

MALATTIE METABOLICHE EREDITARIE e PERCORSI DIAGNOSTICI

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DIAGNOSTICARE UNA MALATTIA METABOLICA EREDITARIA

Clinica

Anamnesi

Esame obiettivo

Semeiotica strumentale

Ecocardio

Ecoepatica

EEG

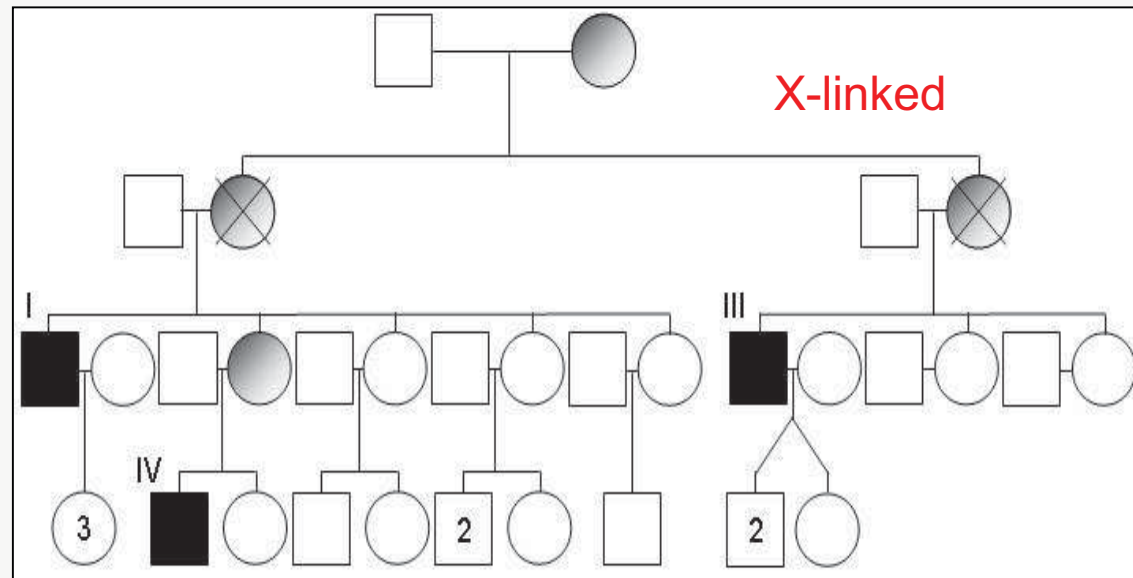
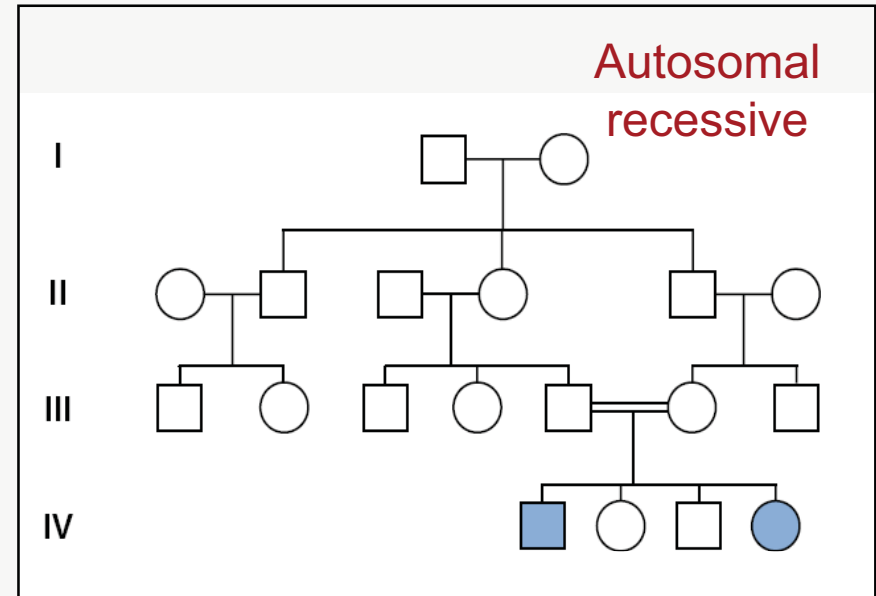
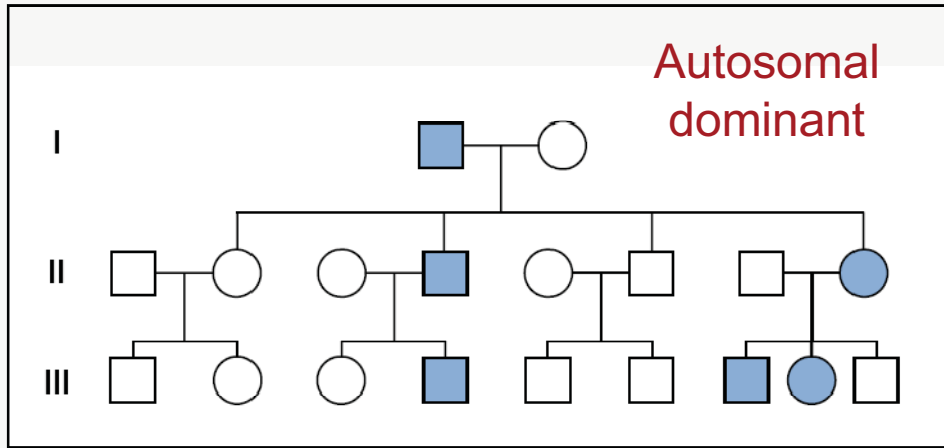
RMN cerebrale

Laboratorio

Screening neonatale esteso

**Patologie non soggette a
screening**

ANAMNESI



■ ● = affected

Epoca Neonatale :Dismorfismi

Lysosomal disorders



Mucopolidosis type II

Peroxisomal disorders



Zellweger syndrome

Disorders of cholesterol synthesis



SLO syndrome

CLINICA DELLE MALATTIE METABOLICHE EREDITARIE

RITARDO DI CRESCITA STATURO-PONDERALE

Vomiti ripetuti

**Epatopatia con aumento delle transaminasi
cardiomiopatie ipertrofiche**

RITARDO DI SVILUPPO PSICOMOTORIO

Micro/macrocefalie inspiegabili

Danno neurologico

**Convulsioni: recidivanti / resistenti al trattamento
altri sintomi neurologici**

Movimenti anomali (distonia, tremori)

