Newborn Screening in Morocco - workshop II

University Hospital of Fes, Morocco

December 9-10, 2014

NBS in **Portugal**: results from a ten years experience with mass spectrometry

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PORTUGAL

Location: Southwestern Europe

Borders: Spain and Atlantic Ocean

Includes Azores and Madeira Islands (Atlantic ocean)

Total area: 92,090 sq km

Population: 10,487,289 persons (December 2012)

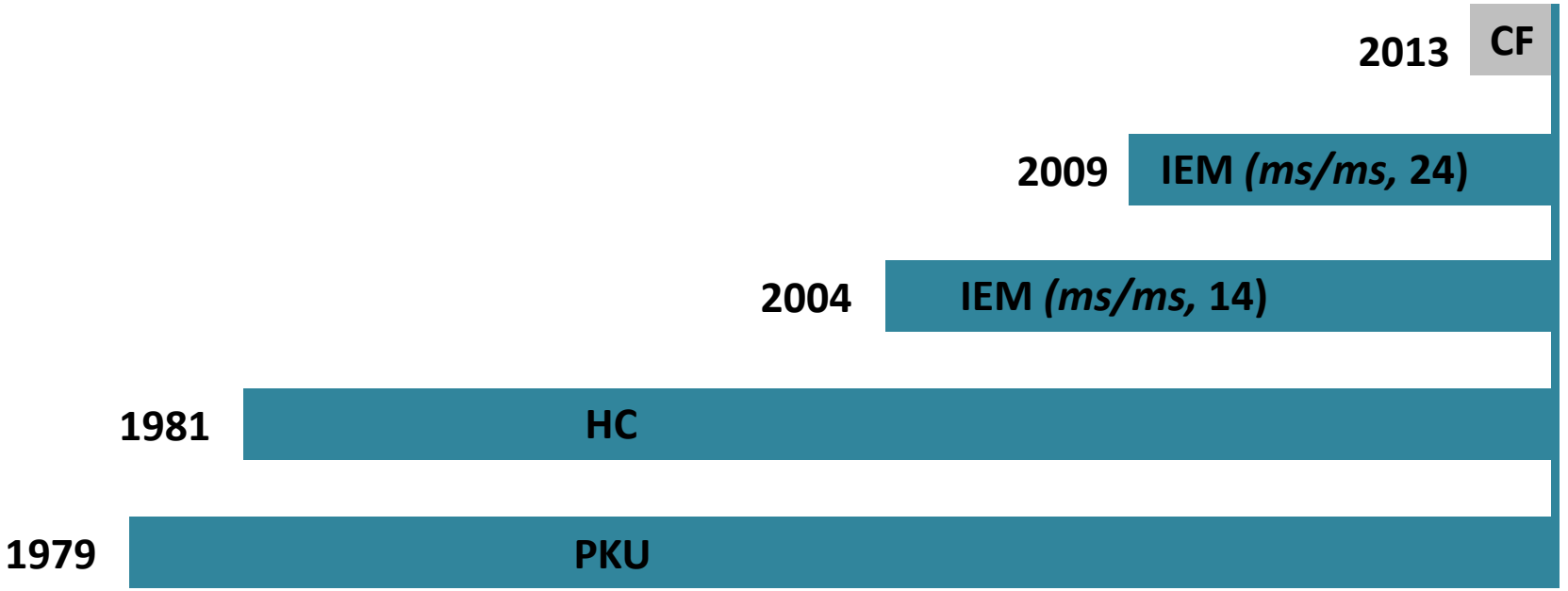
Negative population growth rate: negative natural and migration growth rates.

Portuguese National Program for Newborn Screening

2014

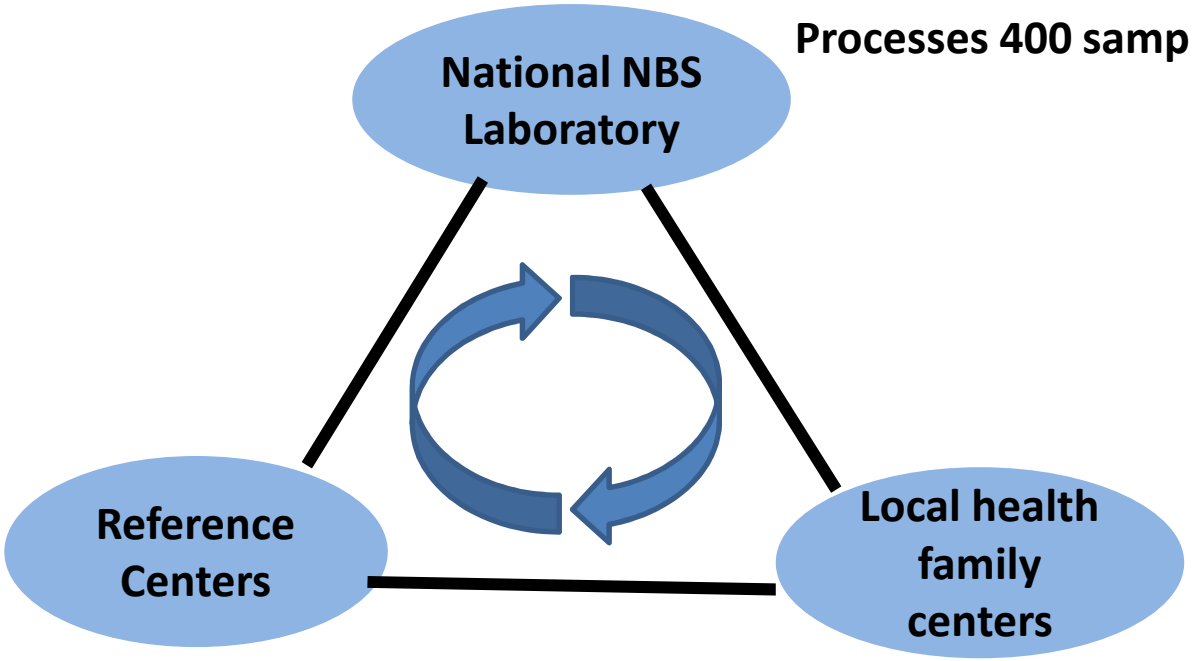
- Congenital hypothyroidism (CH)
- *ms/ms* (24 IEM, PKU included)
- Cystic Fibrosis (CF, pilot study)

Jacinto de Magalhães (1938-1987)



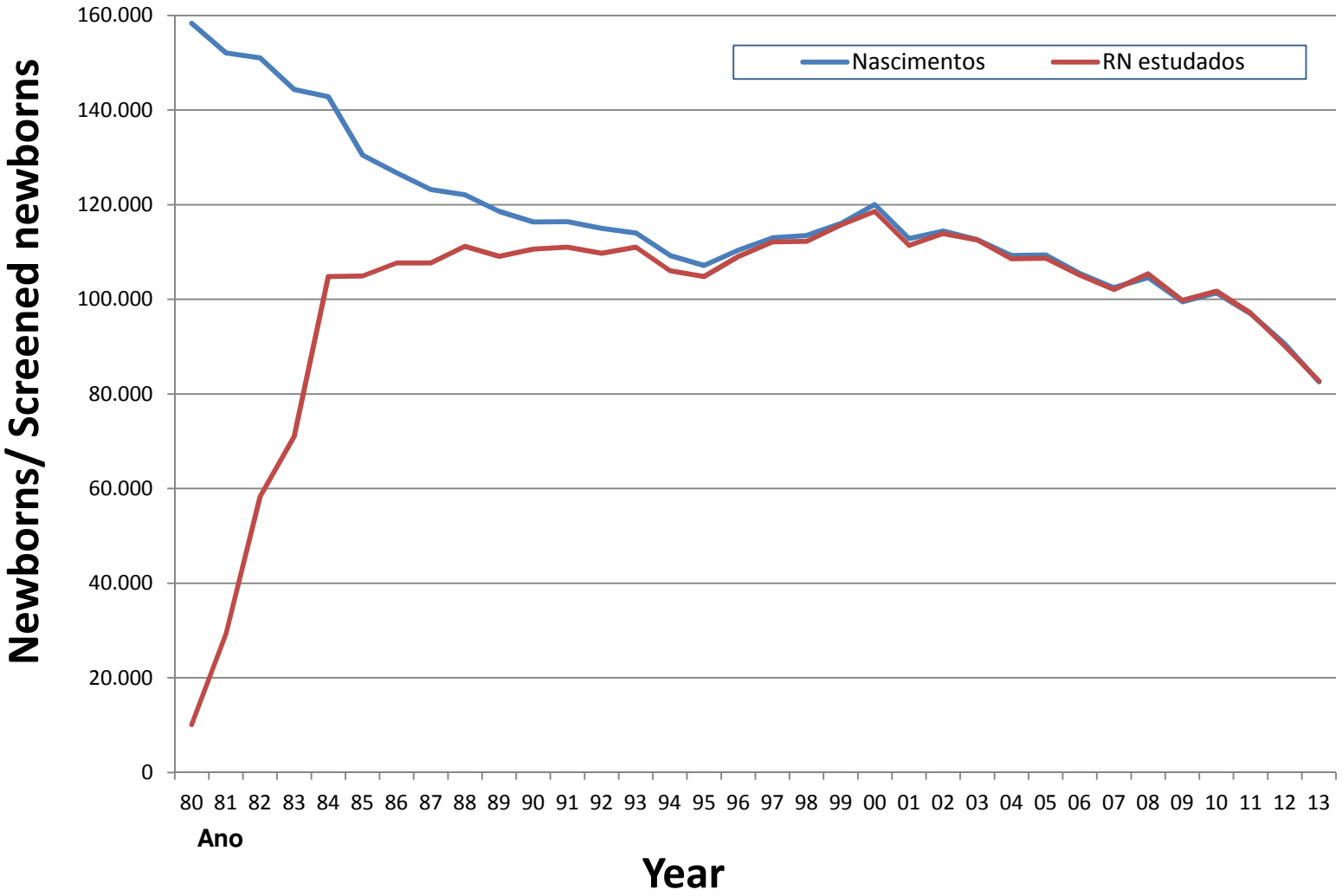
Portuguese National Program for Newborn Screening

