National

Screening Report

Germany 2013

Deutsche Gesellschaft für Neugeborenenscreening e.V.

Uta Nennstiel-Ratzel, Anja Lüders, Oliver Blankenstein, Uta Ceglarek, Regina Ensenauer, Gwendolyn Gramer, Jeannette Klein, Martin Lindner, Cornelia Müller, Michael Peter, Joachim G. Kreuder, Wulf Röschinger, Wolfgang Schultis, Andreas Schulze, Sabine Rönicke, Zoltan Lukacs, Marina Stopsack, Klaus Mohnike

date September 2015

ISSN Nummer 2199-5494

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

Contents

Figures

Abbreviations and Glossary:

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
PT	Preterm < 32 WoG
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
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.

(1) Neugeborenen Screeninglabor Berlin
Dr. med. Oliver Blankenstein
Sylter Str. 2
D 13353 Berlin
030/405 026 391 / Fax: -613
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. Joachim G. Kreuder
Feulgenstr. 12
35392 **Giessen**
0641/ 9943681
Joachim.G.Kreuder@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=neoscreen

(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
PD Dr. med. M. Peter
Dr. med. Dr. rer.nat. Nils Janzen
Postfach 911009
30430 **Hannover**
05108/92163 0
m.peter@metabscreen.de
n.janzen@metabscreen.de
www.metabscreen.de

(9) Neugeborenenscreening Heidelberg
Prof. Dr. med. G.F. Hoffmann
Im Neuenheimer Feld 669
69120 **Heidelberg**
06221/56 8278
gwendolyn.gramer@med.uni-heidelberg.de
www.Neugeborenenscreening.uni-hd.de

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

(12/13) Labor Becker, Olgemöller & Kollegen
Neugeborenenscreening
Laborleitung:
Prof. Dr.med. Dr.rer.nat. Bernhard Olgemöller
Ansprechpartner:
Priv.-Doz. Dr.med. Wulf Röschinger
Ottobrunner Str. 6
81737 **München**
089/544 654 0
Olgemoeller@labor-bo.de
w.roeschinger@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 und Lebensmittelsicherheit
Dr. med. Uta Nennstiel-Ratzel MPH
Veterinärstr.2
85764 **Oberschleißheim**
09131/6808-5-204
screening@lgl.bayern.de
www.lgl.bayern.de/gesundheit/praevention/kindergesundheit/neugeborenenscreening/index.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“) [1] 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 2013. 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:

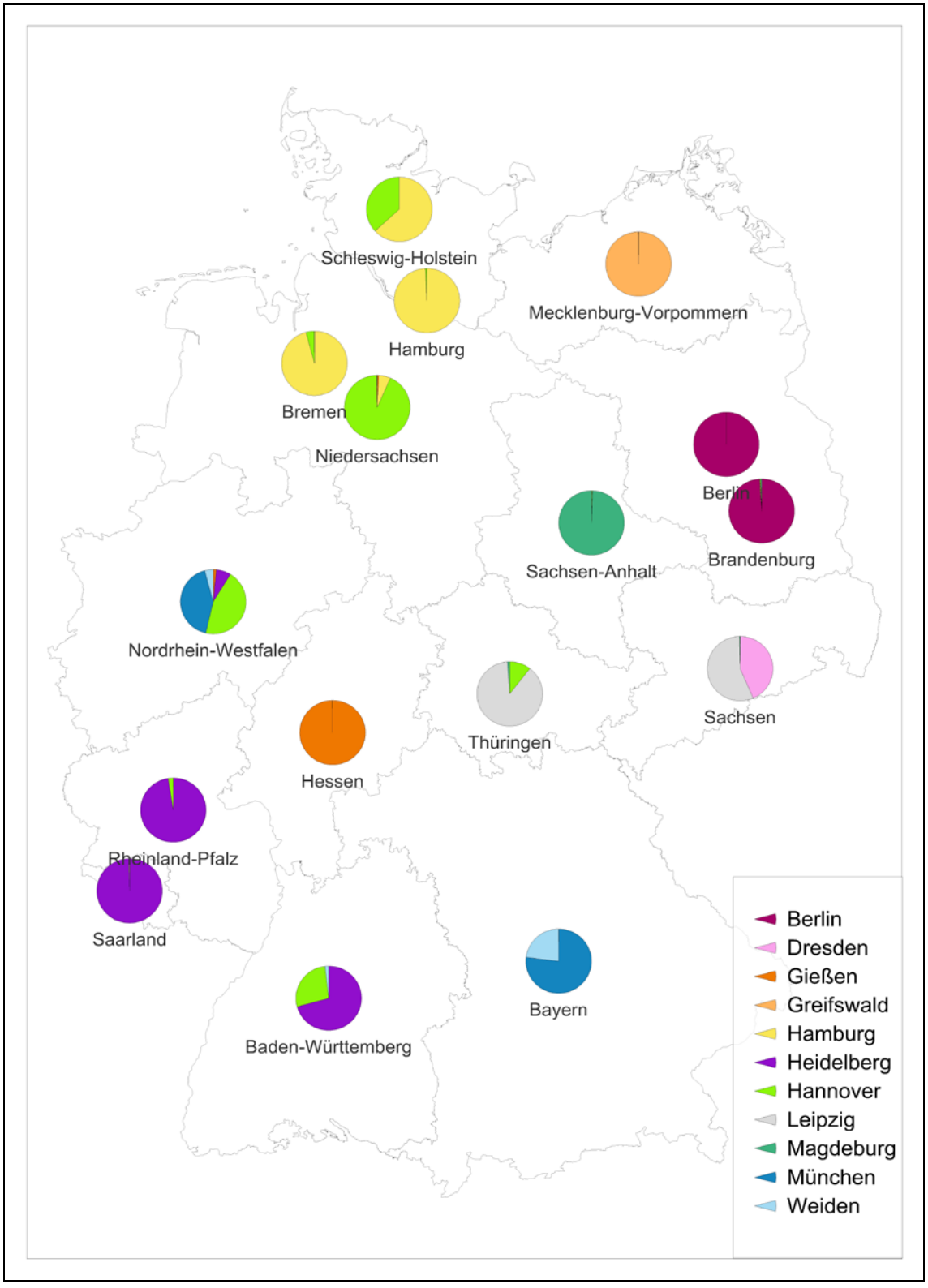
- Total survey of the targeted population
    - Collection method and rate
    - Blank card system
- Completeness of the control and the follow-up studies
- Collection of test parameters and cut offs
- Stratified rates of recall, positive predictive values and prevalence according to laboratory, age 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

On the previous page laboratories were listed which have undertaken the screening in 2013 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 2013, 682.069 children were born in Germany [2]. The total recorded screening of 683.713 exceeds this number. A cause for the additional screening cards cannot be declared. Reasons could be, not as such, registered repeat screening cards, received in another laboratory or cards of births not registered in Germany. Further investigations cannot be undertaken as data exchange is not legalised.

