National

Screening Report

Germany 2009

Deutsche Gesellschaft für Neugeborenenscreening e.V.

Uta Nennstiel-Ratzel, Anja Lüders, Oliver Blankenstein, Uta Ceglarek, Regina Ensenauer, Jeannette Klein, Martin Lindner, Cornelia Müller, Michael Peter, Ernst Rauterberg, Wulf Röschinger,Inge Schneider, Wolfgang Schultis, Andreas Schulze, Irmgard Starke, Maren Stehn, Marina Stopsack, Christoph Fusch

state of July 20th 2011

Correspondence author:
Dr. med Uta Nennstiel-Ratzel MPH
Screeningzentrum
Bayerisches Landesamt für Gesundheit and Lebensmittelsicherheit
Veterinärstr. 2
D-85764 Oberschleißheim
Germany
Email: uta.nennstiel-ratzel@lgl.bayern.de

Contents

Figures

Abbreviations:

CAH	Congenital adrenal hyperplasia
CACT - Deficiency	Carnitin-Acylcarnitin-Translocase-Deficiency
CPTI - Deficiency	Carnitin- Palmitoyl-CoA-Transferase I-Deficiency
CPTII - Deficiency	Carnitin- Palmitoyl-CoA-Transferase II-Deficiency
GA I	Glutaric acidaemia Type I
BW	Birth weight
HPA	Hyperphenylalaninaemia
IVA	Isovaleric anacidaemia
LCHAD Deficiency	Long-Chain-3-Hydroxy-Acyl-CoA-Dehydrogenase-Deficiency
DoL	Day of life
GV 1 - 3	Guide value 1 - 3
MCAD - Deficiency	Medium-Chain-Acyl-CoA-Dehydrogenase-Deficiency
MSUD	Maple syrup urine disease
NBS	New born screening
SP	Secondary parameter
PKU	Phenylketonuria
PPV	Positive predictive value
Second-tier Process	In suspicious results secondary analysis of additional parameter or alternative analytical methods from the same test cards
WoG	Week of gestation
VLCAD Deficiency	Very-Long-Chain-Acyl-CoA-Dehydrogenase-Deficiency

Screening Laboratories and Screening Centres

Screening Centres (laboratories) with different localities or laboratories which are connected to a screening centre are analysised stratified.

(1) Neugeborenen Screeninglabor Berlin
Dr. med. Oliver Blankenstein
Augustenburger Platz 1
13353 **Berlin**
030/450 566678
Oliver.Blankenstein@charite.de

Screeningzentrum Sachsen
Prof. Dr. med. Joachim Thiery,
Universitätsklinikum Leipzig
(3) Standort **Dresden**
PF 160252
01288 Dresden
0351/458 5230 / 5229
marina.stopsack@uniklinikum-dresden.de
(10) Standort **Leipzig**
Paul-Listr-Str. 13-15
04103 Leipzig
0341/9722222 (Leitstelle ILM)
uta.ceglarek@medizin.uni-leipzig.de
http://www.screeningzentrum-sachsen.de/

(5) Screening-Zentrum Hessen
Prof. Dr. med. Ernst W. Rauterberg
Feulgenstr. 12
35392 **Giessen**
0641/9943681
ernst.w.rauterberg@paediat.med.uni-giessen.de

(6) Neugeborenenscreeningzentrum Mecklenburg-Vorpommern,
Prof. Dr. med. Matthias Nauck
Universitätsmedizin Greifswald
Sauerbruchstr.
17475 **Greifswald**
Tel. 03834/ 865501
nauck@uni-greifswald.de
cornelia.mueller@uni-greifswald.de
http://www.medizin.uni-greifswald.de/klinchem/index.php?id=336

(7) Screening-Labor, Universitätskinderklinik
Prof. Dr. med. René Santer
Martinistr. 52
20246 **Hamburg**
040/42803 0
r.santer@uke.uni-hamburg.de

(8) Screening-Labor Hannover
Prof. Dr. med. J. Sander, PD Dr. med. M. Peter
Postfach 911009
D 30430 **Hannover**
05108/92163 0
j.sander@metabscreen.de,
m.peter@metabscreen.de
www.metabscreen.de

(9) Neugeborenenscreening Heidelberg
Prof. Dr. med. G.F. Hoffmann
Im Neuenheimer Feld 153
69120 **Heidelberg**
06221/56 2311
martin.lindner@med.uni-heidelberg.de
www.Neugeborenenscreening.uni-hd.de

(11) Screeninglabor, Universitäts-Kinderklinik
Prof. Dr. med Klaus Mohnike
PSF 140274
39043 **Magdeburg**
0391/6713986
irmgard.starke@med.ovgu.de
http://www.stoffwechselzentrum-magdeburg.de

(12/13) Labor Becker, Olgemöller & Kollegen
Prof. Dr. med. Dr. rer. nat. Bernhard Olgemöller
Ottobrunner Str. 6
81737 **München**
089/544 654 0
Olgemoeller@labor-bo.de
www.labor-bo.de

(14/15) Medizinisches Versorgungszentrum für Laboratoriumsmedizin u. Mikrobiologie
Dr. med. Dr. rer. nat. Hans-Wolfgang Schultis
Zur Kesselschmiede 4
92637 **Weiden**
0961/309 0
schultis@synlab.de
www.mfl-weiden.synlab.de

Screeningzentrum Bayern (12/14)
Bayerisches Landesamt für Gesundheit and Lebensmittelsicherheit
Dr. med. Uta Nennstiel-Ratzel MPH
Veterinärstr.2
85764 **Oberschleißheim**
09131/6808-5-204
screening@lgl.bayern.de
http://www.lgl.bayern.de/gesundheit/neugeborenenscreening.htm

1 Introduction

The newborn screening is a medical population based preventative measure with the aim of early and sufficient detection and high quality therapy of all newborns with treatable endocrine metabolic diseases.

The guidelines of prevention of disease for children up to 6 years of age („Kinder-Richtlinien“) outline the details of newborn screening (NBS) since 1.7.2005.

The National Screening Report 2009 was composed by the “Deutschen Gesellschaft für Neugeborenenscreening (DGNS e.V.)” as well as the German screening laboratories. The statistical analysis of the screening data was according to the guidelines and their quality criteria of the NBS implementation. This report targets only the metabolic and endocrine diseases which are defined in these guidelines. It provides a wide statistical summary of disease related screening numbers, recall numbers at diagnoses for the year 2009. Additionally, data for process quality are presented.

Process quality describes the process flow and its evaluation through specialists according to defined indicators. These are the following for the newborn screening:

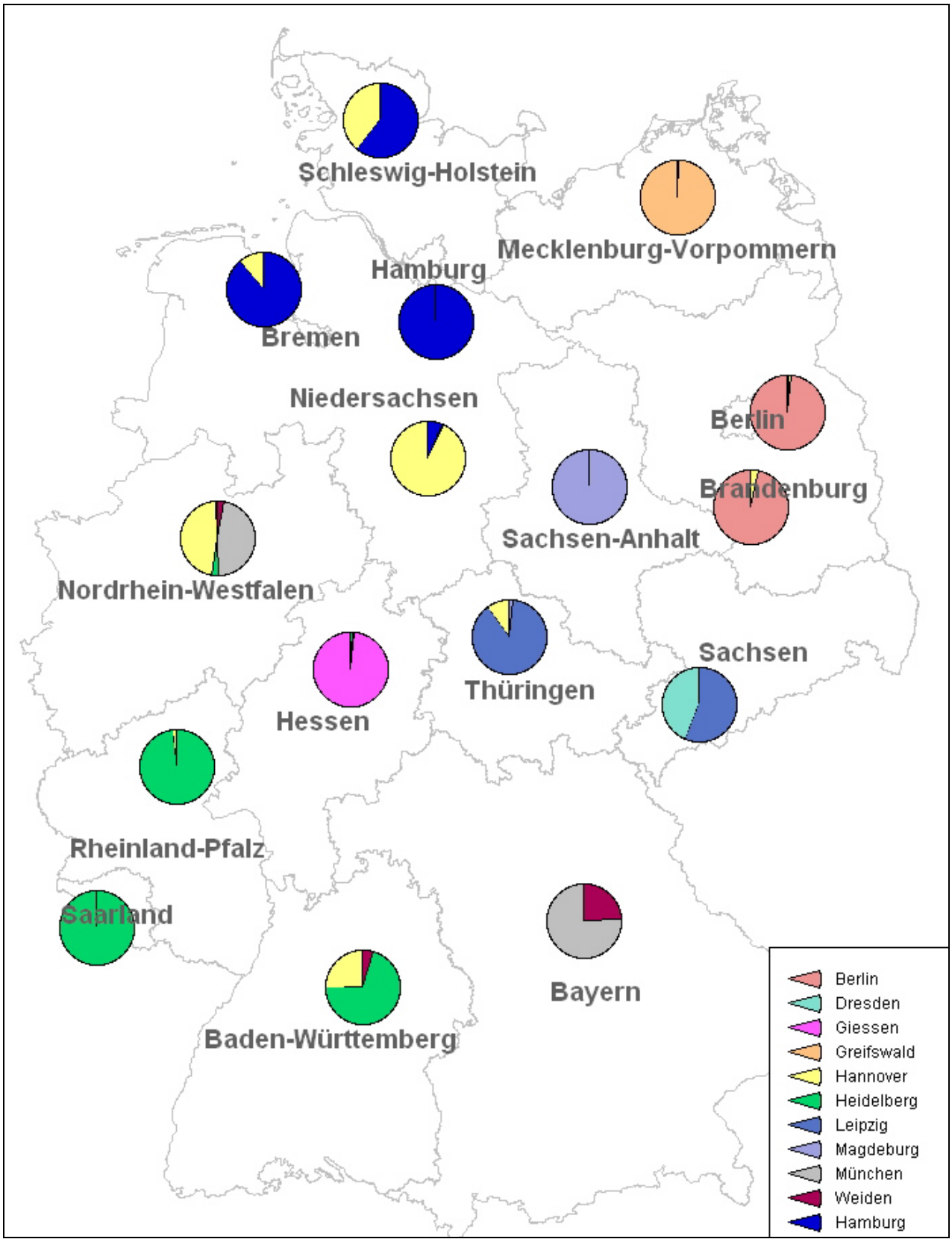
- Total Survey of the population
  - Collection method and rate
  - Blank card system
- Completeness of the control and the follow-up studies
- Collection of test parameters and cut offs
- According to laboratory, age as well as gestational age, stratified rates of recall, positive predictive values and prevalence
- Specificity and sensitivity of diagnostic tests
- Process times (pre analytic and laboratory), age at blood collection, time within blood collections, time of arrival in the laboratory and time of result communication
- Screening values of newborns for which further testing is emphasized
- Diagnostic for confirmation
  - Type of diagnostic
  - Time of diagnostic
- Final diagnosis
- Start of therapy

Previously, laboratories are listed which have undertaken the screening in 2009 for Germany. (12 and 13 relate to the same laboratory, ones with and without the co-operation of the Screening Centre, same for 14 and 15). In the Tables the laboratories are encrypted. Paragraphs in the text relate to the guidelines for children from 21/12/04 (1). Tables are numbered according to the chapters.