Disturbi della marcia / atassia intermittente

Ipotonia muscolare, crampi

Disordini fluttuanti dello stato di coscienza

Dismorfismi cranio-facciali

EPISODIO TIPO ALTE

NEFROLITIASI e nefropatie

ABC DELLA PATOLOGIA METABOLICA : la clinica

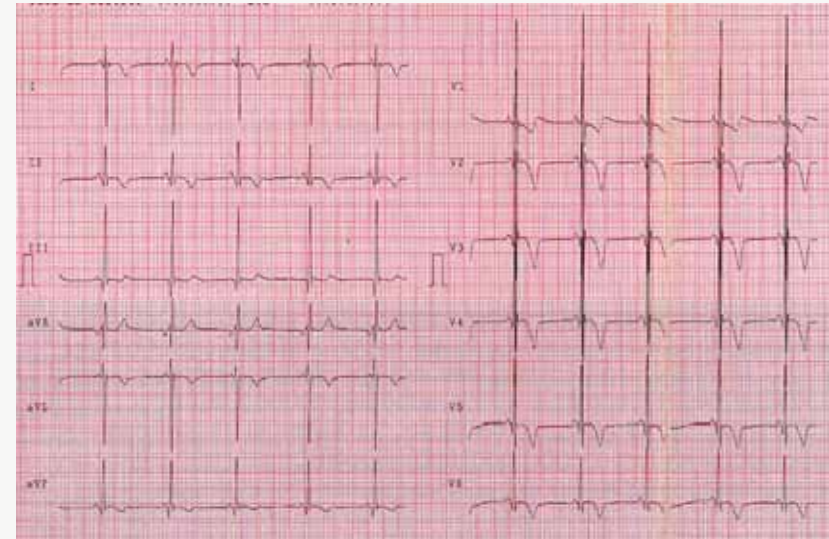
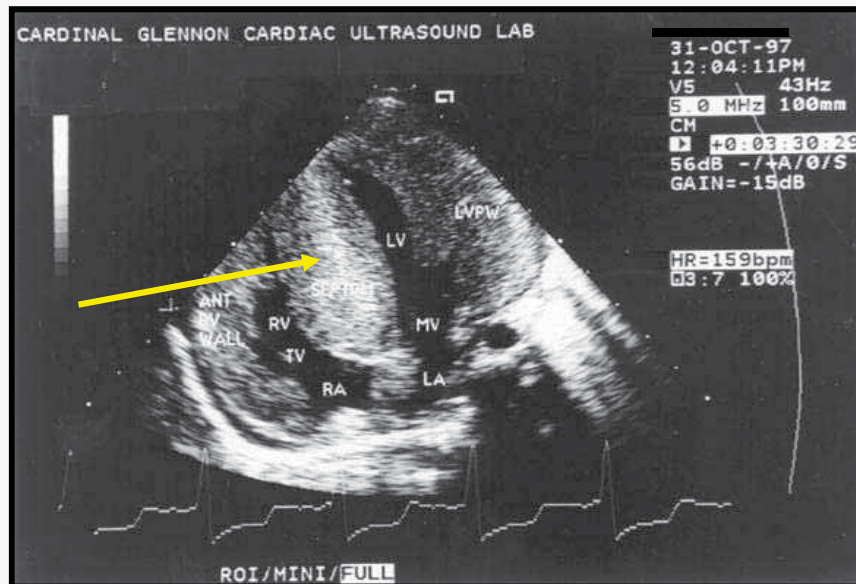
- **MALATTIE DA ACCUMULO** :
decorso cronico, lentamente progressivo, spesso con diversi organi interessati
- **MALATTIE DEL METABOLISMO INTERMEDIO** : presentazione acuta o a decorso intermittente, scatenate da digiuno, infezioni, cambiamento d'alimentazione
- **MALATTIE DEL METABOLISMO ENERGETICO** o poco sintomatiche in epoca pediatrica ma che si presentano clinicamente età adulta.
- lisosomopatie, perossisomi, CDG, difetti del colesterolo, difetti di trasporto
- aminoacidopatie, acidurie organiche, difetti dei carboidrati
- mitocondriopatie, difetti β ossidazione acidi grassi, difetti del metabolismo del piruvato

DIAGNOSI strumentale

PR corto 0.08 sec

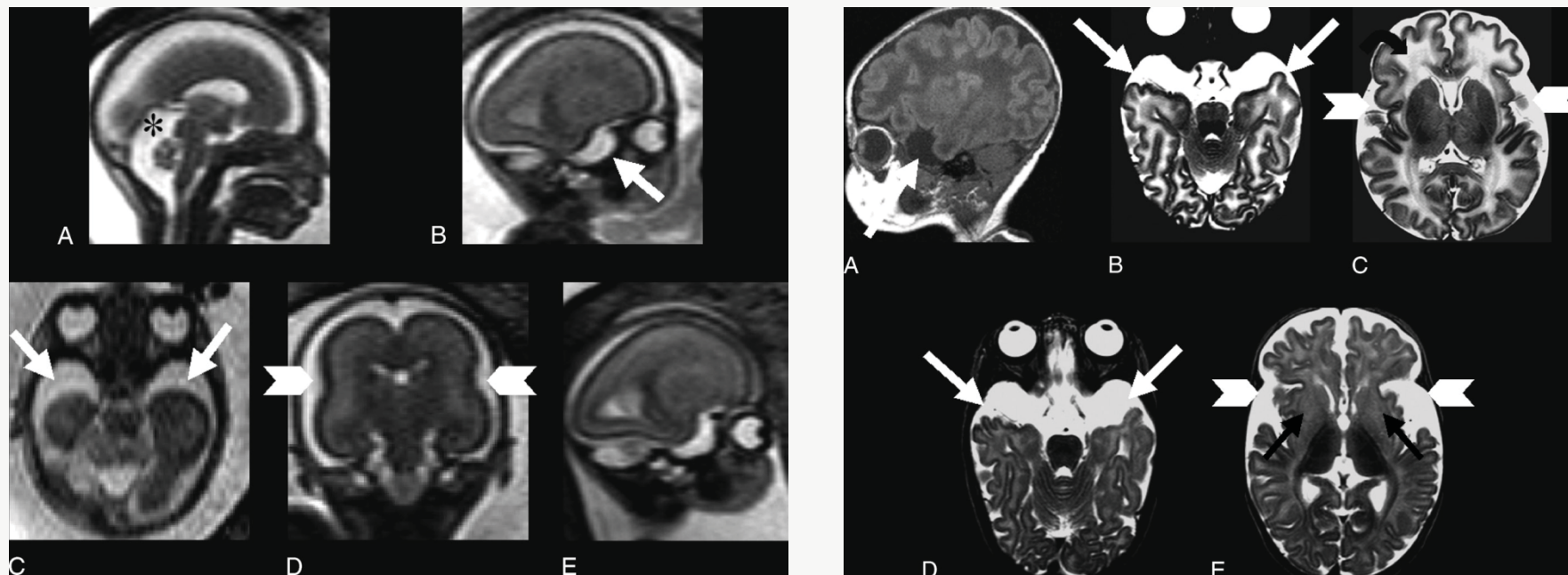
Alti voltaggi settali

Deviazione assiale a $+120^\circ$



Early Prenatal Magnetic Resonance Imaging of Glutaric Aciduria Type 1: Case Report

22-week-gestation fetus, in which prenatalmagnetic resonance imaging revealed findings suggestive of glutaric aciduria type 1 (GA-1),



SOSPETTARE UNA MALATTIA METABOLICA EREDITARIA

Clinica

Anamnesi

Esame obiettivo

Semeiotica strumentale

Ecografia

EEG

Radiografia

TAC

RMN

PET

Laboratorio

Screening neonatale esteso

**Patologie non soggette a
screening**

Screening by MS/MS (Multiplex Testing)