Defined by Health Minister as an integrated Program (2010)
Based in the Portuguese National Institute of Health (INSA)



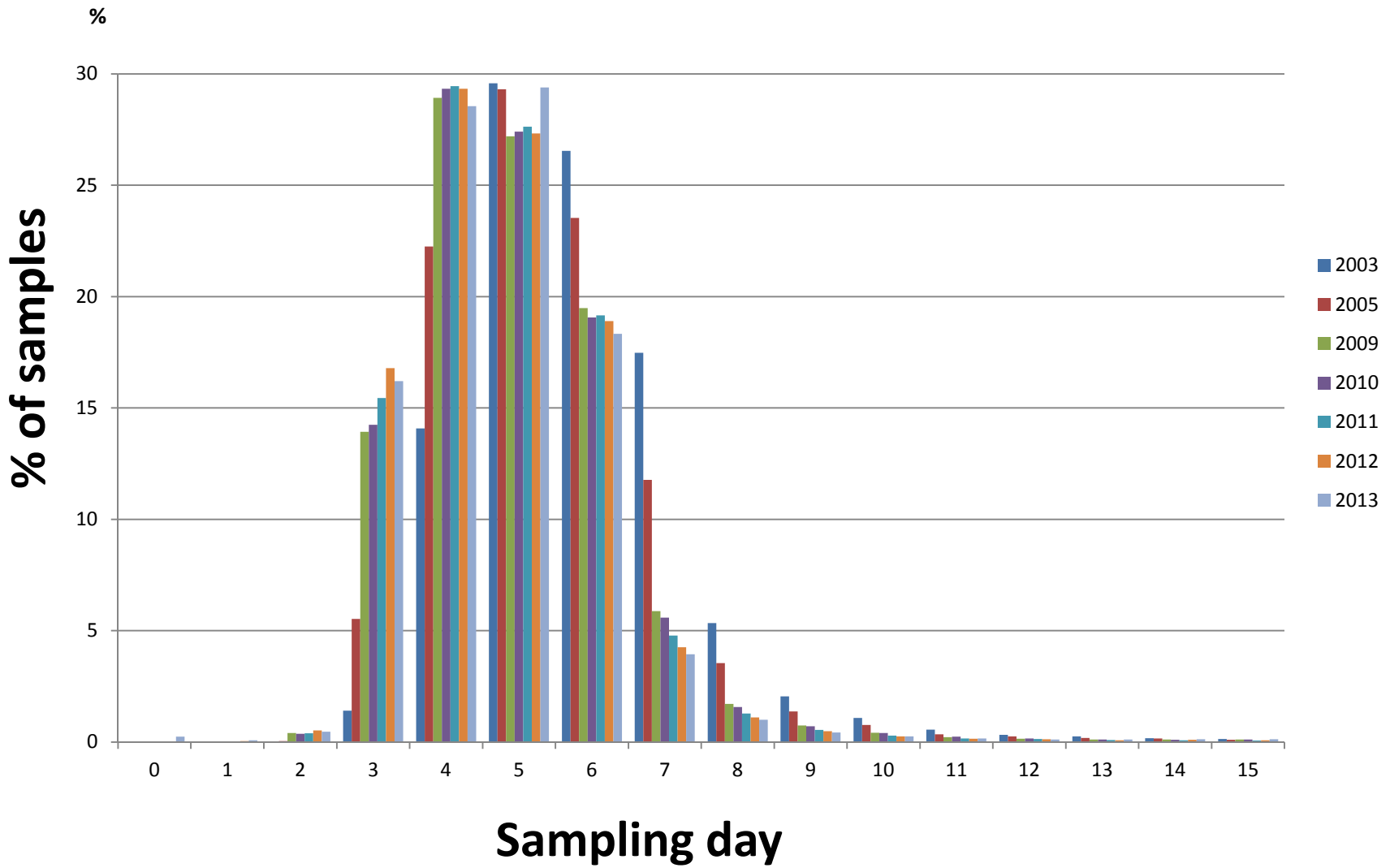
Portuguese National Program for Newborn Screening

Non-mandatory, with 99.8% coverage



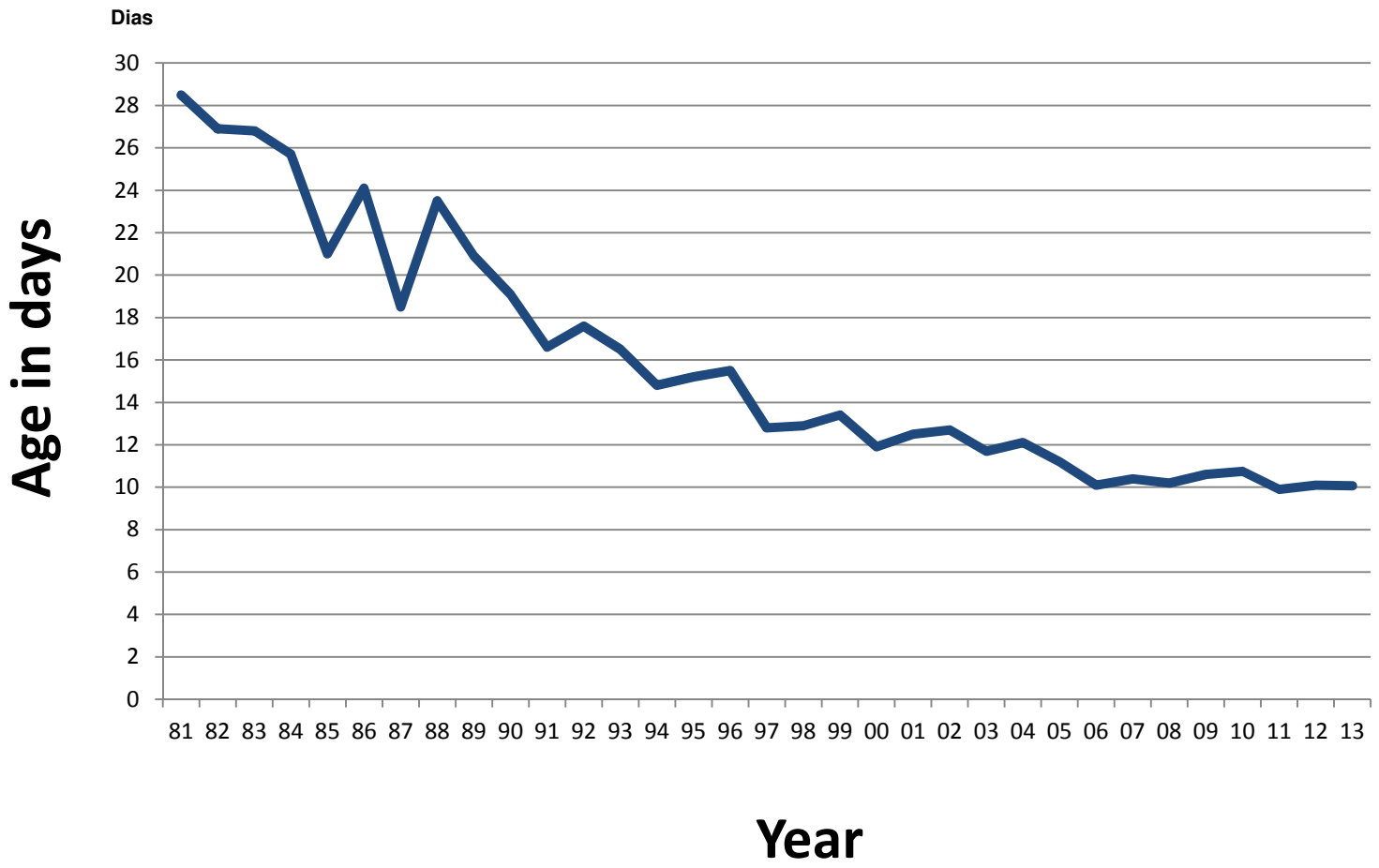
Portuguese National Program for Newborn Screening

Sample collection at hospital or health family centers (3rd-6th day)

