National

Screening Report

Germany 2015

German Society for Neonatal Screening (DGNS)

Uta Nennstiel, 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

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

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Abbreviations and Glossary:

CAH	Congenital adrenal hyperplasia
CACT - Deficiency	Carnitine-Acylcarnitine-Translocase-Deficiency
CPTI - Deficiency	Carnitine-Palmitoyl-CoA-Transferase I-Deficiency
CPTII - Deficiency	Carnitine-Palmitoyl-CoA-Transferase II-Deficiency
PT	Preterm < 32 WoG
GA I	Glutaric acidaemia Type I
BW	Birth weight
HPA	Hyperphenylalaninemia
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 case of abnormal finding, second examination of additional parameters or alternative analysis procedure with the same test card
WoG	Week of gestation
VLCAD - Deficiency	Very-Long-Chain-Acyl-CoA-Dehydrogenase-Deficiency

Screening Laboratories and Screening Centres

The results for screening centres with multiple locations or laboratories which are affiliated with a screening centre are stratified by location / affiliation.

(1) Neugeborenen Screeninglabor Berlin
Dr. med. Oliver Blankenstein
Sylter Str. 2
D 13353 Berlin
030/405 026 391 / Fax: -613
Oliver.Blankenstein@charite.de

(3) Screeningzentrum Sachsen
Prof. Dr. med. Joachim Thiery,
Universitätsklinikum Leipzig
Standort **Dresden**
PF 160252
01288 Dresden
0351/458 5230 / 5229
Contact:
Dr. Marina Stopsack
marina.stopsack@uniklinikum-dresden.de

(10) Standort **Leipzig**
Paul-Listr-Str. 13-15
04103 **Leipzig**
0341/9722222 (Leitstelle ILM)
Contact:
Prof. Dr. Uta Ceglarek
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/ neugeborenenscreening@kgu.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
Dr. med. Dr. rer.nat. Nils Janzen
Postfach 911009
30430 **Hannover**
05108/92163 0
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
www.stwz.ovgu.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
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

(12/14) Screeningzentrum Bayern Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit
Dr. med. Uta Nennstiel 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 complete detection coupled with quality assured therapy for all newborns with treatable endocrine and metabolic diseases.

In the policies for early detection of diseases in children up to 6 years of age, known as the „Children's Guidelines" (Kinder-Richtlinien) [1], the regulations for implementing the newborn screening program (NBS) are defined in §13 - §28 . The National Screening Report was compiled by the "German Society for Neonatal Screening" (DGNS e.V.) together with the German screening laboratories. The statistical analysis of the screening data was performed in accordance with the guidelines and quality criteria of the NBS implementation. This report pertains only to the metabolic and endocrine diseases which are defined in these guidelines. It provides a comprehensive statistical summary of disease-related screening figures, recall rates and confirmed diagnoses for the year 2015. Additionally, the report provides process quality data for all of Germany.

Process quality describes the process sequences and their evaluation by professional bodies according to predefined indicators. These are as follows for the newborn screening:

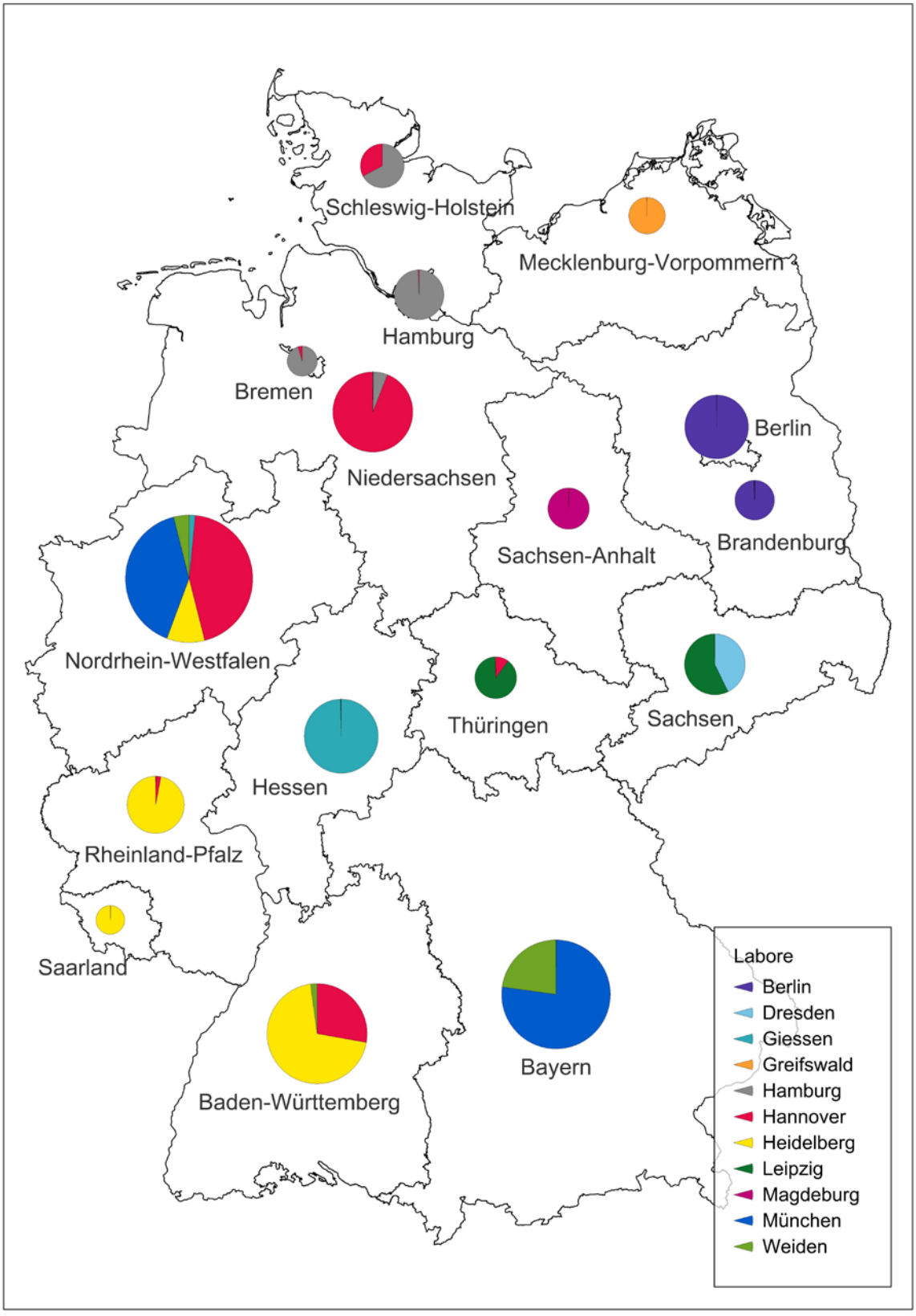
- Total survey of the targeted population
    - Collection method and rate
    - Blank card system
- Completeness of the control (recall) and follow-up examinations
- Recording test parameters and cutoffs
- Stratified recall rates, positive predictive values and prevalence by illness, laboratory, age and gestational age
- Specificity and sensitivity of diagnostic tests
- Processing times (pre-analytic and laboratory only), age at time the blood sample was taken, time between blood collection, arrival in the laboratory and communication of the result
- Individual screening values of newborns for whom further testing is recommended
- Confirmation diagnostics
    - Type of diagnostics
    - Period of diagnostics
- Final diagnosis
- Start of therapy

The laboratories that conducted the screening in 2015 in Germany are listed on the previous page (12 and 13 refer to the same laboratory, once in cooperation with the screening facility and once without; the same is true of 14 and 15). In the tables the laboratories are encrypted. Mentions of sections and subsections in the text refer to the "Children's Guidelines" of November 11, 2016 [1]. For convenience, the tables have not been numbered sequentially but rather in accordance with the related chapters.

We would like to thank all the laboratories for providing their data. The data have been checked for plausibility. In the cases of remaining inconsistencies, the data reported by the laboratories were used in the tables (inconsistencies can sometimes be systemic).

