National

Screening Report

Germany 2012

Deutsche Gesellschaft für Neugeborenenscreening e.V.

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Abbreviations:

CAH	Congenital adrenal hyperplasia
CACT - Deficiency	Carnitin-Acylcarnitin-Translocase-Deficiency
CPT I - Deficiency	Carnitin- Palmitoyl-CoA-Transferase I-Deficiency
CPT II - Deficiency	Carnitin- Palmitoyl-CoA-Transferase II-Deficiency
GA I	Glutaric acidaemia Type I

BW	Birth weight
HPA	Hyperphenylalaninaemia
IVA	Isovaleric acidaemia
LCHAD - Deficiency	Long-Chain-3-Hydroxy-Acyl-CoA-Dehydrogenase-Deficiency
DoL	Day of life
DB	Dried blood
GV 1- 3	Guide value 1 - 3
MCAD - Deficiency	Medium-Chain-Acyl-CoA-Dehydrogenase-Deficiency
MSUD	Maple syrup urine disease
NGS	Newborn screening
SV	Secondary value
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.

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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) in the appendices 2-4.

The National Screening Report 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 and recall numbers at diagnoses for the year 2012. 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:

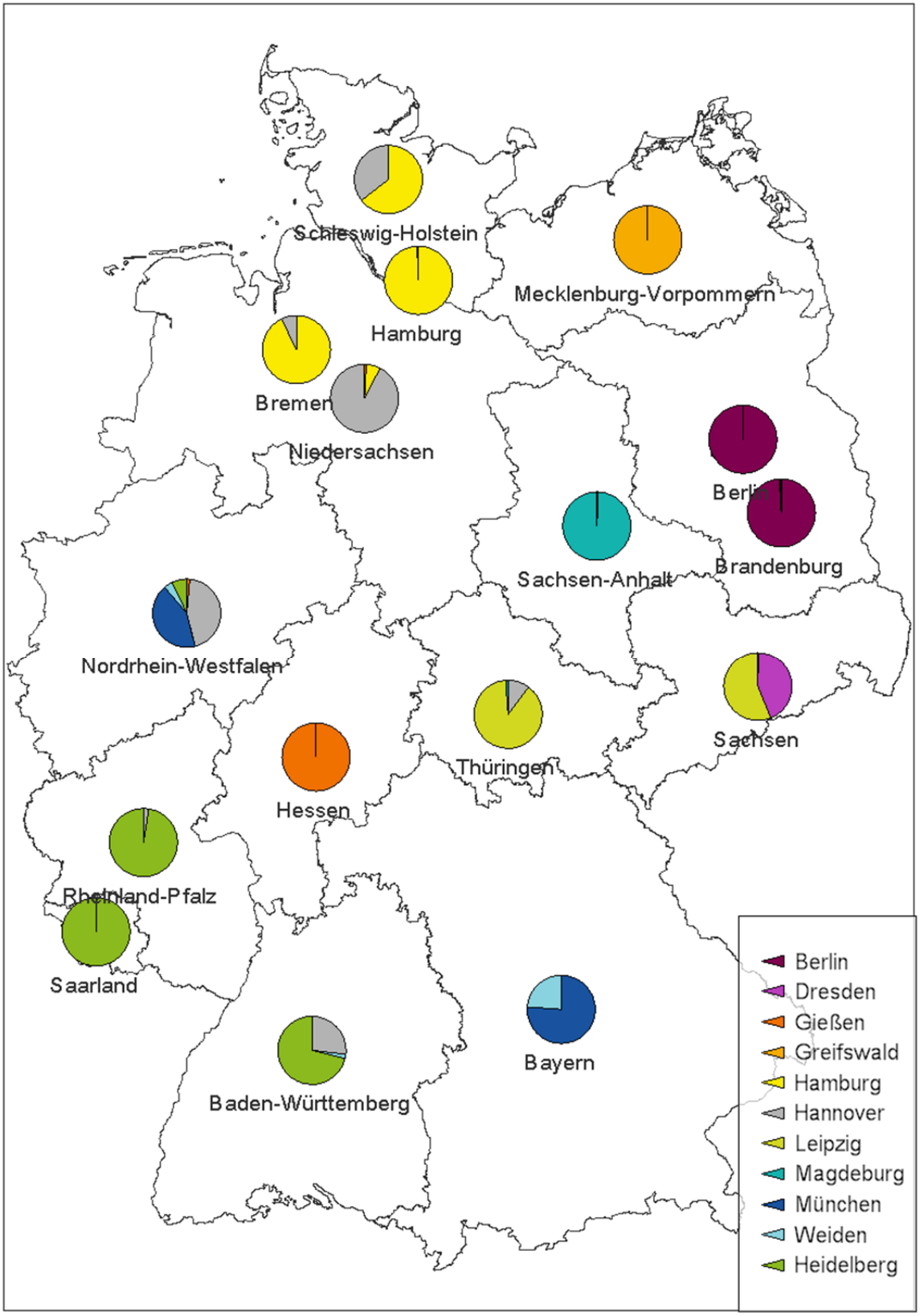
- Total survey of the targeted population
    - Collection method and rate
    - Blank card system
- Completeness of the control and the follow-up studies
- Collection of test parameters and cut offs
- Stratified rates of recall, positive predictive values and prevalence according to laboratory, age as well as gestational age,
- 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
- Diagnostics for confirmation
    - Type of diagnostics
    - Time of diagnostics
- Final diagnosis
- Start of therapy

Previously, laboratories were listed which have undertaken the screening in 2012 for Germany. (12 and 13 relate to the same laboratory, one with and without the cooperation 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 16.12.2010 [1].Tables are numbered according to the chapters.

We would like to thank all the laboratories for provision of their data. The data was checked for plausibility. Remaining inconsistencies of data was analysed according to the reported data. (Inconsistencies can sometimes be 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 2012, 673.544 children were born in Germany [2]. The total recorded screening of 674.926 exceeds this number. A cause for the additional screening cards cannot be declared. Reasons could be, not as such, registered repeat screening cards or cards of births not registered in Germany. Further investigations cannot be undertaken as data exchange is not legalised.

Births [2]: 673.544

First screening: 674.926

Final diagnosis (see Table 3): 516

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

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. Out of 1 in 1.305 newborns, one targeted disease according to the guidelines is found. Table 2 shows the prevalence of targeted diseases in the year 2012 in Germany.

