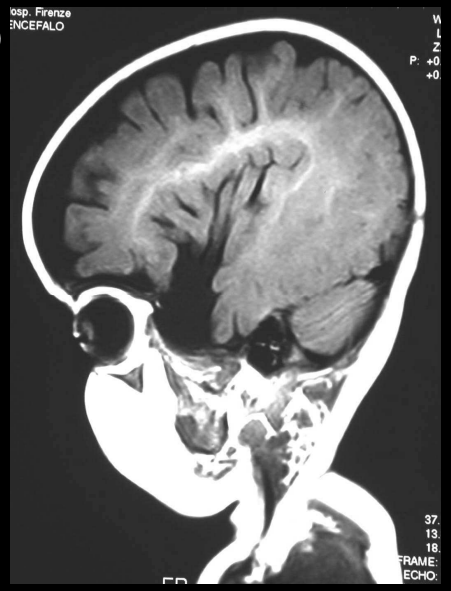
RM a 8 mesi di vita del paziente diagnosticato allo screening a confronto con RM di un paziente GA-I diagnosticato a 8 mesi di vita

A-B)Sequenza T2. In B risulta più evidente il coinvolgimento dei nuclei della base, soprattutto del pallido e del putamen e una maggiore alterazione del segnale della sostanza bianca

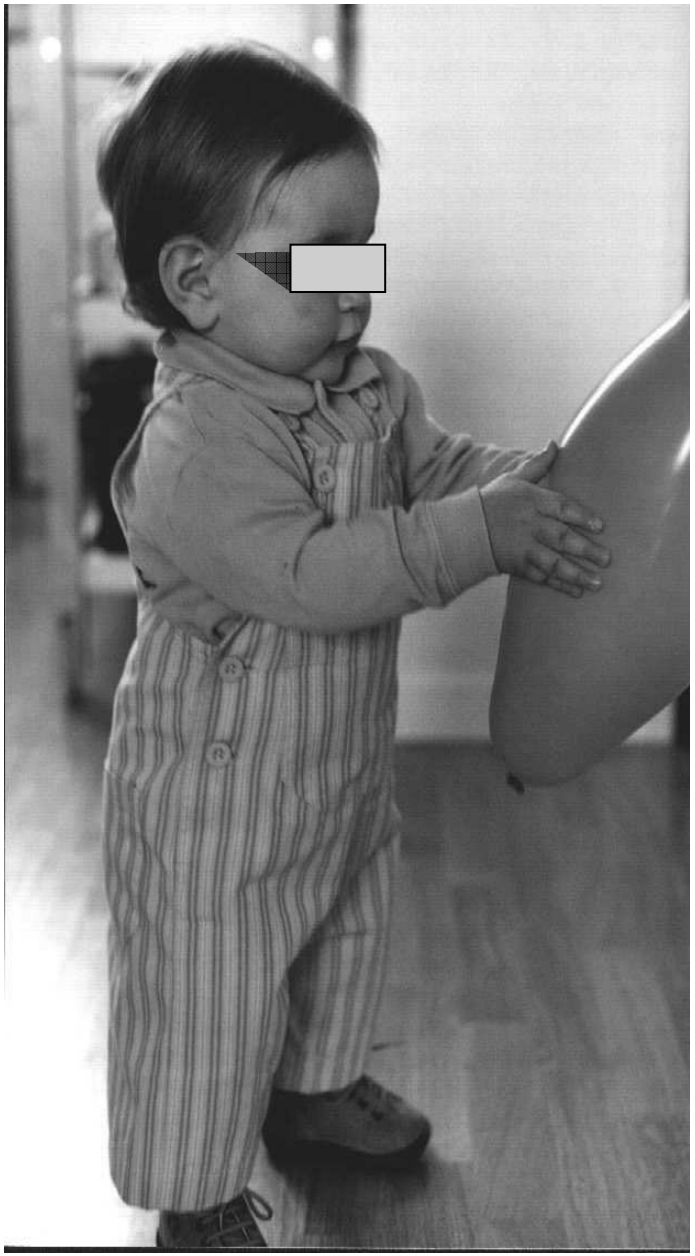
B)



D)



C-D) In D l'ampiezza della valle Silviana e dello spazio temporo-polare anteriore e fronto polare anteriore appare notevolmente più evidente.



GA early diagnosis (NBS)

