National

Screening Report

Germany 2016

German Society for Neonatal Screening (DGNS)

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Abbreviations and Glossary:

BW	Birth weight
CAH	Congenital adrenal hyperplasia
CACT - Deficiency	Carnitine-Acylcarnitine-Translocase-Deficiency
CF	Cystic Fibrosis
CPTI - Deficiency	Carnitine-Palmitoyl-CoA-Transferase I-Deficiency
CPTII - Deficiency	Carnitine-Palmitoyl-CoA-Transferase II-Deficiency
DoL	Day of life
GA I	Glutaric acidaemia Type I
HPA	Hyperphenylalaninemia
IVA	Isovaleric acidaemia
LCHAD - Deficiency	Long-Chain-3-Hydroxy-Acyl-CoA-Dehydrogenase-Deficiency
MCAD - Deficiency	Medium-Chain-Acyl-CoA-Dehydrogenase-Deficiency
MSUD	Maple syrup urine disease
NGS	Newborn screening
PKU	Phenylketonuria
PPV	Positive predictive value
PT	Preterm < 32 WoG
Second-tier Process	In case of abnormal finding, second examination of additional parameters or alternative method of analysis with the same test card
WoG	Week of gestation
VLCAD - Deficiency	Very-Long-Chain-Acyl-CoA-Dehydrogenase-Deficiency

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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 2016. 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:

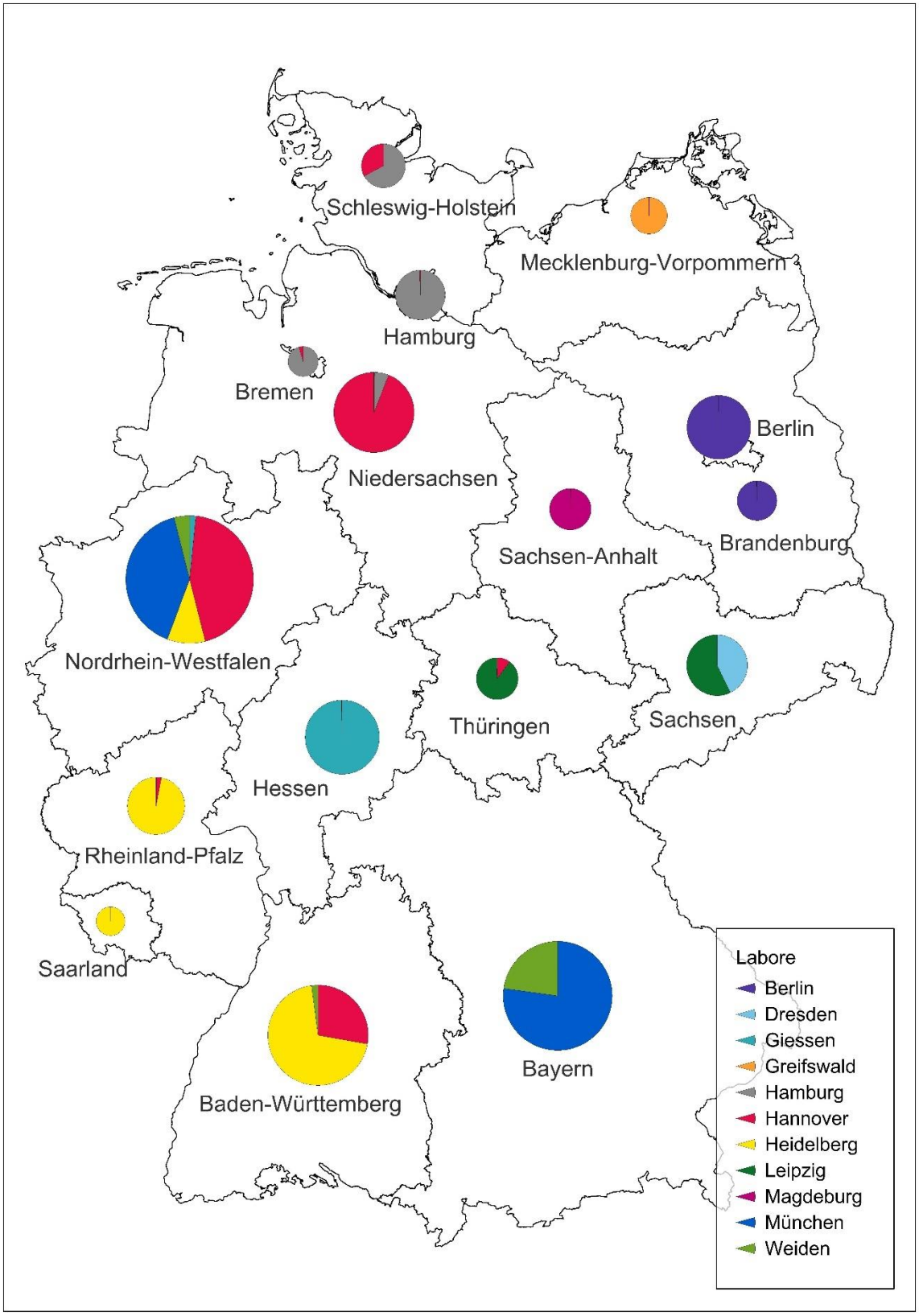
- Total survey of the targeted population
    - Collection method and rate
    - Blank card system
- Completeness of the control (recall) and follow-up examinations
- Recording test parameters and cutoffs
- Stratified recall rates, positive predictive values and prevalence by illness, laboratory, age 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 2016 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" from 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 2016, a total of 792,131 children were born in Germany [2]. The number of recorded screenings (783,873) is slightly lower than the number of births. This results in a screening rate of 98.95%, which is presumably below the true rate. By exception, the official 2016 birth statistics include births from 2015 [3] in 2016 and are therefore higher than the true figure. If the number of hospital births [4] and the number of births outside of hospitals [5] are added together, the total is 785,508 births for the year 2016, resulting in a screening rate of 99.8%.