Table 2: Absolute numbers of detected diseases found by screening 2012

Disease	Confirmed cases	Prevalence
Hypothyroidism	**205**	1: 3 285
Congenital adrenal hyperplasia (CAH)	**48**	1: 14 032
Biotinidase deficiency (incl. partial defect)	**37**	1: 18 204
Galactosaemia (classic)	**9**	1: 74 838
Phenylketonuria (PKU) n=63 / Hyperphenylalaninaemia(HPA) n=63	**126**	1: 5 388
Maple syrup urine disease (MSUD)	**5**	1: 134 709
Medium-Chain-Acyl-CoA-Dehydrogenase (MCAD)-Deficiency	**62**	1: 10 864
Long-Chain-3-OH-Acyl-CoA-Dehydrogenase (LCHAD)-Deficiency	**7**	1: 96 221
(Very-)Long-Chain-Acyl-CoA-Dehydrogenase (VLCAD)-Deficiency	**7**	1: 96 221
Carnitin-Palmitoyl-CoA-Transferase I (CPT I)-Deficiency	**0**	
Carnitin-Palmitoyl-CoA-Transferase II (CPT II)-Deficiency	**0**	
Carnitin-Acylcarnitin-Translocase (CACT)-Deficiency	**0**	
Glutaric aciduria Type I (GA I)	**5**	1: 134 709
Isovalerianacidaemia (IVA)	**5**	1: 134 709
Total	**516**	**1: 1 307**

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

		≥36h and ≥32WoG		<36h and ≥32WoG		<32WoG	
Lab	Total	n	%	n	%	n	%
1	52534	50690	96.49	1152	2.19	692	1.32
3	15538	15229	98.01	160	1.03	149	0.96
5	52547	51137	97.32	847	1.61	563	1.07
6	12742	12275	96.33	315	2.47	152	1.19
7	45018	43525	96.68	774	1.72	719	1.60
8	156526	153215	97.88	1534	0.98	1777	1.14
9	110661	107914	97.52	1156	1.04	1591	1.44
10	34621	33975	98.13	350	1.01	296	0.85
11	16666	16145	96.87	362	2.17	159	0.95
12[a]	80367	78640	97.85	879	1.09	848	1.06
13	64346	62714	97.46	808	1.26	824	1.28
14[a]	25207	24798	98,38	220	0,87	189	0,75
15	8153	7850	96,28	129	1,58	174	2,13
Total	**674926**	**658107**	**97.51**	**8686**	**1.29**	**8133**	**1.21**

[a] Including screening tests that have not been sent to the tracking center (without consent)

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

Table 2.2: Requested and received repeat screenings

Lab	Total[a] [c] requested	Total[a] received	%	Recall requested [c]	Recall received	%
1	2436	2356	96.72	645	632	97.98
3 [b]	400	470	117.50 [d]	98	160	163.27 [d]
5	1865	1818	97.48	455	418	91.87
6	548	548	100.00	62	62	100.00
7 [b]	2352	n.s.	n.s.	875	n.s.	n.s.
8	4407	4072	92.40	926	921	99.46
9	3409	2399	70.37	460	325	70.65
10	936	931	99.47	262	262	100.00
11	581	573	98.62	65	65	100.00
12	2275	2266	99.60	596	595	99.83
13	2074	2023	97.54	442	412	93.21
14	515	514	99.81	112	112	100.00
15	427	326	76.35	84	81	96.43
Total	**22225**	**18296**	**93.96**[b]	**5082**	**4045**	**98.44**[b]

Lab	<36h requested [c]	<36h received	%	<32WOG requested [c]	<32WOG received	%
1	1033	1033	100.00	673	608	90.34
3 [b]	160	170	106.25 [d]	138	140	101.45 [d]
5	847	844	99.65	563	556	98.76
6	314	314	100.00	146	146	100.00
7[b]	771	n.s.	n.s.	706	n.s.	n.s.
8	1525	1348	88.39	1725	1604	92.99
9	1154	728	63.08	1586	1224	77.18
10	348	343	98.56	280	280	100.00
11	361	353	97.78	155	155	100.00
12	873	865	99.08	806	806	100.00
13	808	787	97.40	824	824	100.00
14	219	218	99.54	184	184	100.00
15	135	53	39.26	173	157	90.75
Total	**8548**	**7056**	**92.63** [b]	**7959**	**6684**	**93.94** [b]

[a] Including secondary screening due to blood transfusion, parenteral nutrition or medication
[b] Calculation without labs giving not differentiated numbers
[c] Deaths are not included in the number of requested samples
[d] Figures have been confirmed by the lab

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 screening 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 laboratories receive blank test cards in various numbers. The number of blank screening cards due to refusal is still low but higher than the previous years and in 2012 partly doubled compared to 2010. To what extent this is due to, a better reply or raised true refusals, is not clear.

This system seems to work mainly with the refusals respectively the declined early screening. Both, before screening deceased and the transferred neonates, would give expectations to higher numbers.

Table 2.3: Laboratory received blank cards

		Reasons for blank cards				
	Primary screening Total	Deceased	Screening declined	Transfer of newborn	Early screening declined	Total
Lab	n	n	n	n	n	n
1	52534	48	30	0	3377	3455
3	15538	22	30	0	715	767
5	52547	82	808	1170	833	2893
6	12742	22	2	3	235	262
7[b]	45018	n.s.	n.s.	n.s.	n.s.	n.s.
8	156526	n.s.	n.s.	n.s.	n.s.	1920[a]
9[b]	110661	8	161	68	368	605
10	34621	166	31	0	1846[c]	2043
11	16666	51	8	50	238	347
12	80367	8	23	151	1217	1399
13[b]	64346	n.s.	n.s.	n.s.	n.s.	n.s.
14	25207	0	1	0	50	51
15[b]	8153	n.s.	n.s.	n.s.	n.s.	n.s.
Total	**674926**	**407**	**1094**	**1442**	**10799**	**13742**

[a] Including early screening, transferral, no reason (declared)
[b] No tracking of blank screening cards
[c] No reason declared

Table 2.4: Secondary screening card due to poor sample quality

Lab	Primary screening	Control requested	Control received	received/ requested (%)	Proportion of/ Primary screening (%)
1	52534	418	392	93.78	0.80
3	15538	46	46	100.00	0.30
5	52547	466	460	98.71	0.89
6	12742	15	15	100.0	0.12
7	45018	n.s.	n.s.	n.s.	n.s.
8	156526	233	228	97.85	0.15
9	110661	547	488	89.21	0.49
10	34621	105	101	96.19	0.30
11	16666	2	2	100.00	0.01
12	80367	290	283	97.59	0.36
13	64346	245	243	99.18	0.38
14	25207	24	24	100.00	0.10
15	8153	4	4	100.00	0.05
Total	**674926**	**2395**	**2286**	**95.45**	**0.38***

* Calculation without Lab 7, since no mention of cards with poor sample quality

3 Quality of the screening analysis

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 2012 the recall rate was 0.78%. If we consider only screening cards of term newborns sampled beyond the 36th hour of life, the recall rate is 0.58%, meaning of 1000 tests only 6 are recalled. With sampling before the 36th hour of life or the 32nd WoG a secondary screening has to be done irrespectively of the results.

The total specificity was 99.29%. The sensitivity cannot be quoted, because systematic registration of unscreened neonates is not done.