We thank all the laboratories for provision of their data. The data was checked for plausibility. Finally, the provided, and if necessary corrected, data was analysed. Remaining inconsistencies of data was analysed according to the reported data. (Inconsistency partly due to the system).

The screening samples of the federal states are spread to the laboratories according to Figure1.

Figure 1: Distribution of analysis according to county and laboratory



2 Results

In the year 2009, 665.126 children were born in Germany [2]. The total recorded screening exceeds this number slightly at 665.495. Additional samples should originate from non registered newborns.

A secure statement about the rate of taking part in NGS can only be made by comparison of person related data or the population. By law this is only legal in the county of Bavaria.

Births [2]:	665.126
First screening:	665.495
Final diagnosis (see Table 3):	493

In the German guidelines the targeted diseases are defined for the nationwide screening. Some laboratories will also screen for scientific purposes. These results will not be addressed in this report. Of 1.349 newborns one targeted disease according to the guidelines is found. Table 2 shows the prevalence of targeted diseases in the year 2009 in Germany.

Table: 2 Absolute number of detected diseases found by screening

Disease	Confirmed Cases	Prevalence
Hypothyroidism	195	1: 3.441
Congenital adrenal hyperplasia (CAH)	38	1: 17.503
Biotinidase Deficiency	33	1: 20.155
Galactosaemia (classic)	6	1: 110.854
Phenylketonuria (PKU) n=60 / Hyperphenylalaninaemia (HPA) n=63	123	1: 5.408
Maple syrup urine disease (MSUD)	4	1: 166.282
Medium-Chain-Acyl-CoA-Dehydrogenase (MCAD)-Disease	74	1: 8.988
Long-Chain-3-OH-Acyl-CoA-Dehydrogenase (LCHAD)-Disease	3	1: 221.709
(Very-)Long-Chain-Acyl-CoA-Dehydrogenase (VLCAD)-Disease	7	1: 95.018
Carnitin-Palmitoyl-CoA-Transferase I (CPTI)-Disease	0	
Carnitin-Palmitoyl-CoA-Transferase II (CPTII)-Disease	0	
Carnitin-Acylcarnitin-Translocase (CACT)-Disease	0	
Glutaraciduria Type I (GA I)	4	1: 166.282
Isovaleric acidaemia (IVA)	6	1: 110.854
Total	**493**	1: 1.349

2.1 Data of primary screening

According to the guidelines of children, every newborn should be screened before leaving the birth facility. A reliable screening can only be undertaken with blood sampling beyond the completed 32nd gestational week and 36th hour of life. A primary screening before the 36th hour of life or before the completed 32nd week of gestation should be followed by a repeat screening. The following table shows the stratified results of the primary screening according to age and gestational age.

Table 2.1: Age at primary screening

Laboratory	Total	≥36h and ≥32WOG		<36h and ≥32WOG		<32WOG	
		n	%	n	%	n	%
1	49007	47163	96,24	1239	2,53	605	1,23
3	15195	14779	97,26	252	1,66	164	1,08
5	51600	50784	98,42	321	0,62*	495	0,96
6	12804	12287	95,96	328	2,56	189	1,48
7	42458	40127	94,51	1594	3,75	737	1,74
8	158930	155331	97,74	1683	1,06	1916	1,21
9	105098	102484	97,51	1234	1,17	1380	1,31
10	34145	33321	97,59	424	1,24	400	1,17
11	16968	16314	96,15	443	2,61	211	1,24
12	77969	76264	97,81	856	1,10	849	1,09
13	69476	67725	97,48	889	1,28	862	1,24
14	23905	23356	97,70	329	1,38	220	0,92
15	7940	7724	97,28	131	1,65	85	1,07
Total	**665495**	**647659**	**97,32**	**9723**	**1,46**	**8113**	**1,22**

***** Laboratory declined in 7,5% early screening

2.2 Relation of requested to received repeat screenings

In Table 2.2.1 the repeat screenings are listed stratified according to their base of request defined as:

- **„<32WoG“:** all sample of newborns before 32 WoG, independent of age and result of primary screening
- **„<36h“:** all sample of newborns beyond 32 WoG, but age less than 36h, independent of the result of primary screening
- **Recall:** essential repeat testing due to suspicious primary screening at a gestational age > 32 WoG and age > 36h

Repeat screenings from other laboratories and samples of deceased newborns (especially < 32 WOG) have often not been integrated in the statistics, since in-between laboratories no data transfer is implemented (data protection), resulting in implausible ranges.

Table 2.2: Requested and received repeat screenings

Laboratory	Total[a] requested	Total[a] received	%	Recall requested	Recall received	%
1	2421	2127	87,86	697	609	87,37
3[b]	508			92	92	100
5	1533	1419	92,56	720	718	99,72
6	660	652	98,79	143	143	100
7[b]	3061			730		
8	5114	4366	85,37	1107	1041	94,04
9	3385	2411	71,23	518	492	94,98
10	1141	1108	97,11	318	307	96,54
11	701	665	94,86	47	47	100
12	2250	2247	99,87	599	598	99,83
13[b]	2278			470	438	93,19
14	677	659	97,34	128	128	100
15	296	196	66,22	73	73	100
Total	**24025**	**15850**	**87,19**[b]	**5642**	**4686**	**95,40**[b]

Laboratory	<36h requested	<36h received	%	<32WOG requested	<32WOG received	%
1	1134	1000	88,18	452	388	85,84
3[b]	252			164		
5	320	285	89,06	491	414	84,32
6	328	324	98,78	189	185	97,88
7[b]	1594			737		
8	1683	1403	83,36	1916	1689	88,15
9	1234	752	60,94	1380	994	72,03
10	424	428		382	373	97,64
11	443	410	92,55	211	208	98,58
12	850	848	99,76	801	801	100
13[b]	946			862		
14	329	323	98,18	220	208	94,55
15	131	47	35,88	85	71	83,53
Total	**9668**	**5820**	**84,64**[b]	**7890**	**5331**	**87,01**[b]

[a] Inclusive secondary screening due to blood transfusion, parenteral nutrition or medication
[b] Implausible data were not included in the table and the calculations

2.3 Tracking of completeness of screening

The newborn screening is a measure of public health and should be given to all German born children. To guarantee that the screen is offered to all newborns the tracking of completeness is necessary. For children born in obstetric units, control can be undertaken through hospital records or if permitted by state law through the birth registry.

Currently both measures are not undertaken nationwide. To target the tracking of completeness the following rule was included into the "guidelines". The obstetric unit should document on a blank test card refusal of screening or death of a neonate. This test card should then be sent to the screening centre. The laboratory received blank test cards in various numbers.

Table 2.3: Laboratory received blank cards

Laboratory	Deceased	Screening declined	Transfer	Early screening declined	Total	Relation of declined early screening to total screened
	n	n	n	n	n	%
1	0	0	0	3192	3192	6,51
3	39	15	1109	574	1737	3,78
5	62	0	0	3872	3934	7,50
6	45	3	0	254	261	1,98
7	0	3	0	238	241	0,56
8	0	0	0	1205	1205	0,76
9	15	69	44	529	657	0,50
10	25	1	0	1227	1253	3,59
11	60	2	52	253	367	1,49
12	22	45	79	551	697	0,71
13	n.s.	n.s.	n.s.	n.s.	n.s.	
14	4	14	24	164	206	0,69
15	n.s.	n.s.	n.s.	n.s.	n.s.	
Total	**272**	**152**	**1308**	**12059**	**13750**	**2,05**

Table 2.4: Second screening due to poor quality of primary

Laboratory	Primary screening	Control requested	Control received	received/ requested (%)	Percentage of unprocessed screening cards/ Primary screening (%)
1	49007	305	295	96,72	0,62
3*	15195	29	30		0,19
5	51600	578	578	100	1,12
6	12804	21	20	95,24	0,16
7	42458	96	73	76,04	0,23
8	158930	222	204	91,89	0,14
9	105098	564	524	92,91	0,54
10	34145	129	126	97,67	0,38
11	16968	0	0		0
12	77969	401	395	98,50	0,51
13	69476	336	335	99,70	0,48
14	23905	35	35	100	0,15
15	7940	4	4	100	0,05
Total	**665495**	**2720**	**2619**	**96,29**	**0,41**

***n received > n requested, therefore no proportional data

3 Recall Rate, Prevalence, Positive predictive value specificity

The excellence of a test is measured by the sensitivity, the specificity as well as the positive predictive value. In screening, the sensitivity (true-test positives) but more so the specificity (true-test negatives), should be high to find all diseases and to avoid unnecessary worries and costs. The lower the rate of necessary control screening due to positive first screening (recall rate) the higher the specificity. In 2009 the recall rate accounted for 0,85%, meaning 9 control screenings per 1000. The positive predictive value estimates the risk of disease with a positive test result. It depends on the sensitivity, the specificity and also the prevalence of the targeted disease, meaning the rarer a disease the lower the PPV, even with a high sensitivity and specificity. The sensitivity cannot be quoted, because systematic registration of unscreened neonates is not done. For the calculation of the PPV the sensitivity is estimated 99,5%.