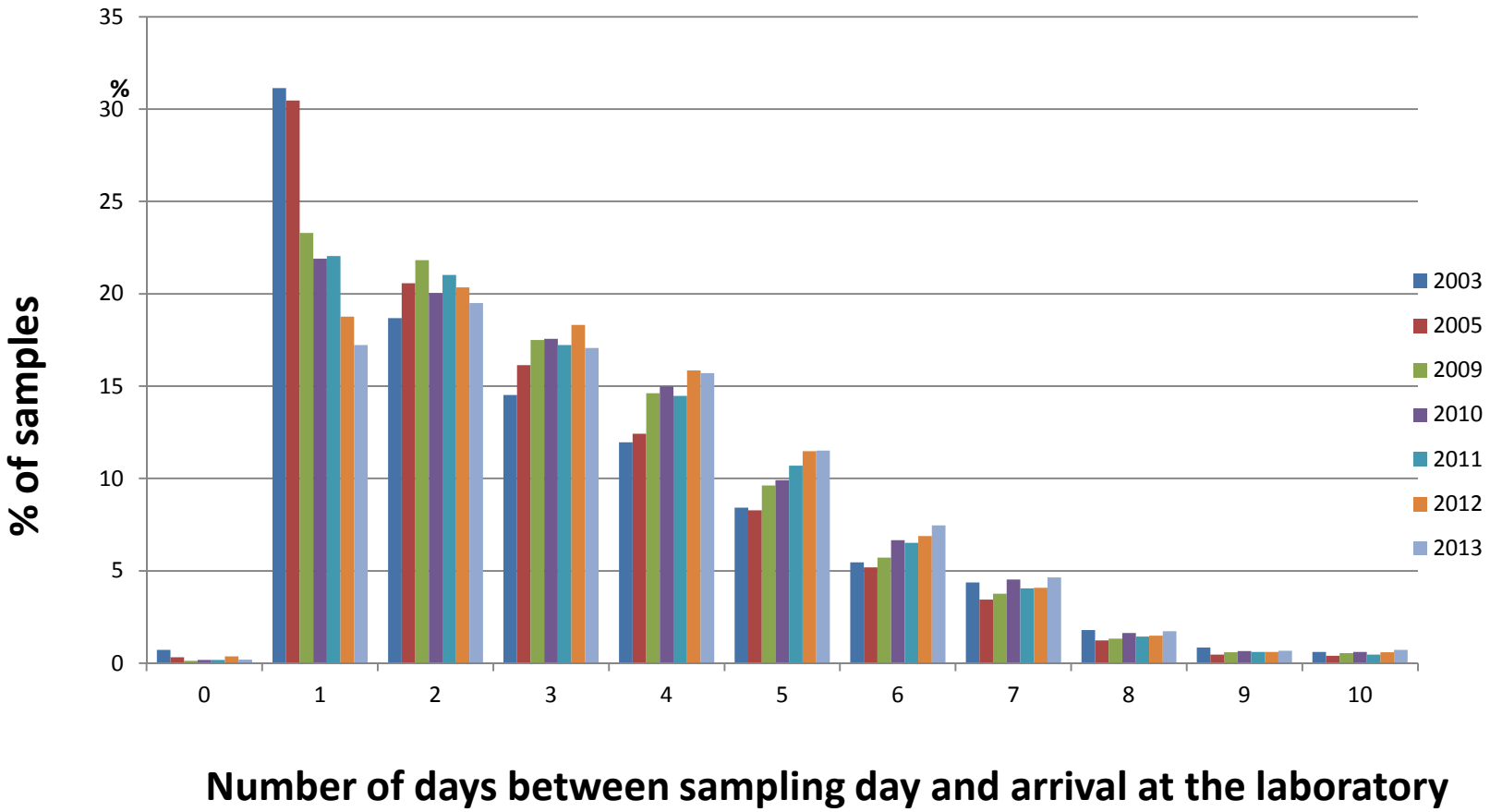


Portuguese National Program for Newborn Screening

Average age for treatment beginning: 10.1 days



Portuguese National Program for Newborn Screening



Portuguese National Program for Newborn Screening

Results communication:

- **Normal cases – www.diagnosticoprecoce.org**
- **Non-urgent 2nd sample request (mail)**
- **Immediate sending to reference centers**

NBS by *ms/ms*: 2004 - 2014

Method

Analysis of amino acids and acylcarnitines as butyl esters (Rashed *et al.*, 1995)

(2 API 2000 triple quadrupole tandem mass spectrometers – Applied Biosystems)

2nd tier test

Succinylacetone (Tyr>210 µM, modified from *Allard et al.*, 2004)

Quality Control Programs

CDC (Quality Control and Proficiency)

ERNDIM

NEQAS UK

SIMMESN

NBS by *ms/ms*: 2004 - 2014

NeoScreen: A Software Application for MS/MS Newborn Screening Analysis

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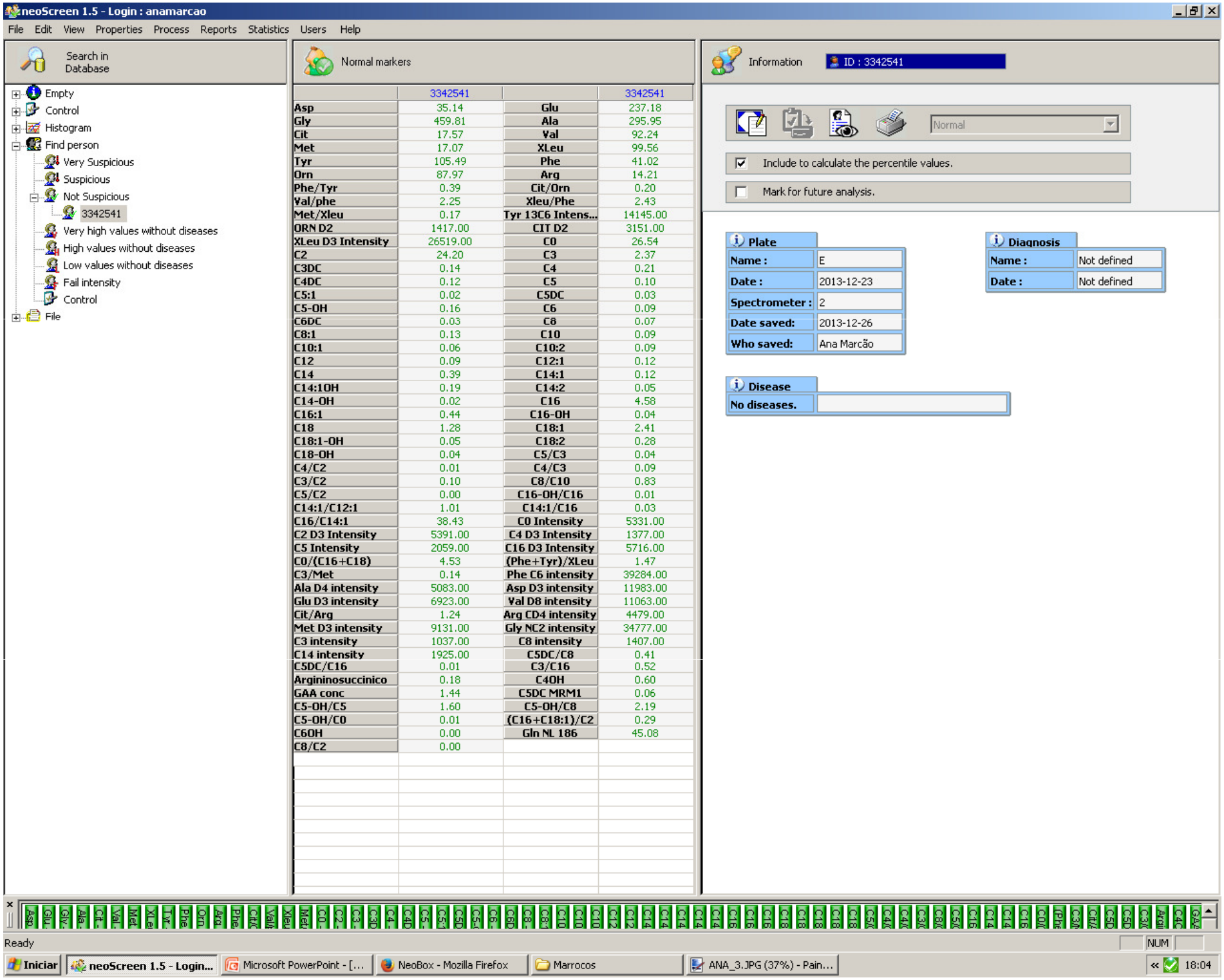
[2] Instituto de Genética Médica Jacinto de Magalhães, Porto, Portugal

Abstract. The introduction of the Tandem Mass Spectrometry (MS/MS), in neonatal screening laboratories, has opened the doors to innovative newborn screening analysis. With this technology the number of metabolic disorders, that can be detected, from dried blood-spot species, increases significantly. However, the amount of information obtained with this technique and the pressure for quick and accurate diagnostics raises serious difficulties in the daily data analysis. To face this challenge we developed a software system, NeoScreen, which simplifies and allow speeding up newborn screening diagnostics.

Keywords: Newborn Screening Software, MS/MS
Paper Domain: Health bioinformatics and genomics Statistical methods and tools for biological and medical data analysis



	3342541		3342541
Asp	35.14	Glu	237.18
Gly	459.81	Ala	295.95
Cit	17.57	Val	92.24
Met	17.07	XLeu	99.56
Tyr	105.49	Phe	41.02
Orn	87.97	Arg	14.21
Phe/Tyr	0.39	Cit/Orn	0.20
Val/phe	2.25	Xleu/Phe	2.43
Met/Xleu	0.17	Tyr 13C6 Intens...	14145.00
ORN D2	1417.00	CIT D2	3151.00
XLeu D3 Intensity	26519.00	C0	26.54
C2	24.20	C3	2.37
C3DC	0.14	C4	0.21
C4DC	0.12	C5	0.10
C5:1	0.02	C5DC	0.03
C5-OH	0.16	C6	0.09
C6DC	0.03	C6	0.07
C8:1	0.13	C10	0.09
C10:1	0.06	C10:2	0.09
C12	0.09	C12:1	0.12
C14	0.39	C14:1	0.12
C14:1OH	0.19	C14:2	0.05
C14-OH	0.02	C16	4.58
C16:1	0.44	C16-OH	0.04
C18	1.28	C18:1	2.41
C18:1-OH	0.05	C18:2	0.28
C18-OH	0.04	C5/C3	0.04
C4/C2	0.01	C4/C3	0.09
C3/C2	0.10	C8/C10	0.83
C5/C2	0.00	C16-OH/C16	0.01
C14:1/C12:1	1.01	C14:1/C16	0.03
C16/C14:1	38.43	C0 Intensity	5331.00
C2 D3 Intensity	5391.00	C4 D3 Intensity	1377.00
C5 Intensity	2059.00	C16 D3 Intensity	5716.00
C0/(C16+C18)	4.53	(Phe+Tyr)/XLeu	1.47
C3/Met	0.14	Phe C6 intensity	39284.00
Ala D4 intensity	5083.00	Asp D3 intensity	11983.00
Glu D3 intensity	6923.00	Val D8 intensity	11063.00
Cit/Arg	1.24	Arg CD4 intensity	4479.00
Met D3 intensity	9131.00	Gly NC2 intensity	34777.00
C3 intensity	1037.00	C8 intensity	1407.00
C14 intensity	1925.00	C5DC/C8	0.41
C5DC/C16	0.01	C3/C16	0.52
Argininosuccinico	0.18	C4OH	0.60
GAA conc	1.44	C5DC MRM1	0.06
C5-OH/C5	1.60	C5-OH/C8	2.19
C5-OH/C0	0.01	(C16+C18:1)/C2	0.29
C6OH	0.00	Gln NL 186	45.08
C8/C2	0.00		

neoScreen 1.5 - Login : anamarcao

File Edit View Properties Process Reports Statistics Users Help

Search in Database

- 2
  - Asp
  - Glu
  - Gly
  - Ala
  - Cit
  - Val
  - Met
  - XLeu
  - Tyr
  - Phe
  - Orn
  - Arg
  - Phe D5 Intensity
  - Tyr 13C6 Intensity
  - ORN D2
  - CIT D2
  - XLeu D3 Intensity
  - C0
  - C2
  - C3
  - C3DC
  - C4
  - C4DC
  - C5
  - C5:1
  - C5DC
  - C5-OH
  - C6
  - C6DC
  - C6DC-OH
  - C8
  - C8:1
  - C10
  - C10:1
  - C10:2
  - C12
  - C12:1
  - C14
  - C14:1
  - C14:1OH
  - C14:2
  - C14-OH
  - C16
  - C16:1
  - C16-OH
  - C18
  - C18:1
  - C18:1-OH