Table 3 : Recall rates and cases found for Germany 2012 N= 674.926*

	Recall ≥36h		Recall <36h		Recall <32WOG		Recall Total	Not found in the screening	Confirmed cases
Disease	n	(%)	n	(%)	n	(%)	(%)	n	n
Hypothyroidism	457	0.07	348	4.01	48	0.59	0.13	5[a]	**205**
CAH	2098	0.32	360	4.14	541	6.65	0.44	1[b]	**48**
Biotinidase-Deficiency	156	0.02	9	0.10	20	0.25	0.03		**37**
Classic Galactosaemia	221	0.03	5	0.06	8	0.10	0.03		**9**
PKU/HPA	210	0.03	16	0.18	33	0.41	0.04		**126**
MSUD	68	0.01	1	0.01	5	0.06	0.01		**5**
MCAD	130	0.02	4	0.05	3	0.04	0.02		**62**
LCHAD	53	0.01	0		2	0.02	0.01		**7**
VLCAD	173	0.03	3	0.03	6	0.07	0.03		**7**
CPT I-Deficiency	10	0.0015	0		0				**0**
CPT II-Deficiency	33	0.01	0		0				**0**
CAT-Deficiency	0		0		0				**0**
GA I	180	0.03	2	0.02	10	0.12	0,03		**5**
IVA	53	0.01	0		9	0.11	0.01		**5**
Total	**3842**	**0.58**	**748**	**8.61**	**685**	**8.42**	**0.78**	**6**	**516**

* Primary screening Total: n= 674.926; Primary screening ≥ 36h and ≥ 32WOG n=658.107; Primary screening <36h n=8.686; Primary screening < 32WOG n=8.133
[a] All preterm infants under 32 WOG
[b] Mutation: I172N

3.1 Recall rate and confirmed cases stratified

The following tables show recall rates ≥36h and confirmed cases stratified for the Laboratory. 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, irrespectively of age and gestational age. The validation of confirmed cases was tested for plausibility of metabolic diseases by Professor Andreas Schulze and Dr. Regina Ensenauer, for endocrine diseases by Dr. Oliver Blankenstein and PD Dr. Heiko Krude. Excluded and therefore not reported are cases with missing data of confirmation diagnostics (n=21) (Tab.3.1.a) and cases where the confirmation diagnostics were negative (n=4). For some diseases 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	11
CAH	3
Biotinidase deficiency	1
MCAD	3
VLCAD	2
GA I	1
Total	21

In the following tables Recall rates <0.01% and very small n are not calculated, small values of large differences would show influence

3.1.1 Hypothyroidism

Lab	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)	Confirmed cases*	Not found in the screening
1	52534	50690	32	0.06	18	1
3	15538	15229	10	0.07	7	0
5	52547	51137	52	0.10	21	1
6	12742	12275	5	0.04	3	0
7	45018	43525	7	0.02	5	0
8	156526	153215	168	0.11	68	3
9	110661	107914	59	0.05	30	0
10	34621	33975	26	0.08	12	0
11	16666	16145	13	0.08	3	0
12	80367	78640	31	0.04	20	0
13	64346	62714	27	0.04	11	0
14	25207	24798	16	0.06	5	0
15	8153	7850	11	0.14	3	0
Total	**674926**	**658107**	**457**	**0.07**	**205**	**5**[a]

* Including transient hypothyroidism n =4,

[a] All premature babies born under 32 WoG (see Table 5.2)

In addition n=7 hyperthyrotropinaemia reported and confirmed. These are not included in the calculation of prevalence.

3.1.2 Congenital adrenal hyperplasia (CAH)

Lab	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)	Confirmed cases	Not found in the screening
1	52534	50690	138	0.27	4	0
3	15538	15229	5	0.03	2	0
5	52547	51137	342	0.67	2	0
6	12742	12275	25	0.20	0	0
7	45018	43525	425	0.98	1	0
8[a]	156526	153215	63	0.04	16	0
9	110661	107914	246	0.23	11	0
10	34621	33975	155	0.46	2	1[b]
11	16666	16145	39	0.24	4	0
12	80367	78640	373	0.47	4	0
13	64346	62714	214	0.34	2	0
14	25207	24798	52	0.21	0	0
15	8153	7850	21	0.27	0	0
Total	**674926**	**658107**	**2098**	**0.32**	**48**	1

[a] Laboratory used second-tier process

[b] Genetics: I172N

3.1.3 Biotinidase deficiency

Lab	Primary screening Total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases	Including complete defect
1	52534	50690	3		0	0
3	15538	15229	0		0	0
5	52547	51137	0		0	0
6	12742	12275	10	0.08	0	0
7	45018	43525	8	0.02	1	0
8	156526	153215	95	0.06	26	9
9	110661	107914	6	0.01	4	3
10	34621	33975	5	0.01	1	1
11	16666	16145	0		0	0
12	80367	78640	8	0.01	1	1
13	64346	62714	12	0.02	3	1
14	25207	24798	1		0	0
15	8153	7850	8	0.10	1	1
Total	**674926**	**658107**	**156**	**0.02**	**37**	**16**

* Recall rate recorded only if ≥ 0.01% and n > 5.

3.1.4 Galactosaemia

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases**	Including classic
1	52534	50690	18	0.04	2	0
3	15538	15229	2		0	0
5	52547	51137	21	0.04	3	0
6	12742	12275	4		1	0
7	45018	43525	6	0.01	2	1
8	156526	153215	33	0.02	8	0
9	110661	107914	5		3	3
10	34621	33975	18	0.05	5	1
11	16666	16145	1		0	0
12	80367	78640	46	0.06	2	1
13	64346	62714	43	0.07	3	3
14	25207	24798	17	0.07	0	0
15	8153	7850	7	0.09	0	0
Total	**674926**	**658107**	**221**	**0.03**	**29**	**9**

* Recall rate recorded only if ≥ 0.01% and n > 5.

** Variants are not comprehensively covered

3.1.5 PKU / HPA

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases	Including PKU
1	52534	50690	19	0.04	15	8
3	15538	15229	8	0.05	5	5
5	52547	51137	13	0.03	8	7
6	12742	12275	2		2	1
7	45018	43525	24	0.06	6	4
8	156526	153215	17	0.01	16	11
9	110661	107914	19	0.02	17	5
10	34621	33975	10	0.03	8	5
11	16666	16145	4		3	1
12	80367	78640	34	0.04	17	6
13	64346	62714	45	0.07	22	8
14	25207	24798	11	0.04	6	2
15	8153	7850	4		1	0
Total	**674926**	**658107**	**210**	**0.03**	**126**	**63**

* Recall rate recorded only if ≥ 0.01% and n > 5.

3.1.6 MSUD

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases
1	52534	50690	38	007	0
3	15538	15229	1		0
5	52547	51137	5		0
6	12742	12275	2		0
7	45018	43525	7	0.02	0
8	156526	153215	2		2
9	110661	107914	6	0.01	0
10	34621	33975	1		0
11	16666	16145	0		0
12	80367	78640	1		1
13	64346	62714	4		1
14	25207	24798	1		1
15	8153	7850	0		0
Total	**674926**	**658107**	**68**	**0.01**	**5**

* Recall rate recorded only if ≥ 0.01% and n > 5.