Births [2]:	682.069
First screening:	683.713
Final diagnosis (seeTable 3):	520

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. In 1 out of 1,312 newborns, one targeted disease according to the guidelines is found. Table 2 shows the prevalence of targeted diseases in the year 2013 in Germany.

Table 2: Absolute numbers of detected diseases found by screening 2013

Disease	Confirmed cases	Prevalence
Hypothyrodism	**211**	1: 3.233
Congenital adrenal hyperplasia (CAH)	**47**	1: 14.512
Biotinidase deficiency (incl. partial defect)	**21**	1: 32.479
Galactosaemia (classic)	**9**	1: 75.785
Phenylketonuria (PKU) n=66 / Hyperphenylalaninaemia (HPA) n=61		
Cofactor-Deficiency n=2	**129**	1: 5.287
Maple syrup urine disease (MSUD)	**5**	1: 136.414
Medium-Chain-Acyl-CoA-Dehydrogenase (MCAD)-Deficiency	**75**	1: 9.094
Long-Chain-3-OH-Acyl-CoA-Dehydrogenase (LCHAD)-Deficiency	**4**	1: 170.517
(Very-)Long-Chain-Acyl-CoA-Dehydrogenase (VLCAD)-Deficiency	**10**	1: 68.207
Carnitin-Palmitoyl-CoA-Transferase I (CPTI)-Deficiency	**0**	
Carnitin-Palmitoyl-CoA-Transferase II (CPTII)-Deficiency	**0**	
Carnitin-Acylcarnitin-Translocase (CACT)-Deficiency	**0**	
Glutaric aciduria Type I (GA I)	**3**	1: 227.356
Isovalerianacidaemia (IVA)	**6**	1: 113.678
Total	**520**	**1: 1.312**

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	52731	51153	97,01	904	1,71	674	1,28
3	15389	15106	98,16	131	0,85	152	0,99
5	53180	51970	97,72	700	1,32	510	0,96
6	12921	12414	96,08	328	2,54	179	1,39
7	45637	44293	97,06	679	1,49	665	1,46
8	159383	156008	97,88	1503	0,94	1872	1,17
9	113335	110468	97,47	1325	1,17	1542	1,36
10	34861	34176	98,04	374	1,07	311	0,89
11	16601	16094	96,95	352	2,12	155	0,93
12	82526	80717	97,81	806	0,98	1003	1,22
13	64253	62674	97,54	746	1,16	833	1,30
14	24826	24304	97,90	265	1,07	257	1,04
15	8070	7792	96,56	114	1,41	164	2,03
Total	**683713**	**667169**	**97,58**	**8227**	**1,20**	**8317**	**1,22**

2.2 Relation of requested to received repeat screenings

In Table 2.2 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	1761	1685	95,68	205	198	96,59
3	542	539	99,45	159	159	100,00
5	2327	1991	85,56	1043	906	86,86
6	576	574	99,65	72	71	98,61
7[b]	1851	n.s.		514	n.s.	
8	4523	4244	93,83	962	958	99,58
9	3590	3008	83,79	548	369	67,34
10	964	956	99,17	245	245	100,00
11	535	534	99,81	37	37	100,00
12	2289	2274	99,34	507	507	100,00
13	1987	1813	91,24	349	334	95,70
14	629	619	98,41	115	115	100,00
15	384	298	77,60	87	87	100,00
Total	21958	18623	92,62[b]	4843	3986	92,08[b]

Lab	<36h requested [c]	<36h received	%	<32WoG requested [c]	<32WoG received	%
1	817	786	96,21	639	605	94,68
3	131	130	99,24	137	136	99,27
5	700	578	82,57	494	454	91,90
6	328	327	99,70	176	176	100,00
7[b]	676	n.s.		661	n.s.	
8	1500	1346	89,73	1818	1719	94,55
9	1321	1015	76,84	1540	1503	97,60
10	372	369	99,19	299	298	99,67
11	349	348	99,71	149	149	100,00
12	798	792	99,25	993	975	98,19
13	805	735	91,30	833	832	99,88
14	265	260	98,11	249	244	97,99
15	116	44	37,93	164	151	92,07
Total	8178	6730	89,71[b]	8152	7242	96,68[b]

[a] Including secondary screening due to blood transfusion or medication
[b] Calculation without laboratories giving not differentiated numbers
[c] Deaths are not included in the number of requested samples

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 the blank screening cards due to refusal is constant related to the total of primary screening.

This system seems to work mainly with the refusals respectively the declined early screening. Due to the data from the perinatal survey, 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	52731	50	106	0	3534	3690
3	15389	33	33	0	844	910
5	53180	32	576	1211	1026	2845
6	12921	9	3	3	261	276
7[b]	45637	n.s.	n.s.	n.s.	n.s.	n.s.
8	159383	n.s.	n.s.	n.s.	n.s.	2043[a]
9	113335	6	115	80	484	685
10	34861	182	26	n.s.	1673[c]	1881
11	16601	70	3	39	277	389
12	82526	n.s.	n.s.	n.s.	1116	1116
13[b]	64253	n.s.	n.s.	n.s.	n.s.	n.s.
14	24826	n.s.	n.s.	n.s.	57	57
15[b]	8070	n.s.	n.s.	n.s.	n.s.	n.s.
Total	**683713**	**382**	**862**	**1333**	**9272**	**13892**

[a] Total number, differentiation not possible
[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	52731	366	343	93,72	0,69
3	15389	13	13	100	0,08
5	53180	504	429	85,12	0,95
6	12921	9	9	100	0,07
7	45637	105	n.s.		0,23
8	159383	248	246	99,19	0,16
9	113335	529	507	95,84	0,47
10	34861	83	81	97,59	0,24
11	16601	4	4	100	0,02
12	82526	319	318	99,69	0,39
13	64253	256	n.s.		0,40
14	24826	27	27	100	0,11
15	8070	6	6	100	0,07
Total	**683713**	**2469**	**1983**	**94,07***	0,36

* Calculation without laboratories 7 and 13 as not specified for the receipt of cards with poor sample quality

3 Quality parameters 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 2013 the recall rate was 0.67%. If we consider only screening cards of term newborns sampled beyond the 36th hour of life, the recall rate is 0.48%, meaning of 1000 tests only 5 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 99.41%. The sensitivity cannot be quoted, because systematic registration of unscreened neonates is not done.