- Molte malattie

- un test 

- Molti metaboliti

- ampio cut-off

(MME)_n



MS/MS



(AA,AC)_n



0.1-1,000 μM

Tecnologia: MS/MS

RIEMPIRE
COMPLETAMENTE
TUTTI I CERCHI

N° 0601 B1

N° 0601 B1

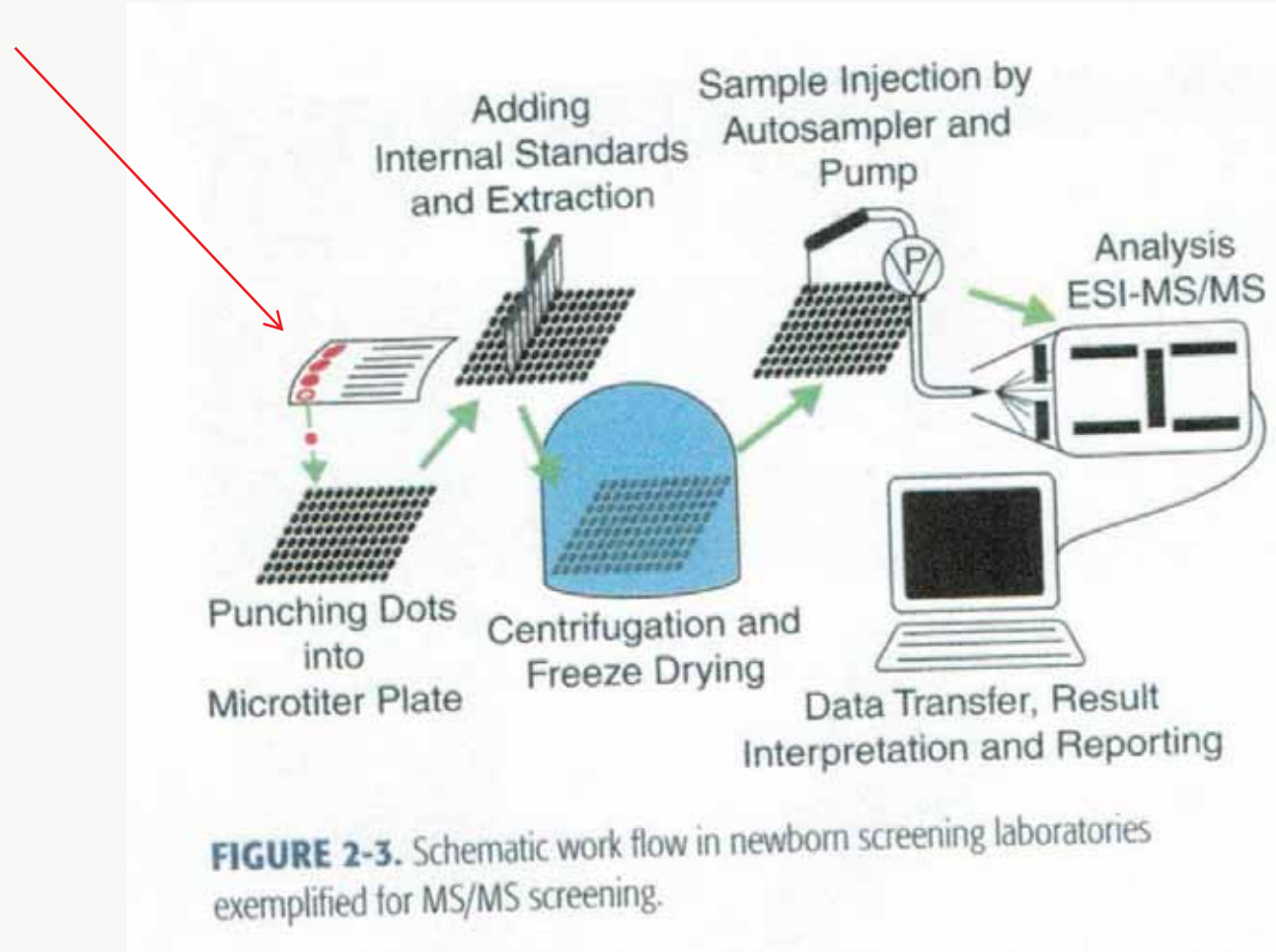
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Nome _____

Nato ___/___/200__ Prelievo ___/___/200__

Peso |_____|gr Sesso |M|F|

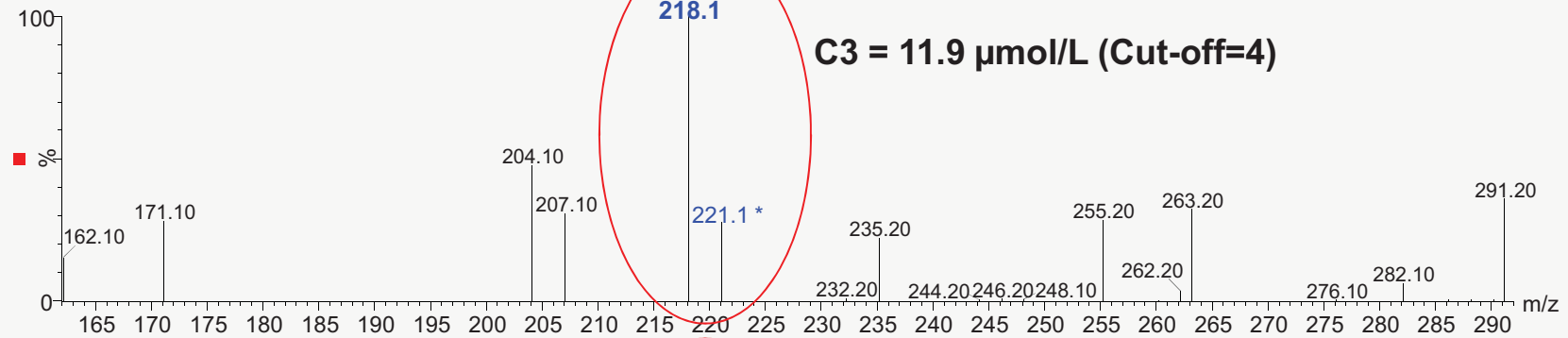
Spedire a:
Centro Regionale Malattie Rare
Sezione Malattie Metaboliche Ereditarie
Dipartimento di Pediatria
Azienda Ospedaliera di Padova
Via Giustiniani, 3 - 35128 PADOVA