Marker histogram

Name of marker : Phe

Average : 53.54 µM

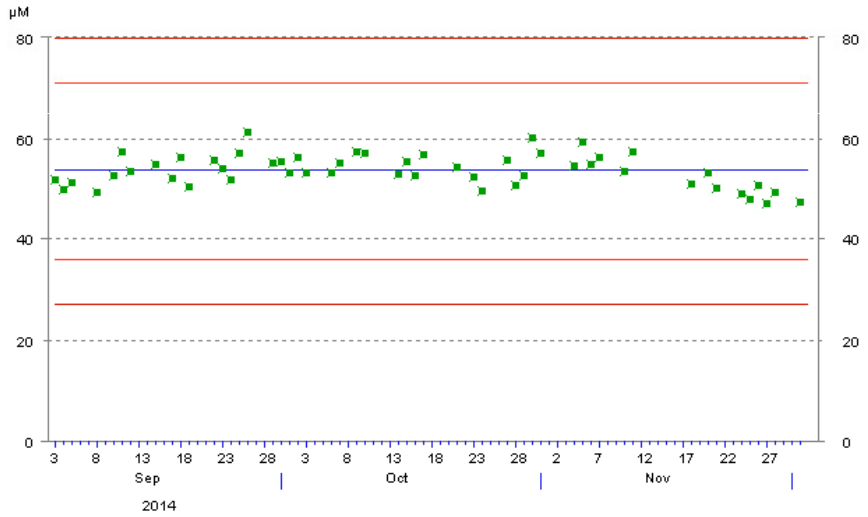
Standard deviation : 8.77 µM

Change histogram

Save data

Average
2 * Standard deviation
3 * Standard deviation

Accepted values
Rejected values
Value accepted but not included in average.
Value rejected but not included in average.



Ready

NUM

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neoScreen 1.5 - Login : anamarcao

File Edit View Properties Process Reports Statistics Users Help

Search in Database

- Empty
- Control
  - All of Spectrometers
  - 1
    - CDC 461
    - CDC 462
    - CDC 463
    - CDC 464
      - Tyr
      - C0
      - C2
      - C3
      - C3DC
      - C4
      - C5
      - C5DC
      - C5-OH
      - C6
      - C8
      - C10
      - C12
      - C14
      - C16
      - C16-OH
      - C18
      - C18-OH
      - C4OH
      - C5DC MRM1
    - CDC 825
    - CDC 826
    - CDC 827
    - CDC 828
    - CDC 261
    - CDC 262
    - CDC 263
    - CDC 264
    - CDC 265
    - CDC 266
    - CDC 267
    - CDC 268
    - CDC 421
    - CDC 422
    - CDC 423
    - CDC 424
  - 2
- Histogram
  - All of Spectrometers
  - 1
  - 2

Marker histogram

Name of marker : C8

Average : 3.06 µM

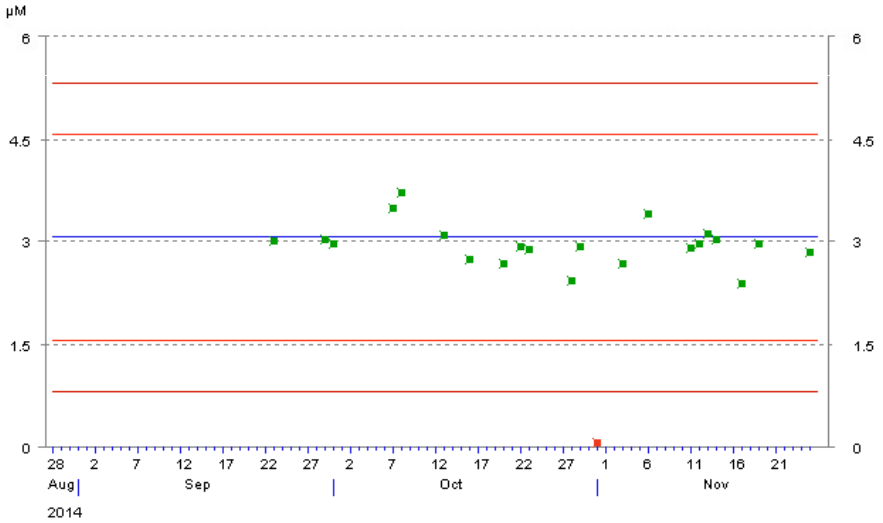
Standard deviation : 0.75 µM

Change histogram

Save data

Average
2 * Standard deviation
3 * Standard deviation

Accepted values
Rejected values
Value accepted but not included in average.
Value rejected but not included in average.



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Identificação : 3420732

Data : 2014-12-2
Placa : C Data da placa : 2014-12-1 Espectrometro : 2

	Valor	Limite -	Limite +
Asp	59.499	0	200
Glu	593.305	0	1369
Gly	487.916	0	3400
Ala	299.962	100	934
Cit	13.957	3	50
Val	132.946	57	285
Met	30.271	7	57
XLeu	158.519	82	270
Tyr	138.162	17	210
Phe	58.503	23	148
Orn	103.522	0	570
Arg	7.212	0	45
Phe/Tyr	0.423	0.18	1.5
Cit/Orn	0.134	0	2
Val/phe	2.272	0	4
Xleu/Phe	2.709	0	5
Met/Xleu	0.19	0	0.4
Tyr 13C6 Intensity	20071	2500	
ORN D2	3403	400	
CIT D2	5632	800	
XLeu D3 Intensity	42155	5000	
C0	30.487	9.13	68.45
C2	24.851	7	49.06
C3	2.888	0	5.25
C3DC	0.087	0	0.35
C4	0.399	0	0.97
C4DC	0.08	0	1
C5	0.245	0	1.8
C5:1	0	0	0.15
C5DC	0	0	0.2
C5-OH	0.253	0	0.57
C6	0.052	0	0.2
C6DC	0.017	0	0.12
C8	0.032	0	0.3
C8:1	0.097	0	0.45
C10	0.129	0	0.44
C10:1	0.032	0	0.36
C10:2	0.048	0	0.35
C12	0.15	0.02	0.51
C12:1	0.145	0	0.46
C14	0.23	0.05	0.59
C14:1	0.053	0.01	0.46
C14:1OH	0.04	0	0.35
C14:2	0.035	0	0.17
C14-OH	0.008	0	0.15

	Valor	Limite -	Limite +
C16	2.968	0.83	7.99
C16:1	0.129	0	0.57
C16-OH	0.03	0	0.15
C18	0.532	0.23	2.28
C18:1	1.24	0.34	3.42
C18:1-OH	0.022	0	0.15
C18:2	0.213	0.03	0.8
C18-OH	0.007	0	0.07
C5/C3	0.084	0	0.97
C4/C2	0.016	0	0.04
C4/C3	0.138	0	0.6
C3/C2	0.116	0	0.25
C8/C10	0.253	0	2.5
C5/C2	0.009	0	0.07
C16-OH/C16	0.01	0	0.04
C14:1/C12:1	0.367	0	4
C14:1/C16	0.017	0	0.15
C16/C14:1	55.677	0	94
C0 Intensity	8933	2000	
C2 D3 Intensity	8777	2500	
C4 D3 Intensity	1641	600	
C5 Intensity	2782	800	
C16 D3 Intensity	6393	1500	
C0/(C16+C18)	8.71	3	30
(Phe+Tyr)/XLeu	1.24	0	3
C3/Met	0.095	0	0.3
Phe C6 intensity	60563	15000	
Ala D4 intensity	13497	600	
Asp D3 intensity	14490	2000	
Glu D3 intensity	7218	1500	
Val D8 intensity	19562	1900	
Cit/Arg	1.935	0	15
Arg CD4 intensity	6835	1300	
Met D3 intensity	18649	3000	
Gly NC2 intensity	62573	100	
C3 intensity	1382	600	
C8 intensity	1503	600	
C14 intensity	2747	750	
C5DC/C8	0	0	3.5
C5DC/C16	0	0	0.09
C3/C16	0.973	0	2.5
Argininosuccinico	0.143	0	1.15
C4OH	0.236	0	0.95
GAA conc	2.025	0	20
C5DC MRM1	0.041	0	0.2
C5-OH/C5	1.032	-1	-1
C5-OH/C8	7.906	-1	-1
C5-OH/C0	0.008	-1	-1
(C16+C18:1)/C2	0.169	0	0.5
C6OH	1.616	0	80
Gln NL 186	55.719	0	120
C8/C2	0.001	-1	-1