Table 3 : Recall rates and cases found for Germany 2013, n= 683.713*

	Recall ≥36h and ≥32WoG		Recall <36h		Recall <32WoG		Recall Total	Confirmed cases
Disease	n	(%)	n	(%)	n	(%)	(%)	n
Hypothyrodism	477	0,07	318	3,87	26	0,31	0,12	211
CAH	1645	0,25	296	3,60	618	7,43	0,37	47
Biotinidase-Deficiency	170	0,03	7	0,09	20	0,24	0,03	21
Classic galactosaemia	209	0,03	5	0,06	5	0,06	0,03	9
PKU/HPA	207	0,03	15	0,18	15	0,18	0,03	129
MSUD	81	0,01	3		8	0,10	0,01	5
MCAD	115	0,02	2		3		0,02	75
LCHAD	20	0,003	0		1		0,00	4
VLCAD	128	0,02	2		0		0,02	10
CPT I-Deficiency	3		0		2		0,00	0
CPT II-Deficiency	11	0,002	0		0		0,002	0
CACT-Deficiency	0		0		0			0
GA I	81	0,01	5	0,06	7	0,08	0,01	3
IVA	27	0,004	0	0,00	16	0,19	0,01	6
Total	**3174**	**0,48**	**653**	**7,94**	**721**	**8,67**	**0,67**	**520**

* Primary screening Total: n= 683.713; Primary screening ≥ 36h and ≥ 32WoG n=667.169; Primary screening <36h n=8.227; Primary screening <32WoG n=8.317

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=19) (Tab.3.1) and cases where the confirmation diagnostics were negative (n=2). For some diseases the true prevalence could be higher. Double reported cases were included only once. Feedback from the treating doctors on the confirmed diagnosis, quality assurance of the laboratory analysis and evaluation of the quality of results are sought. The DGNS provides appropriate consent forms.

Table 3.1 : Cases with missing data of confirmation diagnostics

Disease	Data missing n
Hypothyrodism	10
CAH	5
Galactosaemia (classic)	1
PKU	2
IVA	1
Total	**19**

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 Hypothyrodism

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	52731	51153	32	0,06	14
3	15389	15106	11	0,07	5
5	53180	51970	55	0,11	14
6	12921	12414	3		1
7	45637	44293	30	0,07	7
8	159383	156008	153	0,10	62
9	113335	110468	76	0,07	32
10	34861	34176	21	0,06	12
11	16601	16094	3		2
12	82526	80717	34	0,04	34
13	64253	62674	33	0,05	19
14	24826	24304	17	0,07	4
15	8070	7792	9	0,12	5
Total	**683713**	**667169**	**477**	**0,07**	**211**

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

In addition n=14 hyperthyrotropinaemia were 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
1	52731	51153	13	0,03[a]	9
3	15389	15106	6	0,04	1
5	53180	51970	233	0,45	2
6	12921	12414	37	0,30	0
7	45637	44293	360	0,81	1
8	159383	156008	73	0,05[b]	9
9	113335	110468	299	0,27	12
10	34861	34176	118	0,35	4
11	16601	16094	17	0,11	2
12	82526	80717	263	0,33	5
13	64253	62674	139	0,22	1
14	24826	24304	59	0,24	1
15	8070	7792	28	0,36	0
Total	**683713**	**667169**	**1645**	**0,25**	**47**

[a] Laboratory used second-tier process

[b] Laboratory used second-tier method for screening>36h and <32 WoG

3.1.3 Biotinidase deficiency

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases	Including complete defect / no differentiation
1	52731	51153	8	0,02	2	0
3	15389	15106	3		1	1
5	53180	51970	4		0	0
6	12921	12414	10	0,08	0	0
7	45637	44293	8	0,02	0	0
8	159383	156008	92	0,06	15	5
9	113335	110468	3		0	0
10	34861	34176	1		0	0
11	16601	16094	1		0	0
12	82526	80717	21	0,03	0	0
13	64253	62674	12	0,02	1	1
14	24826	24304	1		0	0
15	8070	7792	6	0,08	2	2
Total	**683713**	**667169**	**170**	**0,03**	**21**	**9**

* 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	52731	51153	14	0,03	3	1
3	15389	15106	2		0	0
5	53180	51970	21	0,04	4	0
6	12921	12414	1		0	0
7	45637	44293	8	0,02	1	0
8	159383	156008	29	0,02	11	3
9	113335	110468	4		1	1
10	34861	34176	11	0,03	8	2
11	16601	16094	3		2	0
12	82526	80717	39	0,05	0	0
13	64253	62674	47	0,07	4	2
14	24826	24304	17	0,07	4	0
15	8070	7792	13	0,17	2	0
Total	**683713**	**667169**	**209**	**0,03**	**40**	**9**

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

** Variants are not comprehensively covered

3.1.5 Phenylketonuria (PKU) / Hyperphenylalaninemia (HPA)

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases	Including PKU
1	52731	51153	23	0,04	10	5
3	15389	15106	7	0,05	5	3
5	53180	51970	12	0,02	11	7
6	12921	12414	4		0	
7	45637	44293	34	0,08	8	3
8	159383	156008	33	0,02	27	17
9	113335	110468	21	0,02	20	10
10	34861	34176	11	0,03	7	4
11	16601	16094	4		3	1
12	82526	80717	21	0,03	20	8
13	64253	62674	19	0,03	11	4
14	24826	24304	11	0,05	4	3
15	8070	7792	7	0,09	3	1
Total	**683713**	**667169**	**207**	**0,03**	**129**	**66**

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

3.1.6 Maple Syrup Urine Disease (MSUD)

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	52731	51153	26	0,05	2
3	15389	15106	1		0
5	53180	51970	12	0,02	0
6	12921	12414	1		0
7	45637	44293	12	0,03	0
8	159383	156008	2		1
9	113335	110468	12	0,01	2
10	34861	34176	1		0
11	16601	16094	4		0
12	82526	80717	0		0
13	64253	62674	7	0,01	0
14	24826	24304	1		0
15	8070	7792	2		0
Total	**683713**	**667169**	**81**	**0,01**	**5**

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

3.1.7 Medium-Chain-Acyl-CoA-Dehydrogenase (MCAD)-Deficiency

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	52731	51153	4		0
3	15389	15106	2		1
5	53180	51970	5	0,01	3
6	12921	12414	8	0,06	0
7	45637	44293	6	0,01	2
8	159383	156008	25	0,02	24
9	113335	110468	26	0,02	15
10	34861	34176	12	0,04	4
11	16601	16094	3		2
12	82526	80717	15	0,02	15
13	64253	62674	4		5[b]
14	24826	24304	4		3
15	8070	7792	1		1
Total	**683713**	**667169**	**115**	**0,02**	**75**