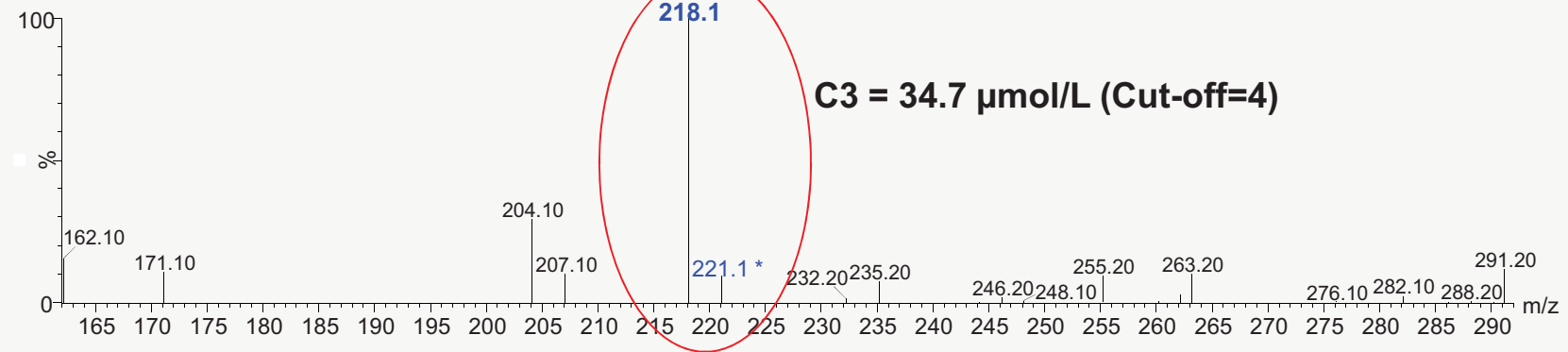
ACIDURIE ORGANICHE

C3 Propionyl carnitine

PROPIONIC ACIDAEMIA

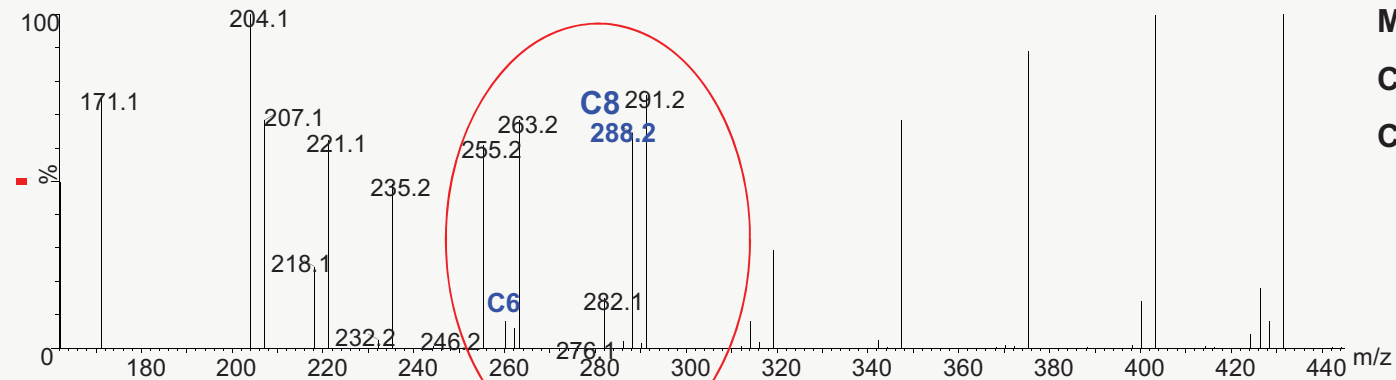


METHYL MALONIC ACIDAEMIA



DIFETTI β -ossidazione ACIDI GRASSI

MCAD

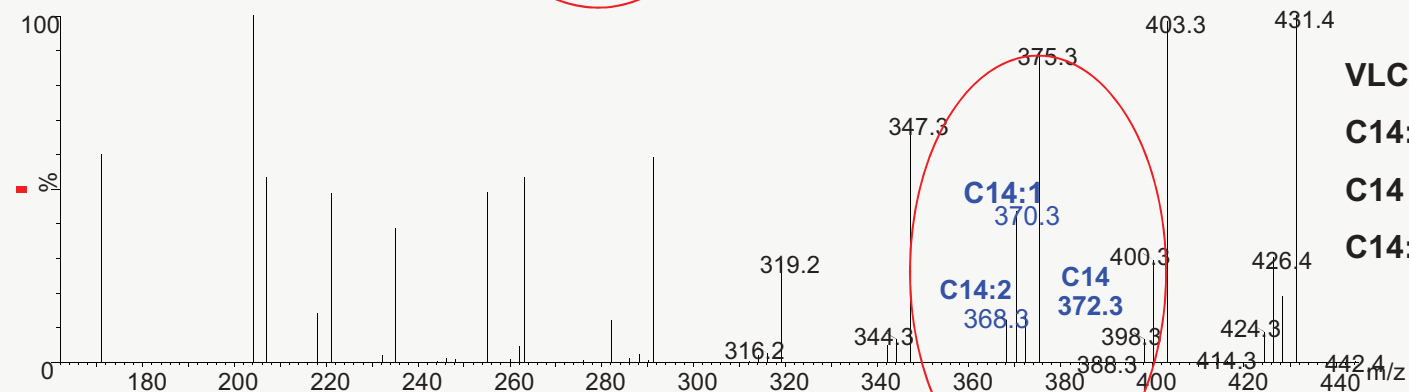


MCAD

C8 = 2.09 $\mu\text{mol/L}$ (Cut-off=0.22)

C6 = 0.30 $\mu\text{mol/L}$ (Cut-off=0.22)

VLCAD



VLCAD

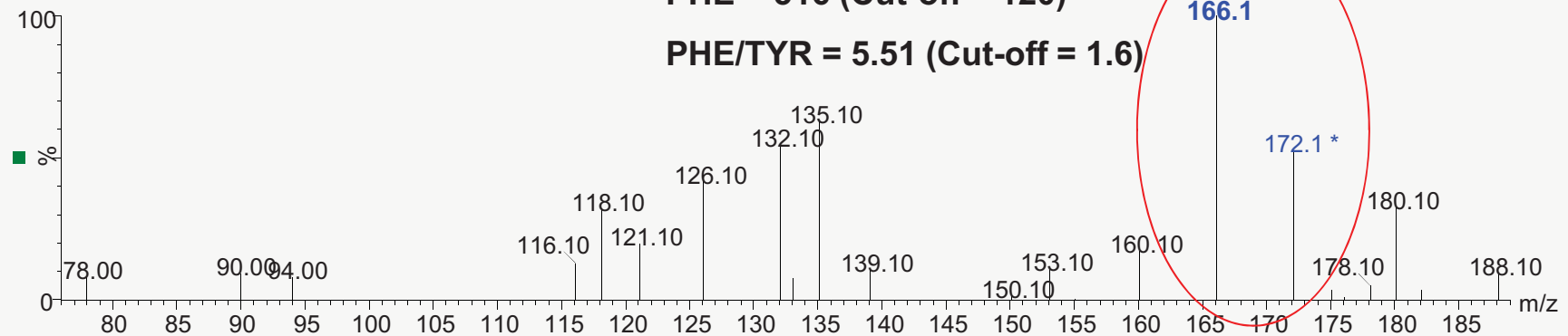
C14:1 = 2.41 $\mu\text{mol/L}$ (Cut-off = 0.44)

C14 = 0.74 $\mu\text{mol/L}$ (Cut-off = 0.5)

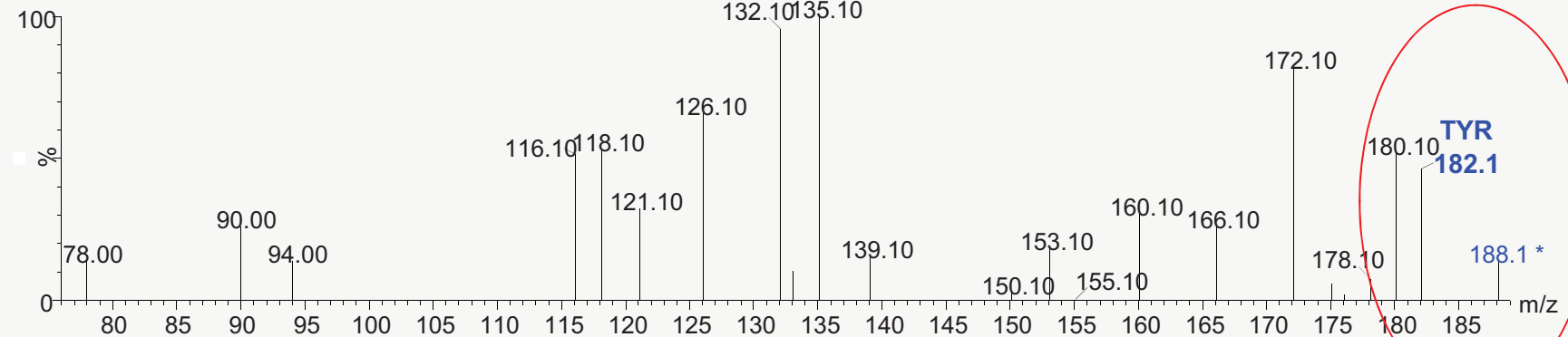
C14:2 = 0.67 $\mu\text{mol/L}$ (Cut-off = 0.10)

aminoacidopatie

PHENYLKETONURIA



TYROSINAEMIA TYPE I



TYR = 614 μ mol/L (Cut-off = 200)

