#### **NEONATAL SCREENINGS**



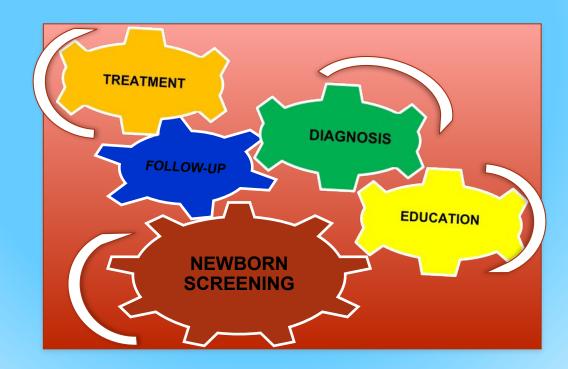
**Prof. ANTONIO ANGELONI** 

## **CRITERIA FOR SCREENING PROGRAMS**

- In order to undertake a screening program for a disease, this must be:
- orelatively frequent;
- serious enough to impose a heavy emotional and financial burden to the family and society;
- othe course of the disease must be partly modifiable by treatments;
- othere must be available tests with good sensitivity and specificity and relative cost.

# Neonatal screening program: a complex network

✓ When developing new organization it should be taken into account that Neonatal Screening is not simply the application of a test but it is a complex system



What you should know before using a test (Sensitivity)

 Property of a test to be altered in patients suffering from a disease. Expresses the capacity to recognize the disease.

Sensitivity = true positives / true positives
 + false negatives (ie, all those sick)

# What you should know before using a test (Specificity)

 Property of a test to be normal in subjects not affected by the disease. Expresses the ability to exclude a disease.

 Specificity = true negatives / true negatives + false positives (i.e. all healthy subjects)

#### Newborn screening: How does it work



A drop of blood is obtained within 48-72 hrs after birth and samples are transferred to a Lab which is capable of highly specialized analyses.



1972 PHENYLKETONURIA
1980 CONGENITAL HYPOTHYROIDISM
1988 CYSTIC FIBROSIS
1999 GALACTOSEMIA
2004 EXTENDED METABOLIC SCREENING
2019 DEFICIT OF BIOTINIDASIS
2021 SPINAL MUSCULAR ATROPHY



# EXTENDED METABOLIC SCREENING

# Law 167/2016: From 2018 is mandate in Italy.

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	GRUPPO AA	MALATTIA Fenilchetonuria	SIGLA				
	AA	Iperfenilalaninemia benigna	H-PHE BIOPT (BS)				
	AA	Deficit biosintesi cofattore tetraidrobiopterina					
	AA	Deficit rigenerazione cofattore tetraidrobiopterina	BIOPT (REG				
	FAO	Deficit dell'acil CoA deidrogenasi a catena media	MCAD				
	OA	Acidemia glutarica tipo I	GAI				
	OA	Acidemia Isovalerica	IVA				
	AA	Malattia delle urine allo sciroppo d'acero	MSUD				
	AA	Tirosinemia tipo I	TYRI				
	FAO	Deficit del trasporto della carnitina	CUD				
	FAO	Deficit dell'idrossiacil CoA deidrogenasi a catena lunga	LCHAD				
	FAO	Deficit della proteina trifunzionale	TFP				
	FAO	Deficit dell'acil CoA deidrogenasi a catena molto lunga	VLCAD				
0	OA	Aciduria 3-Idrossi 3-metil glutarica	HMG				
	OA	Deficit del Beta-chetotiolasi	BKT				
	OA	Acidemia Metilmalonica (CbIA)	CbIA				
	OA	Acidemia Metilmalonica (CbIB)	Cbl B				
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	OA						
	OA						
	AA	Acidemia Argininosuccinica	ASA				
	AA	Citrullinemia tipo I	CIT				
9	AA	Omocistinuria (deficit di CBS)	HCY				
6	AA	Tirosinemia tipo II	TYR II				
ξ.	FAO	Deficit di Carnitina palmitoil-transferasi II	CPTII				
î (	OA	Deficit Multiplo delle carbossilasi	MCD				
	OA	Acidemia Metilmalonica (CbID)	Cbl D				
	AA	Argininemia	ARG				
	AA	Citrullinemia tipo II	CIT II				
	AA	Ipermetioninemia	MET				
1	AA	Tirosinemia tipo III	TYR III				
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	FAO	Acidemia glutarica tipo II	GA2				
1	FAO	Deficit dell'acil CoA deidrogenasi a catena corta	SCAD				
V	FAO	Deficit Carnitina/acil-carnitina translocasi	CACT				
19	OA	Deficit del 3-Metil crotonil-CoA carbossilasi	3MCC				
14	OA	Deficit del 2-Metil butirril-CoA deidrogenasi	2MBG				
16	OA	Aciduria 3-Metil glutaconica (tipo 1, 2, 3, 4 e 5)	3MGA				
1	OA	Deficit del Isobutirril-CoA deidrogenasi	IBG				
<u>o</u>	OA	Aciduria Malonica	MAL				
Pannello Secondario	FAO	Deficit del 3-OH acil-CoA deldrogenasi a catena media/corta	M/SCHAD				
N. K.	OA	Aciduria 2-Metil 3-idrossi butirrico	2M3HBA				
	OA	Encefalopatia Etilmalonica	EE				
Ē.	OA	Deficit di Ornitina transcarbamilasi	OTC				
a l	AA	Deficit di metilene tetraidrofolato reduttasi	MTHER				