The screening samples from the individual federal states are distributed among the laboratories (“Labore”) as illustrated in Figure1.

Figure 1: Distribution of screening samples by state and laboratory



2 Results

In 2015, a total of 737,575 children were born in Germany [2]. The number of recorded screenings (738,864) exceeds the number of births. Reasons for the surplus screening samples could be control cards that were not declared as such and were received by another laboratory, or samples from newborns whose births were not registered in Germany. This cannot be further clarified due to the genetic diagnostics law, which prohibits the exchange of data between screening labs.

Births [2]:	737,575
First screenings:	738,864
Confirmed diagnoses (see Table 3):	539

A reliable statement about the rate of participation in NBS can only be made by reconciling individual data with overall population data. However, due to legal restrictions this is currently only possible in Bavaria.

The diseases targeted for the nationwide screening are defined in the “Children’s Guidelines”. In some laboratories, screenings for additional illnesses are carried out for scientific studies or based on state-level regulations; the results of those screenings are not covered in this report.

One of the targeted disease was found in 1 out of every 1,368 newborns, Table 2 shows the prevalence of the targeted diseases in Germany in 2015.

Table 2: Frequency of diseases detected in screening 2015

Disease	Confirmed cases	Prevalence	
Hypothyroidism	235	1:	3,139
Congenital adrenal hyperplasia (CAH)	36	1:	20,488
Biotinidase deficiency (incl. partial defect)	12	1:	61,465
Galactosaemia (classic)	7	1:	105,368
Phenylketonuria (PKU) n=66 / Hyperphenylalaninemia (HPA) n=66 Cofactor-Deficiency n=1	149	1:	4,950
Maple syrup urine disease (MSUD)	0		
Medium-Chain-Acyl-CoA-Dehydrogenase (MCAD)-Deficiency	72	1:	10,244
Long-Chain-3-OH-Acyl-CoA-Dehydrogenase (LCHAD)-Deficiency	6	1:	122,929
(Very-)Long-Chain-Acyl-CoA-Dehydrogenase (VLCAD)-Deficiency	7	1:	105,368
Carnitine-Palmitoyl-CoA-Transferase I (CPTI)-Deficiency	0		
Carnitine-Palmitoyl-CoA-Transferase II (CPTII)-Deficiency	0		
Carnitine-Acylcarnitine-Translocase (CACT)-Deficiency	0		
Glutaric aciduria Type I (GA I)	5	1:	147,515
Isovalerianacidaemia (IVA)	10	1:	73,758
Total	**539**	**1:**	**1,368**

2.1 Total primary screening figures

According to the "Children's Guidelines", a screening sample should be taken from every newborn before leaving the birth facility. For reliable screening results, blood samples must be collected after 32 weeks of gestation (WoG) and 36 hours of life. If the first screening occurs before the 36th hour of life or before the completed 32nd gestational week, it should be followed by a repeat screening. The following table shows the results of the primary screening stratified by age and gestational age.

Table 2.1: Age at primary screening

		≥36h and ≥32WoG		<36h and ≥32WoG		<32WoG	
Lab	Total	n	%	n	%	n	%
1	56687	55320	97.59	729	1.29	638	1.13
3	15877	15607	98.30	99	0.62	171	1.08
5	57518	56115	97.56	650	1.13	753	1.31
6	13393	12921	96.48	290	2.17	182	1.36
7	49948	48602	97.31	648	1.30	698	1.40
8	171081	167631	97.98	1419	0.83	2031	1.19
9	126680	123595	97.56	1274	1.01	1811	1.43
10	36846	36136	98.07	354	0.96	356	0.97
11	17134	16579	96.76	336	1.96	219	1.28
12	91832	89755	97.74	869	0.95	1208	1.32
13	65892	64247	97.50	849	1.29	796	1.21
14	27178	26564	97.74	415	1.53	199	0.73
15	8798	8506	96.68	99	1.13	193	2.19
Total	**738864**	**721578**	**97.66**	**8031**	**1.09**	**9255**	**1.25**

2.2 Ratio of requested to received repeat screenings

Table 2.2 lists the repeat screenings in total and split by reason, defined as follows:

- **"<32WoG":** all samples of children below 32 WoG, regardless of age and primary screening result
- **"<36h":** all samples of children above 32 WoG, but less than 36 hours old, regardless of the primary screening result
- **Recall:** necessary repeat testing due to abnormal primary screening at a gestational age ≥ 32 WoG and age ≥ 36h

Table 2.2: Requested and received repeat screenings

Lab	Total requested [a]	Total received	%	Recall requested [a]	Recall received	%
1	1542	1509	97.86	208	208	100
3	403	407	100.99	151	151	100
5	1738	1691	97.30	353	352	99.72
6	549	540	98.36	88	87	98.86
7[b]	1866	n/a		527	n/a	
8	4342	4031	92.84	939	924	98.40
9	4090	3211	78.51	1025	878	85.66
10	1070	1046	97.76	360	360	100
11	608	601	98.85	64	64	100
12	2571	2556	99.42	554	553	99.82
13	1931	1884	97.57	286	286	100
14	686	679	98.98	83	83	100
15	308	242	78.57	25	25	100
Total	**21704**	**18397**	**92.74**[b]	**4663**	**3971**	**96.01**[b]

Lab	<36h requested [a]	<36h received	%	<32WoG requested [a]	<32WoG received	%
1	717	684	95.40	617	617	100
3	99	99	100	153	153	100
5	644	598	92.86	741	741	100
6	289	281	97.23	172	172	100
7[b]	647	n/a		692	n/a	
8	1419	1243	87.60	1984	1864	93.95
9	1265	885	69.96	1800	1448	80.44
10	354	345	97.46	356	341	95.79
11	335	329	98.21	209	208	99.52
12	861	847	98.37	1156	1156	100
13	849	807	95.05	796	791	99.37
14	413	406	98.31	190	190	100
15	99	41	41.41	184	176	95.65
Total	**7991**	**6565**	**89.39**[b]	**9050**	**7857**	**94.01**[b]

[a] Deaths are not included in the number of requested samples
[b] Calculation excludes laboratories with undifferentiated or implausible results

2.3 Ensuring completeness of the screening

As a public health measure, the newborn screening is intended to benefit all children born in Germany. To guarantee that the screening is offered to all newborns, it is necessary to track completeness. For children delivered in obstetric units, this can be done in the screening center using the birth registry records, or when permitted by law, by cross-checking the data with the records from residents' registration office.

Currently neither option is available nationwide. With the goal of monitoring the integrity of the screening, the following regulation was added to the "Children's Guidelines" ("Kinderrichtlinie"):

The obstetric unit should use a blank test card to document refusal to participate in the screening or death of a neonate. This test card should then be sent to the screening centre. The laboratories receive blank test cards in varying numbers. The number of the blank cards due to refusal relative to the total number of screening cards has remained approximately constant.

This system seems to work primarily in cases of refusal to either participate in the screening or to have blood samples taken. In cases of death prior to screening or transfer of the newborn, higher numbers would be expected based on the data from the perinatal survey.