Table 1 (continued)

Disease	Methods	Relevance ranking	Screening programs	Test* available	Therapy available	Benefit from early detection	References	Remarks
Galactosemia	Substrate and/or enzyme assay	++	a	y	y	y	[119]	Long-term outcome not as favorable as initially thought in the 1970s
Glucose-6-phosphate dehydrogenase deficiency	Enzyme assay	?	e	?	y	y	[120]	High genetic variability
Disorders of creatine metabolism	TMS	?	p	?	y	?	[121-123]	Feasibility has been demonstrated, results of pilots not available so far
Lysosomal storage disorders	TMS	?	p	?	y	?	[124, 125]	Enzyme replacement therapy is available for M. Fabry, M. Gaucher, M. Krabbe, M. Niemann-Pick A/B, and M. Pompe
Cystic fibrosis	IRT/DNA	++	m	y	y	y	[126-129]	
Diabetes mellitus type I	DNA	?	p	?	?	?	[130]	"Genetic risk" screening
Other diseases								
Hearing deficiency	Otoacoustic	++	m	y	y	y	[131]	Decentralized
Congenital CMV infection	CMV viral load	+	m	y	y	y	[132-138]	Late-onset hearing loss is not detectable by the otoacoustic method in newborns
Congenital toxoplasmosis infection	Toxoplasmosis viral load	--	mat	--	--	--	[139]	Not recommended, (prenatal care)
Congenital syphilis infection	Non-treponemal antibodies	--	mat/epd	--	--	--	[140]	Not recommended, (prenatal care)
Neuroblastoma screening ^b	HPLC	--	d	--	--	n	[141-143]	Not recommended
Duchenne muscular dystrophy	Creatine kinase activity	--	p	y	n	n	[144, 145]	Disposition-screening; no effect on outcome
SCID	T-cell lymphopenia	?	pa	--	--	--	[146]	Not recommended
HBV	Immunoassays	?	epd	--	--	--	[147]	Not recommended
Hepatitis C	Immunoassays	?	epd	--	--	--	[148]	Not recommended, (prenatal care)
Hepatitis B	HBsAg	?	epd	--	--	--	[149]	Not recommended, (prenatal care)

CPT-I carnitine palmitoyl transferase I, *CPT-II* carnitine palmitoyl transferase II, *HBsAg* hepatitis B surface antigen, *HHH* hyperornithinemia-hyperammonemia-homocitrullinuria, *HPLC* high-performance liquid chromatography, *IIF* isoelectric focusing, *IIF* immunoreactive trypsin, *LCHAD* long-chain hydroxyacyl-CoA dehydrogenase, *MCAD* medium-chain acyl-CoA dehydrogenase, *3-MCC* 3-methylcrotonyl-CoA carboxylase, *NBS* newborn screening, *OAT* ornithine amino transferase, *SCAD* short-chain acyl-CoA dehydrogenase, *SCID* severe combined immunodeficiency, *TFF* trifunctional protein, *TLC* thin-layer chromatography, *TMS* tandem mass spectrometry, *VLCAD* very long chain acyl-CoA dehydrogenase, a all, d discontinued, e ethnic, epd epidemiologic, m most, mat recommended as a prenatal screening test, n no, p pilot, pr proposed, y yes, + + unquestioned, + favorable, ? questionable, - unfavorable, -- not recommended

*With sufficient sensitivity and specificity, economically justifiable

^bSpecimen for screening is urine dried on filter paper

Newborn screening for inborn errors of metabolism and endocrinopathies

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Table 1 (continued)

Disease	Methods	Relevance ranking	Screening programs	Test* available	Therapy available	Benefit from early detection	References	Remarks
3-MCC deficiency	TMS	-	m	?	y	?	[95]	Low clinical expressivity and penetrance
3-hydroxyethylglutaryl-CoA lyase deficiency	TMS	?	m	y	y	y	[96]	Reliable discrimination from 3-MCC not possible
Holocarboxylase synthase deficiency	TMS	?	m	y	y	y	[97]	Very rare, but easily treatable with biotin; reliable discrimination from 3-MCC not possible
β -ketothiolase deficiency	TMS	+	m	?	y	y	[98]	Sensitivity and specificity presumably low
Disorders of glutathione metabolism	TMS	?	m	?	?	?	[99]	No prospective data
β -Oxidation defects/disorders of carnitine metabolism								
SCAD deficiency	TMS	--	m	?	?	?	[100]	Causality between enzyme defect and clinical presentation is not proven
MCAD deficiency	TMS	++	a	y	y	y	[101, 102]	Positive effect unquestioned; however, patients that might never become symptomatic are also detected
VLCAD deficiency	TMS	++	m	y	y	y	[103]	Mild variants might be missed when the samples are taken under anabolic conditions
LCHAD/VFPP deficiency	TMS	+	m	y	y	y/f	[104-106]	Information on long-term outcome is still pending; prognosis for VFPP is rather bad
Carnitine transporter deficiency	TMS	+	m	?	y	y	[107]	Sensitivity unclear; free carnitine level can be normal postpartum, depending on maternal supply and renal loss
CPT-I deficiency	TMS	++	m	y	y	y	[108]	Ratio of free carnitine to the sum of palmitoylcarnitine and stercylolethylcarnitine is sensitive and highly specific
CPT-II deficiency	TMS	+	m	?	?	?	[109]	Normal onset form with bad prognosis despite early diagnosis; in the late-onset form mainly skeletal muscle is involved, seems to have normal levels of acylcarnitine in the neonatal period
Translocase deficiency	TMS	+	m	y	?	?	[110]	Bad prognosis despite early diagnosis
Endocrinopathies								
Congenital hypothyroidism	ELISA	++	a	y	y	y	[111]	
Congenital adrenal hyperplasia	ELISA	++	a	y	y	y	[112, 113]	Sensitivity for the salt-wasting form is good, for simple virilizing congenital adrenal hyperplasia approximately 90%
Hemoglobinopathies								
Sickle cell anemia	IEF	++	e	y	y	y	[114-116]	
Hemoglobin S β -thalassemia	IEF	++	e	y	y	y		
Hemoglobin SC disease	IEF	++	e	y	y	y		
Hemoglobin H	IEF	++	e	y	y	y		
Other inborn errors of metabolism								
Biotinidase deficiency	Enzyme assay	++	a	y	y	y	[117, 118]	