Births:	792,131
Primary screenings:	783,873
Confirmed diagnoses:	605

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 diseases was found in 1 out of every 1,309 newborns, Table 2 shows the prevalence of the targeted diseases in Germany in 2016.

Starting Sept 1, 2016, screening for cystic fibrosis (CF) was added to the “Children’s Guidelines”. The results of this screening are not provided in detail in this report as the results are otherwise presented based on analyses for a full year. Furthermore, the outpatient examinations in 2016 were not yet funded and some laboratories had to transfer the algorithm previously used in studies to the the one provided for in the “Children’s Guidelines”.

Initial results already show that the CF screening is very well received by parents. However, for about a third of newborns with a positive CF screening result, it is not known whether this finding was further clarified and, if so, with what result.

Table 2: Frequency of diseases detected in 2016 screening (including milder cases)

Disease	Confirmed cases	Prevalence
Congenital Hypothyroidism	242	1: 3,273
Congenital adrenal hyperplasia (CAH)	54	1: 14,669
Biotinidase deficiency (incl. partial defect)	27	1: 29,338
Galactosaemia (classic)	14	1: 56,581
Phenylketonuria (PKU) n=77 / Hyperphenylalaninemia (HPA) n=77 Cofactor-Deficiency n=1	148	1: 5,352
Maple syrup urine disease (MSUD)	7	1: 113,162
Medium-Chain-Acyl-CoA-Dehydrogenase (MCAD)-Deficiency	76	1: 10,423
Long-Chain-3-OH-Acyl-CoA-Dehydrogenase (LCHAD)-Deficiency	8	1: 99,016
(Very-)Long-Chain-Acyl-CoA-Dehydrogenase (VLCAD)-Deficiency	8	1: 99,016
Carnitine-Palmitoyl-CoA-Transferase I (CPTI)-Deficiency	1	1: 792,131
Carnitine-Palmitoyl-CoA-Transferase II (CPTII)-Deficiency	2	1: 396,066
Carnitine-Acylcarnitine-Translocase (CACT)-Deficiency	1	1: 792,131
Glutaric aciduria Type I (GA I)	5	1: 158,426
Isovalerianacidaemia (IVA)	12	1: 66,011
Total	**605**	**1: 1,309**

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	60681	59374	97.85	698	1.15	609	1.00
3	16464	16237	98.62	114	0.69	113	0.69
5	61072	59885	98.06	548	0.90	639	1.05
6	13500	13095	97.00	245	1.81	160	1.19
7	54925	53283	97.01	756	1.38	886	1.61
8	182945	179378	98.05	1529	0.84	2038	1.11
9	137382	134165	97.66	1393	1.01	1824	1.33
10	37650	36832	97.83	382	1.01	436	1.16
11	17864	17308	96.89	375	2.10	181	1.01
12	92664	90575	97.75	952	1.03	1137	1.23
13	66282	64753	97.69	823	1.24	706	1.07
14	32797	31925	97.34	576	1.76	296	0.90
15	9647	9347	96.89	110	1.14	190	1.97
Total	**783873**	**766157**	**97.74**	**8501**	**1.08**	**9215**	**1.18**

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	1474	95.59	199	195	97.99
3	425	425	100	123	135	109.76 [b]
5	1479	1290	87.22	276	262	94.93
6	467	456	97.64	74	74	100
7	2191	n/a		558	n/a	
8	4766	4384	91.98	921	908	98.59
9	4266	3161	74.10	671	546	81.37
10	1203	1131	94.01	307	304	99.02
11	598	583	97.49	55	55	100
12	2464	2443	99.15	372	371	99.73
13	1790	1660	92.74	214	213	99.53
14	963	949	98.55	106	105	99.06
15	402	304	75.62	80	80	100
Total	**22556**	**18260**	**89.44** [c]	**3956**	**3248**	**95.05** [c]