Table 2.3: Blank cards received by the laboratory

		Reason for blank card			
	Primary screening total	Deceased	Screening declined	Blank cards to due transfer, refusal to provide blood sample and undetermined reasons	Total
Lab	n	n	n	n	n
1	56687	80	144	4056	4280
3	15877	n/a	30	n/a	30
5	57518	27	58	2995	3080
6	13393	9	16	387	412
7[b]	49948	n/a	n/a	n/a	n/a
8	171081	n/a	n/a	2612[a]	2612
9	126680	4	214	759	977
10	36846	120	44	1912	2076
11	17134	71	11	272	354
12	91832	n/a	n/a	1774[a]	1774
13[b]	65892	n/a	n/a	n/a	n/a
14	27178	n/a	n/a	148[a]	148
15[b]	8798	n/a	n/a	n/a	n/a
Total	**738864**	**311**	**517**	**14915**	**15743**

[a] Total number, differentiation not possible
[b] Lab does not track blank cards

Table 2.4: Secondary screening card due to inferior sample quality

Lab	Primary screening	Control requested	Control received	received/ requested (%)	Proportion of samples/ Primary screening (%)
1	56687	646	598	92.57	1.14
3	15877	29	29	100.00	0.18
5	57518	273	260	95.24	0.47
6	13393	5	5	100.00	0.04
7	49948	104	n/a		0.21
8	171081	482	454	94.19	0.28
9	126680	397	346	87.15	0.31
10	36846	122	118	96.72	0.33
11	17134	7	7	100.00	0.04
12	91832	678	661	97.49	0.74
13	65892	587	552	94.04	0.89
14	27178	25	24	96.00	0.09
15	8798	11	11	100.00	0.13
Total	**738864**	**3366**	**3065**	**93.96***	**0.46**

* Calculation without laboratory 7 due to insufficient data regarding cards with poor sample quality

3 Quality parameters of the screening analysis

The quality of a test procedure is measured by the sensitivity, the specificity and the positive predictive value. In a screening procedure, the sensitivity (correct positive test results), but especially the specificity (proportion of healthy persons with negative test results), should be high in order to identify all those affected on the one hand and to cause as little unnecessary worry and subsequent expense as possible on the other. The lower the rate of control screening (recall rate) necessitated by suspicious first screening results, the higher the specificity. In 2015 the recall rate was 0.65%. If we consider only screening samples from full-term newborns collected more than 36 hours after birth, the recall rate is 0.47%, which means that out of 1000 tests only approximately 5 results require a control examination. With samples taken less than 36 hours after birth or before the 32nd WoG a secondary screening has to be done irrespective of the results.

The total specificity was 99.43%. The sensitivity cannot be stated because the number of false negative neonates is not systematically recorded. Here, nationwide registers would be helpful.

Table 3: Recall rates and cases found for Germany 2015, n= 738.864*

	Recall ≥36h and ≥32WoG		Recall <36h		Recall <32WoG		Recall Total	Confirmed cases
Disease	n	(%)	n	(%)	n	(%)	(%)	n
Hypothyroidism	614	0.09	311	4.88	27	0.30	0.13	235
CAH	1669	0.23	217	2.74	624	6.87	0.34	36
Biotinidase-Deficiency	156	0.02	9	0.11	14	0.15	0.02	12
Classic galactosaemia	194	0.03	5	0.06	3	0.03	0.03	7
PKU/HPA	249	0.03	23	0.29	46	0.50	0.04	149
MSUD	48	0.01	1	0.01	10	0.11	0.01	0
MCAD	143	0.02	4	0.05	0		0.02	72
LCHAD	18	0	1	0.01	1	0.01	0	6
VLCAD	147	0.02	4	0.05	3	0.03	0.02	7
CPT I-Deficiency	9	0	0	0	7	0.08	0	0
CPT II-Deficiency	16	0	0	0	0	0.00	0	0
CACT-Deficiency	0	0	0	0	0	0.00	0	0
GA I	126	0.02	6	0.07	15	0.16	0.02	5
IVA	38	0.01	2	0.02	8	0.09	0.01	10
Total	**3427**	**0.47**	**583**	**7.26**	**758**	**8.19**	**0.65**	**539**

* Primary screening Total: n= 738,864; Primary screening ≥ 36h and ≥ 32WoG n=721,578; Primary screening <36h n=8,031; Primary screening <32WoG n=9,255

3.1 Stratified recall rate and confirmed cases

The following tables show recall rates ≥36h and confirmed cases stratified by laboratory. The ≥36 hours category also always includes ≥32 weeks gestational age. The confirmed cases are based on all screening tests, irrespective of age and gestational age. The status of the report is Dec. 12, 2015. Cases from birth year 2015 that were found at a later date are not included in this report. The plausibility check of cases reported as confirmed for metabolic diseases were performed by Prof. Dr. Andreas Schulze and Prof. Dr. Regina Ensenauer and Associate Prof. Dr. Martin Lindner, and for endocrine diseases by Dr. Oliver Blankenstein and Associate Prof. Dr. Heiko Krude.

Excluded, and therefore not reported, are cases with missing confirmation diagnostics data (n=13, table 3.1). As a result, the true prevalence of some diseases may be higher than reported here. Cases reported twice were counted only once. Feedback from the attending physicians regarding the confirmation diagnostics is sought for quality assurance of laboratory analysis and evaluation of the quality of the results. The DGNS provides appropriate forms and consent.

Table 3.1: Cases that could not be confirmed due to missing information

Disease	Data missing n
Hypothyroidism	8
CAH	2
MCAD	2
VLCAD	1
Total	**13**

In the following tables, recall rates <0.01% and n ≤ 5 are not calculated, because for smaller numbers, random fluctuations would have a disproportionately large effect.

3.1.1 Hypothyroidism

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases
1	56687	55320	51	0.09	16
3	15877	15607	7	0.04	2
5	57518	56115	85	0.15	30
6	13393	12921	8	0.06	3
7	49948	48602	34	0.07	8
8	171081	167631	233	0.14	74
9	126680	123595	76	0.06	41
10	36846	36136	17	0.05	9
11	17134	16579	10	0.06	4
12	91832	89755	35	0.04	25
13	65892	64247	39	0.06	19
14	27178	26564	16	0.06	4
15	8798	8506	3		0
Total	**738864**	**721578**	**614**	**0.09**	**235**

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

Of the confirmed and validated cases of congenital Hypothyroidism, n=9 were normal in the primary screening. These are described in Table 3.1.1.1.

In two additional cases, the second card was normal after a suspicious primary screening result. A follow up test after one or two months respectively showed elevated TSH values which were validated in the confirmation diagnostics.

3.1.1.1 Normal primary screening results but confirmed Hypothyroidism

Case	WoG	Birth weight	Control exam at 32 WoG	First suspcious TSH-Value	WoG of first suspicious TSH value*	Comment
1	27	890	normal	23 mU/l	36	Regular checkups with normal primary results; no suspicious control findings until after dismissal. Confirmation diagnostics: TSH 76 µU/l, fT4 0,7 ng/dl
2	30	1730	normal	275 mU/l	40	Regular checkups with normal primary results; no suspicious control findings until after dismissal.
3	29	2100	normal	129,3 mU/l	36	Primary screening under catecholamines
4	31	1480	normal	82 mU/l	36	
5	30	1130	not carried out	95,3 mU/l	34	
6	29	730	not carried out	31,6 mU/l	33	Trisomy 21
7	41	3450	not medically indicated	143 mU/l	44	1st test card normal under catecholamines, control only at approx. 4 weeks of age
8	28	485	suspicious	69,4 mU/l	32	1st test card normal under catecholamines, no further checks after administering catecholamines before 32 WoG
9	34	2420	not medically indicated	40 mU/l	37	Early primary screening, normal results under catecholamines, control exam at 3 weeks of age

*Week of gestation could not be calculated to the day based on the available data.

In addition, n=40 hyperthyrotropinaemia cases 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	56687	55320	9	0.02[a]	1
3	15877	15607	5	0.03	0
5	57518	56115	214	0.38	2
6	13393	12921	31	0.24	0
7	49948	48602	314	0.65	4
8	171081	167631	44	0.03[b]	9
9	126680	123595	630	0.51	8
10	36846	36136	106	0.29	3
11	17134	16579	33	0.20	1
12	91832	89755	186	0.21[a]	4
13	65892	64247	85	0.13[a]	2
14	27178	26564	9	0.03[a]	1
15	8798	8506	3	0.04[a]	1
Total	**738864**	**721578**	**1669**	**0.23**	**36**

[a] Lab uses 2nd tier method [b] Lab uses 2nd tier method for screening >36h and <32 WoG

Two reported cases of congenital adrenal hyperplasia syndrome showed normal results in the primary screening (Case 1: birth at 37 WoG, first sample taken 38 hours after birth, 17-OHP values 24,9 nmol/l, case 2: birth at 38 WoG, first sample taken 51 hours after birth, 17 OHP-values 23 nmol/l). In one case, the mutation I2G/I172N was confirmed, in the other case no information regarding the mutation was provided.
Additionally, one case with a diagnosis of 11β-hydroxylase deficiency was reported and validated but was not included in the calculation of prevalence.