PRECLINICAL DIAGNOSIS

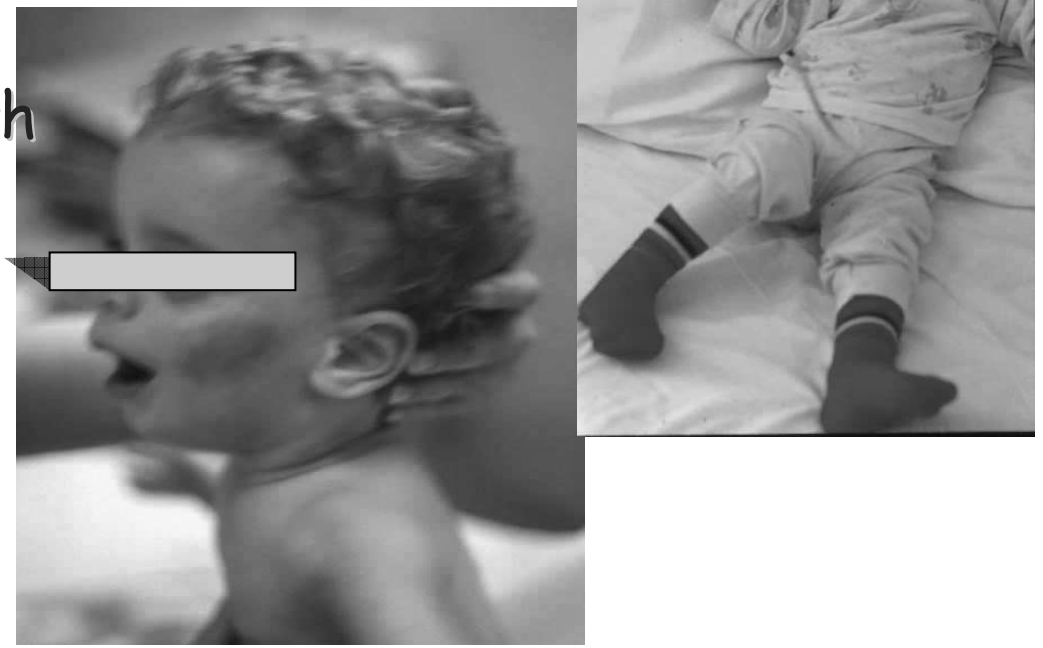
EARLY THERAPY

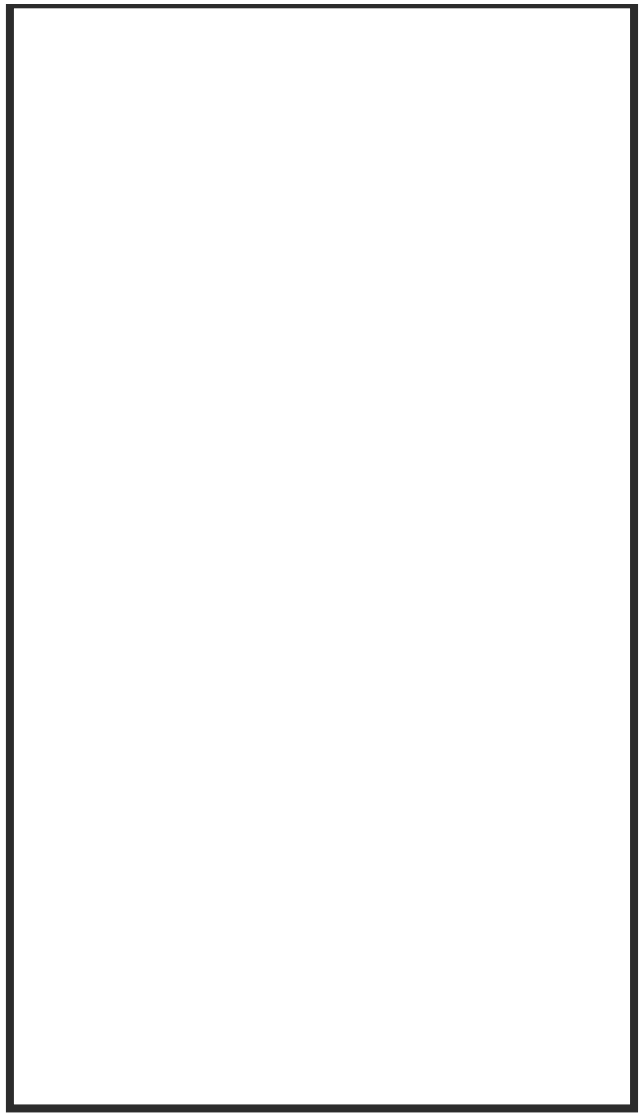
BEST PROGNOSIS

GLUTARIC ACIDURIA TYPE I