Lab	<36h requested [a]	<36h received	%	<32WoG requested [a]	<32WoG received	%
1	688	650	94.48	584	582	99.66
3	114	114	100	128	129	100.78
5	551	409	74.23	628	596	94.90
6	242	231	95.45	151	151	100.00
7	751	n/a		882	n/a	
8	1523	1307	85.82	1978	1879	94.99
9	1382	830	60.06	1810	1460	80.66
10	382	356	93.19	436	393	90.14
11	371	356	95.96	172	172	100.00
12	947	928	97.99	1080	1080	100.00
13	870	742	85.29	706	705	99.86
14	575	562	97.74	282	282	100.00
15	116	37	31.90	190	171	90.00
Total	**8512**	**6522**	**84.04** [c]	**9027**	**7600**	**93.31**

[a] Deaths are not included in the number of requested samples
[b] Results confirmed by lab
[c] 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":

The obstetric unit should use a blank test card to document refusal to participate in the screening or the 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 sent in due to refusal to participate has remained approximately the same relative to the total number of primary screening cards submitted.

This system seems to work primarily in cases of refusal to either participate in the screening or to have blood samples taken. Both in case of death prior to screening and of transfer of the newborn, considerably 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	60681	115	252	4152	4519
3	16464	51	32	954	1037
5	61072	28	119	3245	3392
6	13500	33	18	311	362
7[b]	54925	n/a	n/a	n/a	n/a
8	182945	n/a	n/a	2859[a]	2859
9	137382	7	233	982	1222
10	37650	137	63	1889	2089
11	17864	66	15	286	367
12	92664	n/a	n/a	1759 [a]	1759
13[b]	66282	n/a	n/a	n/a	n/a
14	32797	n/a	n/a	223 [a]	223
15[b]	9647	n/a	n/a	n/a	n/a
Total	**783873**	**437**	**732**	**16660**	**17829**

[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	60681	797	746	93.60	1.31
3	16464	24	24	100.00	0.15
5	61072	424	404	95.28	0.69
6	13500	10	10	100.00	0.07
7	54925	138	n/a		0.25
8	182945	675	664	98.37	0.37
9	137382	598	518	86.62	0.44
10	37650	104	104	100.00	0.28
11	17864	25	25	100.00	0.14
12	92664	696	675	96.98	0.75
13	66282	613	606	98.86	0.92
14	32797	65	65	100.00	0.20
15	9647	27	27	100.00	0.28
Total	**783873**	**4196**	**3868**	**95.32***	**0.54**

* 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 2016 the recall rate was 0.5%. If we consider only screening samples from full-term newborns collected more than 36 hours after birth, the recall rate is 0.36%. This means that out of 1,000 screening examinations, approximately 4 results requiring a control examination can be expected.

The total specificity was 99.58%. The sensitivity cannot be stated because the number of false negatives is not systematically recorded. Here, nationwide registers would be helpful.

Table 3: Recall rates and cases found for Germany 2016 N = 783,873[a]

	Recall ≥36h and ≥32WoG		Recall <36h		Recall <32WoG		Recall Total	Confirmed cases
Disease	n	(%)[d]	n	(%)[d]	n	(%)[d]	(%)[d]	n
Congenital Hypothyroidism	605	0.08	292	3.43	21	0.23	0.12	242
CAH	1119	0.15	228	2.68	425	4.61	0.23	54
Biotinidase-Deficiency	162	0.02	8	0.09	14	0.15	0.02	27
Galactosaemia	169	0.02	7	0.08	1		0.02	14[b]
PKU/HPA	259	0.03	26	0.31	49	0.53	0.04	148
MSUD	61	0.01	4		10	0.11	0.01	7
MCAD	128	0.02	6	0.07	0		0.02	76
LCHAD	22		1		0			8
VLCAD	106	0.01	1		0		0.01	8
CPT I-Deficiency	5		0		1			1
CPT II-Deficiency[c]	9		1		0			2
CACT-Deficiency[c]								1
GA I	81	0.01	2		14	0.15	0.01	5
IVA	46	0.01	4		9	0.10	0.01	12
Total	**2772**	**0.36**	**580**	**6.82**	**544**	**5.90**	**0.50**	**605**

[a] Primary screening Total: n= 783,873; Primary screening ≥ 36h and ≥ 32WoG n=766,157; Primary screening <36h n=8,501; Primary screening <32WoG n=9,215
[b] only classic Galactosaemia,
[c] Recalls for CACT-Deficiency are listed under CPTII-Deficiency,
[d] Recall rate reported only if rate ≥ 0.01% and n > 5.