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K. Engelke, H. Engelke

Table 1 Target diseases for newborn screening

Disease	Methods	Relevance ranking	Screening programs	Test* available	Therapy available	Benefit from early detection	References	Remarks
Amino acidopathies								
Phenylketonuria	TMS	++	a	y	y	y	[54-58]	Alternative therapies for mild phenylketonuria have been introduced recently
Maple syrup urine disease	TMS	++	m	y	y	y	[59-62]	Early blood collection is mandatory
Homocystinuria	TMS	+	m	n	y	y	[13, 63, 64]	Sensitivity and specificity low with methionine as a primary marker; determination of homocysteine could improve NBS
Tyrosinemia type I	TMS	+	m	y?	y	y	[65-69]	Low sensitivity and low specificity with tyrosine as primary marker; determination of succinyl acetone could improve NBS
Citrullinemia	TMS	+	m	?	?	?	[70]	No positive effect on outcome; patients with a mild biochemical phenotype might never develop symptoms
Argininosuccinic acidemia	TMS	+	m	?	?	?	[71]	No positive effect on outcome
Arginase deficiency	TMS	+	m	?	?	y	[72-74]	Very rare; the first results of NBS and early treatment seem promising
Hypornithinemia (OAT deficiency and HHH syndrome)	TMS	?	m	n	?	?	[75]	Normal ornithine levels during the first weeks of life
Nonketotic hyperglycinemia	TMS	--	m	n	n	n	[76]	No therapy available
Hemiparesis	TLC	--	d	--	--	n	[77-81]	Berign, does not require treatment
Hydroxyphenylketonuria	TLC	--	d	--	--	n	[82-84]	Berign, does not require treatment
Organic acidurias								
Glutaric acidemia type I	TMS	++	m	y	y	y	[85, 86]	
Isovaleric acidemia	TMS	++	m	y	y	y	[87, 88]	Screening also detects unaffected patients with mild variants
Propionic acidemia	TMS	+	m	y	y	?	[89, 90]	Acylcarnitine profile indistinguishable from methylmalonic acidemia profile in newborns
Methylmalonic acidemia (mutar)	TMS	+	m	y	y	?	[90]	Acylcarnitine profile indistinguishable from propionic acidemia profile in newborns
Methylmalonic acidemia (disorders of cobalamin metabolism types A-III, F)	TMS	+	m	y	y	?	[91]	Sensitivity unclear; propionylcarnitine level is often only slightly elevated
Cobalamin B12 defect	TMS	--	?	?	?	?	[92]	Low methionine level is the only marker; sensitivity and specificity unknown, but presumably low; determination of homocysteine in dried blood spots could improve NBS
Mahony-CoA decarboxylase deficiency	TMS	+	m	y	y	y	[93, 94]	Very rare; no prospective data

Newborn screening for inborn errors of metabolism and endocrinopathies

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POSSIBILI 60 PATOLOGIE METABOLICHE EREDITARIE

NEWBORN BLOODSPOT SCREENING LSD

Disease (common name)	Deficient enzyme	Age of onset	Corrective therapy*	NBS test status
Fabry	α -Galactosidase A (EC 3.2.1.22)	Childhood - adult	ERT: Begin as early as possible in all symptomatic males with Fabry and in female carriers with significant disease. No consensus on when to begin ERT for presymptomatic male infants.	1, 2, 3
Gaucher	β -Glucocerebrosidase (EC 3.2.1.45)	Type 1: Childhood - Adult Type 2: Infant Type 3: Infant - Adult	ERT: First ERT for LSD. Standard of care for type I Gaucher patients, reduces hepatosplenomegaly, improves bone pain or bone crisis, anemia, and thrombocytopenia. Not indicated in the acute neuronopathic form of Gaucher disease (type II). SRT: Approved for use in mild to moderate type 1 when ERT is not a therapeutic option. New SRTs in clinical trials.	1, 2, 3
Krabbe	β -Galactocerebrosidase (EC 3.2.1.46)	Early onset - Infant Late onset - Adult	HSCT: In presymptomatic infants and older individuals with mild symptoms may improve and preserve cognitive function, but peripheral nervous system function may deteriorate. Significant clinical variability in late-onset forms	1, 3
MPS I (Hurler, Hurler-Scheie, Scheie syndromes)	α -L-Iduronidase (EC3.2.1.76)	Early onset – Hurler Childhood onset – Hurler-Scheie Late onset - Scheie	HSCT: Successful HSCT (before age 2 years) increases survival, reduces facial coarseness, decreases hepatosplenomegaly, improves hearing, and maintains normal heart function. Slows course of cognitive decline if performed before developmental delays are apparent. Minimal to no improvement on the skeletal manifestations, corneal clouding and heart valve involvement. Significant pulmonary and cardiac complications post HSCT. ERT: Treats non-CNS manifestations of MPS I. Improves pulmonary function, six-minute walk, decreases liver volume and lowers urinary glycosaminoglycans. ERT before and after HSCT may alleviate disease manifestations, reduce complications of HSCT. Ongoing investigations of instillation of ERT into CNS.	1, 3
MPS II (Hunter syndrome)	Iduronate-2-sulphatase (EC 3.1.6.13)	Males only. Variable overall; severe forms onset at 2-4 years of age.	HSCT: Poor results to date. Limited data with infants. ERT: Improved 6-minute walk and forced vital capacity. No effect on CNS disease. Ongoing investigations of instillation of ERT into CNS.	3
MPS VI (Maroteaux-Lamy syndrome)	Arylsulfatase B (EC 3.1.6.12)	Generally in childhood; newborn infants may have macrocephaly	HSCT: Limited experience in infants. In older children reduced facial dysmorphism, stabilized cardiac, and mobility. No change in skeletal function. Variable improvement in visual acuity. ERT: Improved 12-minute walk, 3-minute stair climb and reduced urinary glycosaminoglycan excretion. ⁷²	3
Metachromatic leukodystrophy	Arylsulfatase A (EC 3.1.6.8)	Severe in late infantile form, mild in juvenile form; late onset - adult	HSCT: The best outcomes were observed in individuals undergoing transplantation before symptoms occurred. Can slow disease progression but does not seem to alleviate peripheral nervous system manifestations. ERT: In clinical trials.	3
Niemann-Pick A / B	Acid sphingomyelinase (EC 3.1.4.12)	Type A: Neonatal Type B: Childhood	HSCT: Limited experience in infants. Variable response. Improved blood counts and hepatosplenomegaly. Minimal effects on neurological status.	1, 2, 3
Pompe (Glycogen Storage II)	α -Glucosidase (EC 3.2.1.20)	Severe infantile to late onset adult	ERT: Begin as soon as the diagnosis is confirmed. Below 6 months of age had improved ventilator-independent survival, reduced cardiac mass, and improved acquisition of motor skills. Effect on long-term cognition is unknown. Poor prognostic indicators are CRIM negativity and high IgG tiers to exogenous enzyme.	1, 2, 3

TANDEM – MS DISEASE PANELS IN EUROPEAN COUNTRIES

Table 2 Comparison of European Countries (***)excluding Scotland) regarding number of screening centres, total population (year 2001*), screened infants (year 2003**) and metabolic disorders included in MS/MS screening; see Table 1 for abbreviations. The numbers for screening centres, total population and screened infants are partially based on a questionnaire that was initiated by ISNS in 2003. Details can be found on www.isns-neoscreening.org