3.1.7 MCAD-Deficiency

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases
1	52534	50690	47	0.09	8
3	15538	15229	1		1
5	52547	51137	6	0.01	5
6	12742	12275	2		1
7	45018	43525	9	0.02	7
8	156526	153215	20	0.01	17
9	110661	107914	14	0.01	7
10	34621	33975	11	0.03	1
11	16666	16145	2		1
12	80367	78640	7	0.01	6
13	64346	62714	5		5
14	25207	24798	3		1
15	8153	7850	3		2
Total	**674926**	**658107**	**130**	**0.02**	**62**

* Recall rate recorded only if ≥ 0.01% and n > 5.

3.1.8 LCHAD-Deficiency

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases
1	52534	50690	40	0.08	0
3	15538	15229	0		0
5	52547	51137	1		1
6	12742	12275	0		0
7	45018	43525	0		1
8	156526	153215	2		1
9	110661	107914	2		2
10	34621	33975	3		1
11	16666	16145	1		0
12	80367	78640	0		0
13	64346	62714	3		1
14	25207	24798	1		0
15	8153	7850	0		0
Total	**674926**	**658107**	**53**	**0.01**	**7**

* Recall rate recorded only if ≥ 0.01% and n > 5.

3.1.9 VLCAD-Deficiency

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases
1	52534	50690	61	0.12	0
3	15538	15229	1		0
5	52547	51137	6	0.01	0
6	12742	12275	7	0.06	0
7	45018	43525	37	0.09	2
8	156526	153215	6		3
9	110661	107914	27	0.03	0
10	34621	33975	21	0.06	1
11	16666	16145	0		0
12	80367	78640	0		0
13	64346	62714	2		1
14	25207	24798	2		0
15	8153	7850	3		0
Total	**674926**	**658107**	**173**	**0.03**	**7**

* Recall rate recorded only if ≥ 0.01% and n > 5.

3.1.10 No confirmed cases of CPTI-Deficiency and for CPT II-Deficiency

3.1.11 Glutaric aciduria Type I

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases
1	52534	50690	87	0.17	0
3	15538	15229	0		0
5	52547	51137	3		0
6	12742	12275	3		0
7	45018	43525	30	0.07	1
8	156526	153215	2		1
9	110661	107914	49	0.05	1
10	34621	33975	1		0
11	16666	16145	0		0
12	80367	78640	3		2
13	64346	62714	1		0
14	25207	24798	1		0
15	8153	7850	0		0
Total	**674926**	**658107**	**180**	**0.03**	**5**

* Recall rate recorded only if ≥ 0.01% and n > 5.

3.1.12 Isovaleric acidaemia

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases
1	52534	50690	27	0.05	2
3	15538	15229	1		0
5	52547	51137	6	0.01	1
6	12742	12275	1		0
7	45018	43525	6	0.01	0
8	156526	153215	3		2
9	110661	107914	1		0
10	34621	33975	3		0
11	16666	16145	4		0
12	80367	78640	1		0
13	64346	62714	0		0
14	25207	24798	0	,	0
15	8153	7850	0		0
Total	**674926**	**658107**	**53**	**0.01**	**5**

* Recall rate recorded only if ≥ 0.01% and n > 5.

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. Recall rate is recorded only if it exceeds 0.01% and n > 5 since small numbers cause a high variability.

3.2.1 Hypothyroidism

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	50690	32	0.06	1152	8	0.69	692	0	
3	15229	10	0.07	160	0		149	0	
5	51137	52	0.10	847	1		563	3	
6	12275	5		315	1		152	0	
7	43525	7	0.02	774	34	4.39	719	26	3.62
8	153215	168	0.11	1534	155	10.10	1777	7	0.39
9	107914	59	0.05	1156	1		1591	3	
10	33975	26	0.08	350	39	11.14	296	0	
11	16145	13	0.08	362	62	17.13	159	0	
12	78640	31	0.04	879	33	3.75	848	8	0.94
13	62714	27	0.04	808	4		824	1	0.12
14	24798	16	0.06	220	9	4.09	189	0	
15	7850	11	0.14	129	1		174	0	
Total	**658107**	**457**	**0.07**	**8686**	**348**	**4.01**	**8133**	**48**	**0.59**

3.2.2 Congenital adrenal hyperplasia (CAH)

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	50690	138	0.27	1152	23	2.00	692	26	3.76
3	15229	5		160	0		149	1	
5	51137	342	0.67	847	6	0.71	563	35	6.22
6	12275	25	0.20	315	0		152	7	4.61
7	43525	425	0.98	774	74		719	248	34.49
8*	153215	63	0.04*	1534	130	8.47	1777	29	1.63*
9	107914	246	0.23	1156	8	0.69	1591	17	1.07
10	33975	155	0.46	350	12	3.43	296	34	11.49
11	16145	39	0.24	362	18	4.97	159	5	3.14
12	78640	373	0.47	879	80	9.10	848	67	7.90
13	62714	214	0.34	808	1		824	37	4.49
14	24798	52	0.21	220	6	2.73	189	14	7.41
15	7850	21	0.27	129	2		174	21	12.07
Total	**658107**	**2098**	**0.32**	**8686**	**360**	**4.14**	**8133**	**541**	**6.65**

* Laboratory used second-tier process at screening >36h and <32 WoG

3.2.3 Biotinidase deficiency

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	50690	3		1152	5		692	3	
3	15229	0		160	0		149	0	
5	51137	0		847	0		563	0	
6	12275	10	0.08	315	1		152	0	
7	43525	8	0.02	774	0		719	1	
8	153215	95	0.06	1534	2		1777	8	0.45
9	107914	6	0.01	1156	0		1591	2	
10	33975	5	0.01	350	0		296	0	
11	16145	0		362	0		159	0	
12	78640	8	0.01	879	0		848	3	
13	62714	12	0.02	808	1		824	3	
14	24798	1		220	0		189	0	
15	7850	8	0.10	129	0		174	0	
Total	**658107**	**156**	**0.02**	**8686**	**9**	**0.10**	**8133**	**20**	**0.25**

3.2.4 Galactosaemia

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	50690	18	0.04	1152	0		692	0	
3	15229	2		160	0		149	0	
5	51137	21	0.04	847	2		563	0	
6	12275	4		315	0		152	0	
7	43525	6	0.01	774	0		719	0	
8	153215	33	0.02	1534	0		1777	2	
9	107914	5		1156	0		1591	1	
10	33975	18	0.05	350	1		296	1	
11	16145	1		362	0		159	0	
12	78640	46	0.06	879	2		848	3	
13	62714	43	0.07	808	0		824	1	
14	24798	17	0.07	220	0		189	0	
15	7850	7	0.09	129	0		174	0	
Total	**658107**	**221**	**0.03**	**8686**	**5**	**0.06**	**8133**	**8**	**0.10**