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

[b] n=1 bloods taken <36h, therefore not included in the recall

3.1.8 Long-Chain-3-OH-Acyl-CoA-Dehydrogenase (LCHAD)-Deficiency

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	52731	51153	7	0,01	1
3	15389	15106	0		0
5	53180	51970	0		0
6	12921	12414	0		0
7	45637	44293	0		0
8	159383	156008	2		2
9	113335	110468	1		1
10	34861	34176	3		0
11	16601	16094	0		0
12	82526	80717	1		0
13	64253	62674	7	0,01	0
14	24826	24304	0		0
15	8070	7792	0		0
Total	**683713**	**667169**	**21**		**4**

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

3.1.9 (Very-)Long-Chain-Acyl-CoA-Dehydrogenase (VLCAD)-Deficiency

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	52731	51153	16	0,03	2
3	15389	15106	4		1
5	53180	51970	7	0,01	0
6	12921	12414	5	0,04	0
7	45637	44293	26	0,06	0
8	159383	156008	8	0,01	5
9	113335	110468	42	0,04	0
10	34861	34176	17	0,05	1
11	16601	16094	0		0
12	82526	80717	0		0
13	64253	62674	1		1
14	24826	24304	2		0
15	8070	7792	0		0
Total	**683713**	**667169**	**128**	**0,02**	**10**

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

3.1.10 For CPT I-Deficiency, CPT II-Deficiency and CACT-Deficiency, no confirmed cases were reported.

3.1.11 Glutaric aciduria Type I

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	52731	51153	14	0,03	0
3	15389	15106	0		0
5	53180	51970	7	0,01	1
6	12921	12414	1		0
7	45637	44293	22	0,05	0
8	159383	156008	1		1
9	113335	110468	33	0,03	0
10	34861	34176	0		0
11	16601	16094	0		0
12	82526	80717	2		0
13	64253	62674	1		1
14	24826	24304	0		0
15	8070	7792	0		0
Total	**683713**	**667169**	**81**	**0,01**	**3**

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

3.1.12 Isovalerianacidaemia (IVA)

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall-rate(%)*	Confirmed cases
1	52731	51153	4		0
3	15389	15106	0		0
5	53180	51970	0		0
6	12921	12414	2		1
7	45637	44293	8	0,02	0
8	159383	156008	1		0
9	113335	110468	4		2
10	34861	34176	2		1
11	16601	16094	2		0
12	82526	80717	3		2
13	64253	62674	1		0
14	24826	24304	0		0
15	8070	7792	0		0
Total	**683713**	**667169**	**27**		**6**

* 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 before 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 Hypothyrodism

	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	51153	32	0,06	904	6	0,66	674	0	
3	15106	11	0,07	131	0		152	0	
5	51970	55	0,11	700	0		510	1	
6	12414	3		328	0		179	0	
7	44293	30	0,07	679	32	4,71	665	2	
8	156008	153	0,10	1503	168	11,18	1872	5	
9	110468	76	0,07	1325	5		1542	1	
10	34176	21	0,06	374	35	9,36	311	1	
11	16094	3		352	40	11,36	155	1	
12	80717	34	0,04	806	22	2,73	1003	11	1,10
13	62674	33	0,05	746	1		833	2	
14	24304	17	0,07	265	7	2,64	257	2	
15	7792	9	0,12	114	2		164	0	
Total	**667169**	**477**	**0,07**	**8227**	**318**	**3,87**	**8317**	**26**	**0,31**

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[a]	51153	13	0,03	904	1		674	8	1,19
3	15106	6	0,04	131	0		152	0	
5	51970	233	0,45	700	6	0,86	510	34	6,67
6	12414	37	0,30	328	0		179	2	
7	44293	360	0,81	679	48	7,07	665	398	59,85
8[b]	156008	73	0,05	1503	139	9,25	1872	24	1,28
9	110468	299	0,27	1325	8	0,60	1542	33	2,14
10	34176	118	0,35	374	10	2,67	311	25	8,04
11	16094	17	0,11	352	16	4,55	155	10	6,45
12	80717	263	0,33	806	58	7,20	1003	36	3,59
13	62674	139	0,22	746	1		833	16	1,92
14	24304	59	0,24	265	7	2,64	257	17	6,61
15	7792	28	0,36	114	2		164	15	9,15
Total	**667169**	**1645**	**0,25**	**8227**	**296**	**3,60**	**8317**	**618**	**7,43**

[a] Laboratory used second-tier process [b] Laboratory used second-tier process at screening >36h and <32 WoG

3.2.3 Biotinidase deficiency (incl. partial defects)

	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	51153	8	0,02	904	2		674	4	
3	15106	3		131	0		152	0	
5	51970	4		700	1		510	1	
6	12414	10	0,08	328	0		179	0	
7	44293	8	0,02	679	0		665	0	
8	156008	92	0,06	1503	2		1872	8	0,43
9	110468	3		1325	0		1542	1	
10	34176	1		374	0		311	0	
11	16094	1	0,01	352	0		155	0	
12	80717	21	0,03	806	2		1003	1	
13	62674	12	0,02	746	0		833	3	
14	24304	1		265	0		257	0	
15	7792	6	0,08	114	0		164	2	
Total	**667169**	**170**	**0,03**	**8227**	**7**	**0,09**	**8317**	**20**	**0,24**

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	51153	14	0,03	904	0		674	0	
3	15106	2		131	0		152	0	
5	51970	21	0,04	700	1		510	0	
6	12414	1		328	0		179	0	
7	44293	8	0,02	679	0		665	0	
8	156008	29	0,02	1503	0		1872	0	
9	110468	4		1325	0		1542	0	
10	34176	11	0,03	374	0		311	0	
11	16094	3		352	1		155	0	
12	80717	39	0,05	806	2		1003	5	
13	62674	47	0,07	746	1		833	0	
14	24304	17	0,07	265	0		257	0	
15	7792	13	0,17	114	0		164	0	
Total	**667169**	**209**	**0,03**	**8227**	**5**	**0,06**	**8317**	**5**	**0,06**

3.2.5 Phenylketonuria (PKU) / Hyperphenylalaninemia (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	51153	23	0,04	904	6	0,66	674	2	
3	15106	7	0,05	131	0		152	0	
5	51970	12	0,02	700	2		510	0	
6	12414	4		328	0		179	1	
7	44293	34	0,08	679	4		665	8	1,20
8	156008	33	0,02	1503	2		1872	0	
9	110468	21	0,02	1325	0		1542	1	
10	34176	11	0,03	374	0		311	1	
11	16094	4		352	0		155	0	
12	80717	21	0,03	806	0		1003	1	
13	62674	19	0,03	746	0		833	0	
14	24304	11	0,05	265	1		257	1	
15	7792	7	0,09	114	0		164	0	
Total	**667169**	**207**	**0,03**	**8227**	**15**	**0,18**	**8317**	**15**	**0,18**