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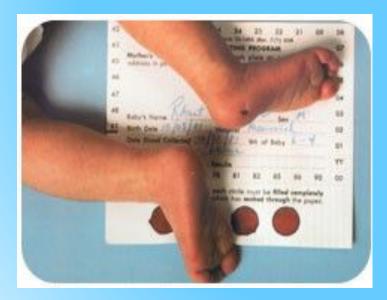
## **CONGENITAL HYPOTHYRODISM**

- □ Incidence: 1/3500 newbors
- Embryonic alterations in the development of the gland
- Genetic defects affecting the enzymes involved in thyroid hormones synthesis
- Hypothalamic/pituitary axis deficit



### **NEONATAL DIAGNOSIS**

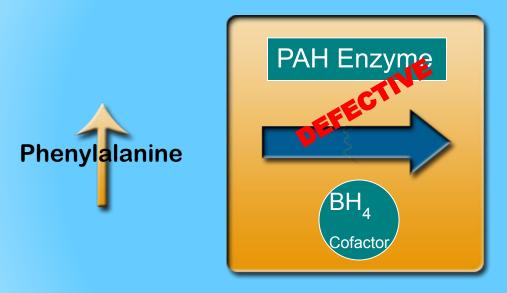
# Determination of TSH within day 3 (PPV 95-98% of the cases).



## What is phenylketonuria?

- Persistent elevated blood phenylalanine (Phe) caused by a deficiency of the **phenylalanine hydroxylase (PAH) enzyme**
- The term PKU is reserved for primary dysfunction of the PAH enzyme due to mutations in the PAH gene
- The degree of impairment varies greatly among patients resulting in a broad continuum of phenotypes
- Categories based on blood Phe at diagnosis
  - Classic PKU > 1200 µmol/L (20 mg/dL)
  - Moderate PKU = 900–1200 µmol/L (15–20 mg/dL)
  - Mild PKU =  $600-900 \mu mol/L (10-15 mg/dL)$
  - Mild HPA = 300–600 µmol/L (5–10 mg/dL)

# Simplified biochemistry of phenylalanine metabolism



Tyrosine

PAH = phenylalanine hydroxylase BH<sub>4</sub> = cofactor tetrahydrobiopterin

# Success of the diet followed newborn screening

- "It is reasonable to presume that the best results of dietetic treatment of PKU will be obtained if treatment is started in infancy and particularly in the neonatal period"<sup>1</sup>
- The first method of testing for PKU was the ferric chloride test<sup>2</sup>
  - Detected ketones in urine
  - Limited use in newborns because appearance of ketones can be delayed
- The Guthrie test<sup>3</sup>
  - Developed by Robert Guthrie in the late 1950s
  - Bacteria inhibition assay worked on newborn blood
  - Simplicity (dried blood spot on filter paper) was ideal for mass screening

## **Consequences of elevated blood** phenylalanine levels vary by age



**PKU Patients Not on Diet** 



When PKU is untreated or treated late, the following may occur

- Mental retardation or reduced IQ
- Seizures and tremors
- **Difficulties in executive function**
- **Psychological and behavioral issues**
- Social difficulties
- Impaired growth
- Irritability
- Eczema

When PKU is poorly controlled, the following may occur

- **Difficulties in executive function**
- **Psychological and behavioral issues**
- Social difficulties
- **Neurological complications**
- Irritability
- Eczema

# Results of the screening and diet on PKU

The combination of newborn screening and Phe-restricted diets has **nearly eliminated** the severe neurocognitive and motor deficits that occur with untreated PKU

In some studies, difficulty in following the diet and maintaining adequate Phe control resulted in poor outcomes.