3.2.5 PKU/HPA

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	50690	19	0.04	1152	3		692	1	
3	15229	8	0.05	160	0		149	0	
5	51137	13	003	847	0		563	0	
6	12275	2		315	0		152	0	
7	43525	24	0.06	774	8	1.03	719	19	2.64
8	153215	17	0.01	1534	1		1777	0	
9	107914	19	0.02	1156	1		1591	0	
10	33975	10	0.03	350	0		296	0	
11	16145	4		362	1		159	0	
12	78640	34	0.04	879	0		848	3	
13	62714	45	0.07	808	2		824	4	
14	24798	11	0.04	220	0		189	4	
15	7850	4		129	0		174	2	
Total	**658107**	**210**	**0.03**	**8686**	**16**	**0.18**	**8133**	**33**	**0.41**

3.2.6 MSUD

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	50690	38	0.07	1152	0		692	5	
3	15229	1		160	0		149	0	
5	51137	5		847	1		563	0	
6	12275	2		315	0		152	0	
7	43525	7	0.02	774	0		719	0	
8	153215	2		1534	0		1777	0	
9	107914	6	0.01	1156	0		1591	0	
10	33975	1		350	0		296	0	
11	16145	0		362	0		159	0	
12	78640	1		879	0		848	0	
13	62714	4		808	0		824	0	
14	24798	1		220	0		189	0	
15	7850	0		129	0		174	0	
Total	**658107**	**68**	**0.01**	**8686**	**1**	**0.01**	**8133**	**5**	**0.06**

3.2.7 MCAD-Deficiency

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	50690	47	0.09	1152	1		692	1	
3	15229	1		160	0		149	0	
5	51137	6		847	0		563	1	
6	12275	2		315	0		152	0	
7	43525	9	0.02	774	3		719	0	
8	153215	20	0.01	1534	0		1777	0	
9	107914	14	0.01	1156	0		1591	1	
10	33975	11	0.03	350	0		296	0	
11	16145	2		362	0		159	0	
12	78640	7	0.01	879	0		848	0	
13	62714	5		808	0		824	0	
14	24798	3		220	0		189	0	
15	7850	3		129	0		174		
Total	**658107**	**130**	**0.02**	**8686**	**4**	**0.05**	**8133**	**3**	**0.04**

3.2.8 LCHAD-Deficiency

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	50690	40	0.08	1152	0		692	0	
3	15229	0		160	0		149	0	
5	51137	1		847	0		563	0	
6	12275	0		315	0		152	0	
7	43525	0		774	0		719	0	
8	153215	2		1534	0		1777	0	
9	107914	2		1156	0		1591	2	
10	33975	3		350	0		296	0	
11	16145	1		362	0		159	0	
12	78640	0		879	0		848	0	
13	62714	3		808	0		824	0	
14	24798	1		220	0		189	0	
15	7850	0		129	0		174	0	
Total	**658107**	**53**	**0.01**	**8686**	**0**		**8133**	**2**	**0.02**

3.2.9 VLCAD-Deficiency

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	50690	61	0.12	1152	2		692	6	0,87
3	15229	1		160	0		149	0	
5	51137	6	0.01	847	0		563	0	
6	12275	7	0.06	315	0		152	0	
7	43525	37	0.09	774	1		719	0	
8	153215	6		1534	0		1777	0	
9	107914	27	0.03	1156	0		1591	0	
10	33975	21	0.06	350	0		296	0	
11	16145	0		362	0		159	0	
12	78640	0		879	0		848	0	
13*	62714	2		808	0		824	0	
14	24798	2		220	0		189	0	
15	7850	3		129	0		174	0	
Total	**658107**	**173**	**0.03**	**8686**	**3**	**0.03**	**8133**	**6**	**0.07**

3.2.10 CPT I-Deficiency

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	50690	7	0.01	1152	0		692	0	
3	15229	0		160	0		149	0	
5	51137	0		847	0		563	0	
6	12275	1		315	0		152	0	
7	43525	0		774	0		719	0	
8	153215	0		1534	0		1777	0	
9	107914	0		1156	0		1591	0	
10	33975	0		350	0		296	0	
11	16145	0		362	0		159	0	
12	78640	0		879	0		848	0	
13	62714	1		808	0		824	0	
14	24798	0		220	0		189	0	
15	7850	1		129	0		174	0	
Total	**658107**	**10**	**0.0015**	**8686**	**0**		**8133**	**0**	

3.2.11 CPT II-Deficiency

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	50690	4		1152	0		692	0	
3	15229	0		160	0		149	0	
5	51137	2		847	0		563	0	
6	12275	0		315	0		152	0	
7	43525	0		774	0		719	0	
8	153215	0		1534	0		1777	0	
9	107914	2		1156	0		1591	0	
10	33975	25	0.07	350	0		296	0	
11	16145	0		362	0		159	0	
12	78640	0		879	0		848	0	
13	62714	0		808	0		824	0	
14	24798	0		220	0		189	0	
15	7850	0		129	0		174	0	
Total	**658107**	**33**	**0.01**	**8686**	**0**		**8133**	**0**	

3.2.12 CACT-Deficiency

No recalls for the CACT deficiency were reported in 2012

3.2.13 Glutaric aciduria Type I

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	50690	87	0.17	1152	1		692	3	
3	15229	0		160	0		149	0	
5	51137	3		847	0		563	2	
6	12275	3		315	0		152	0	
7	43525	30	0.07	774	1		719	3	
8	153215	2		1534	0		1777	0	
9	107914	49	0.05	1156	0		1591	2	
10	33975	1		350	0		296	0	
11	16145	0		362	0		159	0	
12	78640	3		879	0		848	0	
13	62714	1		808	0		824	0	
14	24798	1		220	0		189	0	
15	7850	0		129	0		174	0	
Total	**658107**	**180**	**0.03**	**8686**	**2**	**0.02**	**8133**	**10**	**0.12**

3.2.14 Isovaleric acidaemia

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	50690	27	0.05	1152	0		692	2	
3	15229	1		160	0		149	0	
5	51137	6	0.01	847	0		563	1	
6	12275	1		315	0		152	2	
7	43525	6	0.01	774	0		719	3	
8	153215	3		1534	0		1777	0	
9	107914	1		1156	0		1591	0	
10	33975	3		350	0		296	1	
11	16145	4		362	0		159	0	
12	78640	1		879	0		848	0	
13	62714	0		808	0		824	0	
14	24798	0		220	0		189	0	
15	7850	0		129	0		174	0	
Total	**658107**	**53**	**0.01**	**8686**	**0**		**8133**	**9**	**0.11**

4 Process Periods

4.1 Age at blood collection

According to the guidelines (§8.1) of children, every newborn should be screened beyond the completed 32nd gestational week and 36th hour of life. In 90% of cases, with specification of collection time, the collection was according to the guidelines, in 8.65% (3.15-12.03%) beyond the 72nd hour of life, in 11.56% (1.02-3.72%) 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 9.67 % in 2012 (see figure 2). These numbers clearly imply an improvement of the process quality, since the adherence to the optimal timeframe is of great importance to the efficiency of the screening. Life threatening metabolic or electrolyte crisis can be prevented by early diagnosis and therapy.