3.2.6 Maple Syrup Urine Disease (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	51153	26	0,05	904	0		674	1	
3	15106	1		131	0		152	0	
5	51970	12	0,02	700	0		510	0	
6	12414	1		328	0		179	0	
7	44293	12	0,03	679	2		665	6	0,90
8	156008	2		1503	0		1872	1	
9	110468	12	0,01	1325	0		1542	0	
10	34176	1		374	0		311	0	
11	16094	4		352	0		155	0	
12	80717	0		806	1		1003	0	
13	62674	7	0,01	746	0		833	0	
14	24304	1		265	0		257	0	
15	7792	2		114	0		164	0	
Total	**667169**	**81**	**0,01**	**8227**	**3**	**0,04**	**8317**	**8**	**0,10**

3.2.7 Medium-Chain-Acyl-CoA-Dehydrogenase (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	51153	4		904	0		674	1	
3	15106	2		131	0		152		
5	51970	5	0,01	700	0		510		
6	12414	8	0,06	328	0		179		
7	44293	6	0,01	679	0		665		
8	156008	25	0,02	1503	0		1872		
9	110468	26	0,02	1325	0		1542		
10	34176	12	0,04	374	0		311	2	
11	16094	3	0,02	352	0		155		
12	80717	15	0,02	806	1		1003		
13	62674	4		746	1		833		
14	24304	4		265	0		257		
15	7792	1		114	0		164		
Total	**667169**	**115**	**0,02**	**8227**	**2**	**0,02**	**8317**	**3**	**0,04**

3.2.8 Long-Chain-3-OH-Acyl-CoA-Dehydrogenase (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	51153	7	0,01	904	0		674	0	
3	15106	0		131	0		152	0	
5	51970	0		700	0		510	0	
6	12414	0		328	0		179	0	
7	44293	0		679	0		665	0	
8	156008	2		1503	0		1872	0	
9	110468	1		1325	0		1542	1	
10	34176	3		374	0		311	0	
11	16094	0		352	0		155	0	
12	80717	1		806	0		1003	0	
13	62674	7	0,01	746	0		833	0	
14	24304	0		265	0		257	0	
15	7792	0		114	0		164	0	
Total	**667169**	**21**		**8227**	**0**		**8317**	**1**	**0,01**

3.2.9 (Very-)Long-Chain-Acyl-CoA-Dehydrogenase (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	51153	16	0,03	904	0		674	0	
3	15106	4	0,03	131	0		152	0	
5	51970	7	0,01	700	0		510	0	
6	12414	5		328	0		179	0	
7	44293	26	0,06	679	0		665	0	
8	156008	8	0,01	1503	0		1872	0	
9	110468	42	0,04	1325	2		1542	0	
10	34176	17	0,05	374	0		311	0	
11	16094	0		352	0		155	0	
12	80717	0		806	0		1003	0	
13	62674	1		746	0		833	0	
14	24304	2		265	0		257	0	
15	7792	0		114	0		164	0	
Total	**667169**	**128**	**0,02**	**8227**	**2**	**0,02**	**8317**	**0**	

3.2.10 Carnitin-Palmitoyl-CoA-Transferase I (CPTI)-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	51153	1		904	0		674	2	
3	15106	0		131	0		152	0	
5	51970	1		700	0		510	0	
6	12414	0		328	0		179	0	
7	44293	0		679	0		665	0	
8	156008	1		1503	0		1872	0	
9	110468	0		1325	0		1542	0	
10	34176	0		374	0		311	0	
11	16094	0		352	0		155	0	
12	80717	0		806	0		1003	0	
13	62674	0		746	0		833	0	
14	24304	0		265	0		257	0	
15	7792	0		114	0		164	0	
Total	**667169**	**3**		**8227**	**0**		**8317**	**2**	

3.2.11 Carnitin-Palmitoyl-CoA-Transferase II (CPTII)-Deficiency respectively Carnitin-Acylcarnitin-Translocase (CACT)-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	51153	0		904	0		674	0	
3	15106	0		131	0		152	0	
5	51970	4		700	0		510	0	
6	12414	0		328	0		179	0	
7	44293	0		679	0		665	0	
8	156008	0		1503	0		1872	0	
9	110468	1		1325	0		1542	0	
10	34176	6	0,02	374	0		311	0	
11	16094	0		352	0		155	0	
12	80717	0		806	0		1003	0	
13	62674	0		746	0		833	0	
14	24304	0		265	0		257	0	
15	7792	0		114	0		164	0	
Total	**667169**	**11**		**8227**	**0**		**8317**	**0**	

3.2.12 Glutaric aciduria Type I (GA 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	51153	14	0,03	904	0		674	2	
3	15106	0		131	0		152	0	
5	51970	7	0,01	700	0		510	0	
6	12414	1		328	0		179	0	
7	44293	22	0,05	679	4		665	4	
8	156008	1		1503	0		1872	0	
9	110468	33	0,03	1325	1		1542	1	
10	34176	0		374	0		311	0	
11	16094	0		352	0		155	0	
12	80717	2		806	0		1003	0	
13	62674	1		746	0		833	0	
14	24304	0		265	0		257	0	
15	7792	0		114	0		164	0	
Total	**667169**	**81**	**0,01**	**8227**	**5**	**0,06**	**8317**	**7**	**0,08**

3.2.13 Isovalerianacidaemia (IVA)

	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	51153	4		904	0		674	1	
3	15106	0		131	0		152	0	
5	51970	0		700	0		510	2	
6	12414	2		328	0		179	0	
7	44293	8	0,02	679	0		665	12	1,80
8	156008	1		1503	0		1872	0	
9	110468	4		1325	0		1542	0	
10	34176	2		374	0		311	0	
11	16094	2		352	0		155	1	
12	80717	3		806	0		1003	0	
13	62674	1		746	0		833	0	
14	24304	0		265	0		257	0	
15	7792	0		114	0		164	0	
Total	**667169**	**27**		**8227**	**0**		**8317**	**16**	**0,19**