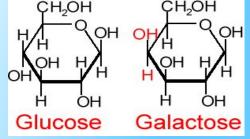
Nutritional deficiencies have been associated with low-Phe diets, suggesting that increasing natural sources of protein may be important.

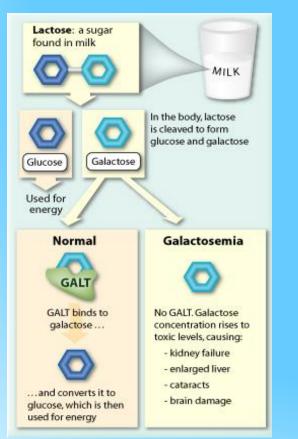
Despite the overall success of the PKU diet, adherence into adulthood continues to be a problem.

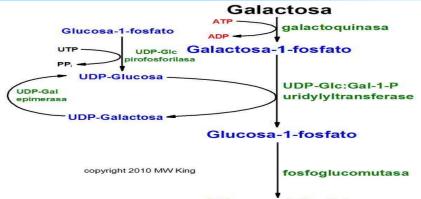
# GALACTOSEMIA

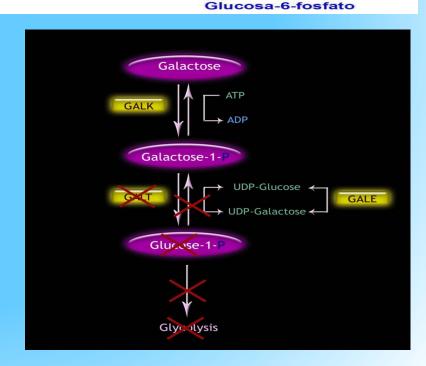
- Galactosemia is an inherited recessive deficiency in enzymes that metabolize galactose
- 1 in 60 000 newborns are diagnosed with Galactosemia every year

# Sources and metabolism of galactose









#### NORMAL GALACTOSE METABOLISM

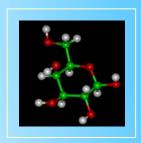
- Dietary lactose is digested into glucose and galactose, and absorbed through the intestine
- Galactose is taken up by a RBC (carrier-mediated), it is phosphorylated to Galactose-1-Phosphate (Gal-1-P) by Galactokinase (GALK)
- Gal-1-P is converted to Glucose-1-Phosphate (Glu-1P) using the epimerization of UDP-Glucose to UDP-Galactose by the enzyme Galactose-1-Phosphate Uridyl Transferase (GALT). That is:
   Gal-1-P + UDP-Glucose GALT UDP-Galactose + Glu-1-P
- Glu-1-P proceeds on to glycolysis
- UDP-Galactose is recycled back to UDP-Glucose by Uridyl Diphosphate Galactose 4-Epimerase (GALE)

## THREE TYPES OF GALACTOSEMIA



# 1. GALT Deficiency

Most severe form: "classic galactosemia" Most prevalent: 95% of cases



# 2. GALK Deficiency

Milder form 5% of cases





rare



DIAGNOSIS

## <u>Tests</u>

<u>Blood tests</u>

Enzyme activity in RBCs
 Normal range for Galactose-1-phosphate uridyl transferase activity is 18.5 to 28.5 U/g Hb.

- Low blood sugar (hypoglycemia)
- Urine analysis
  - Reducing substances accumulation (i.e. galactose & galactose-1-P)

## TREATMENT



- No pharmacological treatment is currently available
- Sources of galactose (especially lactose) must be eliminated from the diet
  - All dairy products (chesses, yogurt, ice cream), breast milk, infant formulas, sweeteners
  - Foods with > 10mg galactose/100g fresh weight must be avoided; dates, papaya, tomatoes, watermelon
- Calcium and vitamin supplementation (vitamin D)

#### **Cystic Fibrosis: Clinical Features**

Cystic fibrosis is a **heterogeneous recessive genetic** disorder with features that reflect mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

Classic cystic fibrosis is characterized by chronic bacterial infection of the airways and sinuses, fat maldigestion due to pancreatic exocrine insufficiency, infertility in males due to obstructive azoospermia, and elevated concentrations of chloride in sweat.