Table. 4.1: Age at blood collection, primary screening

	Total	<36h		36h-<48h		48h-<72h		≥72h	
Lab	n	n	%	n	%	n	%	n	%
1[a]	52472	1285	2.45	11830	22.55	33741	64.30	5616	10.70
3	15538	208	1.34	2848	18.33	11793	75.90	689	4.43
5	52577	899	1.71	35547	67.61	14476	27.53	1655	3.15
6	12742	325	2.55	3999	31.38	7907	62.05	511	4.01
7	45018	1676	3.72	14751	32.77	23740	52.73	4851	10.78
8[a]	146769	1698	1.16	56928	38.79	75868	51.69	12275	8.36
9[a]	110620	1273	1.15	36102	32.64	62223	56.25	11022	9.96
10[a]	34617	364	1.05	8957	25.87	22033	63.65	3263	9.43
11[a]	16659	375	2.25	4689	28.15	10435	62.64	1160	6.96
12[a]	77639	940	1.21	32882	42.35	38012	48.96	5805	7.48
13	64346	888	1.38	25233	39.21	30487	47.38	7738	12.03
14[a]	24315	249	1.02	9734	40.03	12289	50.54	2043	8.40
15	8153	135	1.66	3737	45.84	3664	44.94	617	7.57
Total	**661465**	**10315**	**1.56**	**247237**	**37.38**	**346668**	**52.41**	**57245**	**8.65**

Due to missing data the stated number is smaller than the total number of primary screening. (marked with [a]).

4.2 Period from sampling to laboratory receipt

The time span between sampling and report of suspect results should not exceed 72 hours (paragraph 6. section 3). In 21.75% of cases with statement of the delivery time the probe was received 72 hours after sampling, in 23.55% of the cases between 48 and 72 hours. Shorter periods of delivery times are desirable, especially at the weekend. (Table 4.2)

Table 4.2: Period from sampling to laboratory receipt

	Total	≤24h		>24h-48h		>48h-72h		>72h	
Lab	n	n	%	n	%	n	%	n	%
1[a]	52395	14037	26.79	19836	37.86	10749	20.52	7773	14.84
3	15538	6155	39.61	5828	37.51	2362	15.20	1193	7.68
5	52552	6456	12.28	22630	43.06	14162	26.95	9304	17.70
6[a]	11891	2062	17.34	5324	44.77	3065	25.78	1440	12.11
7	45018	14281	31.72	13902	30.88	8345	18.54	8490	18.86
8[a]	149732	16951	11.32	50126	33.48	40872	27.30	41783	27.91
9[a]	110639	9985	9.02	31059	28.07	29065	26.27	40530	36.63
10[a]	34617	3750	10.83	12723	36.75	10253	29.62	7891	22.80
11[a]	16657	2818	16.92	7275	43.68	4281	25.70	2283	13.71
12[a]	78330	26032	33.23	27571	35.20	15041	19.20	9686	12.37
13	64346	17248	26.81	22615	35.15	13345	20.74	11138	17.31
14[a]	24623	13725	55.74	6767	27.48	2837	11.52	1294	5.26
15	8153	1270	15.58	2990	36.67	2141	26.26	1752	21.49
Total	**664491**	**134770**	**20.28**	**228646**	**34.41**	**156518**	**23.55**	**144557**	**21.75**

Due to missing data the stated number is smaller than the total number of primary screening of the previous tables (marked with [a])

4.3 Period between laboratory receipt and result reporting

In 82% of probes the results get reported within 24 hours. 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 result reporting

	Total	≤24h		>24h-48h		>48h-72h		>72h	
Lab	n	n	%	n	%	n	%	n	%
1	52535	27311	51.99	19949	37.97	4188	7.97	1087	2.07
3	15538	14229	91.58	903	5.81	104	0.67	302	1.94
5	52901	39382	74.44	10274	19.42	2929	5,54	316	0.60
6	12742	4146	32.54	4774	37.47	2419	18.98	1403	11.01
7	n.s.	n.s.		n.s.		n.s.		n.s.	
8	156526	150491	96.14	5525	3.53	382	0.24	128	0.08
9[a]	110456	107234	97.08	2715	2.46	306	0.28	201	0.18
10[a]	34619	29172	84.27	5271	15.23	154	0.44	22	0.06
11	16666	11008	66.05	5229	31.38	409	2.45	20	0.12
12[a]	78388	59033	75.31	13277	16.94	5601	7.15	477	0.61
13	64346	47976	74.56	11109	17.26	4372	6.79	889	1.38
14[a]	24658	15073	61.13	7539	30.57	1215	4.93	831	3.37
15	8153	7950	97.51	201	2.47	2	0.02	0	
Total	**627528**	**513005**	**81.75**	**86766**	**13.83**	**22081**	**3.52**	**5676**	**0.90**

In part, the number of probes is lower than the number of primary screening of previous tables (marked with [a]).