Only for neonates born after the 32nd WoG and screening sampled beyond the 36th the PPV is considered for analysis. Overall the PPV is 10,87% meaning that about 11% of suspicious screening results indicate the targeted disease. For several diseases the PPV is high, e.g. for HPA / PKU 45,82%, for MCAD-Deficiency 37,5% and for hypothyroidism 29,39%. The range of PPV between the single Laboratories is high.

Table 3: Recallrate, Specificity, Prevalence and PPV for Germany 2009 N=665.495*

Disease	Recall ≥36h	Recallrate (%) ≥36h	Confirmed Cases	PPV ≥36h (%)	Specificity (%)	Prevalence (relative to Primary screening)
Hypothyroidism	592	0,09	195	29,39	99,88	1: 3413
AGS	1883	0,29	38	1,75	99,58	1: 17513
Biotinidase-Disease	162	0,03	33	19,14	99,98	1: 20167
classic Galactosaemia	542	0,08	6	0,92	99,93	1: 110916
PKU/HPA	251	0,04	123	45,82	99,97	1: 5411
MSUD	62	0,01	4	6,45	99,99	1: 166374
MCAD	184	0,03	74	37,50	99,98	1: 8993
LCHAD	16		3	18,75	99,99	1: 221832
VLCAD	112	0,02	7	6,25	99,98	1: 95071
CPT I-Disease	9		0			
CPT II-Disease	5		0			
CAT-Disease	0		0			
GA I	253	0,04	4	1,58	99,96	1: 166374
IVA	67	0,01	6	7,46	99,99	1: 110916
Total	**4138**	**0,64**	**491**	**10,87**	**99,23**	**1: 1350**

* Primary screening Total: n= 665.495; Primary screening ≥ 36h and ≥ 32WOG n= 647.659

3.1 Recall rate, prevalence stratified

The following tables show recall rates and prevalence of newborns > 36 hours of age and > 32 weeks gestational age stratified according to laboratories. The reference of > 36 hours automatically includes > 32 weeks gestational age. The confirmed diagnosis, confirmed cases and their prevalence relate to the total screening tests, irrespective of age and gestational age. The validation of confirmed cases was tested for plausibility of metabolic diseases by Andreas Schulze and Regina Ensenauer, for endocrine diseases by Oliver Blankenstein and Heiko Krude. Excluded and therefore not reported are cases with missing data of confirmation diagnostics (n=32) (Tab.3.1.a) and cases where the confirmation diagnostics was negative (n=12). As a result the true prevalence could be higher. Double reported cases were included only once.

Table 3.1 : Cases with missing data of confirmation diagnostics

Disease	Data missing
Hypothyroidism	18
AGS	4
Biotinidase Deficiency	
Galactosaemia (classic)	
PKU/HPA	2
MSUD	1
MCAD	1
LCHAD	2
VLCAD	1
CPT II-Disease	1
GA I	2
IVA	
Total	**32**

The next tables do not show recall rates <0,01% since small n cause a big variability.

In 2009 no cases with false negative screening results were reported.

3.1.1 Hypothyroidism*

Laboratory	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)	Confirmed cases
1	49007	47163	36	0,08	24
3	15195	14779	5	0,03	2
5	51600	50784	153	0,30	11
6	12804	12287	8	0,07	6
7	42458	40127	39	0,10	11
8	158930	155331	190	0,12	52
9	105098	102484	50	0,05	35
10	34145	33321	14	0,04	5
11	16968	16314	9	0,06	5
12	77969	76264	33	0,04	17
13	69476	67725	39	0,06	18
14	23905	23356	13	0,06	8
15	7940	7724	3	0,04	1
Total	**665495**	**647659**	**592**	**0,09**	**195**

* including temporary hypothyroidism n=3

Additionally n=18 persistent elevations of TSH were diagnosed, not counted in the prevalence.

3.1.2 Congenital adrenal hyperplasia (CAH)

Laboratory	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)	Confirmed cases
1	49007	47163	155	0,33	2
3	15195	14779	36	0,24	2
5	51600	50784	253	0,50	0
6	12804	12287	92	0,75	2
7	42458	40127	228	0,57	2
8	158930	155331	37	0,02*	14
9	105098	102484	211	0,21	3
10	34145	33321	143	0,43	0
11	16968	16314	26	0,16	1
12	77969	76264	399	0,52	5
13	69476	67725	227	0,34	6
14	23905	23356	53	0,23	1
15	7940	7724	23	0,30	0
Total	**665495**	**647659**	**1883**	**0,29**	**38**

* Laboratory used Second-tier process

3.1.3 Biotinidase Deficiency

Laboratory	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	49007	47163	11	0,02	2
3	15195	14779	6	0,04	1
5	51600	50784	2		1
6	12804	12287	9	0,07	1
7	42458	40127	9	0,02	1
8	158930	155331	75	0,05	21
9	105098	102484	7	0,01	2
10	34145	33321	4		1
11	16968	16314	2		0
12	77969	76264	12	0,02	1
13	69476	67725	17	0,03	2
14	23905	23356	8	0,03	0
15	7940	7724	0		0
Total	**665495**	**647659**	**162**	**0,03**	**33**

* Recall rate recorded only if ≥ 0,01% and n > 5

3.1.4 Galactosaemia incl. Varients / classic

Laboratory	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	49007	47163	115	0,24	15
3	15195	14779	8	0,05	0
5	51600	50784	55	0,11	11
6	12804	12287	6	0,05	4
	42458	40127	37	0,09	8
8	158930	155331	42	0,03	9
9	105098	102484	11	0,01	0
10	34145	33321	7	0,02	4
11	16968	16314	2		0
12	77969	76264	97	0,13	9
13	69476	67725	98	0,14	1
14	23905	23356	36	0,15	4
15	7940	7724	28	0,36	0
Total	**665495**	**647659**	**542**	**0,08**	**65**

***** Recall rate recorded only if ≥ 0,01% and n > 5

3.1.5 PKU / HPA

Laboratory	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	49007	47163	82	0,17	12
3	15195	14779	6	0,04	2
5	51600	50784	13	0,03	5
6	12804	12287	3		2
7	42458	40127	20	0,05	4
8	158930	155331	26	0,02	24
9	105098	102484	33	0,03	28
10	34145	33321	5		5
11	16968	16314	4		4
12	77969	76264	27	0,04	17
13	69476	67725	17	0,03	17
14	23905	23356	11	0,05	3
15	7940	7724	4		0
Total	**665495**	**647659**	**251**	**0,04**	**123**
Davon PKU					**60**

* Recall rate recorded only if ≥ 0,01% and n > 5

3.1.6 MSUD

Laboratory	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	49007	47163	21	0,04	1
3	15195	14779	6	0,04	0
5	51600	50784	10	0,02	0
6	12804	12287	2		0
7	42458	40127	6	0,01	1
8	158930	155331	2		1
9	105098	102484	11	0,01	0
10	34145	33321	0		0
11	16968	16314	0		0
12	77969	76264	3		0
13	69476	67725	1		1
14	23905	23356	0		0
15	7940	7724	0		0
Total	**665495**	**647659**	**62**	**0,01**	**4**

* Recall rate recorded only if ≥ 0,01% and n >5

3.1.7 MCAD-Deficiency

Laboratory	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	49007	47163	52	0,11	1
3	15195	14779	2		0
5	51600	50784	45	0,09	6
6	12804	12287	3		1
7	42458	40127	13	0,03	8
8	158930	155331	17	0,01	16
9	105098	102484	23	0,02	12
10	34145	33321	5		4
11	16968	16314	3		3
12	77969	76264	6	0,01	8
13	69476	67725	9	0,01	14
14	23905	23356	5		0
15	7940	7724	1		1
Total	**665495**	**647659**	**184**	**0,03**	**74**

* Recall rate recorded only if ≥ 0,01% and n > 5

3.1.8 LCHAD-Deficiency

Laboratory	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	49007	47163	7		0
3	15195	14779	0		0
5	51600	50784	1		0
6	12804	12287	0		0
7	42458	40127	1		0
8	158930	155331	3		2
9	105098	102484	4		1
10	34145	33321	0		0
11	16968	16314	0		0
12	77969	76264	0		0
13	69476	67725	0		0
14	23905	23356	0		0
15	7940	7724	0		0
Total	**665495**	**647659**	**16**	**0,002**	**3**

* Recallrate due to small numbers only in absolute

3.1.9 VLCAD-Deficiency

Laboratory	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	49007	47163	32	0,07	0
3	15195	14779	6	0,04	0
5	51600	50784	12	0,02	0
6	12804	12287	4		0
7	42458	40127	18	0,04	0
8	158930	155331	0		0
9	105098	102484	19	0,02	2
10	34145	33321	1		0
11	16968	16314	1		0
12	77969	76264	16	0,02	3
13	69476	67725	2		2
14	23905	23356	0		0
15	7940	7724	1		0
Total	**665495**	**647659**	**112**	**0,02**	**7**

* Recall rate recorded only if ≥ 0,01% and n>5

3.1.10 No confirmed cases of CPTI-Deficiency, CPTII-Deficiency and for CACT-Deficiency

3.1.11 Glutaric acidaemia Type I

Laboratory	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	49007	47163	9	0,02	0
3	15195	14779	3		0
5	51600	50784	166	0,33	0
6	12804	12287	9	0,07	0
7	42458	40127	44	0,11	1
8	158930	155331	1		0
9	105098	102484	12	0,01	3
10	34145	33321	0		0
11	16968	16314	0		0
12	77969	76264	5		0
13	69476	67725	4		0
14	23905	23356	0		0
15	7940	7724	0		0
Total	**665495**	**647659**	**253**	**0,04**	**4**

* Recall rate recorded only if ≥ 0,01% and n>5

.

3.1.12 Isovaleric acidaemia

Laboratory	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	49007	47163	45	0,10	2
3	15195	14779	1		0
5	51600	50784	9	0,02	0
6	12804	12287	4	0,03	0
7	42458	40127	0		0
8	158930	155331	0		0
9	105098	102484	0[b]		1[b]
10	34145	33321	3		1
11	16968	16314	1		0
12	77969	76264	3		1
13	69476	67725	1		1
14	23905	23356	0		0
15	7940	7724	0		0
Total	**665495**	**647659**	**67**	**0,01**	**6**

* Recall rate recorded only if ≥ 0,01% and n > 5;

[b] Recall was <36 h and is not listed here

3.2 Recall rate stratified according to time of primary screening

The number of positives, especially false positive screening results and therefore the recall rate, depends on age and gestational age. Earlier testing than the 36th hour of life and a gestational age of <32 weeks increases the risk of false negative and false positive results. This differs for the targeted diseases. In the following tables we stratify the recall rates by gestational age and timing of the sampling time. Recall rate is recorded only if it exceeds 0,01% and n > 5, since small numbers cause a big variability.