DiagnosiS aT 23 mth

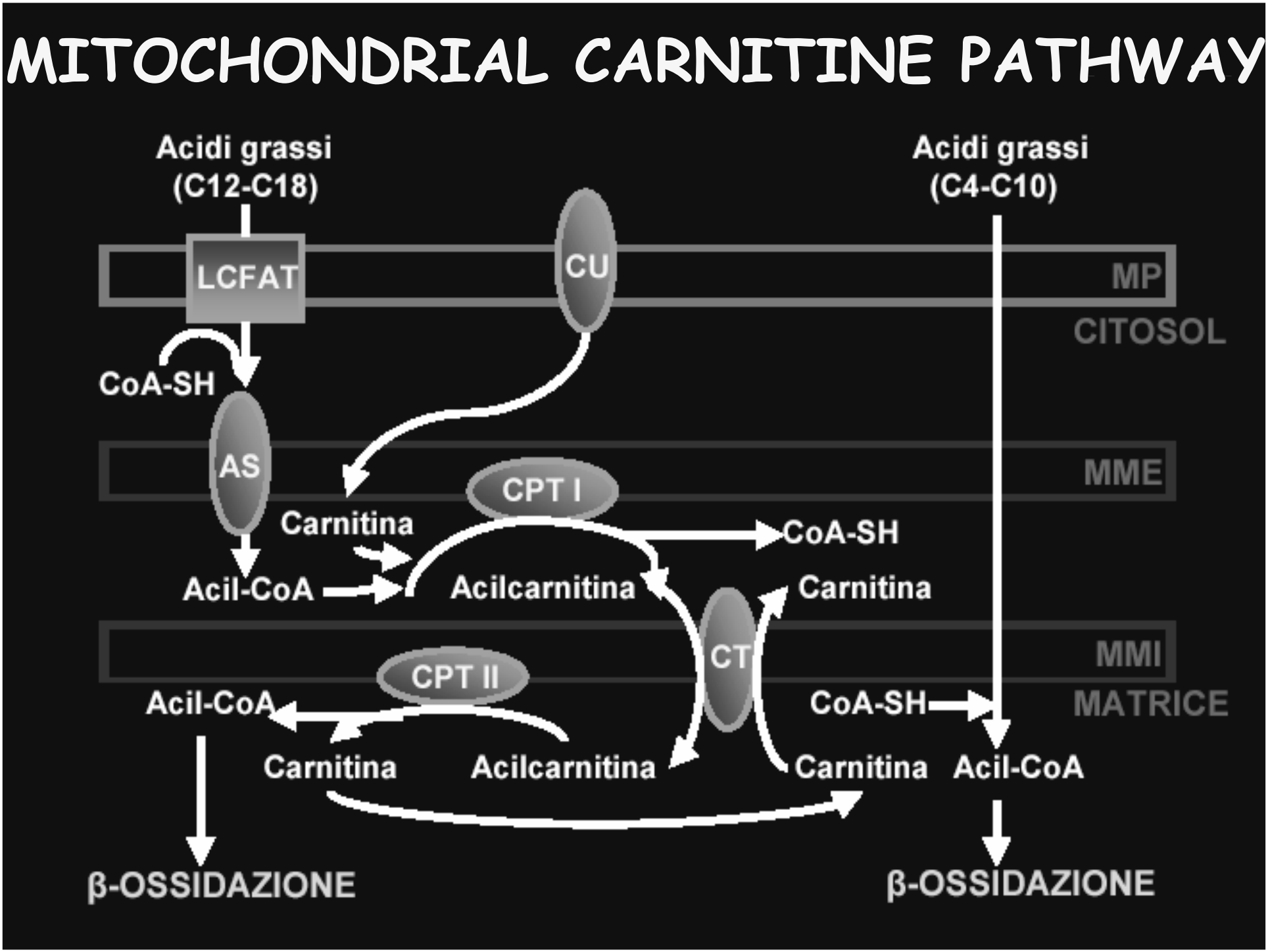
exitus at 32 mth





β-oxidation of fatty acids defects

MITOCHONDRIAL CARNITINE PATHWAY