4 Process Periods

4.1 Age at blood collection

According to the screening-guidelines of children (§8.1), every newborn should be screened beyond the completed 32nd gestational week and 36th hour of life, preferably between 36 and 48 hours. In 91.8% of cases, with specification of collection time, the collection was according to the guidelines, in 6.8% beyond the 72nd hour of life, in 1.3% before the 36th hour of life (Table 4.1). The proportion of samples which were sampled after 72 hours could be lowered from 22.25 % in 2005 to 6.83 % in 2013 (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	52731	1033	1,96	12698	24,08	33703	63,91	5297	10,05
3	15389	160	1,04	2876	18,69	11606	75,42	747	4,85
5	53231	763	1,43	38722	72,74	12617	23,70	1129	2,12
6	12921	350	2,71	5443	42,13	6585	50,96	543	4,20
7	45637	830	1,82	13416	29,40	26751	58,62	4640	10,17
8[a]	158966	1673	1,05	63813	40,14	82686	52,01	10794	6,79
9[a]	113310	1433	1,26	41034	36,21	61534	54,31	9309	8,22
10	34861	406	1,16	9999	28,68	21775	62,46	2681	7,69
11	16601	370	2,23	4920	29,64	10246	61,72	1065	6,42
12[a]	80575	888	1,10	52101	64,66	24547	30,46	3039	3,77
13	64253	824	1,28	27488	42,78	30046	46,76	5895	9,17
14[a]	24258	297	1,22	14604	60,20	8542	35,21	815	3,36
15	8070	116	1,44	3613	44,77	3830	47,46	511	6,33
Total	**680803**	**9143**	**1,34**	**290727**	**42,70**	**334468**	**49,13**	**46465**	**6,83**

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 22.6% of cases with statement of the delivery time the probe was received later than 72 hours after sampling, in 24.4% 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	52731	14198	26,93	17852	33,85	10841	20,56	9840	18,66
3	15389	4912	31,92	6514	42,33	2678	17,40	1285	8,35
5	53212	6329	11,89	21414	40,24	14929	28,06	10540	19,81
6	12921	1300	10,06	5837	45,17	3409	26,38	2375	18,38
7	45637	11155	24,44	13240	29,01	8481	18,58	12761	27,96
8[a]	158966	16471	10,36	55276	34,77	43998	27,68	43221	27,19
9[a]	113327	9884	8,72	31431	27,73	30410	26,83	41602	36,71
10	34861	4670	13,40	12630	36,23	10014	28,73	7547	21,65
11	16601	2555	15,39	7727	46,55	4143	24,96	2176	13,11
12[a]	78700	24554	31,20	29246	37,16	15619	19,85	9281	11,79
13	64253	17311	26,94	21993	34,23	15239	23,72	9710	15,11
14[a]	21715	10928	50,32	6522	30,03	2894	13,33	1371	6,31
15	8070	1365	16,91	3331	41,28	2012	24,93	1362	16,88
Total	**676383**	**125632**	**18,57**	**233013**	**34,45**	**164667**	**24,35**	**153071**	**22,63**

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 80.3% of probes the results get reported within 24 hours. The process time in borderline elevated results can be prolonged due to repeat examinations (quality control) (Table 4.3

Table 4.3 Period between laboratory receipt and result reporting

	Total	≤24h		>24h-48h		>48h-72h		>72h	
Lab	n	n	%	n	%	n	%	n	%
1	52731	25856	49,03	17693	33,55	5745	10,89	3437	6,52
3	15389	14130	91,82	902	5,86	131	0,85	229	1,49
5	53248	38262	71,86	11682	21,94	3082	5,79	222	0,42
6	12921	11670	90,32	753	5,83	280	2,17	218	1,69
7	n.s.	n.s.		n.s.		n.s.		n.s.	
8	159383	152398	95,62	5941	3,73	878	0,55	166	0,10
9[a]	113197	108094	95,49	4289	3,79	660	0,58	154	0,14
10	34861	30221	86,69	4527	12,99	101	0,29	12	0,03
11	16601	10806	65,09	5394	32,49	376	2,26	25	0,15
12[a]	80688	60916	75,50	14128	17,51	5488	6,80	156	0,19
13	64253	48256	75,10	10996	17,11	4436	6,90	565	0,88
14[a]	24344	2257	9,27	16517	67,85	4027	16,54	1543	6,34
15	8070	7812	96,80	255	3,16	3	0,04	0	
Total	**635686**	**510678**	**80,33**	**93077**	**14,64**	**25207**	**3,97**	**6727**	**1,06**

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 2013

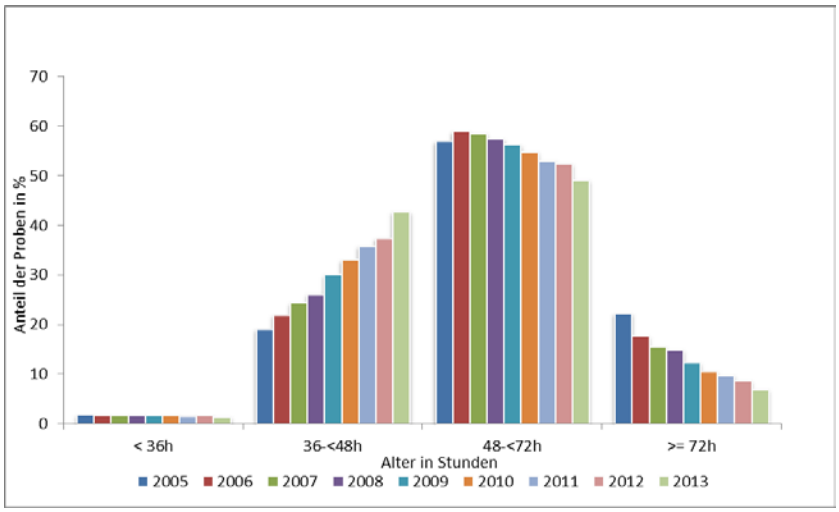


Figure 3: Period between sampling and laboratory receipt 2005 to 2013

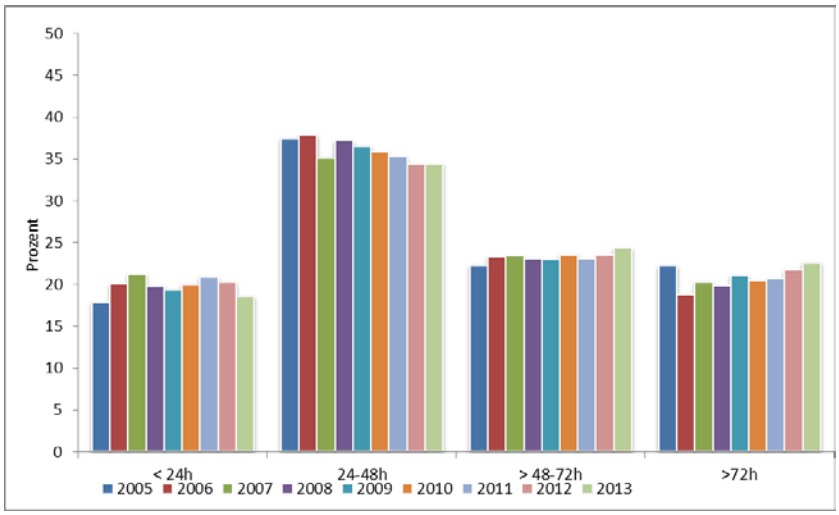
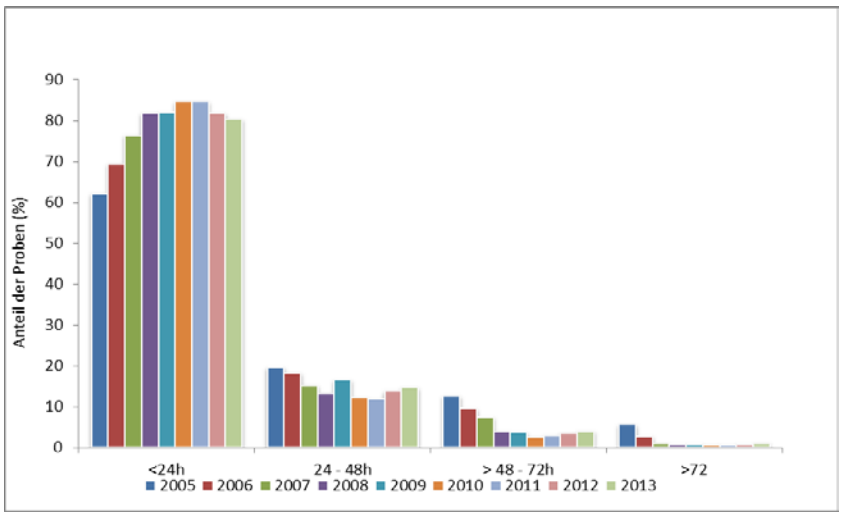