3.2.1 Hypothyroidism

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WOG		
Laboratory	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate
1	47163	36	0,08	1239	13	1,05	605	1	
3	14779	5	0,03	252	0		164	0	
5	50784	153	0,30	321	2		495	1	
6	12287	8	0,07	328	0		189	1	
7	40127	39	0,10	1594	51	3,20	737	0	
8	155331	190	0,12	1683	190	11,29	1916	9	0,47
9	102484	50	0,05	1234	3		1380	3	
10	33321	14	0,04	424	31	7,31	400	0	
11	16314	9	0,06	443	40	9,03	211	1	
12	76264	33	0,04	856	36	4,21	849	2	
13	67725	39	0,06	889	32	3,60	862	1	
14	23356	13	0,06	329	6	1,82	220	0	
15	7724	3		131	3		85	0	
Total	**647659**	**592**	**0,09**	**9723**	**407**	**4,19**	**8113**	**19**	**0,23**

3.2.2 Congenital adrenal hyperplasia (CAH)

Laboratory	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WOG		
	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate
1	47163	155	0,33	1239	49	3,95	605	57	9,42
3	14779	36	0,24	252	1		164	0	
5	50784	253	0,50	321	4		495	23	4,65
6	12287	92	0,75	328	0		189	1	
7	40127	228	0,57	1594	30	1,88	737	220	29,85
8	155331	37	0,02	1683	214	12,72	1916	23	1,20
9	102484	211	0,21	1234	6	0,49	1380	69	5,00
10	33321	143	0,43	424	69	16,27	400	28	7,00
11	16314	26	0,16	443	8	1,81	211	4	
12	76264	399	0,52	856	17	1,99	849	86	10,13
13	67725	227	0,34	889	38	4,27	862	12	1,39
14	23356	53	0,23	329	2		220	6	2,73
15	7724	23	0,30	131	1		85	5	
Total	**647659**	**1883**	**0,29**	**9723**	**439**	**4,52**	**8113**	**534**	**6,58**

3.2.3 Biotinidase Deficiency

Laboratory	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WOG		
	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate*	Primary screening	Recall	Recall-rate*
1	47163	11	0,02	1239	2		605	1	
3	14779	6	0,04	252	0		164	0	
5	50784	2		321	0		495	0	
6	12287	9	0,07	328	0		189	0	
7	40127	9	0,02	1594	2		737	1	
8	155331	75	0,05	1683	4		1916	5	
9	102484	7	0,01	1234	0		1380	1	
10	33321	4		424	0		400	1	
11	16314	2		443	0		211	0	
12	76264	12	0,02	856	1		849	1	
13	67725	17	0,03	889	1		862	0	
14	23356	8	0,03	329	0		220	0	
15	7724	0		131	1		85	0	
Total	**647659**	**162**	**0,03**	**9723**	**11**	**0,11**	**8113**	**10**	**0,12**

3.2.4 Galactosaemia

Laboratory	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WOG		
	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate*
1	47163	115	0,24	1239	0		605	0	
3	14779	8	0,05	252	0		164	0	
5	50784	55	0,11	321	0		495	0	
6	12287	6	0,05	328	0		189	0	
7	40127	37	0,09	1594	0		737	0	
8	155331	42	0,03	1683	0		1916	0	
9	102484	11	0,01	1234	1		1380	0	
10	33321	7	0,02	424	3		400	0	
11	16314	2		443	0		211	0	
12	76264	97	0,13	856	1		849	1	
13	67725	98	0,14	889	0		862	0	
14	23356	36	0,15	329	0		220	1	
15	7724	28	0,36	131	0		85	1	
Total	**647659**	**542**	**0,08**	**9723**	**5**	**0,05**	**8113**	**3**	**0,04**

3.2.5 PKU/HPA

Laboratory	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WOG		
	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate
1	47163	82	0,17	1239	16	1,29	605	12	1,98
3	14779	6	0,04	252	0		164	0	
5	50784	13	0,03	321	0		495	0	
6	12287	3		328	1		189	0	
7	40127	20	0,05	1594	0		737	9	1,22
8	155331	26	0,02	1683	1		1916	2	
9	102484	33	0,03	1234	1		1380	1	
10	33321	5		424	0		400	2	
11	16314	4		443	0		211	0	
12	76264	27	0,04	856	0		849	1	
13	67725	17	0,03	889	0		862	0	
14	23356	11	0,05	329	1		220	2	
15	7724	4		131	0		85	2	
Total	**647659**	**251**	**0,04**	**9723**	**20**	**0,21**	**8113**	**31**	**0,38**

3.2.6 MSUD

Laboratory	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WOG		
	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate*	Primary screening	Recall	Recall-rate*
1	47163	21	0,04	1239	0		605	2	
3	14779	6	0,04	252	0		164	0	
5	50784	10	0,02	321	2		495	0	
6	12287	2		328	0		189	0	
7	40127	6	0,01	1594	0		737	1	
8	155331	2		1683	0		1916	0	
9	102484	11	0,01	1234	0		1380	0	
10	33321	0		424	0		400	0	
11	16314	0		443	0		211	0	
12	76264	3		856	0		849	0	
13	67725	1		889	0		862	0	
14	23356	0		329	0		220	0	
15	7724	0		131	0		85	0	
Total	**647659**	**62**	**0,01**	**9723**	**2**	**0,02**	**8113**	**3**	**0,04**

3.2.7 MCAD-Disease

Laboratory	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WOG		
	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate*	Primary screening	Recall	Recall-rate*
1	47163	52	0,11	1239	0		605	0	
3	14779	2		252	0		164	0	
5	50784	45	0,09	321	0		495	0	
6	12287	3		328	0		189	0	
7	40127	13	0,03	1594	0		737	0	
8	155331	17	0,01	1683	1		1916	1	
9	102484	23	0,02	1234	0		1380	0	
10	33321	5		424	0		400	2	
11	16314	3		443	0		211	0	
12	76264	6	0,01	856	1		849	0	
13	67725	9	0,01	889	0		862	0	
14	23356	5		329	0		220	0	
15	7724	1		131	0		85	0	
Total	**647659**	**184**	**0,03**	**9723**	**2**	**0,02**	**8113**	**3**	**0,04**

3.2.8 LCHAD-Disease

Laboratory	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WOG		
	Primary screening	Recall	Recall-rate*	Primary screening	Recall	Recall-rate*	Primary screening	Recall	Recall-rate
1	47163	7		1239	0		605	0	
3	14779	0		252	0		164	0	
5	50784	1		321	0		495	0	
6	12287	0		328	0		189	0	
7	40127	1		1594	0		737	0	
8	155331	3		1683	1		1916	0	
9	102484	4		1234	0		1380	0	
10	33321	0		424	0		400	0	
11	16314	0		443	0		211	0	
12	76264	0		856	0		849	0	
13	67725	0		889	0		862	0	
14	23356	0		329	0		220	0	
15	7724	0		131	0		85	0	
Total	**647659**	**16**	**0,002**	**9723**	**1**	**0,01**	**8113**	**0**	

* Recallrate due to small numbers only in absolute

3.2.9 VLCAD-Disease

Laboratory	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WOG		
	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate
1	47163	32	0,07	1239	0		605	6	0,99
3	14779	6	0,04	252	0		164	0	
5	50784	12	0,02	321	0		495	4	
6	12287	4		328	0		189	0	
7	40127	18	0,04	1594	0		737	0	
8	155331	0		1683	1		1916	0	
9	102484	19	0,02	1234	0		1380	0	
10	33321	1		424	1		400	0	
11	16314	1		443	1		211	0	
12	76264	16	0,02	856	0		849	0	
13*	67725	2		889	0		862	0	
14	23356	0		329	0		220	0	
15	7724	1		131	0		85	0	
Total	**647659**	**112**	**0,02**	**9723**	**3**	**0,03**	**8113**	**10**	**0,12**

3.2.10 CPTI-Disease

Laboratory	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WOG		
	Primary screening	Recall	Recall-rate*	Primary screening	Recall	Recall-rate*	Primary screening	Recall	Recall-rate*
1	47163	0		1239	0		605	2	
3	14779	0		252	0		164	0	
5	50784	2		321	0		495	0	
6	12287	3		328	0		189	0	
7	40127	0		1594	0		737	0	
8	155331	0		1683	1		1916	0	
9	102484	1		1234	0		1380	0	
10	33321	0		424	0		400	0	
11	16314	0		443	0		211	0	
12	76264	1		856	0		849	0	
13	67725	2		889	0		862	1	
14	23356	0		329	0		220	0	
15	7724	0		131	0		85	0	
Total	**647659**	**9**	**0,001**	**9723**	**1**	**0,01**	**8113**	**3**	**0,04**

* Recallrate due to small numbers only in absolute

3.2.11 CPTII-Disease/CACT-Disease

Laboratory	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WOG		
	Primary screening	Recall	Recall-rate*	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate
1	47163	0		1239	0		605	0	
3	14779	0		252	0		164	0	
5	50784	1		321	0		495	0	
6	12287	0		328	0		189	0	
7	40127	0		1594	0		737	0	
8	155331	1		1683	0		1916	0	
9	102484	0		1234	0		1380	0	
10	33321	2		424	0		400	0	
11	16314	0		443	0		211	0	
12	76264	1		856	0		849	0	
13	67725	0		889	0		862	0	
14	23356	0		329	0		220	0	
15	7724	0		131	0		85	0	
Total	**647659**	**5**	**0,001**	**9723**	**0**		**8113**	**0**	