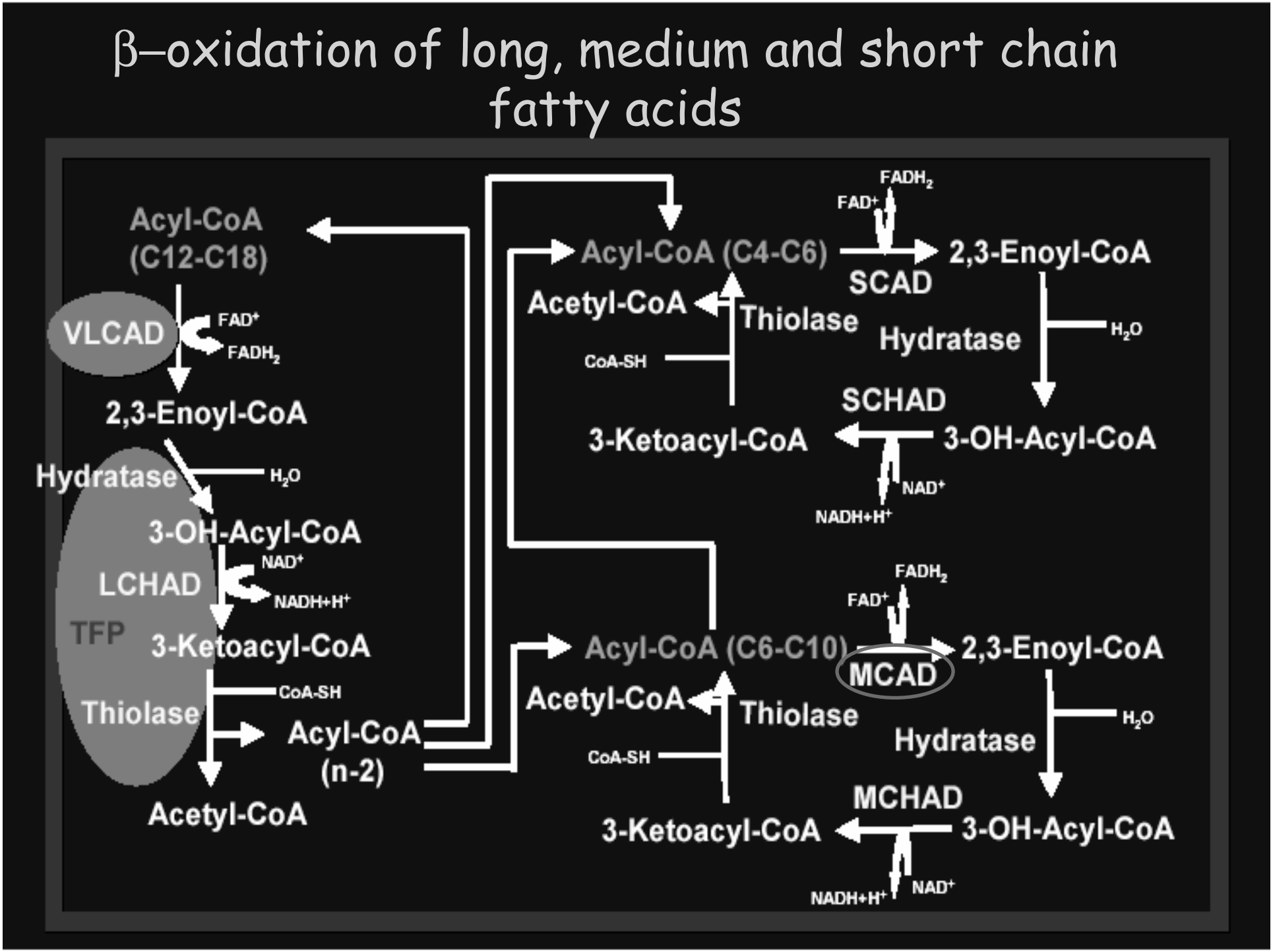


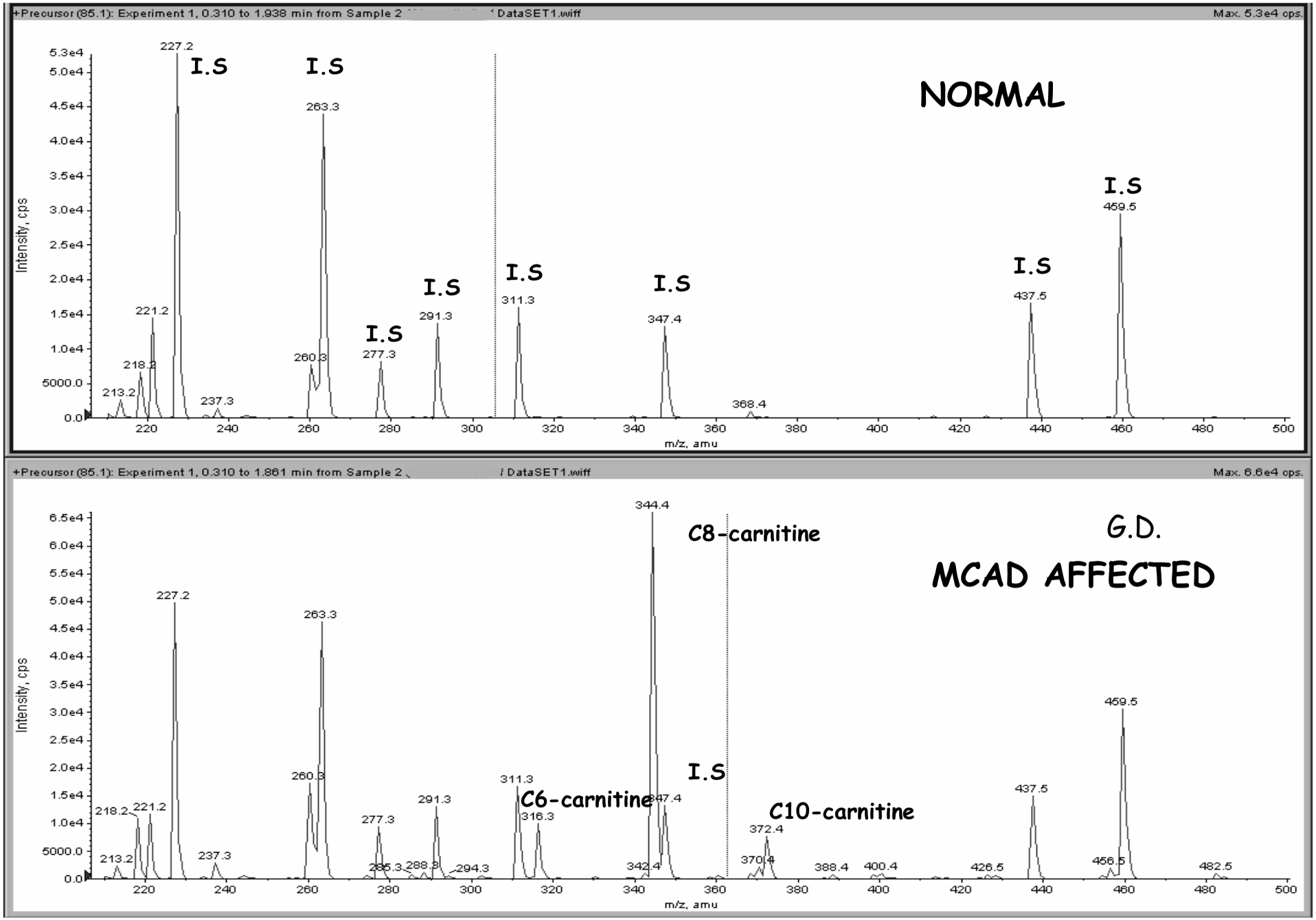
MCADD: Medium-Chain Acyl CoA Dehydrogenase Deficiency