3.1.3 Biotinidase deficiency

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases	of which complete defect / no differentiation
1	56687	55320	7	0.01	1	
3	15877	15607	1		0	
5	57518	56115	4		0	
6	13393	12921	9	0.07	0	
7	49948	48602	16	0.03	1	
8	171081	167631	66	0.04	5	4
9	126680	123595	9	0.01	3	2
10	36846	36136	2		0	
11	17134	16579	1		0	
12	91832	89755	25	0.03	1	1
13	65892	64247	5		1	1
14	27178	26564	1		0	
15	8798	8506	10	0.12	0	
Total	**738864**	**721578**	**156**	**0.02**	**12**	**8**

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

3.1.4 Galactosaemia

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases
1	56687	55320	16	0.03	0
3	15877	15607	2		1
5	57518	56115	27	0.05	1
6	13393	12921	6	0.05	0
7	49948	48602	19	0.04	0
8	171081	167631	33	0.02	1
9	126680	123595	13	0.01	1
10	36846	36136	7	0.02	1
11	17134	16579	1		0
12	91832	89755	52	0.06	1
13	65892	64247	14	0.02	1
14	27178	26564	3		0
15	8798	8506	1		0
Total	**738864**	**721578**	**194**	**0.03**	**7**

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

3.1.5 Phenylketonuria (PKU) / Hyperphenylalaninemia (HPA)

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases	Including PKU
1	56687	55320	29	0.05	16	11
3	15877	15607	4		3	0
5	57518	56115	11	0.02	9	6
6	13393	12921	3		0	0
7	49948	48602	64	0.13	17	5
8	171081	167631	39	0.02	32	18
9	126680	123595	21	0.02	18	6
10	36846	36136	12	0.03	6	3
11	17134	16579	4		4	3
12	91832	89755	24	0.03	18	4
13	65892	64247	28	0.04	20	6
14	27178	26564	8	0.03	6	3
15	8798	8506	2		0	0
Total	**738864**	**721578**	**249**	**0.03**	**149**	**65**

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

3.1.6 Maple Syrup Urine Disease (MSUD) – no cases reported

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

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases
1	56687	55320	4		3
3	15877	15607	6	0,04	1
5	57518	56115	9	0,02	6
6	13393	12921	5		1
7	49948	48602	14	0,03	7
8	171081	167631	17	0,01	16
9	126680	123595	30	0,02	17
10	36846	36136	38	0,11	4
11	17134	16579	2		0
12	91832	89755	9	0,01	8
13	65892	64247	4		4
14	27178	26564	4		5
15	8798	8506	1		0
Total	**738864**	**721578**	**143**	**0,02**	**72**

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

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	56687	55320	1		0
3	15877	15607	0		0
5	57518	56115	1		0
6	13393	12921	2		0
7	49948	48602	0		0
8	171081	167631	2		2
9	126680	123595	9	0.01	2
10	36846	36136	0		1
11	17134	16579	1		1
12	91832	89755	2		0
13	65892	64247	0		0
14	27178	26564	0		0
15	8798	8506	0		0
Total	**738864**	**721578**	**18**	**0.002**	**6**

* Recall rate recorded only if rate ≥ 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	56687	55320	18	0.03	1
3	15877	15607	1		0
5	57518	56115	12	0.02	1
6	13393	12921	4		0
7	49948	48602	26	0.05	0
8	171081	167631	3		2
9	126680	123595	68	0.06	2
10	36846	36136	10	0.03	0
11	17134	16579	0		0
12	91832	89755	1		1
13	65892	64247	0		0
14	27178	26564	4		0
15	8798	8506	0		0
Total	**738864**	**721578**	**147**	**0.02**	**7**

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

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

3.1.11 Glutaric aciduria Type I

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases
1	56687	55320	7	0.01	1
3	15877	15607	0		0
5	57518	56115	0		0
6	13393	12921	1		0
7	49948	48602	27	0.06	0
8	171081	167631	0		0
9	126680	123595	86	0.07	1
10	36846	36136	0		0
11	17134	16579	1		0
12	91832	89755	2		2
13	65892	64247	2		1
14	27178	26564	0		0
15	8798	8506	0		0
Total	**738864**	**721578**	**126**	**0.02**	**5**

* 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	56687	55320	4		2
3	15877	15607	1		0
5	57518	56115	3		2
6	13393	12921	1		0
7	49948	48602	4		1
8	171081	167631	0		0
9	126680	123595	3		3
10	36846	36136	13	0.04	1
11	17134	16579	4		0
12	91832	89755	3		0
13	65892	64247	2		1
14	27178	26564	0		0
15	8798	8506	0		0
Total	**738864**	**721578**	**38**	**0.01**	**10**

* 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 is dependent on age and gestational age. Testing less than the 36 hours after birth and at gestational age of <32 weeks increases the risk of false negative and false positive results. This differs for the various targeted diseases. Therefore, 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 because for smaller numbers, random fluctuations would have a disproportionately large effect.

3.2.1 Hypothyroidism

	Primary Screening ≥ 36h			Primary Screening < 36h			Primary Screening < 32SSW		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	55320	51	0.09	729	9	1.23	638	3	
3	15607	7	0.04	99	n/a[a]		171	n/a[c]	
5	56115	85	0.15	650	1		753	6	0.80
6	12921	8	0.06	290	n/a[a]		182	n/a[c]	
7	48602	34	0.07	648	36	5.56	698	0	
8	167631	233	0.14	1419	137	9.65	2031	9	0.44
9	123595	76	0.06	1274	n/a[a]		1811	1	
10	36136	17	0.05	354	51	14.41	356	2	
11	16579	10	0.06	336	59	17.56	219	0	
12	89755	35	0.04	869	2		1208	1	
13	64247	39	0.06	849	1		796	0	
14	26564	16	0.06	415	11	2.65	199	5	
15	8506	3		99	2		193	0	
Total	**721578**	**614**	**0.09**	**8031**	**311**	**4.88[b]**	**9255**	**27**	**0.30[d]**

[a] For labs 3, 6 und 9 no data available about the number of cases with a TSH level above the set cutoff. Elevated TSH levels are monitored here during the second screening after 36 hours.

[b] Calculations exclude Labs 3, 6 and 9.

[c] For labs 3 and 6 no data available about the number of cases with a TSH level above the set cutoff. Elevated TSH levels are monitored during the second screening after the end of the 32nd WoG.

[d] Calculations exclude Labs 3 and 6.

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]	55320	9	0.02	729	2	0.27	638	9	1.41
3	15607	5	0.03	99	n/a[c]		171	n/a[d]	
5	56115	214	0.38	650	0	0.00	753	10	1.33
6	12921	31	0.24	290	2	0.69	182	4	2.20
7	48602	314	0.65	648	67	10.34	698	484	69.34
8[b]	167631	44	0.03	1419	100	7.05	2031	23	1.13
9	123595	630	0.51	1274	7	0.55	1811	39[f]	2.15
10	36136	106	0.29	354	16	4.52	356	14	3.93
11	16579	33	0.20	336	20	5.95	219	18	8.22
12	89755	186	0.21	869	0		1208	0	
13	64247	85	0.13	849	1	0.12	796	14	1.76
14	26564	9	0.03	415	1	0.24	199	4	2.01
15	8506	3	0.04	99	1	1.01	193	5	2.59
Total	**721578**	**1669**	**0.23**	**8031**	**217**	**2.74**[e]	**9255**	**624**	**6.87**[e]

[a] Laboratory used 2nd-tier process [b] Laboratory used 2nd-tier process for screening >36h and <32 WoG

[c] For lab 3 no data available about the number of cases with 17OHP levels above the set cutoff. Elevated 17OHP levels are monitored here during the second screening after 36 hours.

[d] For lab 3 no data available about the number of cases with 17OHP levels above the set cutoff. Elevated 17OHP levels are monitored here during the second screening after 32 WoG

[e] Calculations exclude Lab 3

[f] The lab recommends follow-up during the second screening after the end of 32 WoG provided there is no clinical suspicion of CAH and regular electrolyte testing is performed.