Patients with non-classic cystic fibrosis have at least one copy of a mutant gene that confers partial function of the CFTR protein, and such patients usually have no overt signs of maldigestion because some pancreatic exocrine function is preserved.

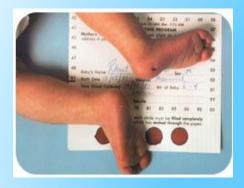
## **Genetics of Cystic Fibrosis**

- Autosomal recessive
- Gene located on chromosome 7
- Prevalence- varies with ethnic origin
  - 1 in 3000 live births in Caucasians in North America and Northern Europe
  - 1 in 17,000 live births of African Americans
  - 1 in 90,000 live births in Hawaiian Asians

# Changes in Protein structure

- CFTR functions principally as a cAMP-induced chloride channel and appears capable of regulating other ion channels.
- Besides the most common mutation, ΔF508, accounting for about 70% of CF chromosomes worldwide, more than 850 mutant alleles have been reported to the CF Genetic Analysis Consortium.
- These mutations affect CFTR through a variety of molecular mechanisms which can produce little or no functional CFTR at the apical membrane.

## **Screening test for cystic fibrosis**



Few blood drops from the newborn heel between 48-72 hours are spotted on an absorbent card (Guthrie test)

#### Trypsin dosage is a test:

High sensitivity L Among 100 newbors affected by CF, 98 show high levels of trypsin

#### Low specificity

Trypsin levels are increased also in newborns showing:
-respiratory distress syndrome;
-prematurity;
-malformations

## **Second level tests:**

#### Sweat chloride test



Sweat stimulation with pilocarpine Sweat collection for 30 min CI and Na dosage in the sample Negative < 40 mEq/l ??? 40 – 70 mEq/l Positive > 70 mEq/l

## **GENETIC TESTS FOR CYSTIC FIBROSIS**

- FIRST LEVEL (search of the 32 most common mutations that cause cystic fibrosis) through:
  - reverse dot blot
  - amplification refractory mutation systems (ARMS)
  - oligonuclotide specific allele (ASO)
- SECOND LEVEL (identification of 90% of the mutations that cause cystic fibrosis) through:
  - -DHPLC
  - -full sequence of the gene

#### PANNELLO DM 13 ottobre 2016

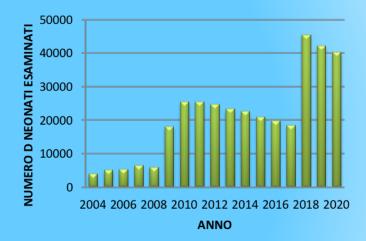
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oldemia metitimationica (DE-B) oldemia metitimationica con omocisticuma (deficit CM D) edebia metitimationica con omocisticuma (deficit CM D) edicita a metitimatica de destingenasi olduria malonica edica da 2-metitica destingenasi olduria malonica edica da destina destina ciduria malonica edica da destina destina induinemia tipo i edica del trasporto della carristina edict di carristina patimitoi-trasferasi i	Cel B Cel C CeliC ZMBG MAL MCD CIT I CIT I CIT I ASA ARG CUD CPT Ia	251110 277400 277410 610006 606781 253270 215700 806914 207000 207600 212140 212140			RCG999	C3 C3 C3 dis Met tosso C3 dis elo Met tosso C3 dis elo Met tosso C3 DC C3 DC C3 DC C5 OH C8 C8 C8 C8 C8 C8 C8 C8 C8 C8 C8 C8 C8	elenc T D Deficit	eate in tabella <sup>*</sup> I in quanto condividono I bi <b>9 condizioni:</b> <b>seconda</b> •4 Aminoacidopa •5 Acidurie organ it d S adenosionecisteina idrelasi arie 3-metil gutaconiche ait di 3-metilectoral CoA carbossiasi	omarcatori ) pan ario tie iche saun 3MGCA	613762 210200	0 10 10 10 10 10 10 10 10 10 10 10 10 10	-	alattosemia	GALT	MIM 230400 253260 Gala	DISTURBIO DISTURBIO DEL TR DISTURBIO DEL TR DISTURBIO DEL TRA AN	atologi 9/2001 / EL MET/ ASPORT RBOIDR EL MET/ SPORT MINOACI	ia AIL N.1) ABOLISMO E TO DEI ATT ABOLISMO E TO DEGLI CIDI	(D.M 279/200 RCG0/ RCG0/