AUTOSOMAL RECESSIVE

Estimated occurrence ~1:15000
Caucasian births

β–oxidation of long, medium and short chain fatty acids





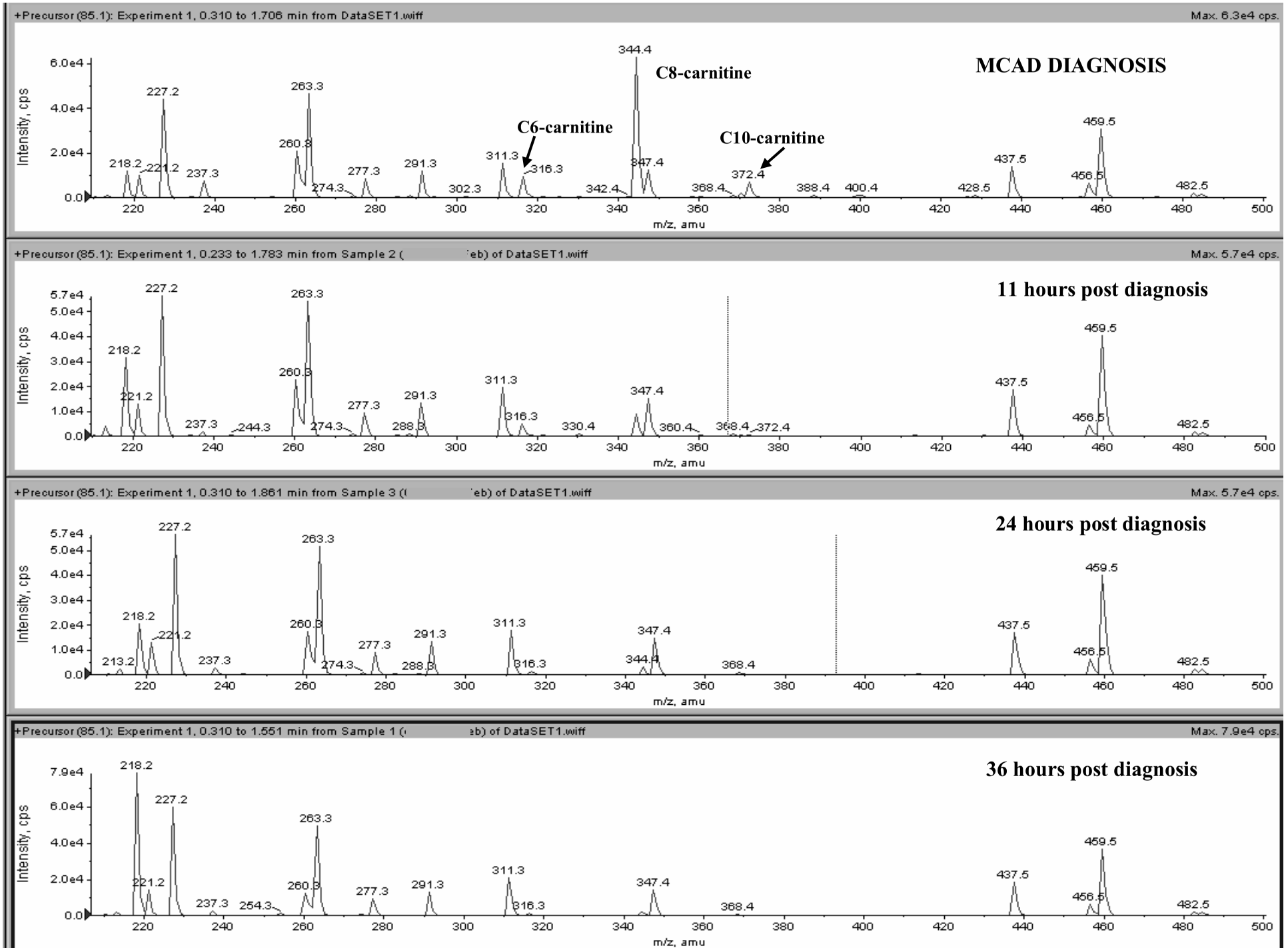
G.la Marca et al, Rapid Comm Mass Spectrom, 17, 2003

EMERGENCY THERAPY

Glucose i.v 7-10 mg/Kg/min

No activation of lipolitic pathway

Supplementation with carnitine is currently done (30-50 mg/Kg/die)


+Precursor (85.1): Experiment 1, 0.310 to 1.706 min from DataSET1.wiff
Max. 6.3e4 cps.
MCAD DIAGNOSIS
C8-carnitine
C6-carnitine
C10-carnitine
Intensity, cps
m/z, amu
+Precursor (85.1): Experiment 1, 0.233 to 1.783 min from Sample 2 (eb) of DataSET1.wiff
Max. 5.7e4 cps.
11 hours post diagnosis
+Precursor (85.1): Experiment 1, 0.310 to 1.861 min from Sample 3 (eb) of DataSET1.wiff
Max. 5.7e4 cps.
24 hours post diagnosis
+Precursor (85.1): Experiment 1, 0.310 to 1.551 min from Sample 1 (eb) of DataSET1.wiff
Max. 7.9e4 cps.
36 hours post diagnosis