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	55320	7	0.01	729	1		638	2	
3	15607	1		99	0		171	0	
5	56115	4		650	0		753	4	
6	12921	9	0.07	290	0		182	0	
7	48602	16	0.03	648	1		698	1	
8	167631	66	0.04	1419	3		2031	0	
9	123595	9	0.01	1274	1		1811	0	
10	36136	2		354	0		356	0	
11	16579	1		336	0		219	0	
12	89755	25	0.03	869	1		1208	3	
13	64247	5		849	2		796	3	
14	26564	1		415	0		199	0	
15	8506	10	0.12	99	0		193	1	
Total	**721578**	**156**	**0.02**	**8031**	**9**	**0.11**	**9255**	**14**	**0.15**

3.2.4 Galactosaemia

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32WoG		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recal l rate	Primary screening	Recall	Recall rate
1	55320	16	0.03	729	2		638	0	
3	15607	2		99	0		171	0	
5	56115	27	0.05	650	0		753	0	
6	12921	6	0.05	290	0		182	0	
7	48602	19	0.04	648	0		698	1	
8	167631	33	0.02	1419	0		2031	0	
9	123595	13	0.01	1274	0		1811	0	
10	36136	7	0.02	354	1		356	0	
11	16579	1		336	0		219	0	
12	89755	52	0.06	869	0		1208	2	
13	64247	14	0.02	849	0		796	0	
14	26564	3		415	2		199	0	
15	8506	1		99	0		193	0	
Total	**721578**	**194**	**0.03**	**8031**	**5**	**0.06**	**9255**	**3**	**0.03**

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	55320	29	0.05	729	3		638	5	
3	15607	4		99	0		171	0	
5	56115	11	0.02	650	0		753	0	
6	12921	3		290	3		182	0	
7	48602	64	0.13	648	13	2.01	698	38	5.44
8	167631	39	0.02	1419	0		2031	0	
9	123595	21	0.02	1274	0		1811	1	
10	36136	12	0.03	354	0		356	0	
11	16579	4		336	0		219	0	
12	89755	24	0.03	869	1		1208	1	
13	64247	28	0.04	849	0		796	1	
14	26564	8	0.03	415	2		199	0	
15	8506	2		99	1		193	0	
Total	**721578**	**249**	**0.03**	**8031**	**23**	**0.29**	**9255**	**46**	**0.50**

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	55320	4		729	0		638	0	
3	15607	1		99	0		171	0	
5	56115	3		650	0		753	0	
6	12921	4		290	0		182	0	
7	48602	9	0.02	648	1		698	7	1.00
8	167631	2		1419	0		2031	1	
9	123595	16	0.01	1274	0		1811	2	
10	36136	7	0.02	354	0		356	0	
11	16579	1		336	0		219	0	
12	89755	0		869	0		1208	0	
13	64247	0		849	0		796	0	
14	26564	1		415	0		199	0	
15	8506	0		99	0		193	0	
Total	**721578**	**48**	**0.01**	**8031**	**1**	**0.01**	**9255**	**10**	**0.11**

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	55320	4		729	2		638	0	
3	15607	6	0.04	99	0		171	0	
5	56115	9	0.02	650	0		753	0	
6	12921	5		290	0		182	0	
7	48602	14	0.03	648	0		698	0	
8	167631	17	0.01	1419	0		2031	0	
9	123595	30	0.02	1274	0		1811	0	
10	36136	38	0.11	354	0		356	0	
11	16579	2		336	0		219	0	
12	89755	9	0.01	869	0		1208	0	
13	64247	4		849	0		796	0	
14	26564	4		415	2		199	0	
15	8506	1		99	0		193	0	
Total	**721578**	**143**	**0.02**	**8031**	**4**	**0.05**	**9255**	**0**	

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	55320	1		729	1		638	0	
3	15607	0		99	0		171	0	
5	56115	1		650	0		753	1	
6	12921	2		290	0		182	0	
7	48602	0		648	0		698	0	
8	167631	2		1419	0		2031	0	
9	123595	9	0.01	1274	0		1811	0	
10	36136	0		354	0		356	0	
11	16579	1		336	0		219	0	
12	89755	2		869	0		1208	0	
13	64247	0		849	0		796	0	
14	26564	0		415	0		199	0	
15	8506	0		99	0		193	0	
Total	**721578**	**18**	**0.002**	**8031**	**1**	**0.01**	**9255**	**1**	**0.01**

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

	Primary screening≥ 36h			Primary screening< 36h			Primary screening< 32SSW		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	55320	18	0.03	729	0		638	0	
3	15607	1		99	0		171	0	
5	56115	12	0.02	650	0		753	0	
6	12921	4		290	0		182	0	
7	48602	26	0.05	648	3		698	3	
8	167631	3		1419	0		2031	0	
9	123595	68	0.06	1274	1		1811	0	
10	36136	10	0.03	354	0		356	0	
11	16579	0		336	0		219	0	
12	89755	1		869	0		1208	0	
13	64247	0		849	0		796	0	
14	26564	4		415	0		199	0	
15	8506	0		99	0		193	0	
Total	**721578**	**147**	**0.02**	**8031**	**4**	**0.05**	**9255**	**3**	**0.03**

3.2.10 Carnitine-Palmitoyl-CoA-Transferase I (CPTI)-Deficiency

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32SSW		
Lab	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate
1	55320	4		729	0		638	3	
3	15607	0		99	0		171	0	
5	56115	1		650	0		753	1	
6	12921	2		290	0		182	0	
7	48602	0		648	0		698	0	
8	167631	0		1419	0		2031	0	
9	123595	0		1274	0		1811	0	
10	36136	1		354	0		356	1	
11	16579	0		336	0		219	0	
12	89755	1		869	0		1208	0	
13	64247	0		849	0		796	0	
14	26564	0		415	0		199	2	
15	8506	0		99	0		193	0	
Total	**721578**	**9**	**0.001**	**8031**	**0**		**9255**	**7**	**0.08**

3.2.11 Carnitine-Palmitoyl-CoA-Transferase I (CPTI)-Deficiency or Carnitine-Acylcarnitine-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	55320	5		729	0		638	0	
3	15607	0		99	0		171	0	
5	56115	0		650	0		753	0	
6	12921	1		290	0		182	0	
7	48602	0		648	0		698	0	
8	167631	2		1419	0		2031	0	
9	123595	7	0.01	1274	0		1811	0	
10	36136	1		354	0		356	0	
11	16579	0		336	0		219	0	
12	89755	0		869	0		1208	0	
13	64247	0		849	0		796	0	
14	26564	0		415	0		199	0	
15	8506	0		99	0		193	0	
Total	**721578**	**16**	**0.002**	**8031**	**0**		**9255**	**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	55320	7	0.01	729	0		638	1	
3	15607	0		99	0		171	0	
5	56115	0		650	0		753	1	
6	12921	1		290	0		182	2	
7	48602	27	.06	648	3		698	6	0.86
8	167631	0		1419	0		2031	0	
9	123595	86	0.07	1274	3		1811	5	
10	36136	0		354	0		356	0	
11	16579	1		336	0		219	0	
12	89755	2		869	0		1208	0	
13	64247	2		849	0		796	0	
14	26564	0		415	0		199	0	
15	8506	0		99	0		193	0	
Total	**721578**	**126**	**0.02**	**8031**	**6**	**0.07**	**9255**	**15**	**0.16**

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	55320	4		729	0		638	0	
3	15607	1		99	0		171	0	
5	56115	3		650	0		753	0	
6	12921	1		290	0		182	0	
7	48602	4		648	2		698	2	
8	167631	0		1419	0		2031	0	
9	123595	3		1274	0		1811	0	
10	36136	13	0.04	354	0		356	6	1.69
11	16579	4		336	0		219	0	
12	89755	3		869	0		1208	0	
13	64247	2		849	0		796	0	
14	26564	0		415	0		199	0	
15	8506	0		99	0		193	0	
Total	**721578**	**38**	**0.01**	**8031**	**2**	**0.02**	**9255**	**8**	**0.09**