* Recallrate due to small numbers only in absolute

3.2.12 Glutaric acidaemia Type I

Laboratory	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WOG		
	Primary screening	Recall	Recall-rate*	Primary screening	Recall	Recall-rate*	Primary screening	Recall	Recall-rate*
1	47163	9		1239	1		605	0	
3	14779	3		252	0		164	0	
5	50784	166	0,33	321	3		495	7	1,41
6	12287	9		328	0		189	0	
7	40127	44	0,11	1594	0		737	1	
8	155331	1		1683	0		1916	0	
9	102484	12	0,01	1234	0		1380	2	
10	33321	0		424	0		400	0	
11	16314	0		443	0		211	0	
12	76264	5		856	0		849	0	
13	67725	4		889	0		862	0	
14	23356	0		329	0		220	0	
15	7724	0		131	0		85	0	
Total	**647659**	**253**	**0,04**	**9723**	**4**	**0,04**	**8113**	**10**	**0,12**

3.2.13 Isovaleric acidaemia

Laboratory	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WOG		
	Primary screening	Recall	Recall-rate	Primary screening	Recall	Recall-rate*	Primary screening	Recall	Recall-rate*
1	47163	45	0,10	1239	2		605	16	2,64
3	14779	1		252	0		164	0	
5	50784	9	0,02	321	1		495	2	
6	12287	4		328	0		189	1	
7	40127	0		1594	0		737	0	
8	155331	0		1683	0		1916	0	
9	102484	0		1234	1		1380	0	
10	33321	3		424	0		400	0	
11	16314	1		443	0		211	0	
12	76264	3		856	0		849	0	
13	67725	1		889	0		862	0	
14	23356	0		329	0		220	0	
15	7724	0		131	0		85	0	
Total	**647659**	**67**	**0,01**	**9723**	**4**	**0,04**	**8113**	**19**	**0,23**

4 Process Periods

4.1 Age at blood collection

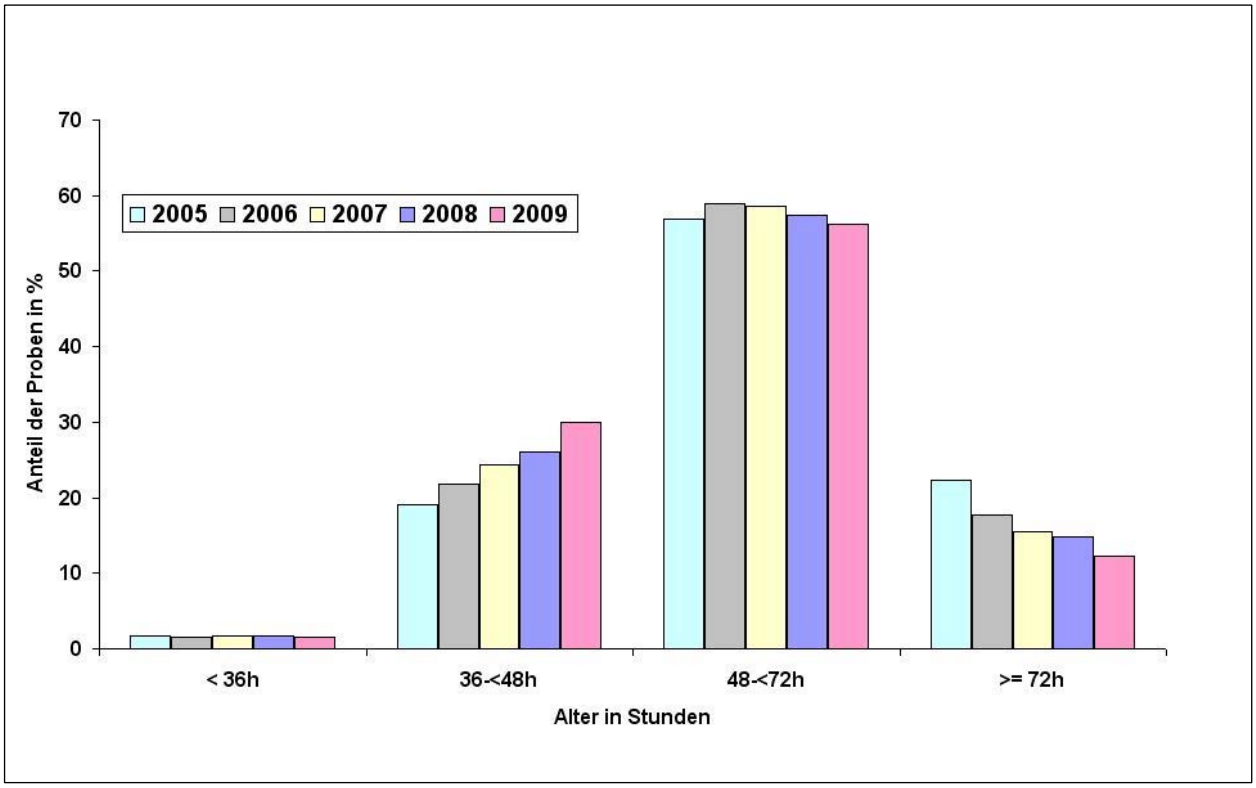
According to the guidelines (Kinderrichtlinien, section 8, paragraph 1) the sampling should be performed between the 36th and 72nd hour of life. In 86,17% of cases, with specification of collection time, the collection was according to the guidelines, in 12,28% (5,03-19,19%) beyond the 72nd hour of life, in 1,55% (0.69-2,79%) before the 36th hour of life (see Table 4.1). The proportion of samples which were sampled after 72 hours could be lowered from 22,25% in 2005 to 12,28% in 2009 (see figure 2), meaning a significant improvement in process quality, as the adherence to the optimal sampling time improves the efficacy of screening. Life threatening metabolic or electrolyte crisis can be prevented by early diagnosis and therapy.

Table 4.1: Age at blood collection, primary screening

Lab.	Total	<36h		36h-<48h		48h-<72h		≥72h	
	n	n	%	n	%	n	%	n	%
1[a]	48897	1325	2,71	8376	17,13	30866	63,12	8330	17,04
3	15195	275	1,81	2262	14,89	11812	77,74	846	5,57
5[a]	51573	355	,69	29322	56,86	19300	37,42	2596	5,03
6	12804	346	2,70	2993	23,38	8182	63,90	1283	10,02
7[b]	43146	1063	2,46	10541	24,43	23732	55,00	7810	18,10
8[a]	146039	1874	1,28	53280	36,48	75117	51,44	15768	10,80
9[a]	105090	1346	1,28	18502	17,61	65071	61,92	20171	19,19
10[a]	34144	438	1,28	7933	23,23	21616	63,31	4157	12,17
11[a]	16964	473	2,79	3709	21,86	11470	67,61	1312	7,73
12[a]	75295	913	1,21	25450	33,80	40871	54,28	8061	10,71
13[a]	69533	1227	1,76	21262	30,58	40810	58,69	6234	8,97
14[a]	23225	313	1,35	8346	35,94	12311	53,01	2255	9,71
15	7940	134	1,69	2720	34,26	4119	51,88	967	12,18
Total	**649845**	**10082**	**1,55**	**194696**	**29,96**	**365277**	**56,21**	**79790**	**12,28**

The number of samples with unrecorded sampling time is smaller than the totally primary screening (marked with [a]). In other laboratories the number of samples with recorded sampling time exceeds the totally primary screening, an explanation could be the consideration of unidentified secondary screening cards (marked with [b])

Figure 2: Comparison: Age at blood collection 2005 and 2009



4.2 Period from sampling to laboratory receipt

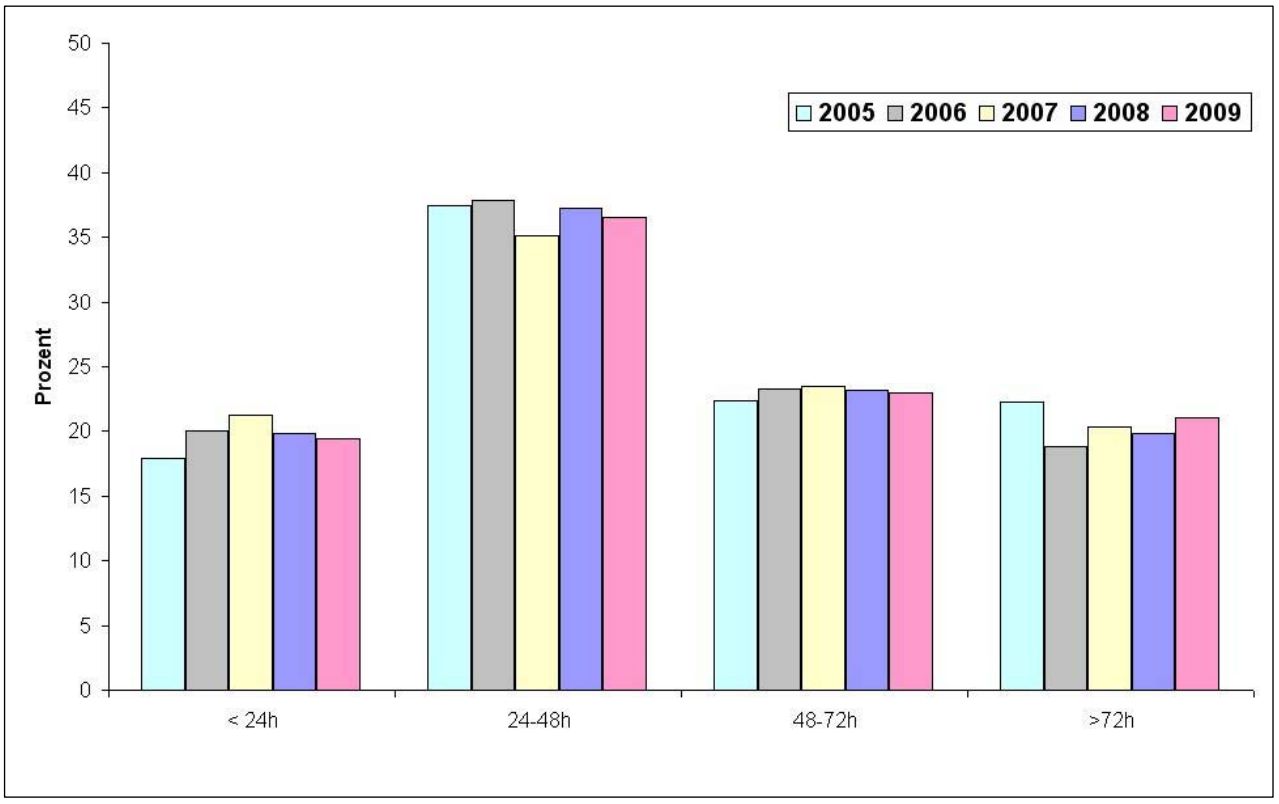
The time span between sampling and conveyance of suspect results should not exceed 72 hours (section 6, paragraph 3). In 21,08% (3,89-36,75%) of cases with statement of the delivery time the probe was received after 72 hours of sampling. In further 22,96% (10,75-26,78%) of the cases a period between 48 and 72 hours. Shorter periods of delivery times are desirable, especially on the weekends. (Table 4.2, figure 3)