Country	No of centres	Population*(millions)	Number of infants screened**(average sample number/ screening laboratory)	Disorders included in extended screening by MS/MS
Austria(including South Tyrol, Italy)	1	8.18	77 186(77 186)	PKU, MSUD, TyrI, Cit, ASLD, Homocyst, MCADD, LCHADD, VLCADD, CPT ID CPT IID/CACT, CTD, KTD, HMG-CoA LD, MMA, PA, IVA, GA I, 3-MCCD
Belgium	6	10.29	105 335(17 555)	PKU, MSUD, TyrI, MCADD, LCHADD, VLCADD, CPT ID CPT IID/CACT, CTD, KTD, HMG-CoA LD, MMA, PA, IVA, GA I, 3-MCCD
Bulgaria	1	7.55	63 190	None
Croatia	1	4.43	No information	None
Czech Republic	4	10.25	93 685(23 421)	None
Denmark	1	5.38	66 657(66 657)	PKU, MSUD, Cit, ASLD, ArginaseD, MCADD, LCHADD, VLCADD, CPT ID CPT IID/CACT, CTD, KTD, HMG-CoA LD, MMA, PA, IVA, GA I, 3-MCCD (pilot study, not 100% population coverage)
Finland	40	5.19	56 000(1 400)	None
France	22	59.94	764 212(34 737)	None
Germany	13	83.43	725 125(60 427)	PKU, MSUD, MCADD, LCHADD, VLCADD, CPT ID, CPT IID/CACT, IVA, GA I
Great Britain***	20	54.78	625 749(32 287)	MCADD (pilot project, not 100% population coverage)
Hungary	4	10.05	approx. 100 000(25 000)	None
Iceland	1	0.308	4 000(4 000)	None
Ireland	1	3.92	62 000(62 000)	None
Italy	22	57.74	566 169(25 734)	No information
Netherlands	5	16.14	200 635(40 127)	PKU, MSUD, Homocyst, TyrI, MCADD, LCHADD, VLCADD, HMG-CoA LyaseD, IVA, GA I, 3-MCCD
Norway	1	4.54	50 840(50 840)	None
Poland	8	38.62	352 152(44 019)	PKU, MSUD, TyrI, MCADD, LCHADD, VLCADD, CPT ID, CPT IID/CACT, CTD, IVA, GA I; one centre screens for 30% of population
Portugal	1	10.10	112 557(112 557)	PKU, MSUD, MCADD, LCHADD, VLCADD, CPT ID, CPT IID/CACT, IVA, GA I, GAMTD
Romania	No information	22.28	No information	None
Serbia	1	10.50	57 354(57 354)	None
Slovakia	1	5.43	No information	None
Slovenia	1	1.94	14 000(14,000)	None
Spain	20	40.11	441 297(22,064)	PKU, MSUD, MCADD, LCHADD, VLCADD, CPT ID, CPT IID/CACT, IVA, GA I; one centre screens <10% of population)
Switzerland	1	7.32	74 450 74 450	PKU, MCADD
Total	176	478 418	4 618 599	

Netherlands
9 Metabolic disorders
 PKU, MSUD, Hcys, Tyr I, MCAD, LCHAD, VLCAD, HMG-CoAL, MMA, PA, GA 1, IVA, 3-MCC

UK
2 Metabolic disorders
 PKU, MCAD
 Considering Hcys
 GA 1, MSUD, IVA, LCHAD, Biotinidase

Germany
9 Metabolic disorders
 PKU, MSUD, MCAD, LCHAD, VLCAD, CPT I, CPT II/CACT, GA 1, IVA,

Neonatal Screening for Treatable and Untreatable Disorders: Prospective Parents' Opinions

Anne Marie Catharina Plass, Carla Geertruida van El, Toine Pieters and Martina Cornelia Cornel

Pediatrics 2010;125:e99-e106; originally published online Dec 21, 2009;

TABLE 1 Information Presented to the Respondents

Category I: treatable disorders

An example of a treatable disorder is the hereditary metabolic disorder PKU (phenylketonuria). This disorder can cause serious brain damage, but early treatment (ie, diet) can prevent this. Children affected with PKU are therefore able to live healthy. At present, all disorders included in the neonatal screening program are comparable to PKU.

Category II: less treatable disorders

An example of a less treatable disorder is cystic fibrosis (CF). CF is an inherited disorder that causes obstruction in the lungs and other organs, which leads to infections. CF cannot be cured, but early treatment can mitigate the disease. Timely intervention results in reduced symptoms and improved life expectancy. In the Netherlands, newborns are not screened for CF.^a

Category III: untreatable disorders

An example of an untreatable disorder is Duchenne muscular dystrophy (DMD). DMD is a genetic disorder causing a progressive loss of muscle function. Most affected children are confined to a wheelchair and will die by the time they reach maturity. DMD cannot be treated. In the Netherlands, newborns are not screened for this disease.

TABLE 2 Arguments Presented to the Respondents in the Questionnaire Combined With the Mean Scores on Extent of Agreement (Disagree-Agree) With These Arguments

Parameter	Newborns Should be Tested on ...		
	Category I: Treatable Disorders, Mean (SD)	Category II: Less Treatable Disorders, Mean (SD)	Category III: Untreatable Disorders, Mean (SD)
Arguments in favor			
Because the disease can be prevented or cured through early diagnosis	4.5 (1.2)	NA	NA
Because, through early diagnosis, the symptoms of the disease can be cured or delayed	4.7 (1.0)	NA	NA
To fight the symptoms of the disease as soon as possible	NA	4.4 (1.1)	NA
Because, through early diagnosis, the child will live longer	NA	4.4 (1.0)	3.5 (1.4)
To enable parents to adjust their future expectations to their child's condition	4.1 (1.2)	3.9 (1.2)	3.6 (1.2)
To prevent a long diagnostic quest ^a	4.7 (0.8)	4.5 (0.9)	4.4 (1.1)
To inform parents in time about the reproductive choices they have, because a future child in the same family might be affected as well	4.3 (1.1)	4.2 (1.1)	4.2 (1.2)
Arguments against			
Because the disease cannot be prevented or cured	NA	2.1 (1.3)	2.5 (1.4)
Because parents of an affected child would be worried before the disease has come to expression	2.3 (1.3)	2.5 (1.3)	2.7 (1.4)
Because the parents of an affected child would be afraid to get too strongly attached to their child	1.4 (0.9)	1.6 (1.0)	1.7 (1.1)
Because a lot of parents would be worried, whereas only a few children will be affected	2.0 (1.2)	2.2 (1.2)	2.4 (1.3)
Because this is way too expensive ^b	1.3 (0.7)	1.4 (0.9)	1.5 (1.0)
Because you have to take life the way it is	1.8 (1.1)	2.0 (1.2)	2.0 (1.2)

PROCESSO DI SCREENING : NOTE PRATICHE

RACCOLTA DEL CAMPIONE

GIORNALIERO

< 48 ORE DI VITA

PREMATURITA'

< 1500 G RIPETERE A 2,6,10 SETTIMANE

RISULTATO PATOLOGICO

OSSERVAZIONE E VALIUTAZIONE DELLA PATOLOGIA

CURE INTENSIVE

CENTRI e COMPETENZE SPECIALISTICHE

CONFERMA DIAGNOSTICA

MALATTIA ACUTA

STATO DI MALATTIA ASINTOMATICO

FORME LIEVI

MALATTIA	COSA DEVE FARE IL PEDIATRIA
MSUD	Trasferimento immediato Centro Metabolico
TIROSIMEIA TIPO I	Asintomatica – Ricovero Immediato
OMOCISTINURIA	Asintomatica – Contattare Centro
MCAD	Asintomatica – Contattare centro Letargico – Ricovero Immediato
VLCAD	Asintomatica – Contattare cento Letargico – Ricovero Immediato
IVA	Trasferimento immediato- Centro metabolico
GA I	Trasferimento immediato- Centro metabolico
MMA	Trasferimento immediato- Centro metabolico
PA	Trasferimento immediato- Centro metabolico
CPT I e CPT II	Asintomatica – Contattare Centro
CITRULLINEMIA	Trasferimento immediato-Centro Metabolico
ARGININSUCCINICO ACIDURIA	Trasferimento immediato-Centro Metabolico

SOSPETTARE UNA MALATTIA METABOLICA EREDITARIA

Clinica

Anamnesi

Esame obiettivo

Semeiotica strumentale

Ecografia

EEG

Radiografia

TAC

RMN

PET

Laboratorio

Screening neonatale esteso

**Patologie non soggette a
screening**

diagnosi biochimica

diagnosi molecolare

Division of Metabolic Diseases - Padua (1999-2011)