Figure 4: Period from laboratory receipt to report 2005 to 2013



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 36th to the 48th hour of life (guidelines until 72 h). 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 4.2% 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[a]	Not specified[b]	Total
Hypothyrodism	178	7		5	14	3	4	**211**
CAH	38	2		6			1	**47**
Biotinidase	20			1				**21**
Galactosaemia	6	2					1	**9**
PKU/HPA	117	5	1	5			1	**129**
MSUD	5							**5**
MCAD	64	4	1	2		1	3	**75**
LCHAD	3			1				**4**
VLCAD	10							**10**
GA I	3							**3**
IVA	6							**6**
Total	**450**	**20**	**2**	**20**	**14**	**4**	**10**	**520**

* ≥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 First Test card and diagnosis with confirmed hypothyroidism

The following tables show in detail the relationship between the first test card (TC) and diagnosis in a confirmed validated hypothyroidism. Table 5.2 applies to all cases and Table 5.3 only to the cases in which the primary screening was performed before reaching 32 weeks of gestation.

Table 5.2 Evaluation TSH-value 1. TC and Diagnosis

	Evalulation TSH value of the first test card				
Diagnosis	**True positive**	**False negative**	**Confounding, possibly false negative**	**Unremarkable, no known cause**	**Total**
Congenital hypothyroidism	191 (incl. 2 PT)	0	3 (incl. 2 PT)	7 (all PT)	**201**
Transient hypothyroidism	2	2[b]	1	1 (PT)	**6**
Other diagnosis[a]	3	0	0	1 (PT)	**4**
Total	**196** (incl. 2 PT)	**2**	**4** (incl. 2 PT)	**9** (all PT)	**211**

PT = Preterm < 32 WoG

[a] at time of testing not clear if transient or permanent, [b] both cases with 2nd TC suspicious, after exposure to iodine

Table 5.3 Preterm < 32 WoG - Correlation of primary screening and diagnosis after completed weeks of gestation (WoG), Total n=14 cases

	1st TC Noticeable	1st TC Unremarkable				
	Congenital hypothyroidism	**Transient hypothyroidism**		**Congenital hypothyroidism**		
WoG		2nd TC after exposure to iodine	No known impact	No known impact	TC after catecholamine / Transfusion	Mother autoimmune thyroiditis
23-24				24 WoG 24 WoG	23 WoG	
25-26				25 WoG 25 WoG		26 WoG
27-28		27 WoG	27 WoG	27 WoG	27 WoG	
29-30				29 WoG 29 WoG		
31-32	31 WoG 31 WoG					
Total	**2**	**1**	**1**	**7**	**2**	**1**

From 14 preterm infants <32 WoG with confirmed congenital hypothyroidism, only 2 children (both 31 WoG) had a first noticeable test card. After the time specified in the German guidelines algorithm for the screening procedure (repeat screening with 32 WoG) 2 out of the 12 preterm infants were tested without a pathological finding at their first test card. In one case (25 WoG) the control at 32 WoG was unremarkable. Only a screening with 37 WoG was noticeable. This shows that a control at discharge would be necessary in preterm infants.

In the second case (29 WoG) the 32 WoG control was undertaken at 34 weeks. The cause of the unremarkable first levels is unknown in both cases.

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 2013, 28 out of 520 confirmed cases had no detailed information about the confirmation diagnostics available, the available data though allows a plausible analysis. In a further 19 cases only limited information is given that confirmation can not be accepted and we therefore do not list it in our analysis.

6.1 Congenital hypothyroidism

Lab	Confirmed cases	TSH	T3	fT3	T4	fT4	Ultrasound	Thyroid antibodies
1	14	14	n.s.	2	n.s.	14	14	1
3	5	5	4	3	2	5	4	5
5	14	12	n.s.	9	n.s.	10	11	7
6	1	1	n.s.	1	n.s.	1	1	1
7	7	2	n.s.	n.s.	n.s.	n.s.	1	n.s.
8	62	61	n.s.	49	n.s.	60	55	50
9	32	29	7	18	7	28	9	1
10	12	12	n.s.	9	n.s.	12	8	8
11	2	2	n.s.	2	n.s.	2	2	1
12	34	34	n.s.	23	n.s.	33	22	19
13	19	19	1	n.s.	n.s.	19	n.s.	n.s.
14	4	4	n.s.	2	n.s.	4	n.s.	n.s.
15	5	5	n.s.	5	n.s.	5	3	2
Total	**211***	**200**	**12**	**123**	**9**	**193**	**130**	**95**

* incl n=10 cases without detailed information of confirmation diagnostics

6.2 Congenital adrenal hyperplasia (CAH)

Lab	Confirmed cases	17-OHP (Serum)	Steroid (Serum/TB)	Urinary steroids	Molecular genetic testing
1	9	9	8	1	9
3	1	1	1	n.s.	n.s.
5	2	n.s.	1	2	n.s.
7	1	n.s.	n.s.	n.s.	n.s.
8	9	9	8	1	7
9	12	10	9	2	5
10	4	4	3	2	3
11	2	1	1	n.s.	2
12	5	4	3	1	4
13	1	n.s.	n.s.	n.s.	1
14	1	1	1	n.s.	n.s.
Total	**47***	**39**	**35**	**9**	**31**