Doenças :

Diagnóstico : Normal

Identificação : 3392015

Data : 2014-12-2
Placa : A Data da placa : 2014-8-5 Espectrometro : 1

	Valor	Limite -	Limite +
Asp	67.84	0	200
Glu	482.579	0	1369

	Valor	Limite -	Limite +
C16	1.156	0.83	7.99
C16:1	0.087	0	0.57

C4/C2	0.014	0	0.04
C4/C3	0.306	0	0.6
C3/C2	0.048	0	0.3
C8/C10	**11.275**	0	2.5
C5/C2	0.011	0	0.07
C16-OH/C16	0.03	0	0.04

CIT D2	12108	500	
XLeu D3 Intensity	62710	6000	
C0	34.391	9.13	68.45
C2	20.508	9.13	49.06
C3	0.992	0	6.23
C3DC	0.134	0	0.35
C4	0.304	0	0.97
C4DC	0.259	0	1

C2 D3 Intensity	8691	1900	
C4 D3 Intensity	2955	600	
C5 Intensity	3611	700	
C16 D3 Intensity	5598	1500	
C0/(C16+C18)	20.83	3	30
(Phe+Tyr)/XLeu	0.969	0	3
C3/Met	0.075	0	0.3
Phe C6 intensity	110178	15000	

C5-OH	0.202	0	0.57	
C6	**0.707**	0	0.2	10
C6DC	0.078	0	0.12	
C8	**3.011**	0	0.3	
C8:1	0.145	0	0.45	3.5
C10	0.267	0	0.44	0.09
C10:1	**0.599**	0	0.29	2.5
C10:2	0.056	0	0.35	1.14
C12	0.061	0.05	0.51	0.95
C12:1	0.032	0	0.46	20
				-1
				-1
				-1
				0.5
				80
				120
				-1

NBS by *ms/ms*: 2004 - 2014

Amino acid disorders

*Phenylketonuria (PKU) / HPA
*Maple syrup urine disease (MSUD)
Tyrosinemia type I
Tyrosinemia type II
Homocystinuria (CBS deficiency)
MAT I/III deficiency

Urea cycle disorders

*Citrullinemia type I
*Argininosuccinate lyase deficiency (ASA)
Arginase deficiency (ARG 1)

Organic acid disorders

3-Methylcrotonyl-CoA carboxylase def. (3MCC)
*Isovaleric aciduria (IVA)
*Propionic aciduria (PA)
*Methylmalonic aciduria (mut$^{-/0}$ and Cbl C, D)
*Glutaric aciduria type I (GA1)
*3-Hydroxy-3-methylglutaryl CoA lyase def. (3HMG)
Malonic aciduria

Fatty acid oxidation disorders

SCHAD deficiency
*MCAD deficiency
*LCHAD deficiency
*VLCAD deficiency
MADD deficiency
*CPT I deficiency
*CPT II deficiency
Carnitine transport defect (CUD)

*Started in 2004

NBS by *ms/ms*: 2004 - 2014

Amino acid disorders and urea cycle disorders

Disorders	Positive screening criteria
Phenylketonuria (PKU) / Hyperphenylalaninaemia	Phe >150µM and Phe/Try >1,5
Maple syrup urine disease (MSUD)	XLeu >342µM and Val >350µM
Tyrosinemia type I	Tyr >210µM and succinylacetone (+)
Tyrosinemia type II	Tyr >850µM and succinylacetone (-)
Homocystinuria (CBS deficiency)	Met >57µM
Methionine adenosyltransferase deficiency (MAT I/III deficiency)	Met >57µM
Citrullinemia type I	Cit >200µM
Argininosuccinate lyase deficiency (Argininosuccinic aciduria)	ASA >1µM
Arginase deficiency	Arg >50µM

NBS by *ms/ms*: 2004 - 2014

Organic acid disorders

Disorders	Positive screening criteria
3-Methyl crotonyl-CoA carboxylase deficiency (3MCCD)	C5OH >1µM
Isovaleric aciduria (IVA)	C5 >2µM
Propionic aciduria (PA)	C3 >5,2µM and C3/C2 >0,3
Methylmalonic aciduria (mut $^{-}$/^{0})	C3 >5,2µM and C3/C2 >0,3
Glutaric acidemia type I GA 1)	C5DC (>0.2µM)
Methylmalonic aciduria (Cbl C, D)	C3 >5,2µM, C3/C2 >0,3 and C3/Met >0,4
3-Hydroxy-3-methylglutaryl CoA lyase deficiency (3HMG)	C5OH >1µM and C6DC >0,07µM
Malonic aciduria	C3DC >0,4µM

NBS by *ms/ms*: 2004 - 2014

Fatty acid oxidation disorders

Disorders	Positive screening criteria
Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)	C8 >0,3µM and C8/C10 > 2,5
Long-chain 3-OH acyl-CoA dehydrogenase deficiency (LCHAD)	C16OH >0,10µM, C18:1OH >0,07µM, C18OH >0,06µM and C16OH/C16 >0,04
Multiple acyl-CoA dehydrogenase deficiency (MADD)	Multiple elevations from C4 to C18
Carnitine transport defect (CUD)	C0 <7µM
Very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	C14:1 >0,46µM and C14:2 >0,17µM
Carnitine palmitoyl-transferase I deficiency (CPT I)	C0/(C16+C18) >30
Carnitine palmitoyl-transferase II deficiency (CPT II)	C0/(C16+C18)<3 and (C16+C18:1)/C2>0.5
Short-chain 3-OH acyl-CoA dehydrogenase deficiency (SCHAD)	C4OH >1,0µM

NBS by *ms/ms*: 2004 - 2014

Confirmation of positive cases

- Plasmatic aminoacids analysis (ionic change chromatography)
- Urinary organic acids (GC-MS)
- Acylcarnitines (dry blood spots, *ms/ms*)
- Molecular analysis
- Urinary orotic acid (HPLC)
- Urinary succinylacetone (GC-MS)

ms/ms positive cases and birth prevalence: 2004-2014

Disorder	Positive cases	Birth prevalence
Amino acid disorders	**127**	**1: 6 460**
Phenylketonuria (PKU)	65	1: 12 622
Hyperphenylalaninaemia	20	1: 41 022
Maple syrup urine disease (MSUD)	4	1: 205 108
Tyrosinemia type I	6	1: 136 739
Tyrosinemia type III	1	1: 820 433
Homocystinuria (CBS deficiency)	2	1: 410 217
Methionine adenosyltransferase deficiency (MAT I/III deficiency)	29	1: 28 291
Urea cycle disorders	**16**	**1: 51 277**
Citrullinemia type I	9	1: 91 159
Argininosuccinate lyase deficiency	2	1: 410 217
Arginase deficiency	5	1: 164 087

ms/ms positive cases and birth prevalence: 2004-2014

Disorder	Positive cases	Birth prevalence
Organic acid disorders	**66**	**1: 12 431**
3-Methyl crotonyl-CoA carboxylase deficiency (3MCCD)	23	1: 35 671
Isovaleric aciduria	4	1: 205 108
Holocarboxylase synthetase deficiency	2	1: 410 217
Propionic aciduria	3	1: 273 478
Methylmalonic aciduria ($mut^{-}/^{0}$)	4	1: 205 108
Glutaric aciduria type I	12	1: 68 369
Methylmalonic aciduria (Cbl C/ D)	8+1	1: 91 159
3-Hydroxy-3-methylglutaryl CoA lyase deficiency	8	1: 102 554
Malonic aciduria	1	1: 820 433

ms/ms positive cases and birth prevalence: 2004-2014

Disorder	Positive cases	Birth prevalence
Fatty acid oxidation disorders	**133**	**1: 6 169**
Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)	98	1: 8 372
Long-chain 3-OH acyl-CoA dehydrogenase deficiency (LCHAD)	7	1: 117 205
Multiple acyl-CoA dehydrogenase deficiency (MADD)	5	1: 164 087
Carnitine transport defect (CUD)	8	1: 102 554
Very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	8	1: 102 554
Carnitine palmitoyl-transferase I deficiency (CPT I)	2	1: 410 217
Carnitine palmitoyl-transferase II deficiency (CPT II)	3	1: 273 478
Short-chain 3-OH acyl-CoA dehydrogenase deficiency (SCHAD)	2	1: 410 217

ms/ms positive cases and birth prevalence: 2004-2014

Screened Newborns (ms/ms)	Positive cases	Birth prevalence
820 433	342	1: 2 399

NBS by *ms/ms* – Performance metrics0

Number of samples	820.433
Sensitivity	99.42%
Specificity	99.81%
Positive Predictive Value (PPV)	18%
Positive detection rate	1: 2.399
False positive rate	0.19%

NBS by *ms/ms*: 2004 - 2014

Major causes for false positive cases
C5↑
C3↑
C5DC↑ (premature NB)
Arg↑ (premature NB)

NBS by *ms/ms*: 2004 - 2014

Additional findings (ms/ms)	
3MCCD mothers	9
CUD mothers	4
GA 1 mothers	3
Galactosemias (Phe + Tyr ↑)	5

Additional findings (family studies)
MCAD mothers (2) and brothers MAT I/III deficient relatives (>30) MADD father (1)

NBS by *ms/ms*: 2004 - 2014

False negative results

Methylmalonic aciduria (Cbl D)

C3= 6.1 µM (N<6.2)
Met= 15.2 µM (N>6)
C3/met=0.40 (N<0.4)
C3/C2=0.35 (N< 0.3)

Present-day cut-off: N<5.2 µM

(p.R250X/ p.R250X)

CPT II deficiency

C0= 15.1µM (N: 9.1-68)
C2 = 17.2µM (N: 7.0-49)
C16= 2.26µM(N: 0.83-7.99)
C18= 1.0µM(N: 0.23-2.28)
C18:1=1.51µM(N: 0.34-3.4)
C18:2= 0.13µM(N: 0-0.8)
C0/(C16 + C18)= 4.6(N: 3-30)
(C16+C18:1)/C2= 0.22(N <0.5)