Table 4.2: Period between sampling and laboratory receipt

Laboratory	Total	≤24h		>24h-48h		>48h-72h		>72h	
	n	N	%	n	%	n	%	n	%
1[a]	48882	12625	25,83	18995	38,86	9893	20,24	7369	15,08
3	15195	3083	20,29	6294	41,42	3806	25,05	2012	13,24
5[a]	51569	6539	12,68	24119	46,77	13360	25,91	7551	14,64
6	12804	1878	14,67	5284	41,27	3134	24,48	2508	19,59
7[b]	43146	10003	23,18	13571	31,45	8422	19,52	11150	25,84
8[a]	149520	18880	12,63	54028	36,13	38768	25,93	37844	25,31
9[a]	105091	7499	7,14	33270	31,66	27889	26,54	36433	34,67
10	34145	4570	13,38	12189	35,70	9144	26,78	8242	24,14
11[a]	16964	2682	15,81	7849	46,27	4328	25,51	2105	12,41
12[a]	75647	26679	35,27	27051	35,76	13704	18,12	8213	10,86
13[b]	69533	18468	26,56	27389	39,39	13094	18,83	10582	15,22
14[a]	23319	13736	58,90	6169	26,45	2506	10,75	908	3,89
15	7940	197	2,48	2785	35,08	2040	25,69	2918	36,75
Total	**653755**	**126839**	**19,40**	**238993**	**36,56**	**150088**	**22,96**	**137835**	**21,08**

The number of samples with unrecorded sampling time is smaller than the totally primary screening (marked with [a]). In other laboratories the number of samples with recorded sampling time exceeds the totally primary screening, an explanation could be the consideration of unidentified secondary screening cards (marked with [b])

Figure 3: Period between sampling and laboratory receipt: Comparison 2005 to 2009



4.3 Period between laboratory receipt and conveyance

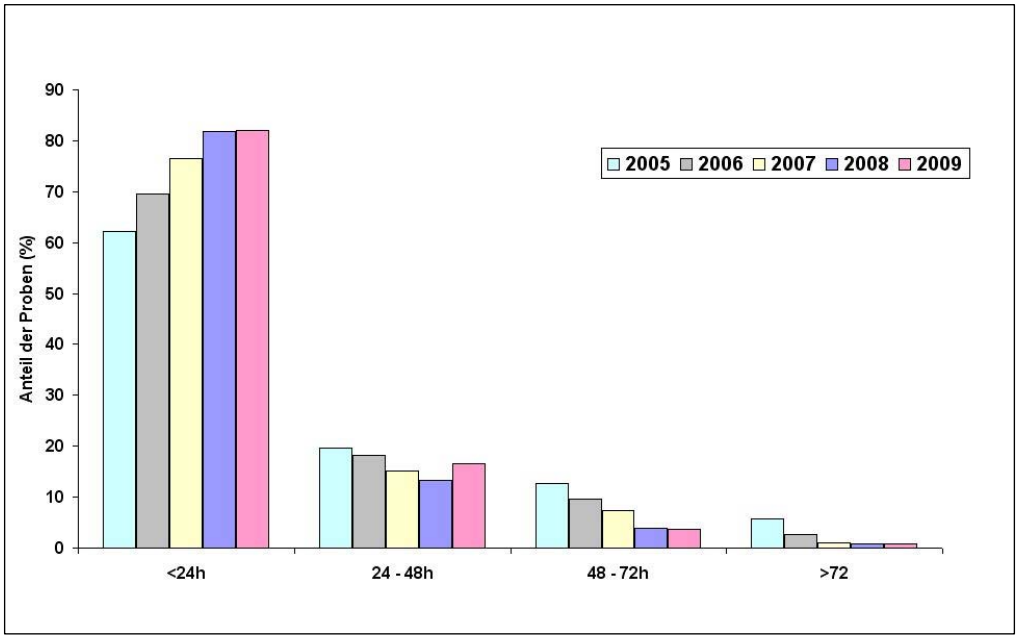
According to §14 paragraph 3 analysis, as well as reporting suspicious results of the screening card have to be conducted on the same day as receipt. Generally suspicious results are firstly notified by telephone or fax (Table 4.3). This standard is met in more than three quarters of screening. The process time in borderline elevated results can be prolonged due to repeat testing (quality control) (Table 4.3, figure 4)

Table 4.3 Period between laboratory receipt and conveyance

Lab	Total	≤24h		>24h-48h		>48h-72h		>72h	
	n	N	%	n	%	n	%	n	%
1[a]	49005	30260	61,75	14410	29,41	3346	6,83	989	2,02
3	15195	8695	57,22	5319	35,00	697	4,59	484	3,19
5[a]	51760	32322	62,45	11391	22,01	7578	14,64	469	0,91
8	158930	150936	94,97	7050	4,44	298	0,19	646	0,41
9[a]	105022	98900	94,17	4993	4,75	632	0,60	497	0,47
10	34145	29292	85,79	4264	12,49	487	1,43	102	0,30
11	16968	11008	64,88	5609	33,06	351	2,07	0	
12[a]	76445	60041	78,54	11438	14,96	4534	5,93	432	0,57
13[b]	69533	56013	80,56	9757	14,03	2882	4,14	881	1,27
14[a]	23312	22913	98,29	392	1,68	6	0,03	1	0,004
15	7941	7779	97,96	160	2,01	2	0,03	0	
Total	**608256**	**508159**	**83,54**	**74783**	**12,29**	**20813**	**3,42**	**4956**	**0,74**

The number of samples with unrecorded sampling time is smaller than the totally primary screening (marked with [a]). In other laboratories the number of samples with recorded sampling time exceeds the totally primary screening, an explanation could be the consideration of unidentified secondary screening cards (marked with [b]). Listed are only laboratories which provide data.

Figure : Period from laboratory receipt to conveyance, comparison of 2005 to 2008



5 Time of screening in the confirmed cases

5.1 Primary Screening

Crucial for successful screening are the reliability of results and the promptness of further diagnostic evaluation and therapy in suspect cases. The optimal sampling time is the 48th to the 72nd hour of life. The probe should not be sampled before the 36th and not after the 72nd hour of life. Any delay means a potential risk for affected children.

The time of primary screening is shown for the targeted disease in Table 5.1. For clarity reasons the description >72 hours of age is reported in days. About 10% of diseased children were at the time of sampling older than 72 hours.

Table 5.1 Time of primary screening in confirmed cases

Disease	36-72h	4-7d	>7d	<36h	<32WOG	≥36h, n.s. Time *	No information**	Total
Hypothyroidism	153	21		6	12		3	**195**
AGS	31	2		3	2			**38**
Biotinidase	25	5		2		1		**33**
classic Galactosaemia	4	1		1				**6**
PKU/HPA	106	8		1	4	1	3	**123**
MSUD	4							**4**
MCAD	59	9	1	2	2		1	**74**
LCHAD	2	1						**3**
VLCAD	7							**7**
GA I	4							**4**
IVA	4	1		1				**6**
Total	**399**	**48**	**1**	**16**	**20**	**2**	**7**	**493**

*≥ 36h n.s. does not include repeat testing with early sampling or preterm birth, but exact age of sampling time not stated.
** No information, neither WOG nor age at sampling.

5.2 Indication for request of repeat testing in the confirmed cases.

An indication for a second screening could be early sampling before the 32nd week of pregnancy or before the 36th hour of life, even in children with confirmed diagnosis. In Table 6.2 the indications for repeat testing are shown.

Table 5.2 : Indication for request of repeat testing in the confirmed cases

	Indication for repeat screening				
Disease	suspicoius Primary screening	< 36h	<32WOG	n.s.	Total
Hypothyroidism	174	6[a]	12[b]	3	**195**
AGS	33	3	2		**38**
Biotinidase	31	2			**33**
classic Galactosaemia	5	1			**6**
PKU/HPA	115	1	4	3	**123**
MSUD	4				**4**
MCAD	69	2	2	1	**74**
LCHAD	3				**3**
VLCAD	7				**7**
GA I	4				**4**
IVA	5	1			**6**
Total	**450**	**16**	**20**	**7**	**493**

[a] n=1 TSH < 10 mU/l, Time of sampling 35 hours of life
[b] n=4 TSH <10 mU/l Premature births 24, 26, 28 u. 29 WOG;
n=2 TSH < 10 mU/l, Decrease in Catecholamine therapy;
n=1 TSH <10 mU/l, Decrease after Transfusion.

6 Confirmation of pathological results

The following chapter outlines the diagnostic measures for confirmation of the suspected diagnosis as known to the laboratories. This information is used for quality control by the individual laboratories; unfortunately feedback by the Clinicians is not always warranted. For the year 2009 in 24 out of 493 confirmed cases no detailed information about the confirmation diagnostics is available, the available data though allows a plausible analysis. In a further 32 cases only limited information is given, that confirmation can not be accepted and we therefore do not list it in our analysis.