3.2.14 Abnormal MS/MS results that could not conclusively be attributed to one of the target diseases

	Primary screening ≥ 36h			Primary screening < 36h			Primary screening < 32SSW		
Labor	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate	Primary screening	Recall	Recall rate*
1	55320	4		729	3		638	4	
3	15607	97	0.62	99	0		171	1	
5	56115	37	0.07	650	0		753	8	
6	12921	0		290	0		182	0	
7	48602	n/a		648	n/a		698	n/a	
8	167631	306	0.18	1419	2		2031	188	9.26
9	123595	0		1274	0		1811	0	
10	36136	163	0.45	354	14	3.95	356	60	16.85
11	16579	7	0.04	336	0		219	1	
12	89755	38	0.04	869	2		1208	12	0.99
13	64247	n/a		849	n/a		796	n/a	
14	26564	5		415	0		199	5	
15	8506	0		99	0		193	0	
Total	**721578**	**657**	**0.11**[a]	**8031**	**21**	**0.32**[a]	**9255**	**279**	**3.59**[a]

[a] Calculation excludes laboratories undifferentiated data

4 Process Time

4.1 Age at blood sample collection

According to the “Children’s Guidelines” (§ 20 paragraph 1) blood samples should be collected between 36 and 72 hours after birth, ideally between 36 and 48 hours. In 93% of cases in which the time of blood sampling was provided, collection took place in the designated time frame, in 5.8% not on until after 72 hours and in 1.2% before 36 hours (table 4.1). The proportion of samples which were collected after 72 hours - i.e. outside the designated time frame – has been reduced from 22.3 % in 2005 to 5.8% in 2015 (Figure 2).

This means a marked improvement in process quality, as adherence to the optimal time frame is of great importance for the effectiveness of the screening. Potentially life-threatening metabolic or electrolyte crises can be avoided through very early diagnosis and initiation of therapy in affected children.

Table 4.1: Age at blood sample collection - primary screening

	Total	<36h		36h-<48h		48h-<72h		≥72h	
Lab	n	n	%	n	%	n	%	n	%
1[a]	56651	821	1.45	15931	28.12	35538	62.73	4361	7.70
3[a]	15876	117	0.74	3803	23.95	11441	72.06	515	3.24
5	57518	707	1.23	43573	75.76	11781	20.48	1457	2.53
6	13393	314	2.34	5656	42.23	6977	52.09	446	3.33
7	49948	766	1.53	19720	39.48	23566	47.18	5896	11.80
8[a]	170625	1591	0.93	72102	42.26	86962	50.97	9970	5.84
9	126680	1408	1.11	53493	42.23	63815	50.37	7964	6.29
10	36846	382	1.04	11604	31.49	22481	61.01	2379	6.46
11	17134	357	2.08	5264	30.72	10527	61.44	986	5.75
12[a]	89341	960	1.07	39859	44.61	43935	49.18	4587	5.13
13	65892	831	1.26	39015	59.21	23471	35.62	2575	3.91
14[a]	25931	422	1.63	12068	46.54	12023	46.37	1418	5.47
15	8798	105	1.19	4702	53.44	3718	42.26	273	3.10
Total	**734633**	**8781**	**1.20**	**326790**	**44.48**	**356235**	**48.49**	**42827**	**5.83**

The number of samples for which times are known is below the total number of initial screening samples in some laboratories (indicated with [a]) due to missing data.

4.2 Period between sample collection and receipt by the lab

The time interval between taking blood samples and reporting abnormal results should not exceed 72 hours (§ 18 paragraph 3). However, in 26.5% of cases in which the delivery times were provided, the sample did not reach the lab until more than 72 hours after the blood sample was taken. In another 23.4% of the cases, the time period ranged from 48 to 72 hours. Efforts should be made to shorten the time span for sending samples, particularly on weekends (table 4.2, fig. 3).

Table 4.2: Period between sample collection and receipt by the lab

	Total	≤24h		>24h-48h		>48h-72h		>72h	
Lab	n	n	%	n	%	n	%	n	%
1[a]	56577	15749	27,84	20200	35,70	10779	19,05	9849	17,41
3[a]	15796	4463	28,25	6957	44,04	2971	18,81	1405	8,89
5	57518	14298	24,86	11840	20,58	15981	27,78	15399	26,77
6	13393	1708	12,75	6285	46,93	3111	23,23	2289	17,09
7	49948	11263	22,55	13800	27,63	9904	19,83	14981	29,99
8[a]	170626	15265	8,95	51184	30,00	45035	26,39	59142	34,66
9	126680	10026	7,91	30349	23,96	32801	25,89	53504	42,24
10	36846	4960	13,46	14142	38,38	9744	26,45	8000	21,71
11	17134	2617	15,27	7385	43,10	4237	24,73	2895	16,90
12[a]	90090	30578	33,94	29814	33,09	16992	18,86	12706	14,10
13	65892	18451	28,00	20120	30,53	16073	24,39	11248	17,07
14[a]	26389	15155	57,43	6607	25,04	3069	11,63	1558	5,90
15	8798	1281	14,56	3913	44,48	1524	17,32	2080	23,64
Total	**735687**	**145814**	**19,82**	**222596**	**30,26**	**172221**	**23,41**	**195056**	**26,51**

The number of samples for which times are known is below the total number of initial screening samples in some laboratories (indicated with [a]) due to missing data.

4.3 Period between receiving the sample and reporting the results

84% of the findings are reported within 24 hours. In the case of borderline elevated findings, the time in the laboratory can be extended by internal repeat examinations (quality assurance) (Table 4.3, Fig.4).

Table 4.3 Period between receiving the sample and reporting the results

	Total	≤24h		>24h-48h		>48h-72h		>72h	
Lab	n	n	%	n	%	n	%	n	%
1[a]	56687	35055	61.84	15689	27.68	3278	5.78	2665	4.70
3[a]	15877	15058	94.84	506	3.19	98	.62	215	1.35
5	57518	46394	80.66	9657	16.79	1276	2.22	191	0.33
6	13393	12952	96.71	312	2.33	78	0.58	51	0.38
7	n/a	n/a		n/a		n/a		n/a	
8	171081	165064	96.48	5741	3.36	113	0.07	163	0.10
9[a]	126594	116255	91.83	9176	7.25	990	0.78	173	0.14
10	36846	30075	81.62	6110	16.58	409	1.11	252	0.68
11	17134	11889	69.39	4603	26.86	623	3.64	19	0.11
12[a]	90286	67168	74.39	15120	16.75	7357	8.15	641	0.71
13	65892	49403	74.98	10453	15.86	5479	8.32	557	0.85
14[a]	26394	23772	90.07	2189	8.29	305	1.16	128	0.48
15	8798	3304	37.55	5328	60.56	157	1.78	9	0.10
Total	**686500**	**576389**	**83.96**	**84884**	**12.36**	**20163**	**2.94**	**5064**	**0.74**

The number of samples for which times are known is below the total number of initial screening samples in some laboratories (indicated with [a]) due to missing data.