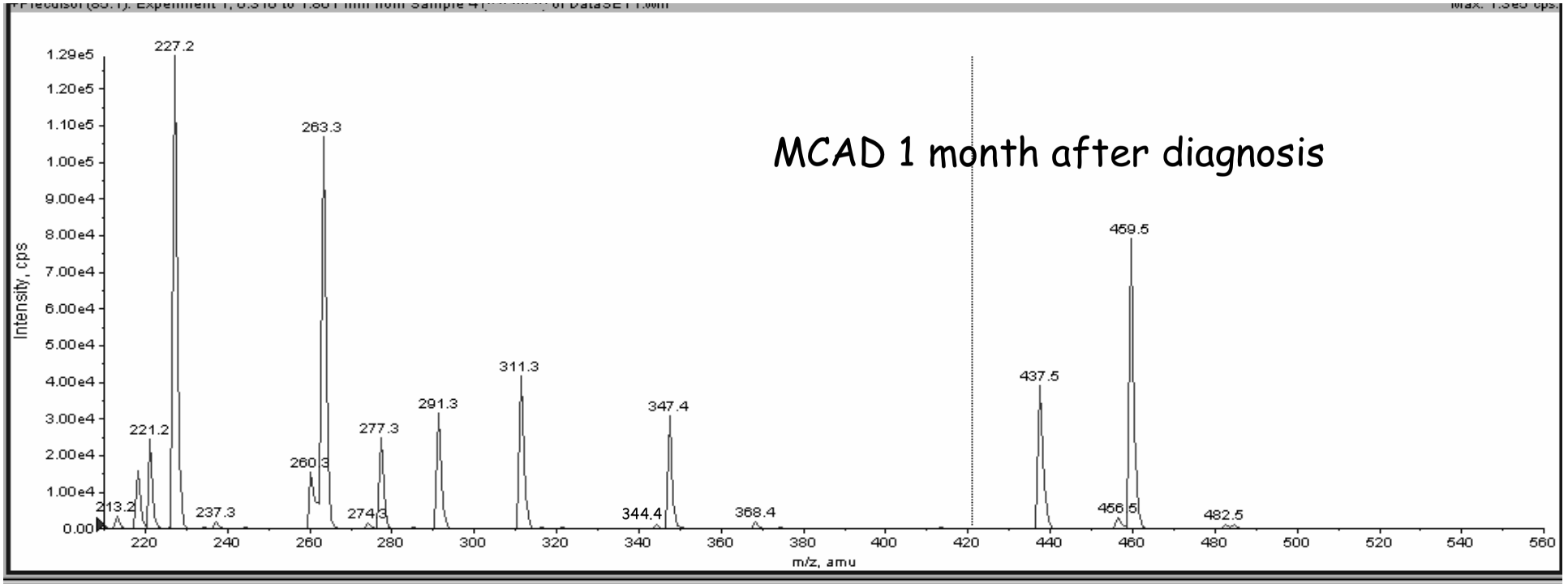
LONG TERM MANAGEMENT

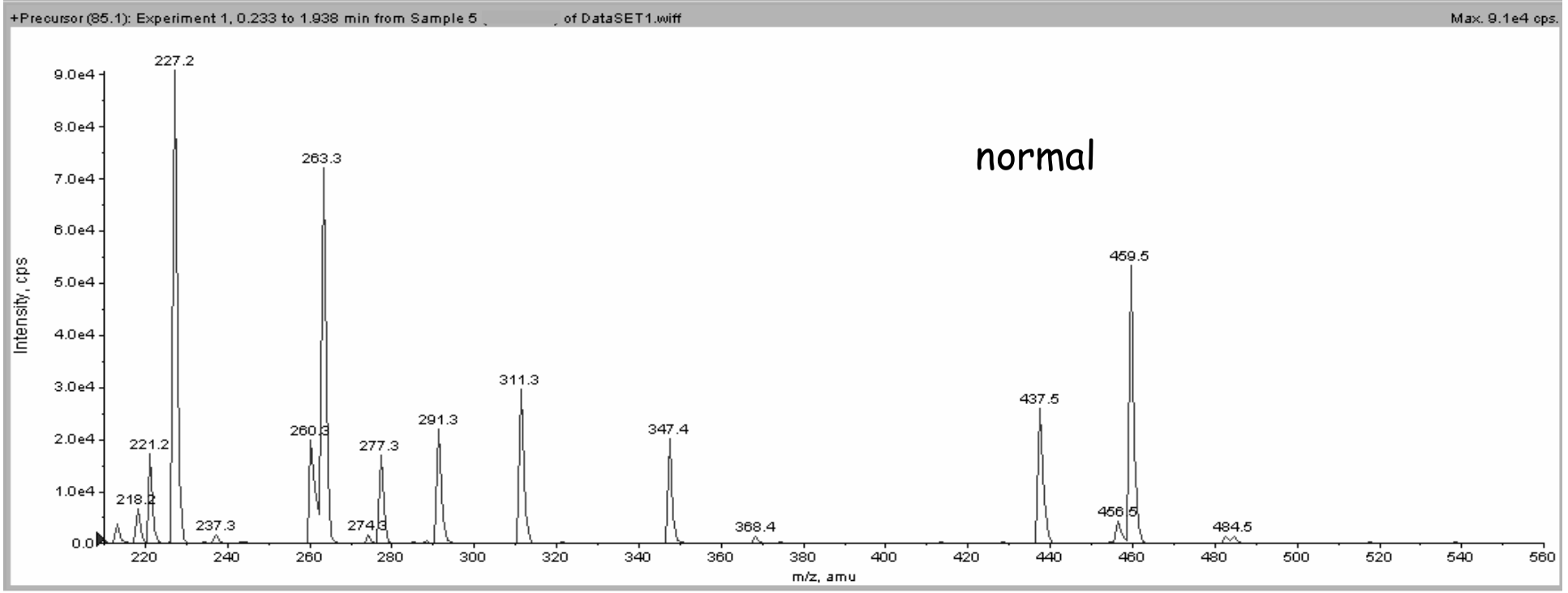
avoid fasting;

adequate caloric intake;

frequent meals;

carnitine supplementation (30-50 mg/Kg/die)


MCAD 1 month after diagnosis
Intensity, cps
m/z, amu
227.2
263.3
459.5
311.3
437.5
347.4
291.3
277.3
221.2
260.3
213.2
237.3
274.3
344.4
368.4
456.5
482.5


+Precursor (85.1): Experiment 1, 0.233 to 1.938 min from Sample 5 , of DataSET1.wiff
Max. 9.1e4 cps.
normal
Intensity, cps
m/z, amu
227.2
263.3
459.5
311.3
437.5
347.4
291.3
277.3
221.2
260.3
218.2
237.3
274.3
368.4
456.5
484.5

DEFICIT DI MCAD

- Episodi di ipoglicemia ipochetotica
- Epatomegalia
- Episodi Reye like

} dopo digiuno prolungato / dopo infezione

DIAGNOSI POSTSINTOMATICA (120 paz.)