Figure 2: Age at blood collection 2005 to 2012

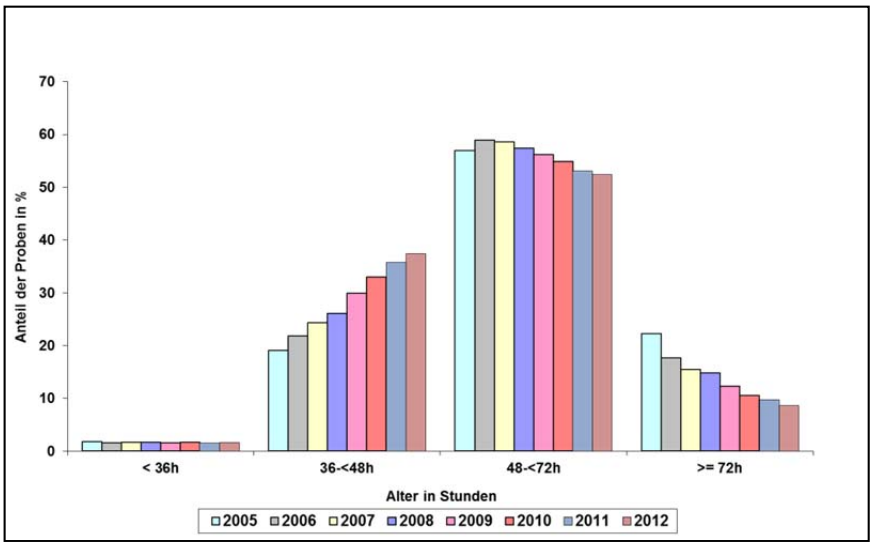


Figure 3: Period between sampling and laboratory receipt 2005 to 2012

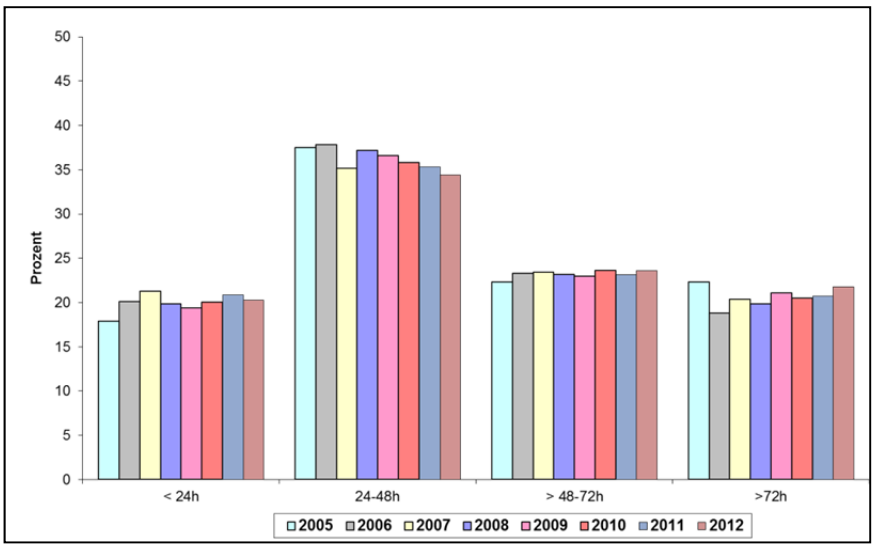
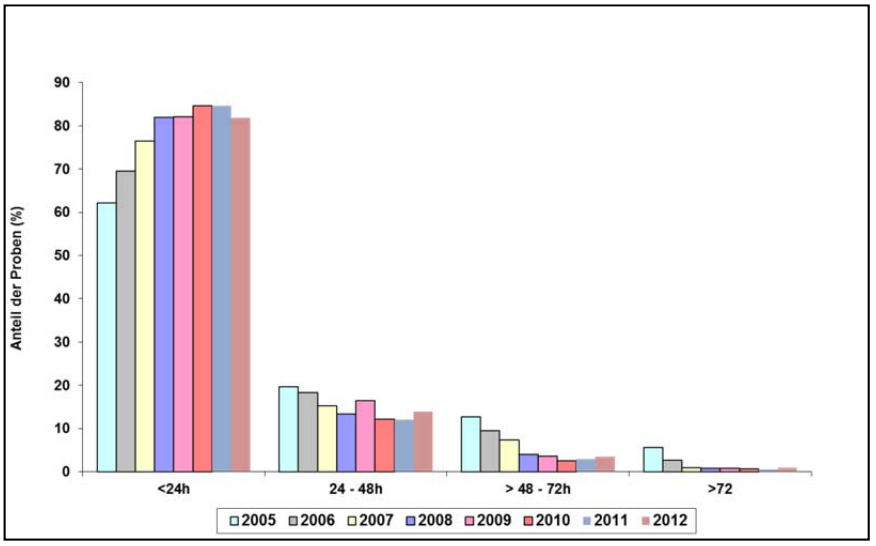


Figure 4: Period from laboratory receipt to report 2005 to 2012



5 Time of screening in the confirmed cases

5.1 Primary screening

Crucial for a successful screening is 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 6.9% 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, Time not specified *	Not specified**	Total
Hypothyroidism	171	13			5	16		**205**
CAH	37	2			7	1	1	**48**
Biotinidase	36	1						**37**
Classic Galactosaemia	9							**9**
PKU/HPA	109	11		1	4		1	**126**
MSUD	5							**5**
MCAD	50	6	2		3	1		**62**
LCHAD	4	1				2		**7**
VLCAD	7							**7**
GA I	5							**5**
IVA	5							**5**
Total	**438**	**34**	**2**	**1**	**19**	**20**	**2**	**516**

* ≥36h Not specified does not include repeat testing with early sampling or preterm birth, exact age of sampling time not stated.

** No information, neither WoG nor age at sampling.

5.2 Result of the primary testing and time of sampling in the confirmed cases

We stratified in the confirmed cases the results of the primary test card according to sampling time and result. For premature infants for whom the test was performed before the 32nd week of gestation we itemised the sufficiency of the control algorithm. In two cases of hypothyroidism the control beyond 32nd week of gestation showed a normal result. These children were diagnosed later. In 3 children the compulsory screening control was not undertaken timely. It is not known if and how many premature infants below the 32nd week of gestation with congenital hypothyroidism have been undiagnosed due to unremarkable secondary or missed screening.

Table 5.2 : Confirmed cases: Result of the primary testing and time of sampling

Disease	Full term, sampling ≥36h		Sampling <36h	First sampling <32 WOG				Not specified
	Prim. screen suspicious	Prim. screen not suspicious	Prim. screen suspicious	Prim. screen suspicious	Prim. screen not suspicious, screening at 32 WOG suspicious	Prim. screen not suspicious, missed screening at 32 WOG	Prim. screen not suspicious, screening at 32 WOG not suspicious	
Hypothyroidism	184		5	4	7	3	2	
CAH	38	1[a]	7	1				1
Biotinidase	37							
Classic Galactosaemia	9							
PKU/HPA	121		4					1
MSUD	5							
MCAD	58		3	1				
LCHAD	5			2				
VLCAD	7							
GA I	5							
IVA	5							
Total	**474**	**1**	**19**	**8**	**7**	**3**	**2**	**2**

[a] Mutation: I172N

6 Confirmation of pathological results

The following chapter outlines the diagnostic measures for confirmation of the diagnosis, as known to the laboratories. This information is used for quality control by the individual laboratories but does not always get reported by the physicians taking care of the patient. For the year 2012, 24 out of 516 confirmed cases had no detailed information about the confirmation diagnostics available, the available data though allows a plausible analysis. In a further 22 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

Lab	Confirmed cases*	TSH (Serum)	T3	fT3	T4	fT4	Ultrasound	Thyroid antibodies
1	18	18	1	2	3	16	18	13
3	7	7	4	3	n.s.	7	7	7
5	21	19	1	11	1	11	16	14
6	3	3	n.s.	3	n.s.	3	3	3
7	5	2	n.s.	2	n.s.	2	1	1
8	68	67	1	59	1	65	60	47
9	30	30	12	18	9	30	13	8
10	12	12	n.s.	7	1	12	8	6
11	3	3	n.s.	n.s.	n.s.	2	3	2
12	20	20	n.s.	16	n.s.	19	18	12
13	11	11	n.s.	n.s.	n.s.	11	n.s.	n.s.
14	5	5	1	1	n.s.	4	4	4
15	2	2	n.s.	2	n.s.	2	1	n.s.
Total	**205**	**200**	**20**	**124**	**15**	**185**	**153**	**117**

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

6.2 Congenital adrenal hyperplasia (CAH)

Lab	Confirmed cases*	17-OHP (Serum)	Steroid (Serum/DB)	Urinary steroids	Molecular genetic testing
1	4	4	2	n.s.	4
3	2	2	2	2	2
5	2	2	n.s.	2	n.s.
7	1	1	1	n.s.	n.s.
8	16	14	7	4	11
9	11	10	8	n.s.	3
10	2	2	1	n.s.	1
11	4	4	3	n.s.	4
12	4	1	1	1	3
13	2	1	1	n.s.	n.s.
Total	**48**	**41**	**26**	**9**	**28**