Figure 2: Age at the time the blood sample was collected 2005 to 2015

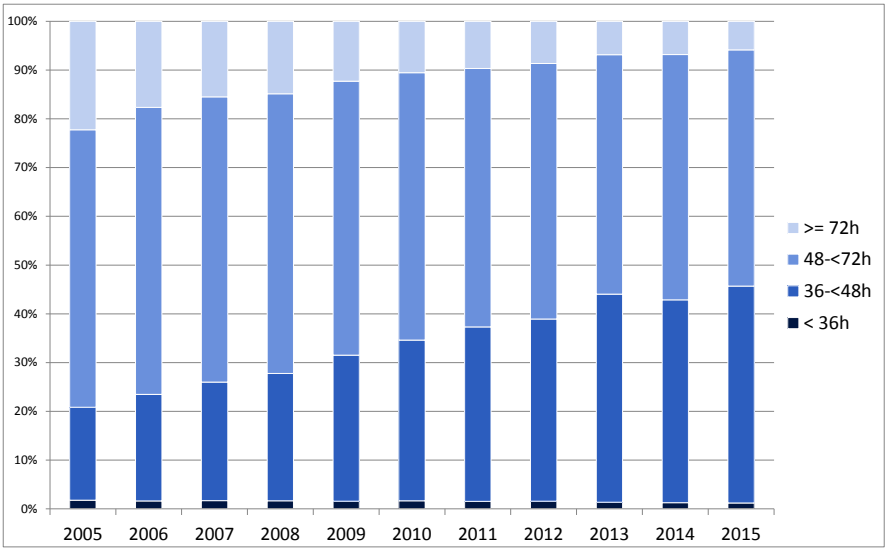


Figure 3: Time between sample collection and receipt by the lab 2005 to 2015

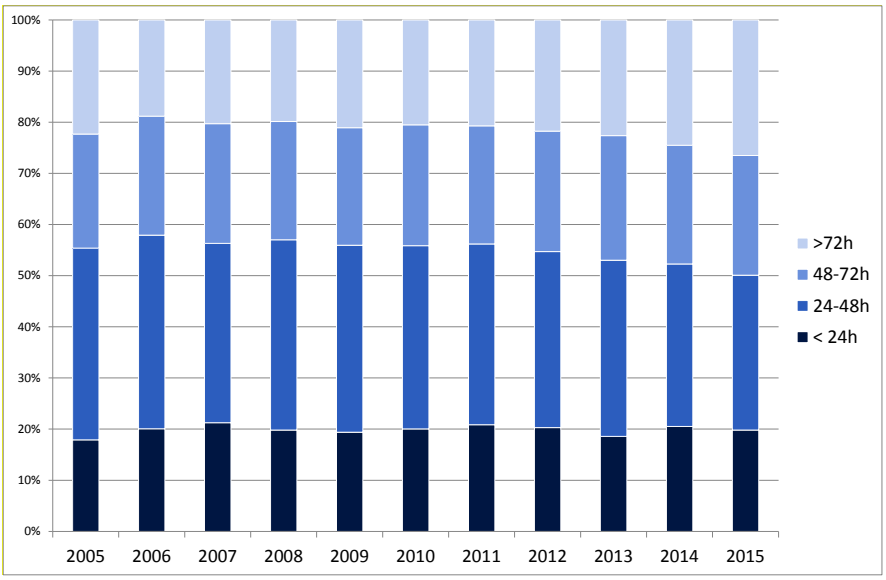
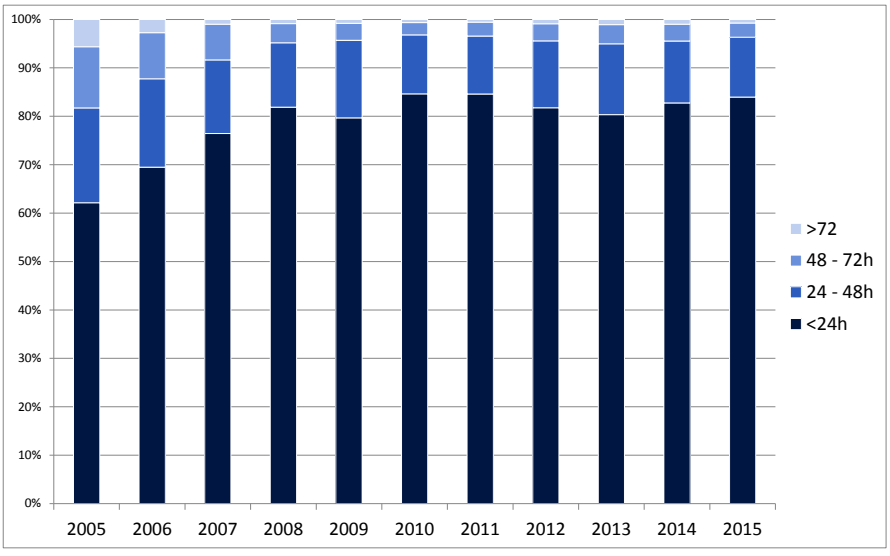


Figure 4: Time between receipt by the lab and report of the results 2005 to 2015



5 Time of screening in the confirmed cases

Decisive for the success of the screening are the reliability of the findings and the speed with which confirmation diagnostics are carried out and therapeutic measures are initiated in suspected cases. In accordance with the guidelines, the blood sample should not be collected less than 36 hours before or more than 72 after birth except in the case of early release. Any delay means a potential risk for affected children.

Table 5.1 shows the age at initial screening for children with one of the target diseases. For the sake of clarity, ages above 72 hours are reported in days; 3.7% of the affected children were already more than 72 hours old at the time the blood sample was taken.

Table 5: Time of primary screening in confirmed cases

Disease	36-72h	4-7d	>7d	<36h	<32WoG	≥36h, time not specified[a]	Not specified[b]	Total
Hypothyroidism	196	4	3	9	21	2	0	**235**
CAH	30	2	1	3	0	0	0	**36**
Biotinidase	11	0	0	0	1	0	0	**12**
Galactosaemia	5	1	0	1	0	0	0	**7**
PKU/HPA	139	4	2	2	1	1	0	**149**
MCAD	65	2	0	4	0	0	1	**72**
LCHAD	6	0	0	0	0	0	0	**6**
VLCAD	7	0	0	0	0	0	0	**7**
GA I	5	0	0	0	0	0	0	**5**
IVA	9	1	0	0	0	0	0	**10**
Total	**473**	**14**	**6**	**19**	**23**	**3**	**1**	**539**

[a] ≥36h Not specified does not mean a repeat examination for premature or premature birth, but exact age at blood collection not specified

[b] Not specified here means neither gestational age nor age at the time of blood collection is known.

6 Confirmation of pathological final results

The following chapter describes the diagnostic measures taken to confirm the diagnosis, as far as they were known to the laboratories. This information is important for quality assurance in the laboratory but is not always communicated to the laboratories by the attending physicians. For example, for 2015 no detailed information on confirmation diagnosis is available for 37 of the 539 confirmed cases, but the information available makes it possible to assess the case as plausibly positive. Where n/a is indicated in the table it means the laboratory does not know whether this diagnosis has been carried out. There is so little information available about an additional 13 children that the diagnosis cannot be regarded as confirmed. The latter have not been included in the evaluations.

6.1 Congenital hypothyroidism

Lab	Confirmed cases	TSH	T3	fT3	T4	fT4	Ultrasound	Thyroid antibodies
1	16	15	2	15	14	12	**1**	16
3	2	2	n/a	2	2	1	**3**	2
5	30	29	26	29	21	22	**5**	30
6	3	3	3	3	3	3	**6**	3
7	8	n/a	n/a	n/a	1	n/a	**7**	8
8	74	70	63	72	64	58	**8**	74
9	41	39	30	39	13	1	**9**	41
10	9	9	5	8	6	6	**10**	9
11	4	4	4	4	4	4	**11**	4
12	25	25	21	24	17	15	**12**	25
13	19	18	10	18	n/a	n/a	**13**	19
14	4	4	2	3	4	2	**14**	4
Total	**235***	**218**	**166**	**217**	**149**	**124**	**235***	**218**

* of which n=10 cases without detailed information about confirmation diagnostics

6.2 Congenital adrenal hyperplasia (CAH)

Lab	Confirmed cases	17-OHP (Serum)	Steroid (Serum/TB)	Urinary steroids	Molecular genetic testing
1	1	n/a	1	n/a	1
5	2	2	n/a	n/a	n/a
7	4	n/a	n/a	n/a	n/a
8	9	6	9	1	6
9	8	7	2	n/a	4
10	3	3	2	n/a	2
11	1	n/a	1	n/a	1
12	4	4	3	n/a	3
13	2	1	n/a	n/a	n/a
14	1	1	1	n/a	1
15	1	n/a	1	1	1
Total	**36***	**24**	**20**	**2**	**19**

* of which n=5 cases without detailed information about confirmation diagnostics

6.3 Biotinidase deficiency

Labor	Confirmed cases	Biotinidase (Serum/TB)	Molecular genetic testing
1	1	1	n/a
7	1	1	1
8	5	5	n/a
9	3	3	n/a
12	1	1	n/a
13	1	n/a	n/a
Total	**12***	**11**	**1**