6.1 Hypothyroidism

Laboratory	Confirmed cases*	TSH (Serum)	T3	fT3	T4	fT4	ultrasound	Thyroid antibodies
1	24	24	13	n.s.	12	24	23	10
3	2	1	1	n.s.	n.s.	1	n.s.	n.s.
5	11	11	1	8	n.s.	11	10	4
6	6	6	n.s.	6	n.s.	6	4	4
7	11	8	2	3	n.s.	6	6	4
8	52	47	3	41	1	50	45	31
9	35	34	16	18	19	34	4	1
10	5	5	n.s.	4	n.s.	5	4	3
11	5	5	n.s.	3	n.s.	4	3	n.s.
12	17	17	1	12	1	15	11	9
13	18	18	n.s.	n.s.	n.s.	17	1	1
14	8	8	2	6	1	7	3	4
15	1	n.s.	n.s.	1	n.s.	1	1	1
Total	**195**	**184**	**39**	**102**	**34**	**181**	**115**	**72**

*incl n=3 cases without detailed information of confirmation diagnostics

6.2 Congenital adrenal hyperplasia (CAH)

Laboratory	Confirmed Cases*	17-OHP (Serum)	Serum-steroids	Urinary steroids	Molecular genetic testing
1	2	2	2	n.s.	2
3	2	1	n.s.	n.s.	n.s.
6	2	2	2	n.s.	2
7	2	n.s.	n.s.	n.s.	2
8	14	8	12	4	13
9	3	2	2	n.s.	1
11	1	1	1	n.s.	n.s.
12	5	3	4	2	4
13	6	2	2	n.s.	3
14	1	1	1	n.s.	1
Total	**38**	**22**	**26**	**6**	**28**

* incl n=4 cases without detailed information of confirmation diagnostics

6.3 Biotinidase Deficiency

Laboratory	Confirmed cases*	Serum Biotinidase	Molecular genetic testing
1	2	2	n.s.
3	1	1	n.s.
5	1	n.s.	n.s.
6	1	n.s.	n.s.
7	1	1	1
8	21	20	n.s.
9	2	1	n.s.
10	1	1	n.s.
12	1	1	1
13	2	n.s.	n.s.
Total	**33**	**27**	**2**

* incl n=6 cases without detailed information of confirmation diagnostics

6.4 Classic Galactosaemia

Laboratory	Confirmed cases	Red cell GALT	Molecular genetic testing
1	1	1	n.s.
5	2	1	2
6	1	1	n.s.
8	1	n.s.	1
12	1	1	1
Total	**6**	**4**	**4**

6.5 PKU / HPA

Laboratory	Confirmed cases*	Phe (Serum)	Phe/Tyr	BH4-Test	BH4 sensitive	Molecular genetic testing	Pterine im Urine	DHPR in dried blood
1	12	12	n.s.	5	1	11	12	12
3	2	2	2	2	1	n.s.	n.s.	n.s.
5	5	5	5	5	3	n.s.	5	5
6	2	1	2	1	1	n.s.	1	1
7	4	3	3	3	n.s.	1	4	4
8	24	14	10	12	3	6	19	19
9	28	15	20	6	1	2	19	19
10	5	2	4	4	n.s.	2	3	3
11	4	2	3	3	n.s.	n.s.	3	3
12	17	13	3	14	5	2	14	10
13	17	n.s.	n.s.	11	n.s.	n.s.	15	15
14	3	2	n.s.	3	1	n.s.	3	2
Total	**123**	**71**	**52**	**69**	**16**	**24**	**98**	**93**

* incl n=4 cases without detailed information of confirmation diagnostics

6.6 MSUD

Laboratory	Confirmed cases	Confirmation Serum	Urinary organic acids	Enzyme activity	Molecular genetic testing
1	1	1	1	n.s.	n.s.
7	1	1	1	n.s.	n.s.
8	1	1	n.s.	n.s.	n.s.
13	1	1	n.s.	n.s.	n.s.
Total	**4**	**4**	**2**	**n.s.**	**n.s.**

6.7 MCAD-Disease

Laboratory	Confirmed cases*	Confirmation Serum	Urinary organic acids	Enzyme activity	Molecular genetic testing
1	1	1	1	1	1
5	6	n.s.	1	n.s.	5
6	1	n.s.	1	n.s.	1
7	8	n.s.	5	1	5
8	16	13	7	1	14
9	12	12	9	n.s.	4
10	4	4	4	n.s.	3
11	3	3	3	n.s.	1
12	8	7	4	n.s.	8
13	14	n.s.	n.s.	3	11
15	1	n.s.	n.s.	n.s.	1
Total	**74**	**40**	**35**	**6**	**54**

* incl n=7 cases without detailed information of confirmation diagnostics

6.8 LCHAD-Disease

Laboratory	Confirmed cases	Confirmation Serum	Urinary organic acids	Enzyme activity	Molecular genetic testing
8	2	2	1	2	n.s.
9	1	1	n.s.	n.s.	n.s.
Total	**3**	**3**	**1**	**2**	**n.s.**

6.9 VLCAD-Disease

Laboratory	Confirmed cases	Confirmation Serum	Urinary organic acids	Enzyme activity	Molecular genetic testing
9	2	2	2	1	n.s.
12	3	3	n.s.	2	2
13	2	n.s.	n.s.	2	2
Total	**7**	**5**	**2**	**5**	**4**

6.10 No confirmed cases of CPT I-deficiency, CPT II- deficiency, CACT- deficiency

6.11 Glutaric acidaemia Type I

Laboratory	Confirmed cases	Confirmation Serum	Urinary organic acids	Enzyme activity	Molecular genetic testing
7	1	n.s.	1	1	1
9	3	3	3	n.s.	n.s.
Total	**4**	**3**	**4**	**1**	**1**

6.12 Isovaleric acidaemia

Laboratory	Confirmed cases	Confirmation Serum	Urinary organic acids	Enzyme activity	Molecular genetic testing
1	2	2	2	n.s.	n.s.
9	1	1	1	n.s.	n.s.
10	1	1	n.s.	n.s.	n.s.
12	1	1	1	n.s.	n.s.
13	1	n.s.	1	n.s.	n.s.
Total	**6**	**5**	**5**	**n.s.**	**n.s.**

7 Methods and cut offs in screening

7.1 Filter paper for sampling

Laboratory	Filterpaper
1	ID Biological (Ahlstrom 226)
3	other
5	other
6	ID Biological (Ahlstrom 226)
7	WS 903
8	TFN (Munktell)
9	WS 903
10	WS 903
11	WS 903
12	Macherey and Nagel
13	Macherey and Nagel
14	WS 903
15	WS 903

7.2 Hypothyroidism

Laboratory	Parameter	Cutoff	Method
1	TSH	15 mU/l	AutoDELFIA
3	TSH	15 mU/l	AutoDELFIA
5	TSH	13 mU/l	AutoDELFIA
6	TSH	15 mU/l	DELFIA
7	TSH	15 nmol/l	AutoDELFIA
8	TSH	> 15 mU/l	DELFIA
9	TSH	15 mU/l	AutoDELFIA
10	TSH	15 mU/l	AutoDELFIA
11	TSH	15 mU/l	DELFIA
12	TSH	>20 mU/l	AutoDELFIA
13	TSH	>20 mU/l	AutoDELFIA
14	TSH	> 20 mU/l	AutoDELFIA
15	TSH	> 20 mU/l	AutoDELFIA

7.3 Biotinidase Deficiency

Laboratory	Parameter	Cutoff	Method
1	Biotinidase	30% board mean	Colorimetrie qualitative
3	Biotinidase	30 % day mean	Colorimetrie qualitative
5	Biotinidase	n.s.	n.s.
6	Biotinidase	70 U	Flurometrie (PE)
7	Biotinidase	2,7 U/g Hb	Colorimetrie quantitative
8	Biotinidase	< 30% day mean	Colorimetrie quantitative
9	Biotinidase	< 30%	Colorimetrie qualitative
10	Biotinidase	< 30%	Colorimetrie qualitative
11	Biotinidase	n.s.	Colorimetrie qualitative
12	Biotinidase	< 30%	Fluorometrie quantitative
13	Biotinidase	< 30%	Fluorometrie quantitative
14	Biotinidase	< 30 %	Colorimetrie quantitative
15	Biotinidase	< 30 %	Colorimetrie quantitative

7.4 Galactosaemia

Laboratory	Parameter	Cutoff	Method
1	GALT Galactose	3,5 U/gHb 15 mg/dl	Fluorometrie(PE) BIORAD Quantase
3	GALT Galactose	2,3 Ug/Hb 15 mg/dl	BIORAD Quantase
5	GALT Galactose	n.s.	n.s.
6	GALT	3,5 U/g Hb	Fluorometrie (PE)
7	GALT	3,5 U/g Hb	Fluorometrie quantitativ
8	GALT Galactose	<20 % Tagesmittel >30mg/dl	Fluorometrie quantitativ Colorimetrie quatitativ
9	GALT Galactose*	<2,3 U/gHb 20 mg/dl	BIORAD Quantase BIORAD Quantase
10	GALT Galactose	2,3 U/gHb 1111 µmol/l	BIORAD Quantase BIORAD Quantase
11	GALT	3,5 U/gHb	Fluorometrie quantitativ
12	GALT Galactose	< 30% 15 mg/dl	Fluoro. quant.(non-kit) Colorimetrie non Kit
13	GALT Galactose	< 30% 15 mg/dl	Fluoro. quant.(non-kit) Colorimetrie non Kit
14	GALT Galactose	<2,3 U/g Hb >15 mg/dl	BIORAD Quantase BIORAD Quantase
15	GALT Galactose	<2,3 U/g Hb >15 mg/dl	BIORAD Quantase BIORAD Quantase

* galactose as second-tier process

7.5 MS/MS

Laboratory	Method
1	derivative Chromsystems
3	non-derivat. non Kit
5	non-derivat. non Kit
6	non-derivat. PE Kit
7	derivative PE Kit
8	derivative non Kit
9	derivative non Kit
10	derivative non Kit
11	non-derivat. non Kit
12	derivative non Kit
13	derivative non Kit
14	derivative non Kit
15	derivative non Kit

7.6 Congenital adrenal hyperplasia (CAH)

Term babies

Laboratory	Parameter	Method	Dependent on age	Dependent on WOG	Dependent on BW	Formula	Constant value
1	17 OHP	AutoDELFIA	yes			ln(OHP)=2,90798-0,40653ln(age)	
3	17 OHP	AutoDELFIA	yes			ln (OHP) = 1,868 - 0,374(ln age	
5	17 OHP	AutoDELFIA		yes		Value from B 24-112	
6	17 OHP	DELFIA	yes				
7	17 OHP	AutoDELFIA					30
8*	17 OHP	DELFIA	yes				
9	17 OHP	AutoDELFIA		yes			
10	17 OHP	AutoDELFIA	yes				
11	17 OHP	DELFIA	yes				
12	17 OHP	AutoDELFIA	yes		yes		
13	17 OHP	AutoDELFIA	yes		yes		
14	17 OHP	AutoDELFIA	yes		yes		
15	17 OHP	AutoDELFIA	yes		yes		

*Laboratory 8: with raised Delfia 17OHP TMS Steroidprofil with 17OHP, 21-Desoxycortisol, 11-Desoxycortisol, Cortisol and Androstendion.