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 figures were reported as of December 1, 2017. Cases from birth year 2016 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=15, 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
Congenital Hypothyroidism	7
CAH	2
Classic Galactosaemia	1
MCAD	3
VLCAD	2
Total	**15**

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 Congenital Hypothyroidism

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate (%)*	Confirmed cases
1	60681	59374	44	0.07	17
3	16464	16237	6	0.04	3
5	61072	59885	67	0.11	29
6	13500	13095	6	0.05	2
7	54925	53283	63	0.12	18
8	182945	179378	187	0.10	58
9	137382	134165	81	0.06	41
10	37650	36832	20	0.05	6
11	17864	17308	9	0.05	3
12	92664	90575	34	0.04	23
13	66282	64753	43	0.07	24
14	32797	31925	36	0.11	14
15	9647	9347	9	0.10	4
Total	**783873**	**766157**	**605**	**0.08**	**242**

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

Of the 242 confirmed and validated cases of congenital Hypothyroidism, 20 were normal in the primary screening. Among them were seven severely ill newborns, some of whom had received dopamine before their first blood sample was collected, one child with autoimmune thyroiditis and eight premature babies under 32 WoG, in whom the control exam at 32 WoG showed an increased level of TSH.

In two children the control examination was carried out in the 37th WoG instead of at 32 WoG and in one case the treating clinic did not react to the very high TSH value at 32 WoG. One case remains unclear.

In addition, n= 20 hyperthyrotropinemia cases were reported and validated as confirmed. These were not included in the calculation of prevalence.

3.1.2 Congenital adrenal hyperplasia (CAH)

Labor	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate (%)*	Confirmed cases
1[a]	60681	59374	9	0.02	3
3	16464	16237	8	0.05	4
5	61072	59885	138	0.23	2
6	13500	13095	34	0.26	4
7	54925	53283	341	0.64	3
8[b]	182945	179378	57	0.03	14
9	137382	134165	329	0.25	11
10	37650	36832	133	0.36	3
11[a]	17864	17308	27	0.16	0
12[a]	92664	90575	25	0.03	6
13[a]	66282	64753	16	0.02	2
14[a]	32797	31925	0		0
15[a]	9647	9347	2		2
Total	**783873**	**766157**	**1119**	**0.15**	**54**

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

* Recall rates are only given for recall rates ≥ 0.01% and n > 5.

3.1.3 Biotinidase deficiency

Labor	Primary Screening Total	Primary Screening ≥36h	Recall ≥36h	Recall rate (%)*	bestätigte Fälle	of which complete defect/ no differentiation
1	60681	59374	16	0.03	3	3
3	16464	16237	1		1	
5	61072	59885	3		0	
6	13500	13095	8	0.06	0	
7	54925	53283	11	0.02	4	3
8	182945	179378	45	0.03	7	5
9	137382	134165	11	0.01	1	1
10	37650	36832	5		1	1
11	17864	17308	4		1	
12	92664	90575	25	0.03	3	3
13	66282	64753	18	0.03	2	2
14	32797	31925	3		1	1
15	9647	9347	12	0.13	3	3
Total	**783873**	**766157**	**162**	**0.02**	**27**	**8**

* Recall rate reported 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[a]
1	60681	59374	25	0.04	1
3	16464	16237	0		0
5	61072	59885	19	0.03	1
6	13500	13095	3		0
7	54925	53283	16	0.03	1
8	182945	179378	40	0.02	2
9	137382	134165	13	0.01	3
10	37650	36832	6	0.02	2
11	17864	17308	3		0
12	92664	90575	31	0.03	1
13	66282	64753	5	0.01	2
14	32797	31925	7	0.02	1
15	9647	9347	1		0
Total	**783873**	**766157**	**169**	**0.02**	**14**

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

[a] Only classic Galactosaemia

3.1.5 Phenylketonuria (PKU) / Hyperphenylalaninemia (HPA)

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate (%)*	Confirmed cases	of which PKU
1	60681	59374	26	0,04	16	9
3	16464	16237	4		4	3
5	61072	59885	16	0,03	13	7
6	13500	13095	7	0,05	3	1
7	54925	53283	71	0,13	9	4
8	182945	179378	26	0,01	26	10
9	137382	134165	25	0,02	21	13
10	37650	36832	12	0,03	10	4
11	17864	17308	4		5	3
12	92664	90575	24	0,03	20	8
13	66282	64753	29	0,04	13	4
14	32797	31925	10	0,03	7	3
15	9647	9347	5		1	1
Total	**783873**	**766157**	**259**	**0,03**	**148**	**70**

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

3.1.6 Maple Syrup Urine Disease (MSUD)

Labor	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall-rate (%)*	Confirmed cases
1	60681	59374	6	0.01	0
3	16464	16237	0		0
5	61072	59885	2		2
6	13500	13095	1		0
7	54925	53283	7	0.01	0
8	182945	179378	4		4
9	137382	134165	35	0.03	0
10	37650	36832	4		0
11	17864	17308	0		0
12	92664	90575	0		0
13	66282	64753	2		1
14	32797	31925	0		0
15	9647	9347	0		0
Gesamt	**783873**	**766157**	**61**	**0.01**	**7**

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

One case with confirmed maple syrup disease was unremarkable in the initial screening and was diagnosed at the age of 45 days. Detailed information on the diagnosis is not available.