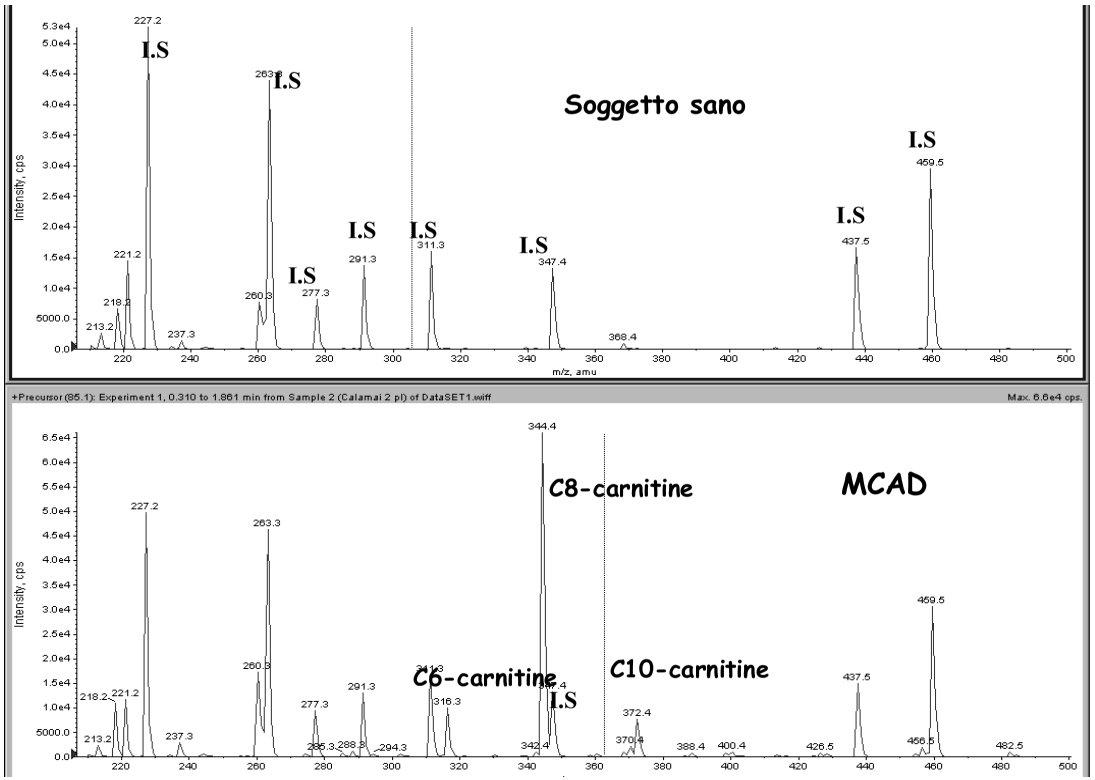
Coma	84%
Patologia neurologica residua	40%
Mortalita'	20%

SCREENING NEONATALE in LC-MS/MS

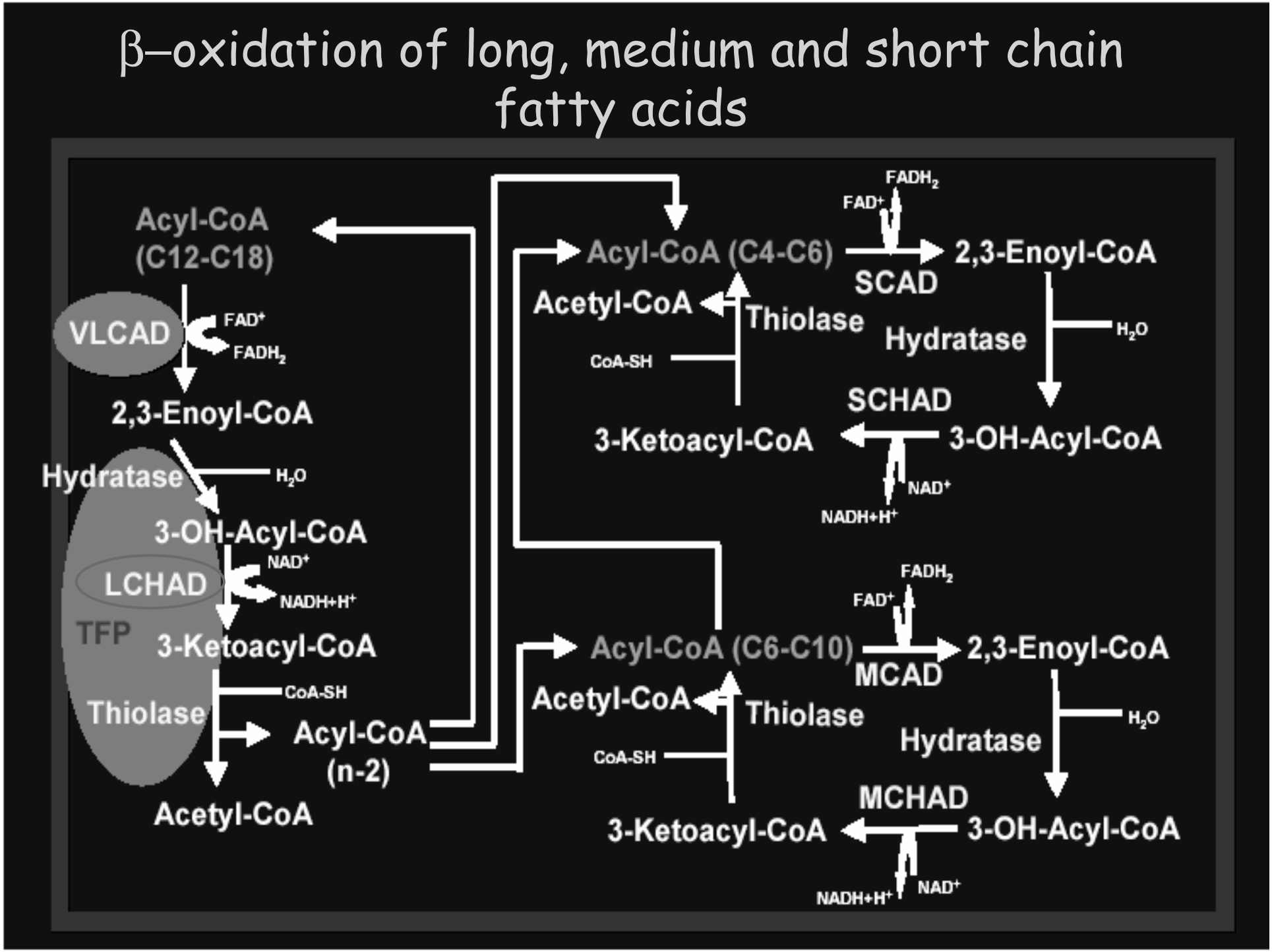
DIAGNOSI PRESINTOMATICA (62 paz.)