Preterm babies

Laboratory	Parameter	Method	Dependent on age	Dependent on WOG	Dependent on BW	Formula	Constant value
1	17 OHP	AutoDELFIA	yes	yes		ln(OHP)=3,470-0,121ln(tage)	
3	17 OHP	AutoDELFIA	yes	yes		ln (OHP) = -118,7 + 75,164(corrected GA)) -11,564(ln(corr GA)²)	
5	17 OHP	AutoDELFIA		yes		Before discharge, analogue 36-38 WOG	
6	17 OHP	DELFIA	yes	yes			
7	17 OHP	AutoDELFIA			yes		
8*	17 OHP	DELFIA	yes	yes	yes		
9	17 OHP	AutoDELFIA		yes			
10	17 OHP	AutoDELFIA	yes	yes			
11	17 OHP	DELFIA	yes	yes			
12	17 OHP	AutoDELFIA	yes		yes		
13	17 OHP	AutoDELFIA	yes		yes		
14	17 OHP	AutoDELFIA		yes			
15	17 OHP	AutoDELFIA		yes			

* Laboratory 8: with raised Delfia 17OHP TMS steroidprofile with 17-OHP, 21-Desoxycortisol, 11-Desoxycortisol, Cortisol and Androstendion.

7.7 MS/MS Parameter

Guide (GV) and secondary (SP) parameters are listed. If the laboratory has given the cut off value for their guide value, it is taken as a guide value. Laboratory 12 accounts for laboratory 12 and 13 (one lab) and laboratory 14 accounts for laboratory 14 and 15 (one lab)

Remarks to testing for parameters in MS/MS

Laboratory	note
3	Half yearly actualisation of cutoff values dependent on kit charge and machine status on the base of all results > 32. WOG and > 36 hours of life
6	All cutoffs calculated from percentiles and are therefore dynamic

7.7.1 PKU

Parameter /Cut off	1	3	5	6	7	8	9	10	11	12	14
Phe	112	120	150	144	139	151	123	150	123	120	129
Tyr								NW		NW	NW
Phe/Tyr	NW	NW	NW	NW	2,5	2,5	NW	NW	2,0	2,0	NW

7.7.2 MSUD

Parameter / Cut off	1	3	5	6	7	8	9	10	11	12[b]	14
Ala				NW				NW		LW	
Val	NW	NW	NW	291	280	NW	NW	NW	185	LW	NW
Leu/Ile	294	310	z ≥ 3,5[a]	340	300	400	299	314	289	LW	350
Fischer-Q	NW	4,0		NW					3,3	LW	3
Leu/Ile:Phe	NW		z ≥ 3,5[a]			10		NW		LW	NW
Val/Phe			NW					NW		LW	NW
Leulle/Ala	NW	NW	z ≥ 3,5[a]	NW			NW	NW	NW	LW	

[a] z ≥ 3,5 means: measured value ≥ mean + z-mal SD

[b] Multi analyte pattern recognition

7.7.3 MCAD-Disease

Parameter / Cut off	1	3	5	6	7	8	9	10	11	12[b]	14
C0								NW			
C6	NW	NW	NW	NW	0,18	NW	NW	NW	NW	LW	NW
C8	0,18	0,32	z ≥ 3,5[a]	0,388	0,4	0,2	0,28	0,3	0,24	LW	0,34
C8/C10	NW	4,0	NW	NW		2,5	NW	NW	2,0	LW	NW
C8/C12	NW		NW	NW		5	NW		NW	LW	
C8/C16					NW			NW		LW	
C10	NW	NW	NW	NW		NW	NW	NW	NW	LW	NW
C10:1	NW	NW	NW	NW	0,15	NW	NW	NW	0,11	LW	NW
C8/C2	NW			NW		0,02	NW				NW
C8/C6			NW							LW	

[a] z ≥ 3,5 means: measured value ≥ mean + 3,5
[b] Multi analyte pattern recognition

7.7.4 LCHAD-Disease

Parameter / Cut off	1	3[a]	5	6	7	8	9	10	11	12[b]	14
C0								NW			
C14:1			NW	NW		NW		NW		NW	
C14OH			NW	0,052			NW	NW	NW	LW	
C16OH	0,069	0,07	z ≥ 3,5	0,082	0,11	0,1	0,1	0,15	0,048	LW	0,60
C16:1OH			NW	NW			NW	NW		LW	NW
C18OH	0,027	NW		0,06	0,1	NW	0,07	NW	0,031	LW	NW
C18:1OH	0,033	NW	z ≥ 3,5	0,077	0,1	0,1	0,11	NW	0,042	LW	NW
C18:2OH						NW		NW			NW
C16OH/C16	NW	0,02	NW						0,018		

[a] Ratio C16OH/C16 at sampling > 7 d; [b] Multi analyte pattern recognition

7.7.5 VLCAD-Disease

Parameter / Cut off	1	3	5	6	7	8	9	10	11	12[a]	14
C0								NW			
C12			NW							LW	
C14	NW	NW	NW	NW	0,65	NW	NW	NW	0,459	LW	NW
C14:1	0,34	0,35	z ≥ 3,5	0,294	0,4	0,25	0,43	0,36	0,32	LW	0,25
C16:1		NW					NW	NW			
C14:2	NW	NW	NW	NW	NW	NW			0,048	LW	NW
C14:1/C16	NW	0,10	NW	NW					0,125		0,1
C14/C4								NW			NW
C14:1/C4			NW				NW	NW		LW	NW
C14:1/C12			NW								
C14:1/C12:1			NW			5,0					

[a] Multi analyte pattern recognition

7.7.6 CPT I-Disease

Parameter / Cut off	1	3	5	6	7	8	9	10	11	12[a]	14
C0	NW	5,7	NW	57,39	70	80	65,49	50	NW	NW	>70
C8											
C16	0,87	NW	NW	0,333	<0,6		LW	0,56	0,69	LW	<1
C18	0,23	NW	NW	0,137	<0,3		LW	0,21	0,2	LW	NW
C18:1	0,30			0,298				NW	0,315	LW	
C16/C2											
(C16+C18:1)/C2				NW							
C0/(C16+C18)	NW	1,3	≥ 70	NW		40	LW		19,3	LW	LW

[a] Multi analyte pattern recognition

7.7.7 CPT II-Disease

Parameter / Cut off	1	3	5	6	7	8	9	10	11	12[a]	14
AC ges								NW			
C0	NW	NW		4,6	<10			NW	5,1	NW	NW
C16	5,55	8,73	NW	8,819	8,0	8	7,65	8,83	7,5	LW	>6
C16:1					0,6		0,67	NW		LW	NW
C18	1,45			2,139	2,6		2,34	3,65	1,94	LW	>2,5
C18:1	2,22	2,76	NW	3,604	3,5	3,4	1,92	NW	3,27	LW	NW
(C16+C18:1)/C2	NW	NW	z ≥ 3,5	NW		0,3	NW	20,3	NW		
C18:2								NW		LW	
C16/C2			NW								
C0/(C16+C18)			NW	NW			NW	NW			

[a] Multi analyte pattern recognition

7.7.8 CACT-Disease

Parameter / Cut off	1	3	5	6	7	8	9	10	11	12[a]	14
AC ges								NW			
C0	NW	NW		NW	<10	<0,25		NW	5,1	LW	NW
C16	5,55	8,73	NW	8,819	8,0	8,0	6,85	8,83	7,5	LW	
C16:1							NW	NW		LW	>6
C18	1,45			2,139	2,6	2,5	2,34	2,65	1,94	LW	NW
C18:1	2,22	2,76	NW	3,604	3,5			3,9	3,27	LW	NW
(C16+C18:1)/C2	NW	NW	z ≥ 3,5	NW				NW	NW		
C18:2										LW	
C0/AC ges								NW			
C16/C2			z ≥ 3,5								
C0/(C16+C18)			NW	NW			NW	NW			
C0/(C16+C18:1)							NW	NW			

[a] Multi analyte pattern recognition

7.7.9 Glutaric acidaemia Type I

Parameter / Cut off	1	3	5	6	7	8	9	10	11	12[a]	14
C5DC (Glut)	0,26	0,5	z ≥ 0,13	0,778	0,33	0,20	0,17	0,25	0,45	LW	<0,15
C5DC/C0			NW	NW		0,005					
C5DC/C2										LW	
C5DC/C4				NW				NW		LW	
C5DC/C8		NW		NW	5,9		NW	NW			NW
C5DC/C12	NW	NW							NW	LW	
C5DC/C16	NW		NW	NW			NW	NW	NW	LW	NW
C5DC/(C8+C10)			NW								

[a] Multi analyte pattern recognition

7.7.10 Isovaleric acidaemia

Parameter / Cut off	1	3	5	6	7	8	9	10	11	12[a]	14
C0		NW						NW			
C5	0,36	0,5	z ≥ 3,5	0,6	1	0,5	0,63	0,6	0,57	LW	0,6
C5/C2			NW	NW		0,02	NW				
C5/C3								NW			NW
C5/C8	NW	NW	NW	NW	NW			NW	NW	LW	NW
C5/C4	NW	NW	NW	NW				NW	NW	LW	NW

[a] Multi analyte pattern recognition

Literature

1) Beschluss über eine Änderung der Richtlinien des Bundesausschusses der Ärzte und Krankenkassen über die Früherkennung von Krankheiten bei Kindern bis zur Vollendung des 6. Lebensjahres (Kinder-Richtlinien) zur Einführung des erweiterten Neugeborenen-Screenings vom 21. Dezember 2004; Dt. Ärzteblatt 2005, 102: A1158-63

1) Statistisches Jahrbuch 2009 Herausgeber: Statistisches Bundesamt, Wiesbaden www.destatis.de