* of which n=1 case without detailed information about confirmation diagnostics

6.4 Classic Galactosaemia

Lab	Confirmed cases	Enzyme assay	Galactose. Gal1P	Molecular genetic testing
3	1	n/a	1	1
5	1	1	1	n/a
8	1	1	1	n/a
9	1	1	n/a	1
10	1	1	1	1
12	1	1	1	1
13	1	1	1	n/a
Total	**7**	**6**	**6**	**4**

6.5 Phenylketonuria (PKU) / Hyperphenylalaninemia (HPA)

Lab	Confirmed cases	Phe (Serum/TB)	Phe/Tyr	BH4-Test	BH4 sensitive	Molecular genetic testing	Pterine in Urine/TB	DHPR in dried blood
1	16	16	14	11	1	1	16	16
3	3	3	3	1	1	n/a	1	1
5	9	5	2	3	1	n/a	7	7
7	17	2	n/a	n/a	n/a	11	11	11
8	32	26	20	10	2	13	18	18
9	18	13	12	1	n/a	4	17	17
10	6	6	4	1	2	4	5	6
11	4	4	3	2	n/a	1	2	3
12	18	18	12	5	2	7	17	16
13	20	15	6	6	n/a	1	10	10
14	6	6	5	3	n/a	n/a	6	6
Total	**149***	**114**	**81**	**43**	**9**	**42**	**110**	**111**

*of which n= 15 cases without detailed information about confirmation diagnostics

6.6 Maple syrup urine disease (MSUD)

No cases of maple syrup urine disease (MSUD) were reported.

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

Lab	Confirmed cases	Confirmation Serum/TB	Urinary organic acids	Enzyme activity	Molecular genetic testing
1	3	3	3	3	2
3	1	1	1	n/a	n/a
5	6	n/a	1	n/a	5
6	1	1	1	n/a	1
7	7	n/a	7	n/a	6
8	16	5	4	2	12
9	17	12	7	9	14
10	4	4	3	4	4
12	8	5	2	n/a	3
13	4	2	n/a	n/a	n/a
14	5	5	1	n/a	4
Total	**72***	**38**	**30**	**18**	**51**

* of which n=6 cases without detailed information about 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
8	2	1	2	n/a	2
9	2	2	n/a	n/a	1
10	1	1	n/a	1	1
11	1	1	1	n/a	1
Total	**6**	**5**	**3**	**1**	**5**

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	1	1	1	1	1
5	1	n/a	1	1	1
8	2	n/a	1	2	1
9	2	n/a	1	2	1
12	1	1	n/a	1	1
Total	**7**	**2**	**4**	**7**	**5**

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

No cases of CPT I-Deficiency. CPT II-Deficiency and CACT-Deficiency were reported

6.11 Glutaric aciduria Type I (GA I)

Lab	Confirmed cases	Confirmation Serum/TB	Urinary organic acids	Enzyme activity	Molecular genetic testing
1	1	n/a	1	n/a	1
9	1	1	1	n/a	1
12	2	1	2	n/a	1
13	1	n/a	n/a	n/a	n/a
Total	**5**	**2**	**4**	**n/a**	**3**

6.12 Isovalerianacidaemia (IVA)

Lab	Confirmed cases	Confirmation Serum	Urinary organic acids	Enzyme activity	Molecular genetic testing
1	2	1	2	n/a	2
5	2	1	2	n/a	n/a
7	1	n/a	1	n/a	1
9	3	1	3	n/a	n/a
10	1	1	1	n/a	1
13	1	1	1	n/a	n/a
Total	**10**	**5**	**10**	**n/a**	**4**

7 Methods and Cutoffs used in Screening

7.1 Filter paper for sampling

Lab	Filter paper
1	ID Biological (Ahlstrom 226)
3	ID Biological (Ahlstrom 226)
5	Munktell
6	ID Biological (Ahlstrom 226)
7	PE 266
8	Munktell
9	WS 903
10	WS 903
11	ID Biological (Ahlstrom 226)
12	Munktell
13	Munktell
14	ID Biological (Ahlstrom 226)
15	ID Biological (Ahlstrom 226)

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 nmol/l	GSP
8	TSH	15 mU/l (≤ 7 days) 10 mU/l (>7 days)	DELFIA
9	TSH	15 µU/ml	GSP
10	TSH	15 mU/l	AutoDELFIA
11	TSH	15 mU/l	DELFIA
12 /13	TSH	<20 mU/l (1 day) <15 mU/l (2-4 days) <10 mU/l (≥ 5 days)	AutoDELFIA
14 /15	TSH	<20 mU/l (1 day) <15 mU/l (2-4 days) <10 mU/l (≥ 5 days)	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 uses 2nd tier process

7.4 Biotinidase deficiency

Lab	Parameter	Cutoff	Method
1	Biotinidase	30%	Qualitative colorimetry
3	Biotinidase	30%	Qualitative colorimetry
5	Biotinidase	% of panel mean	Qualitative colorimetry
6	Biotinidase	60 U	Flurometry (PE)
7	Biotinidase	2.7 U/g Hb	Quantitative colorimetry
8	Biotinidase	<30% Daily mean	Quantitative colorimetry
9	Biotinidase	0.2	Qualitative colorimetry
10	Biotinidase	30%	Qualitative colorimetry
11	Biotinidase	30%	Quantitative colorimetry
12	Biotinidase	30%	Quantitative fluorometry
13	Biotinidase	30%	Quantitative fluorometry
14	Biotinidase	30%	Quantitative colorimetry
15	Biotinidase	30%	Quantitative colorimetry

7.5 Galactosaemia

Lab	Parameter	Cutoff	Method
1	GALT	3.5 U/g Hb	Quantitative fluorometry
	Galactose	<20 mg/dl	BIORAD Quantase
3	GALT	2.3 U/g Hb	Fluorometry (PE)
	Galactose	15 mg/dl	
5	GALT	3.5 U/g Hb	Quantitative colorimetry
	Galactose	15 mg/dl	BIORAD Quantase
6	GALT	3.5 U/g Hb	Fluorometry (PE)
7	GALT	3.5 U/g Hb	Quantitative fluorometry
8	GALT	<20% daily mean	Quantitative fluorometry
	Galactose	30 mg/dl	Colorimetry non kit
9	GALT	<2.3 U/g Hb	Fluorometry (PE)
	Galactose	20 mg/dl	BIORAD Quantase
10	GALT	> 3.5 U/gHb	Fluorometry (PE)
	Galactose	1111 µmol/l	BIORAD Quantase
11	GALT	3.5 U/g Hb	Fluorometry (PE)
12	GALT / Galactose	<30%	Colorimetry (not-kit) / Quant. fluorometry (non-kit)
13	GALT / Galactose	<30%	Colorimetry (not-kit) / Quant. fluorometry (non-kit)
14	GALT	<3.5 U/g Hb	BIORAD Quantase
	Galactose	>15 mg/dl	BIORAD Quantase
15	GALT	<3.5 U/g Hb	BIORAD Quantase
	Galactose	>15 mg/dl	BIORAD Quantase

7.6 MS/MS

Lab	Method
1	non derivatized Chromsystems Kit
3	non derivatized Chromsystems
5	derivatized non Kit
6	non derivatized PE Kit
7	derivatized PE Kit
8	derivatized non Kit
9	derivatized non Kit
10	derivatized CS Kit
11	non derivatized Chromsystems Kit
12	derivatized non Kit
13	derivatized non Kit
14	derivatized non Kit
15	derivatized non Kit

Literature

1) Decision on an amendment to the guidelines of the Federal Committee of Physicians and Health Insurance Companies on the early detection of diseases in children up to the age of 6 ("Children's Guidelines") for the introduction of the extended newborn screening of Nov. 24, 2016; https://www.g-ba.de/downloads/62-492-1333/RL_Kinder_2016-11-24_iK-2017-01-28.pdf (Access on 1 May 2016)

2) Statistical Yearbook 2015. Publisher: Federal Statistical Office, Wiesbaden www.destatis.de