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

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate (%)*	Confirmed cases
1	60681	59374	4		4
3	16464	16237	9	0.06	4
5	61072	59885	2		1
6	13500	13095	3		1
7	54925	53283	8	0.02	3
8	182945	179378	20	0.01	20
9	137382	134165	33	0.02	13
10	37650	36832	19	0.05	5
11	17864	17308	2		2
12	92664	90575	15	0.02	14
13	66282	64753	6	0.01	5
14	32797	31925	6	0.02	3
15	9647	9347	1		1
Total	**783873**	**766157**	**128**	**0.02**	**76**

* Recall rate reported 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	60681	59374	1		0
3	16464	16237	0		0
5	61072	59885	3		2
6	13500	13095	2		0
7	54925	53283	1		1
8	182945	179378	4		2
9	137382	134165	7	0.01	1
10	37650	36832	2		1
11	17864	17308	0		0
12	92664	90575	1		0
13	66282	64753	1		1
14	32797	31925	0		0
15	9647	9347	0		0
Total	**783873**	**766157**	**22**		**8**

* Recall rate reported 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	60681	59374	10	0.02	1
3	16464	16237	0		0
5	61072	59885	6	0.01	0
6	13500	13095	8	0.06	0
7	54925	53283	18	0.03	1
8	182945	179378	7		4
9	137382	134165	48	0.04	1
10	37650	36832	6	0.02	0
11	17864	17308	2		0
12	92664	90575	0		1
13	66282	64753	0		0
14	32797	31925	1		0
15	9647	9347	0		0
Total	**783873**	**766157**	**106**	**0.01**	**8**

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

3.1.10 CPT I-Deficiency

Labor	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall-rate (%)*	Confirmed cases
1	60681	59374	3		0
3	16464	16237	0		0
5	61072	59885	0		0
6	13500	13095	0		0
7	54925	53283	0		0
8	182945	179378	1		1
9	137382	134165	1		0
10	37650	36832	0		0
11	17864	17308	0		0
12	92664	90575	0		0
13	66282	64753	0		0
14	32797	31925	0		0
15	9647	9347	0		0
Gesamt	**783873**	**766157**	**5**		**1**

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

3.1.11 CPT II-Deficiency and CACT-Deficiency

Labor	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall-rate (%)*	Confirmed cases
1	60681	59374	1		0
3	16464	16237	0		0
5	61072	59885	1		1[a]
6	13500	13095	0		0
7	54925	53283	0		0
8	182945	179378	2		0
9	137382	134165	4		2[b]
10	37650	36832	0		0
11	17864	17308	0		0
12	92664	90575	0		0
13	66282	64753	1		0
14	32797	31925	0		0
15	9647	9347	0		0
Gesamt	**783873**	**766157**	**9**		**3**

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

[a] CACT-deficiency, [b] CPTII-deficiency

3.1.12 Glutaric aciduria Type I

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases
1	60681	59374	1		1
3	16464	16237	1		0
5	61072	59885	4		0
6	13500	13095	1		0
7	54925	53283	16	0.03	0
8	182945	179378	2		2
9	137382	134165	51	0.04	0
10	37650	36832	2		0
11	17864	17308	0		0
12	92664	90575	0		0
13	66282	64753	3		2
14	32797	31925	0		0
15	9647	9347	0		0
Total	**783873**	**766157**	**81**	**0.01**	**5**

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

3.1.13 Isovalerianacidaemia (IVA)

Lab	Primary screening total	Primary screening ≥36h	Recall ≥36h	Recall rate(%)*	Confirmed cases
1	60681	59374	15	0.03	4
3	16464	16237	0		0
5	61072	59885	1		1
6	13500	13095	2		0
7	54925	53283	6	0.01	0
8	182945	179378	4		4
9	137382	134165	2		1
10	37650	36832	8	0.02	1
11	17864	17308	1		0
12	92664	90575	2		0
13	66282	64753	4		1
14	32797	31925	1		0
15	9647	9347	0		0
Total	**783873**	**766157**	**46**	**0.01**	**12**

* Recall rate reported 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	59374	44	0.07	698	8	1.15	609	3	
3	16237	6	0.04	114	n/a [a]		113	n/a [c]	
5	59885	67	0.11	548	1		639	1	
6	13095	6	0.05	245	n/a [a]		160	n/a [c]	
7	53283	63	0.12	756	30	3.97	886	3	
8	179378	187	0.10	1529	123	8.04	2038	2	
9	134165	81	0.06	1393	n/a [a]		1824	1	
10	36832	20	0.05	382	55	14.40	436	3	
11	17308	9	0.05	375	45	12.00	181	0	
12	90575	34	0.04	952	4		1137	3	
13	64753	43	0.07	823	2		706	1	
14	31925	36	0.11	576	21	3.65	296	4	
15	9347	9	0.10	110	3		190	0	
Total	**766157**	**605**	**0.08**	**8501**	**292**	**4.33 [b]**	**9215**	**21**	**0.23 [d]**