(p.S113L/ p.S113L)

Argininosuccinic aciduria

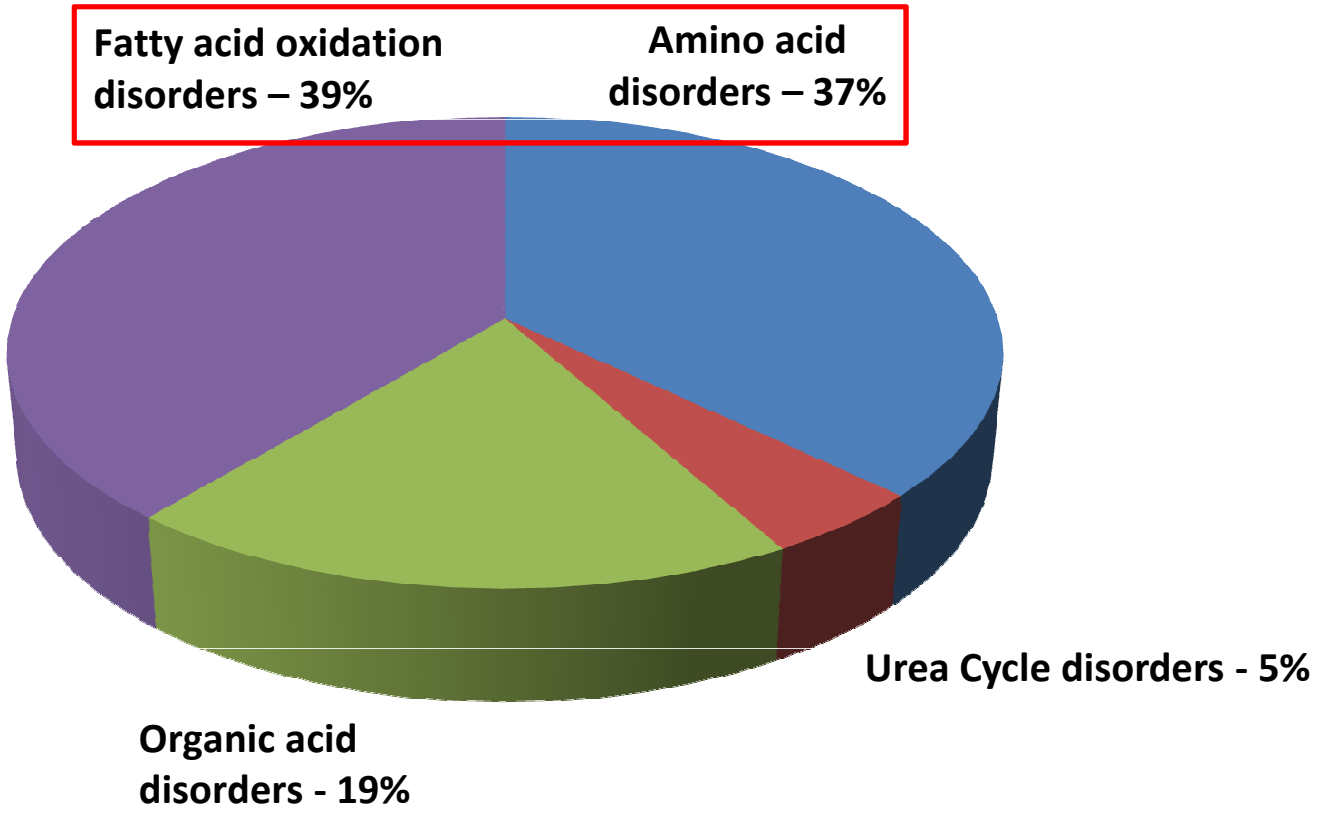
Patient 1
Cit=23µM (N<50µM)
ASA=0.90µM (N<1.1µM)

Patient 2
Cit= 24 µM (N<50)
ASA= 0.26 µM (N<1.1)

(p.R12Q/ p.R12Q)