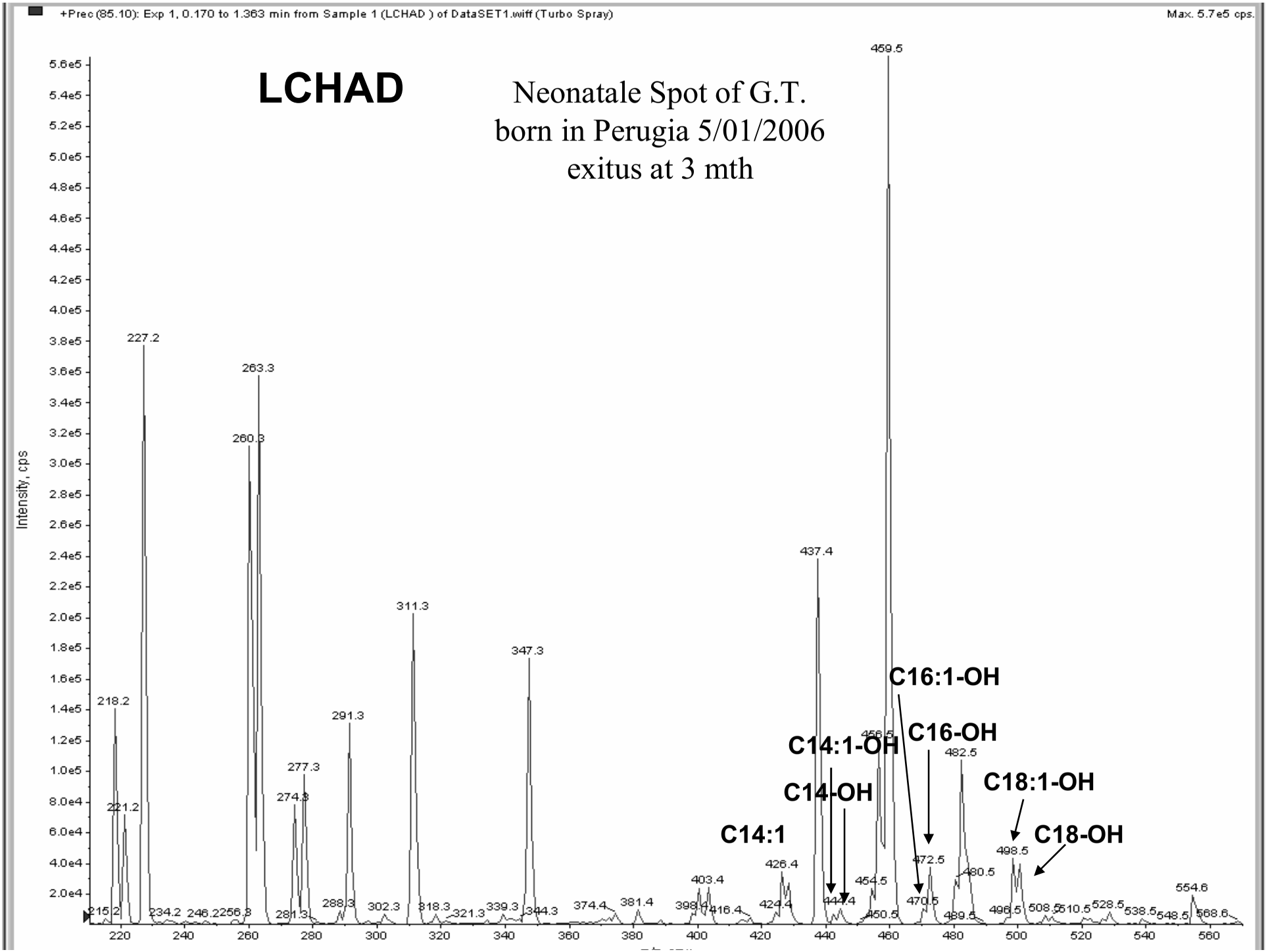
Coma	0%
Ritardo mentale	0%
Mortalità	0%

Muntau 1999-2003



β–oxidation of long, medium and short chain fatty acids




+Prec (85.10): Exp 1, 0.170 to 1.363 min from Sample 1 (LCHAD) of DataSET1.wiff (Turbo Spray)
Max. 5.7e5 cps.
LCHAD
Neonatale Spot of G.T.
born in Perugia 5/01/2006
exitus at 3 mth
Intensity, cps
C14:1
C14:1-OH
C14-OH
C16:1-OH
C16-OH
C18:1-OH
C18-OH

Circa 1 euro a difetto/neonato = 50 euro test per il programma se la spesa viene razionalizzata con la creazione di centri screening interregionali