[a] For labs 3, 6 und 9 no data available about the number of cases with a TSH level above the set cut-off. 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 defined cut-off. 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]	59374	9	0.02	698	2		609	2	
3[c]	16237	8	0.05	114	n/a		113	n/a	
5	59885	138	0.23	548	1		639	8	1.25
6	13095	34	0.26	245	2		160	6	3.75
7	53283	341	0.64	756	56	7.41	886	313	35.33
8[b]	179378	57	0.03	1529	108	7.06	2038	23	1.13
9	134165	329	0.25	1393	6	0.43	1824	4 [d]	
10	36832	133	0.36	382	24	6.28	436	48	11.01
11	17308	27	0.16	375	19	5.07	181	13	7.18
12[a]	90575	25	0.03	952	2		1137	3	
13[a]	64753	16	0.02	823	0		706	4	
14[a]	31925	0		576	6	1.04	296	1	
15[a]	9347	2		110	2		190	0	
Total	**766157**	**1119**	**0.15**	**8501**	**228**	**2.72**[e]	**9215**	**425**	**4.67**[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 cut-off. Elevated 17OHP levels are monitored here during the second screening after 36 hours and after 32 WoG.

[d] 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.

[e] Calculations exclude Lab 3

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	59374	16	0.03	698	1		609	2	
3	16237	1		114	0		113	0	
5	59885	3		548	0		639	3	
6	13095	8	0.06	245	0		160	0	
7	53283	11	0.02	756	2		886	2	
8	179378	45	0.03	1529	1		2038	1	
9	134165	11	0.01	1393	1		1824	1	
10	36832	5	0.01	382	0		436	0	
11	17308	4		375	0		181	1	
12	90575	25	0.03	952	1		1137	2	
13	64753	18	0.03	823	2		706	1	
14	31925	3		576	0		296	0	
15	9347	12	0.13	110	0		190	1	
Total	**766157**	**162**	**0.02**	**8501**	**8**	**0.09**	**9215**	**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	Recall rate	Primary screening	Recall	Recall rate
1	59374	25	0.04	698	3		609	0	
3	16237	0		114	0		113	0	
5	59885	19	0.03	548	2		639	0	
6	13095	3		245	0		160	0	
7	53283	16	0.03	756	1		886	0	
8	179378	40	0.02	1529	0		2038	1	
9	134165	13	0.01	1393	0		1824	0	
10	36832	6	0.02	382	0		436	0	
11	17308	3		375	0		181	0	
12	90575	31	0.03	952	1		1137	0	
13	64753	5	0.01	823	0		706	0	
14	31925	7	0.02	576	0		296	0	
15	9347	1		110	0		190	0	
Total	**766157**	**169**	**0.02**	**8501**	**7**	**0.08**	**9215**	**1**	

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	59374	26	0.04	698	2		609	2	
3	16237	4		114	0		113	0	
5	59885	16	0.03	548	1		639	1	
6	13095	7	0.05	245	2		160	0	
7	53283	71	0.13	756	14	1.85	886	38	4.29
8	179378	26	0.01	1529	1		2038	0	
9	134165	25	0.02	1393	2		1824	1	
10	36832	12	0.03	382	0		436	1	
11	17308	4		375	1		181	0	
12	90575	24	0.03	952	3		1137	1	
13	64753	29	0.04	823	0		706	1	
14	31925	10	0.03	576	0		296	3	
15	9347	5	0.05	110	0		190	1	
Total	**766157**	**259**	**0.03**	**8501**	**26**	**0.31**	**9215**	**49**	**0.53**

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	59374	6	0.01	698	1		609	0	
3	16237	0		114	0		113	0	
5	59885	2		548	0		639	0	
6	13095	1		245	0		160	0	
7	53283	7	0.01	756	2		886	7	
8	179378	4		1529	0		2038	0	
9	134165	35	0.03	1393	1		1824	2	
10	36832	4		382	0		436	0	
11	17308	0		375	0		181	0	
12	90575	0		952	0		1137	0	
13	64753	2		823	0		706	0	
14	31925	0		576	0		296	0	
15	9347	0		110	0		190	1	
Total	**766157**	**61**	**0.01**	**8501**	**4**	**0.05**	**9215**	**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	59374	4		698	0		609	0	
3	16237	9	0.06	114	0		113	0	
5	59885	2		548	0		639	0	
6	13095	3		245	0		160	0	
7	53283	8	0.02	756	0		886	0	
8	179378	20	0.01	1529	1		2038	0	
9	134165	33	0.02	1393	2		1824	0	
10	36832	19	0.05	382	1		436	0	
11	17308	2		375	0		181	0	
12	90575	15	0.02	952	1		1137	0	
13	64753	6	0.01	823	0		706	0	
14	31925	6	0.02	576	0		296	0	
15	9347	1		110	1		190	0	
Total	**766157**	**128**	**0.02**	**8501**	**6**	**0.07**	**9215**	**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	59374	1		698	0		609	0	
3	16237	0		114	0		113	0	
5	59885	3		548	0		639	0	
6	13095	2		245	0		160	0	
7	53283	1		756	0		886	0	
8	179378	4		1529	1		2038	0	
9	134165	7	0.01	1393	0		1824	0	
10	36832	2		382	0		436	0	
11	17308	0		375	0		181	0	
12	90575	1		952	0		1137	0	
13	64753	1		823	0		706	0	
14	31925	0		576	0		296	0	
15	9347	0		110	0		190	0	
Total	**766157**	**22**		**8501**	**1**		**9215**	**0**	