* incl n=2 cases without detailed information of confirmation diagnostics

6.3 Biotinidase deficiency

Lab	Confirmed cases*	Biotinidase (Serum/DB)	Molecular genetic testing
7	1	1	n.s.
8	26	26	n.s.
9	4	4	n.s.
10	1	1	n.s.
12	1	1	1
13	3	2	n.s.
15	1	1	n.s.
Total	**37**	**36**	**1**

* incl n=1 cases without detailed information of confirmation diagnostics

6.4 Classic Galactosaemia

Lab	Confirmed cases*	Enzyme assay	Galactose, Gal1P	Molecular genetic testing
7	1	1	1	1
9	3	1	1	1
10	1	n.s.	n.s.	n.s.
12	1	1	1	n.s.
13	3	2	2	2
Total	**9**	**5**	**5**	**4**

* incl n=1 cases without detailed information of confirmation diagnostics

6.5 PKU / HPA

Lab	Confirmed cases*	Phe (Serum/DB)	Phe/Tyr	BH4-Test	Molecular genetic testing	Pterine in urine/DB	DHPR in DB
1	15	15	10	8	15	15	15
3	5	4	4	3	n.s.	5	5
5	8	8	8	8	1	8	8
6	2	2	2	1	n.s.	2	2
7	6	4	4	n.s.	n.s.	4	4
8	16	14	9	7	1	8	8
9	17	16	15	2	n.s.	17	16
10	8	7	7	n.s.	5	3	5
11	3	3	2	1	n.s.	1	1
12	17	17	16	9	5	16	13
13	22	21	8	4	n.s.	19	19
14	6	6	4	2	1	6	6
15	1	1	1	n.s.	1	1	1
Total	**126**	**118**	**90**	**45**	**29**	**105**	**103**

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

6.6 MSUD

Lab	Confirmed cases	Confirmation Serum	Urinary organic acids	Enzyme activity	Molecular genetic testing
8	2	2	n.s.	n.s.	n.s.
12	1	1	n.s.	n.s.	n.s.
13	1	1	n.s.	n.s.	n.s.
14	1	1	n.s.	n.s.	n.s.
Total	**5**	**5**	**n.s.**	**n.s.**	**n.s.**

6.7 MCAD-Deficiency

Lab	Confirmed cases*	Confirmation Serum/DB	Urinary organic acids	Enzyme activity	Molecular genetic testing
1	8	8	7	7	8
3	1	n.s.	1	n.s.	n.s.
5	5	4	n.s.	n.s.	4
6	1	1	n.s.	n.s.	1
7	7	n.s.	n.s.	n.s.	n.s.
8	17	4	6	4	13
9	7	4	6	2	3
10	1	1	n.s.	1	1
11	1	n.s.	1	n.s.	1
12	6	4	4	n.s.	2
13	5	1	n.s.	2	4
14	1	1	1	n.s.	1
15	2	n.s.	n.s.	n.s.	2
Total	**62**	**28**	**26**	**16**	**40**

* incl n=13 cases without detailed information of confirmation diagnostics

6.8 LCHAD-Deficiency

Lab	Confirmed cases	Confirmation Serum/DB	Urinary organic acids	Enzyme activity	Molecular genetic testing
5	1	1	n.s.	n.s.	1
7	1	1	1	n.s.	1
8	1	n.s.	1	n.s.	n.s.
9	2	1	1	n.s.	2
10	1	1	1	1	1
13	1	n.s.	n.s.	n.s.	1
Total	**7**	**4**	**4**	**1**	**6**

6.9 VLCAD-Deficiency

Lab	Confirmed cases	Confirmation Serum/DB	Urinary organic acids	Enzyme activity	Molecular genetic testing
7	2	n.s.	n.s.	2	2
8	3	3	2	3	2
10	1	1	1	1	1
13	1	n.s.	n.s.	1	n.s.
Total	**7**	**4**	**3**	**7**	**5**

6.10 No confirmed cases of CPT I-Deficiency, CPT II-Deficiency and CACT-Deficiency

6.11 Glutaric aciduria Type I

Lab	Confirmed cases	Confirmation Serum/DB	Urinary organic acids	Enzyme activity	Molecular genetic testing
7	1	n.s.	1	n.s.	1
8	1	n.s.	1	n.s.	1
9	1	1	1	n.s.	1
12	2	n.s.	2	n.s.	1
Total	**5**	**1**	**5**	**n.s.**	**4**

6.12 Isovaleric acidaemia

Lab	Confirmed cases	Confirmation Serum	Urinary organic acids	Enzyme activity	Molecular genetic testing
1	2	2	2	n.s.	n.s.
5	1	1	1	n.s.	n.s.
8	2	1	2	n.s.	1
Total	**5**	**4**	**5**	**n.s.**	**1**

7 Methods and cut offs in screening

7.1 Filter paper for sampling

Lab	Filter paper
1	ID Biological (Ahlstrom 226)
3	ID Biological (Ahlstrom 226)
5	TFN (Munktell)
6	ID Biological (Ahlstrom 226)
7	WS 903
8	TFN (Munktell)
9	WS 903
10	WS 903
11	ID Biological (Ahlstrom 226)
12	Munktell
13	Munktell
14	WS 903
15	WS 903

7.2 Hypothyroidsm

Lab	Parameter	Cut off	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 mU/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 Congenital adrenal hyperplasia (CAH)

Lab	Parameter	Method
1	17 OHP	AutoDELFIA
3	17 OHP	AutoDELFIA
5	17 OHP	AutoDELFIA
6	17 OHP	DELFIA
7	17 OHP	AutoDELFIA
8*	17 OHP	DELFIA
9	17 OHP	AutoDELFIA
10	17 OHP	AutoDELFIA
11	17 OHP	DELFIA
12	17 OHP	AutoDELFIA
13	17 OHP	AutoDELFIA
14	17 OHP	AutoDELFIA
15	17 OHP	AutoDELFIA

* Full term and premature babies – at elevated Delfia 17OHP TMS Steroid profile with 17OHP, 21-Desoxycortisol, 11-Desoxycortisol, Cortisol und Androstendion.

7.4 Biotinidase deficiency

Lab	Parameter	Cut off	Method
1	Biotinidase	30% Flat mean	Colorimetrie qualitative
3	Biotinidase	30% Median days	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% daily 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

7.5 Galactosaemia

Lab	Parameter	Cut off	Method
1	GALT Galactose	3,5 U/gHb 20 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 quantitative
8	GALT Galactose	20% daily mean 30 mg/dl	Fluorimetrie quantitative Colorimetrie non kit
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 quantitative
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 a second-tier method

7.6 MS/MS

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

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 16.6.2010; https://www.g-ba.de/downloads/62-492-506/RL_Kinder_2010-12-16.pdf (Zugriff am 30.5.2014)

2) Statistisches Jahrbuch 2012 Herausgeber: Statistisches Bundesamt, Wiesbaden www.destatis.de