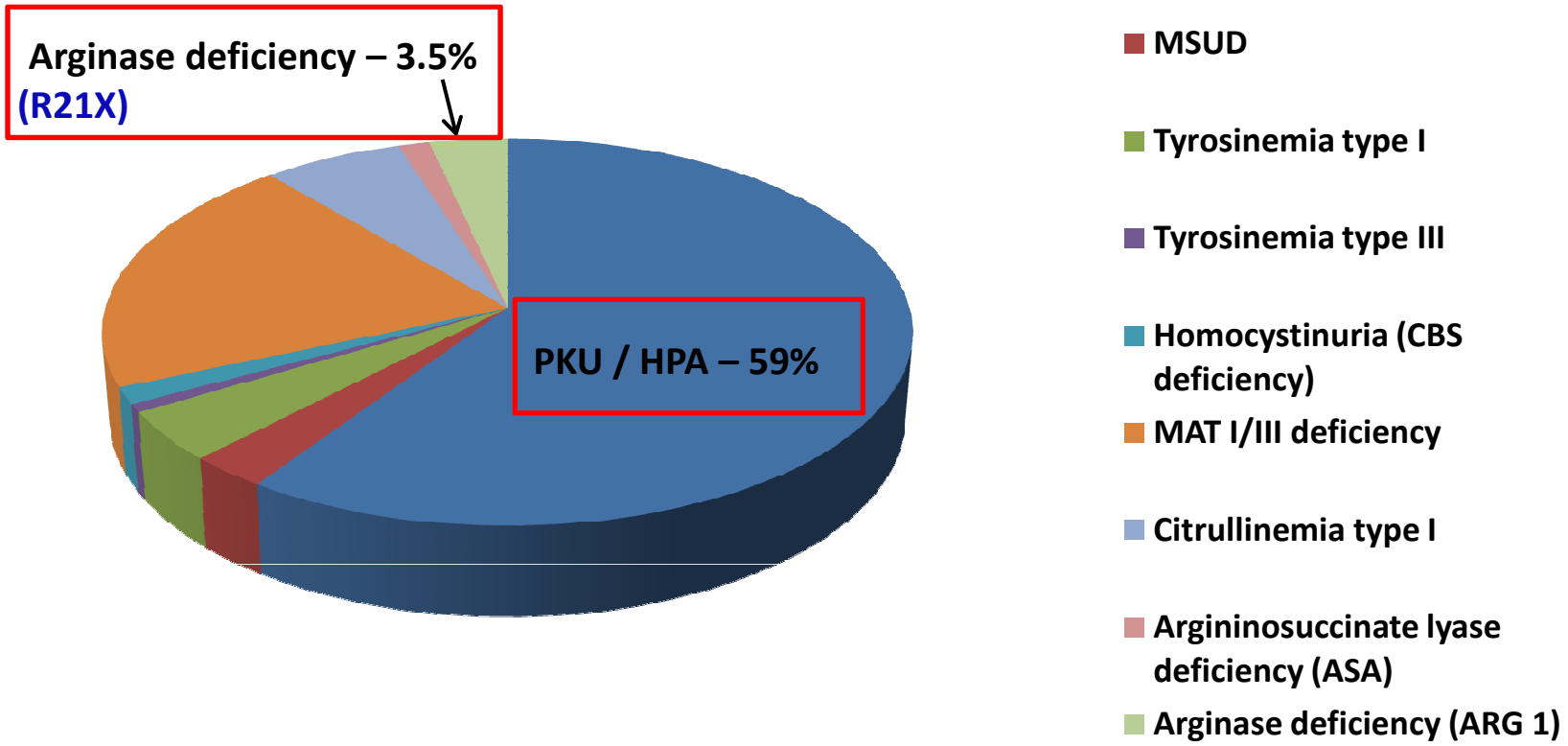
Late-onset forms

NBS by *ms/ms*: 2004 - 2014



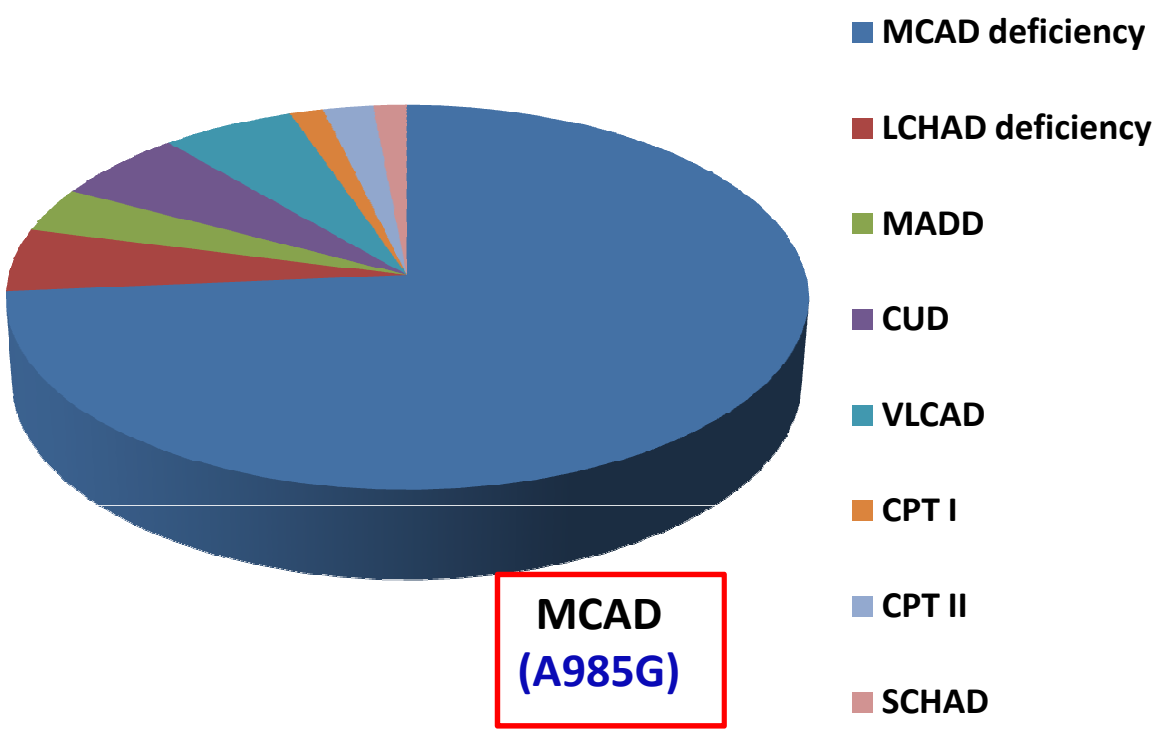
NBS by *ms/ms*: 2004 - 2014

Amino acid disorders



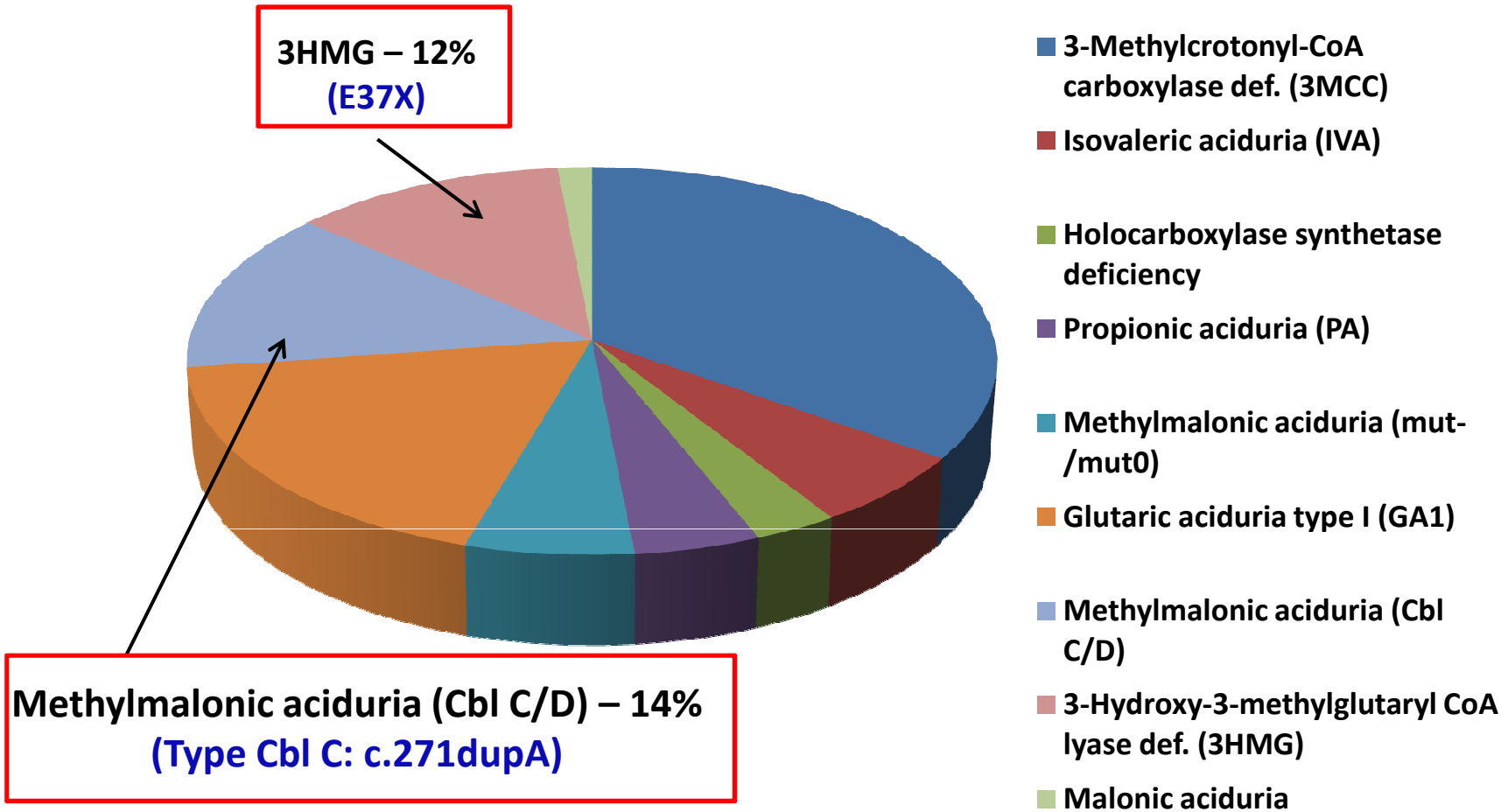
NBS by *ms/ms*: 2004 - 2014

Fatty acid oxidation disorders



NBS by *ms/ms*: 2004 - 2014

Organic acid disorders



Portuguese National Program for Newborn Screening

Total birth prevalence for all screened disorders: 1: 1.659

Total positive cases: 1.727

Newborns	Disorders	Birth prevalence
3.375.266	PKU / HPA	1: 10.459
3.343.098	HC	1: 2.986
820.433	IEM	1: 2.399

IEM screening group (*ms/ms*)

Laura Vilarinho (group leader)
Ana Marcão
Carmen Sousa
Helena Fonseca
Hugo Rocha

Newborn Screening, Genetics and Metabolism Unit

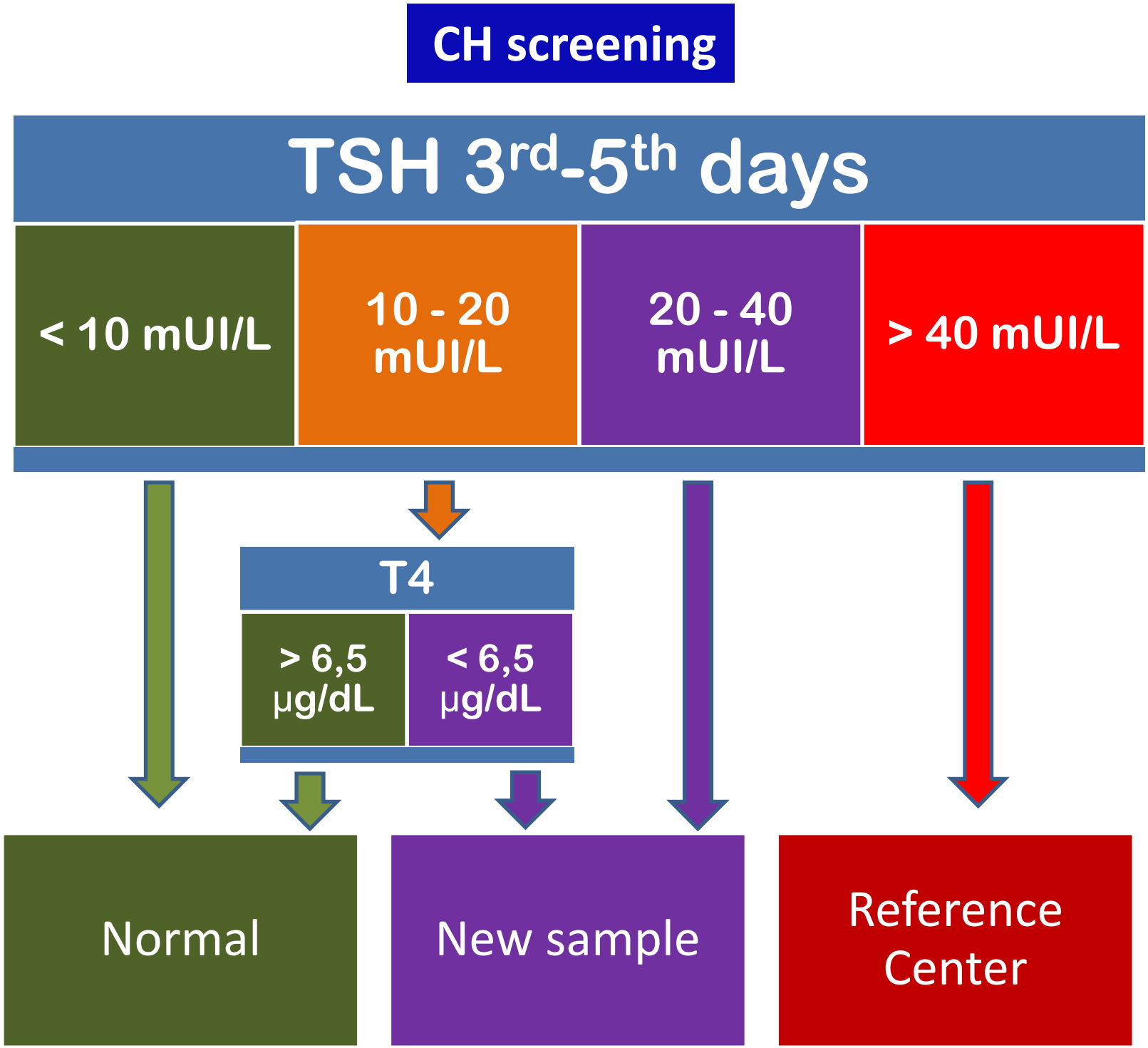
Human Genetics Department
National Institute of Health Dr Ricardo Jorge
Porto - Portugal