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	59374	10	0.02	698	0		609	0	
3	16237	0		114	0		113	0	
5	59885	6	0.01	548	0		639	0	
6	13095	8	0.06	245	0		160	0	
7	53283	18	0.03	756	1		886	0	
8	179378	7	0.00	1529	0		2038	0	
9	134165	48	0.04	1393	0		1824	0	
10	36832	6	0.02	382	0		436	0	
11	17308	2		375	0		181	0	
12	90575	0		952	0		1137	0	
13	64753	0		823	0		706	0	
14	31925	1		576	0		296	0	
15	9347	0		110	0		190	0	
Total	**766157**	**106**	**0.01**	**8501**	**1**		**9215**	**0**	

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	59374	3		698	0		609	1	
3	16237	0		114	0		113	0	
5	59885	0		548	0		639	0	
6	13095	0		245	0		160	0	
7	53283	0		756	0		886	0	
8	179378	1		1529	0		2038	0	
9	134165	1		1393	0		1824	0	
10	36832	0		382	0		436	0	
11	17308	0		375	0		181	0	
12	90575	0		952	0		1137	0	
13	64753	0		823	0		706	0	
14	31925	0		576	0		296	0	
15	9347	0		110	0		190	0	
Total	**766157**	**5**		**8501**	**0**		**9215**	**1**	

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	59374	1		698	1		609	0	
3	16237	0		114	0		113	0	
5	59885	1		548	0		639	0	
6	13095	0		245	0		160	0	
7	53283	0		756	0		886	0	
8	179378	2		1529	0		2038	0	
9	134165	4		1393	0		1824	0	
10	36832	0		382	0		436	0	
11	17308	0		375	0		181	0	
12	90575	0		952	0		1137	0	
13	64753	1		823	0		706	0	
14	31925	0		576	0		296	0	
15	9347	0		110	0		190	0	
Total	**766157**	**9**		**8501**	**1**		**9215**	**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	59374	1		698	1		609	0	
3	16237	1		114	0		113	0	
5	59885	4		548	0		639	1	
6	13095	1		245	0		160	0	
7	53283	16	0.03	756	0		886	4	
8	179378	2		1529	0		2038	0	
9	134165	51	0.04	1393	1		1824	9	
10	36832	2		382	0		436	0	
11	17308	0		375	0		181	0	
12	90575	0		952	0		1137	0	
13	64753	3		823	0		706	0	
14	31925	0		576	0		296	0	
15	9347	0		110	0		190	0	
Total	**766157**	**81**	**0.01**	**8501**	**2**		**9215**	**14**	**0.15**

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	59374	15	0.03	698	0		609	2	
3	16237	0		114	0		113	0	
5	59885	1		548	0		639	0	
6	13095	2		245	0		160	0	
7	53283	6	0.01	756	3		886	5	0.56
8	179378	4		1529	0		2038	0	
9	134165	2		1393	0		1824	0	
10	36832	8	0.02	382	0		436	0	
11	17308	1		375	0		181	0	
12	90575	2		952	1		1137	1	
13	64753	4		823	0		706	1	
14	31925	1		576	0		296	0	
15	9347	0		110	0		190	0	
Total	**766157**	**46**	**0.01**	**8501**	**4**	**0.05**	**9215**	**9**	**0.10**

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	59374	0		698	0		609	0	
3	16237	50	0.31	114	1		113	1	
5	59885	0		548	0		639	0	
6	13095	0		245	0		160	0	
7	53283	n/a		756	n/a		886	n/a	
8	179378	333	0.19	1529	7	0.46	2038	191	9.37
9	134165	1		1393	0		1824	0	
10	36832	162	0.44	382	9	2.36	436	47	10.78
11	17308	10	0.06	375	2		181	4	
12	90575	48	0.05	952	3		1137	16	1.41
13	64753	0		823	0		706	0	
14	31925	2		576	0		296	5	
15	9347	0		110	0		190	0	
Total	**766157**	**606**	**0.09[a]**	**8501**	**22**	**0.28[a]**	**9215**	**264**	**3.17[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 5.2% not 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 5.2% in 2016 (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 may 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]	60649	774	1.28	17849	29.43	37724	62.2	4302	7.09
3[a]	16447	131	0.8	4177	25.4	11652	70.85	487	2.96
5[a]	61009	548	0.9	45715	74.93	13075	21.43	1671	2.74
6	13500	261	1.93	6159	45.62	6664	49.36	416	3.08
7	54925	864	1.57	22622	41.19	24406	44.44	7033	12.8
8[a]	182305	1697	0.93	80252	44.02	90895	49.86	9461	5.19
9	137382	1555	1.13	61445	44.73	67354	49.03	7028	5.12
10	37650	419	1.11	12484	33.16	22682	60.24	2065	5.48
11	17864	407	2.28	5960	33.36	10518	58.88	979	5.48
12	90084	1033	1.15	43360	48.13	41655	46.24	4036	4.48
13	66282	535	0.81	41578	62.73	22321	33.68	1848	2.79
14	31127	600	1.93	15808	50.79	13514	43.42	1205	3.87
15	9647	116	1.2	5114	53.01	4227	43.82	190	1.97
Total	**778871**	**8940**	**1.15**	**362523**	**46.54**	**366687**	**47.08**	**40721**	**5.23**