#### SCREENING NEONATALE ESTESO NEL POLICLINICO UMBERTO I: DAL PROGETTO PILOTA AL PROGRAMMA OPERATIVO

- 2004 inizio dello studio pilota: applicazione dello screening esteso a circa il 20 % della nostra popolazione (nati nelle AOU Policlinico Umberto I, S. Eugenio e S .Giovanni)
- da Giugno 2009 screening pilota è stato esteso a tutto il bacino di utenza del centro: 49 % Lazio e 100% Molise
- dal 01/01/2018 avvio del programma di screening neonatale esteso per tutti i nati nel Lazio e Molise



#### Neonati esaminati per anno

#### NEONATI SOTTOPOSTI A SCREENING ESTESO: 313776



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**AOU Policlinico Umberto 1** 



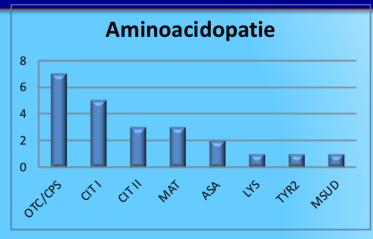
#### SCREENING ESTESO NEL LAZIO: DAL PROGETTO PILOTA AL PROGRAMMA OPERATIVO

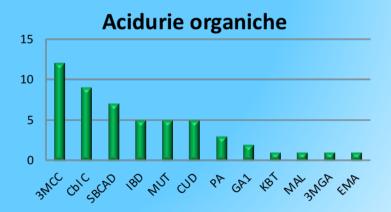
#### **128 NEONATI POSITIVI CONFERMATI**

	2004-2017	2018-2020
Campioni analizzati	226473	128011
Positivi	83	45
INCIDENZA COMPLESSIVA	1:2729	1:2845
SPECIFICITA'	98.5 %	99.1%
SENSIBILITA'	100 %	100%

#### Difetti della β-ossidazione degli acidi grassi







#### **NEWBORN SCREENING (DATA FROM 2010)**

ANNO	NEONATI ESAMINATI	5				DIAGNOSI* SCREENING						
		НРА	IC	FC	GAL	BIOTINIDASI	METABOLICO					
2010	25550	12	24	3	1		11					
2011	25509	9	22	5	1		7					
2012	24748	9	24	2	3		7					
2013	23330	8	29	4	4		11					
2014	22585	9	28	3	1		10					
2015	21017	11	26	7	2		9					
2016	<b>016</b> 19756		24	8	2		9					
2017	18448	9	17	5	1		8					
2018	45499 §	19	40	10	7		18					
2019	42235	17	61	11	2@	12	14					
2020	40277	13	46	8	4	11	13					
TOT parziale (dal 2010)	308954	124	341	66	28	23	117					
		IN CIDENZA COM PLESSIVA 2010-2019 1:442										



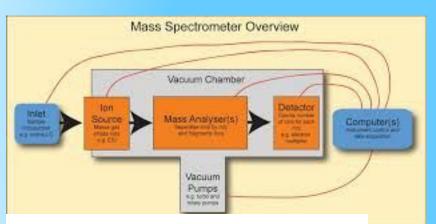
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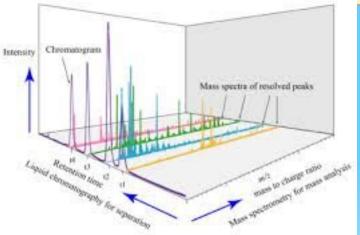
AOU Policlinico Umberto 1



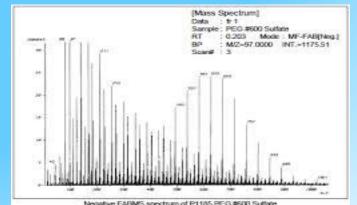
# EXTENDED METABOLIC SCREENING

# Mass spectrometry for • How it looks like EMS









#### **Newborn screening for SMA**

SMA is a genetic neuromuscular disease.

- It is caused by a mutation affecting the SMN gene which code a defective protein, thus affecting surviving of motoneurons.
- In severe SMA (type I) clinical evidences are present at 6 months ffcting all the neuromuscular districts, not only bein responsible for impairment of the movements but also for respiratory activity. If untreated it leads to death within 2 years.



#### **Screening for SMA**

- ✓ A pilot study has been carried out in Lazio and Tuscany from 2019-2021.
- Risultati: Compliance of the screening has been about 90%. 60.000 newborns have been screened and 8 identified as affected by the disease. All of them have been treated and are currently in good health. Incidence has been calculated about 1/7500