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

6.3 Biotinidase deficiency

Lab	Confirmed cases	Biotinidase (Serum/TB)	Molecular genetic testing
1	2	2	n.s.
3	1	n.s.	n.s.
8	15	12	1
13	1	1	n.s.
15	2	2	n.s.
Total	**21***	**17**	**1**

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

6.4 Classic Galactosaemia

Lab	Confirmed cases	Enzyme assay	Galactose, Gal1P	Molecular genetic testing
1	1	1	1	n.s.
8	3	3	3	1
9	1	1	1	n.s.
10	2	2	2	2
13	2	1	2	1
Total	**9**	**8**	**9**	**4**

6.5 Phenylketonuria (PKU) / Hyperphenylalaninaemia (HPA)

Lab	Confirmed cases	Phe (Serum/TB)	Phe/Tyr	BH4-Test	Molecular genetic testing	Pterine im Urine/TB	DHPR in dried blood
1	10	10	4	4	n.s.	10	10
3	5	4	4	3	n.s.	3	3
5	11	9	8	7	n.s.	7	7
7	8	3	2	n.s.	2	2	2
8	27	24	12	13	6	18	19
9	20	18	11	1	4	14	14
10	7	7	6	n.s.	5	6	7
11	3	3	n.s.	1	n.s.	1	1
12	20	20	15	10	8	19	18
13	11	10	2	4	1	10	10
14	4	4	4	3	n.s.	2	2
15	3	3	n.s.	n.s.	n.s.	3	3
Total	**129***	**115**	**68**	**46**	**26**	**95**	**96**

* incl n=10 cases without detailed information of confirmation diagnostics

6.6 Maple syrup urine disease (MSUD)

Lab	Confirmed cases	Confirmation Serum	Urinary organic acids	Enzyme activity	Molecular genetic testing
1	2	2	2	n.s.	n.s.
8	1	1	1	n.s.	1
9	2	2	n.s.	n.s.	n.s.
Total	**5**	**5**	**3**	**n.s.**	**1**

6.7 Medium-Chain-Acyl-CoA-Dehydrogenase (MCAD)-Deficiency

Lab	Confirmed cases	Confirmation Serum/TB	Urinary organic acids	Enzyme activity	Molecular genetic testing
3	1	n.s.	1	n.s.	n.s.
5	3	3	n.s.	n.s.	3
7	2	n.s.	2	1	2
8	24	6	6	3	19
9	15	8	9	2	9
10	4	4	3	2	3
11	2	1	2	n.s.	1
12	15	9	7	1	10
13	5	2	n.s.	2	4
14	3	3	n.s.	1	2
15	1	n.s.	1	1	1
Total	**75***	**36**	**31**	**13**	**54**

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

6.8 Long-Chain-3-OH-Acyl-CoA-Dehydrogenase (LCHAD)-Deficiency

Lab	Confirmed cases	Confirmation Serum/TB	Urinary organic acids	Enzyme activity	Molecular genetic testing
1	1	1	1	n.s.	1
8	2	n.s.	2	n.s.	2
9	1	1	1	1	n.s.
Total	**4**	**2**	**4**	**1**	**3**

6.9 (Very-)Long-Chain-Acyl-CoA-Dehydrogenase (VLCAD)-Deficiency

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

6.10 CPT I-Deficiency, CPT II-Deficiency and CACT-Deficiency

No cases of the CPT I-Deficiency, CPT II-Deficiency and CACT-Deficiency reported

6.11 Glutaric aciduria Type I (GA I)

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

6.12 Isovalerianacidaemia (IVA)

Lab	Confirmed cases	Confirmation Serum	Urinary organic acids	Enzyme activity	Molecular genetic testing
6	1	n.s.	1	n.s.	n.s.
9	2	2	2	n.s.	1
10	1	1	1	n.s.	1
12	2	n.s.	2	n.s.	1
Total	**6**	**3**	**6**	**n.s.**	**3**

7 Methods and cutoffs 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 Hypothyrodism

Lab	Parameter	Cutoff	Method
1	TSH	15 mU/l	AutoDELFIA
3	TSH	15 mU/l	AutoDELFIA
5	TSH	15 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 (<4 Days) 15 mU/l (<7 Days) <10 mU/l (≥7 Days)	AutoDELFIA
13	TSH	20 mU/l (<4 Days) 15 mU/l (<7 Days) <10 mU/l (≥7 Days)	AutoDELFIA
14	TSH	15 mU/l	AutoDELFIA
15	TSH	15 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

* Laboratory used 2nd tier process

7.4 Biotinidase deficiency

Lab	Parameter	Cutoff	Method
1	Biotinidase	30% panel mean	Colorimetrie qualitative
3	Biotinidase	30% median days	Colorimetrie qualitative
5	Biotinidase	30% panel mean	Colorimetrie quantitative
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	Cutoff	Method
1	GALT	3,5 U/g Hb	Fluorometrie(PE)
	Galactose	20 mg/dl	BIORAD Quantase
3	GALT	2,3 U/g Hb	BIORAD Quantase
	Galactose	15 mg/dl	
5	GALT	3,5 U/g Hb	BIORAD Quantase
	Galactose	15 mg/dl	BIORAD Quantase
6	GALT	3,5 U/g Hb	Fluorometrie (PE)
7	GALT	3,5 U/g Hb	Fluorometrie quantitative
8	GALT	20% daily mean	Fluorimetrie quantitative
	Galactose	30 mg/dl	Colorimetrie non kit
9	GALT	<2,3 U/g Hb	BIORAD Quantase
	Galactose as 2nd tier process	20 mg/dl, decreased <48h: 6 mg/dl	BIORAD Quantase
10	GALT	2,3 U/g Hb	BIORAD Quantase
	Galactose	1111 µmol/l	BIORAD Quantase
11	GALT	3,5 U/g Hb	Fluorometrie quantitative
12	GALT	<30%	Fluoro. quant.(non kit)
	Galactose	15 mg/dl	Colorimetrie non Kit
13	GALT	<30%	Fluoro. quant.(non kit)
	Galactose	15 mg/dl	Colorimetrie non Kit
14	GALT	<2,3 U/g Hb	BIORAD Quantase
	Galactose	>15 mg/dl	BIORAD Quantase
15	GALT	<2,3 U/g Hb	BIORAD Quantase
	Galactose	>15 mg/dl	BIORAD Quantase

7.6 MS/MS

Lab	Method
1	non derivat. Kit
3	non derivat. non Kit
5	derivat. non Kit
6	non derivat.PE Kit
7	derivatisiert PE Kit
8	derivatisiert non Kit
9	derivatisiert non Kit
10	derivatisiert non Kit
11	non derivat. non Kit
12	derivatisiert non Kit
13	derivatisiert non Kit
14	derivatisiert non Kit
15	derivatisiert 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 2013 Herausgeber: Statistisches Bundesamt, Wiesbaden www.destatis.de