Newborn Screening in Portugal

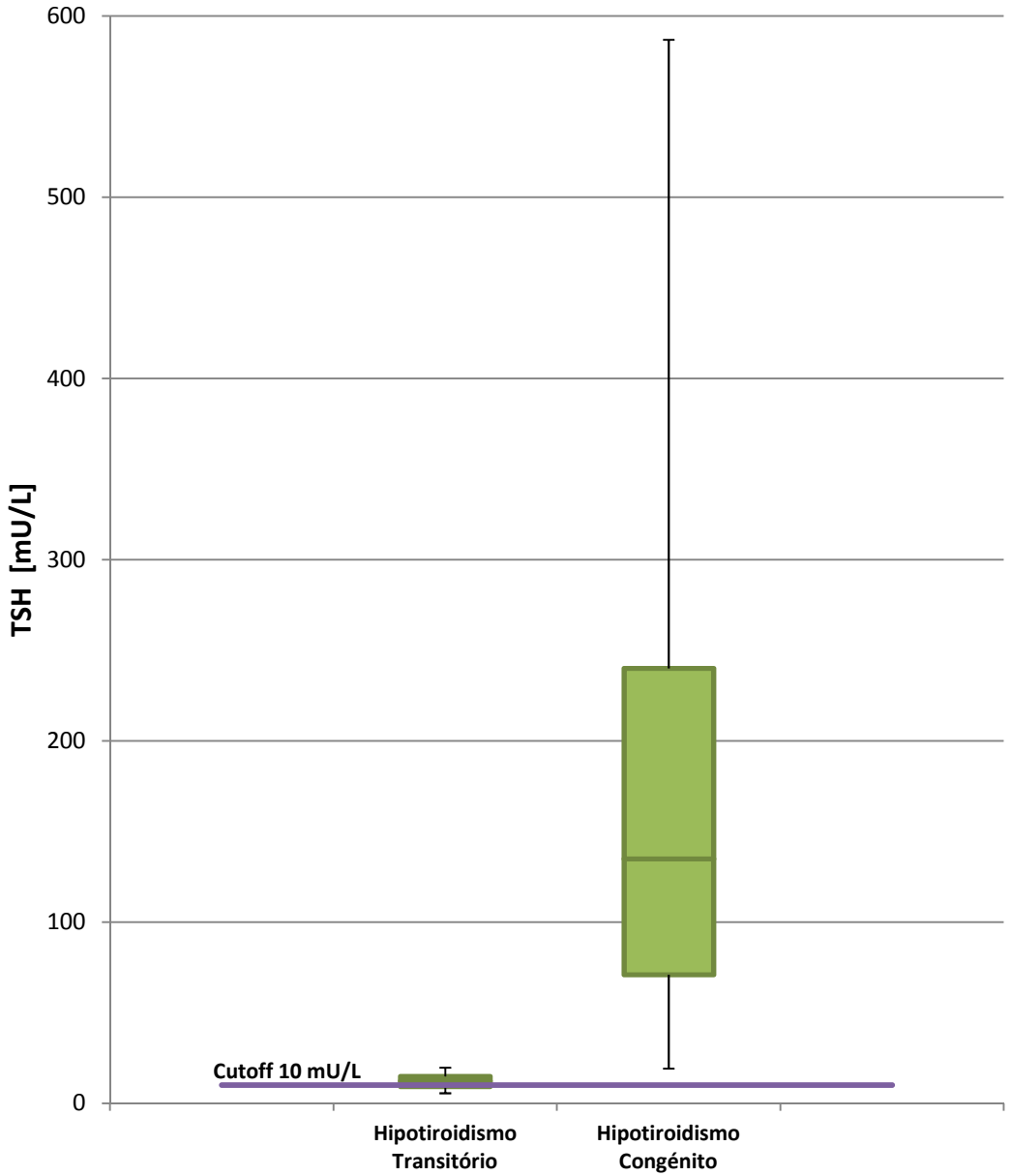
Total number of Screened Newborns: 3.374.671

Total number of positive cases: 1.727

Diseases	Newborns	Positive cases	Prevalence
PKU 1979 – 2013	3.374.671	324	1 : 10.415
CH 1981 – 2013	3.342.429	1.123	1 : 2.976


CH screening
TSH 3rd-5th days
< 10 mUI/L
10 - 20 mUI/L
20 - 40 mUI/L
> 40 mUI/L
T4
> 6,5 µg/dL
< 6,5 µg/dL
Normal
New sample
Reference Center

CH Screening



CH Screening

TSH quantification

AutoDELFIA® Neonatal TSH kit - PerkinElmer

T4 quantification

AutoDELFIA® Neonatal T4 kit – PerkinElmer

Newborn Screening in Portugal

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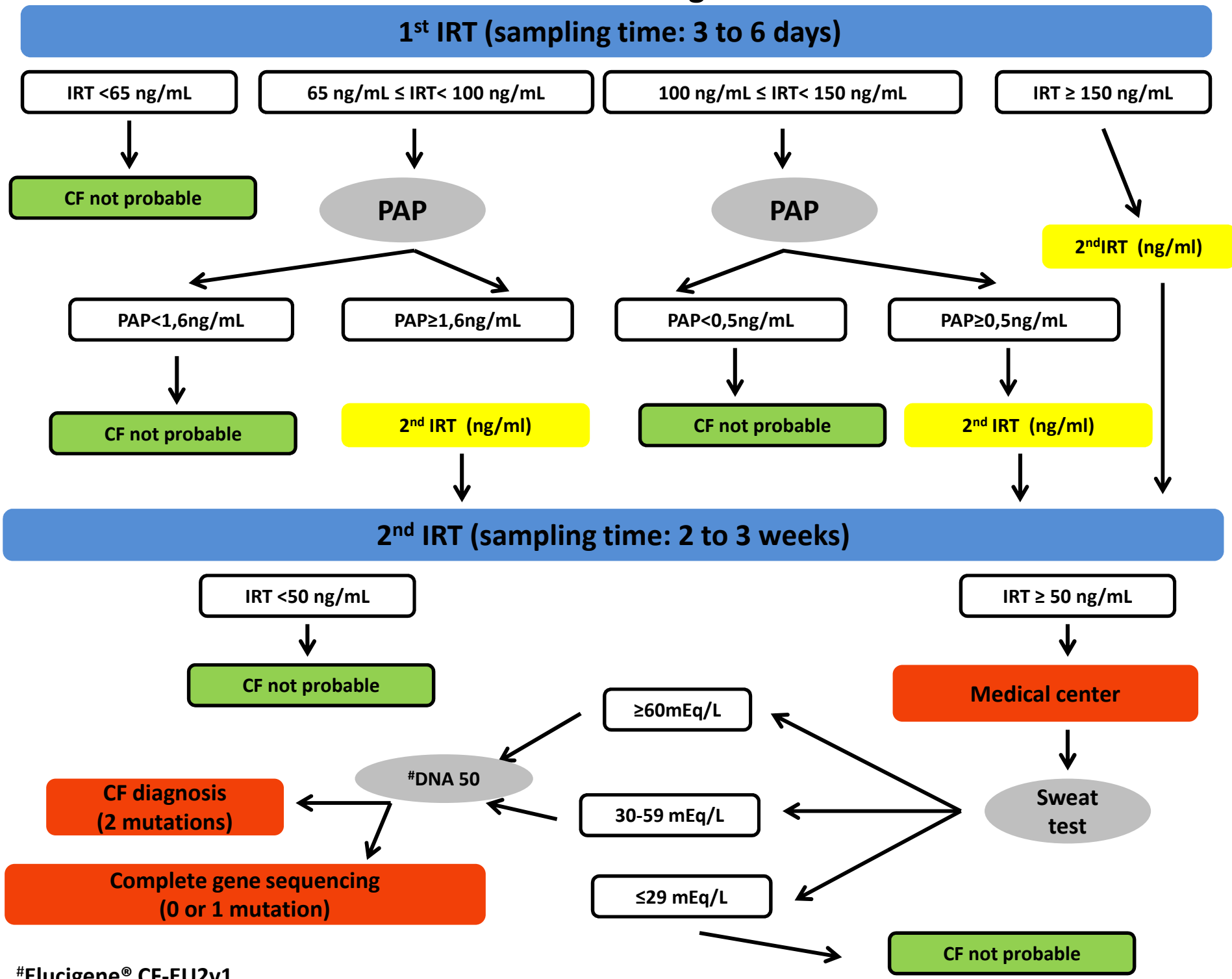
Neonatal Screening for CF



#Elucigene® CF-EU2v1

FQ Neonatal Screening

IRT quantification

AutoDELFIA® Neonatal IRT kit - PerkinElmer

PAP quantification

Kit MucoPAP-F - Dynabio
(adapted to system DELFIA® - Perkin Elmer)

Molecular study

Elucigene CF-EU2v1 (50 mutations)

FQ Neonatal Screening

Screened NB	80 000
Confirmed patients	11
Birth prevalence	1: 7 273

IRT > 65 ng/mL	665 (0,83%)
PNA (IRT+PAP ↑)	277 (0,35%)
2º IRT < 50 ng/mL	250 (0,31% false positives)

NB referred to sweat test	27
Confirmed patients	11
Waiting for confirmation	5
False positives	1 1 (0,014%)

FQ Neonatal screening

Patients (sampling day)	1º IRT (N<65ng/mL)	PAP (N<0,5ng/mL)*	2º IRT (N<50ng/mL)	Genotype
D1 (5d, 18d)	94	5,4	158	F508del/F508del
D2 (21d, --)	129	3,9	n.d.	F508del/F508del
D3 (6d, 14d)	210	>8,8	287	F508del/?
D4 (23d, 28d)	190	>8,8	195	F508del/F508del
D5 (3d, 13d)	260	4,3	344	F508del/F508del
D6 (4d, 27d)	266	>8,8	360	F508del/F508del
D7 (5d, 15d)	443	>8,8	480	F508del/F508del
D8 (4d, --)	202	2,7	n.d.	F508del/N1303K
D9 (2d, 5d)	101	>8,8	85	F508del/F508del
D10 (4d, 30d)	110	4,6	123	F508del/F508del
D11 (3d, 16d)	414	>8,8	265	F508del/F508del

* If IRT<100ng/mL, PAP<1,6 ng/mL