ENERGY METABOLISM DISORDERS (80 pts)

PC e PDH :4

RCD: 26

FAO: 15

GSD & HI :35

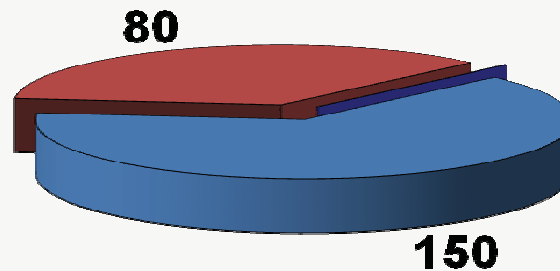
DISORDERS WITH ACUTE INTOXICATION (150pts)

UCD : 61

OA : 45

MSUD: 14

AA :20



Anche se considerate rare, le malattie metaboliche ereditarie sono causa frequente di patologia cronica ad alta complessità assistenziale

Mastroiacovo, Una Pediatria per la società che cambia, 2007

EMOCROMO

DATO	SOSPETTO
Anemia (macrocitica)	Difetti di cobalamina, folati
Reticolocitosi	Difetti glicolisi, difetti del ciclo acido γ -glutammico
Linfociti vacuolati	Malattie lisosomiali

PROFILO BIOCHIMICO (I)

DATO	SOSPETTO
↑ α-Fetoproteina	Atassia teleangiectasia, tirosinemia
↓ Glucosio in CSF	Mitocondriopatie, deficit del trasportatore GLUT -1
↑ Acido urico	Glicogenosi, difetti del metabolismo delle purine, difetti β-ossidazione acidi grassi, mitocondriopatie
↓ Acido urico	Difetti del metabolismo delle purine, difetti del cofattore molibdeno
↑ ACE	Malattia di Gaucher
↓ Creatinina	Difetti di sintesi della creatina

PROFILO BIOCHIMICO (II)

DATO	SOSPETTO
↑ Sideremia, transferrina	Emocromatosi, malattie perossisomiali
↓ Cupremia	Malattia di Wilson, malattia di Menkes
↑ Cupremia	Malattie perossisomiali
↑ Cupruria	Malattia di Wilson, perossisomopatie
↓ Ceruloplasmina	Malattia di Wilson, malattia di Menkes, aceruloplasminemia
Ipotiroidismo, Ipoparatiroidismo	Mitocondriopatie, sindromi CDG

PROFILO BIOCHIMICO (III)

DATO	SOSPETTO
↑ Fosfatasi alcalina	Ipoparatiroidismo, defecti sintesi acidi biliari
↓ Colesterolo	α- ipobetalipoproteinemia, difetto sintesi steroli, difetti perossisomali
↑ Trigliceridi	Glicogenosi, difetti lipoproteine (deficit lipoprotein lipasi)
↑ CK	Difetti mitocondriali, difetti β-ossidazione acidi grassi, glicogenosi tipo II, III and IV, difetti glicolisi, difetto muscolare AMP-deaminasi, distrofinopatie

AMMONIEMIA



VALORI NORMALI: < 80 μ MOL/l

SORGENTE: intestino, batteri, metabolismo proteico

VALORI METABOLICI: > 200 μ mol/l (organico aciduria)

> 500 μ mol/l (difetto del ciclo dell'urea)

VALORI DUBBI (< 200 μ mol/l)

Acido valproico e tossine

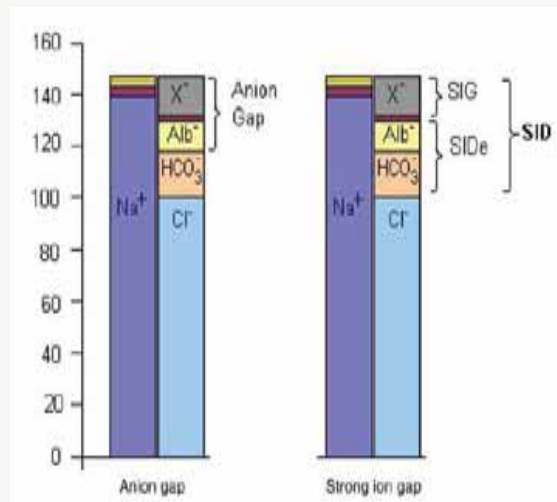
Herpes simplex (neonato)

Emodialisi e insuff epatica

ACIDOSI METABOLICA

• ANION GAP

$$AG = [Na^+] + [K^+] - [Cl^-] - [HCO_3^-]$$



$$AG = [\text{protein}] = 8 - 16 \text{ mmol/l}$$

$$AG = [\text{protein}] + [\text{lactate}^-]$$

Albumin corrected AG = AG

+ (0.25 × [40 - measured albumin g/l])

• LATTATO <2.5 MMOL/L (ESCLUDERE MALATTIE CARDIACHE ED IPOSSIA)

• PIRUVATO : NO : L/P CAVE

TEST METABOLICI

•TEST BASALI

ammonio, glucosio, anion gap, lattato, chetoni urinari

•TEST SPECIFICI (guidati dal sospetto clinico)

AMINO ACIDI (plasma e urine)

ACIDI ORGANICI (urine)

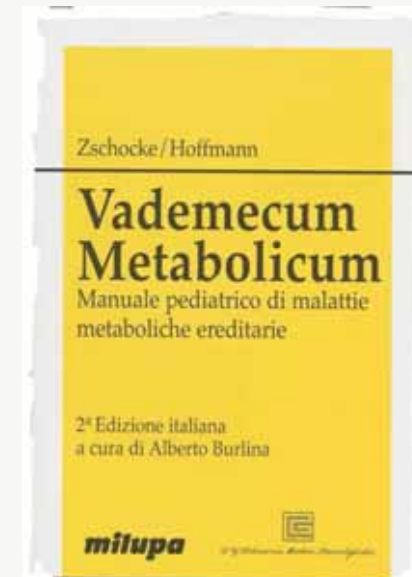
ACILCARNITINE (plasma)

VLCFA (plasma)

DOSAGGIO OLIGOSACCARIDI (urine)

DOSAGGIO PURINE E PIRIMIDINE (urine)

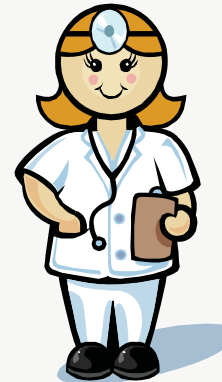
DOSAGGIO SIALOTRANSFERRINE (siero)



QUANDO NON SOSPETTARE UNA MALATTIA METABOLICA EREDITARIA

Sintomo isolato o multiorgano

Decorso clinico statico o progressivo



RITARDO MENTALE LIEVE

RITARDO DEL LINGUAGGIO ISOLATO E PRECOCE

SCARSA CRSCITA (altezza e c.c. normale)

INFEZIONI FREQUENTI

CONVULSIONI OCCASIONALI (con febbre)

SINDROMI EPILETTICHE

SIDS (asintomatiche)

Nyhan WL, Inherited Metabolic Diseases, 2010

Indications for a genetic test

Primary diagnosis, confirmation of diagnosis

- No (reliable) biochemical or enzymatic test
- Advantageous ratio work/benefit
(simple test, small gene, common mutations)

Information on disease course, treatment options and prognosis

- Good genotype-phenotype correlation

Risk calculation and prenatal diagnosis in a family

Predictive testing in a family

*No indication: Carrier testing of minors
in the absence of medical consequences during childhood.*

Epoca Neonatale :Dismorfismi