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 25.7% of cases in which the shipping times were provided, the sample did not reach the lab until more than 72 hours after the blood sample was taken. In another 23.5% 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]	60583	16447	27.15	22170	36.59	12003	19.81	9963	16.45
3[a]	16265	5039	30.98	7408	45.55	2736	16.82	1082	6.65
5[a]	61043	2152	3.53	21842	35.78	19198	31.45	17851	29.24
6	13500	1833	13.58	6182	45.79	3234	23.96	2251	16.67
7	54925	11920	21.70	15974	29.08	11225	20.44	15806	28.78
8[a]	182305	17062	9.36	58276	31.97	47511	26.06	59456	32.61
9	137382	9564	6.96	33239	24.19	35718	26.00	58861	42.84
10	37650	5214	13.85	13922	36.98	10337	27.46	8177	21.72
11	17864	2920	16.35	8060	45.12	4434	24.82	2450	13.71
12[a]	90592	30149	33.28	32733	36.13	16966	18.73	10744	11.86
13	66282	18910	28.53	22603	34.10	14787	22.31	9982	15.06
14[a]	32211	19401	60.23	7830	24.31	3317	10.30	1663	5.16
15	9647	1568	16.25	3971	41.16	1971	20.43	2137	22.15
Total	**780249**	**142179**	**18.22**	**254210**	**32.58**	**183437**	**23.51**	**200423**	**25.69**

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

82% 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]	60654	33339	54.97	20607	33.97	3842	6.33	2866	4.73
3[a]	16448	15735	95.67	444	2.70	87	0.53	182	1.11
5[a]	60901	41297	67.81	13259	21.77	6090	10.00	255	0.42
6	13500	12994	96.25	366	2.71	77	0.57	63	0.47
7	n/a	n/a		n/a		n/a		n/a	
8	182945	175341	95.84	6836	3.74	203	0.11	565	0.31
9	137382	122128	88.90	13203	9.61	1702	1.24	349	0.25
10	37650	33241	88.29	3940	10.46	348	0.92	121	0.32
11	17864	12200	68.29	4723	26.44	721	4.04	220	1.23
12[a]	91362	67431	73.81	14677	16.06	8208	8.98	1046	1.14
13	66282	49229	74.27	10551	15.92	5883	8.88	619	0.93
14[a]	32214	28876	89.64	2497	7.75	357	1.11	484	1.50
15	9647	2712	28.11	6829	70.79	100	1.04	6	0.06
Total	**726849**	**594523**	**81.79**	**97932**	**13.47**	**27618**	**3.80**	**6776**	**0.93**

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 2016

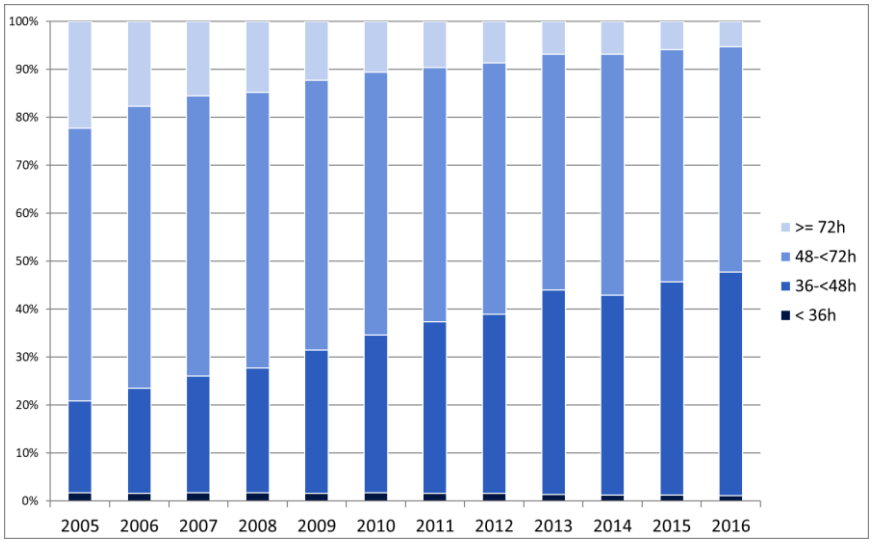


Figure 3: Time between sample collection and receipt by the lab 2005 to 2016

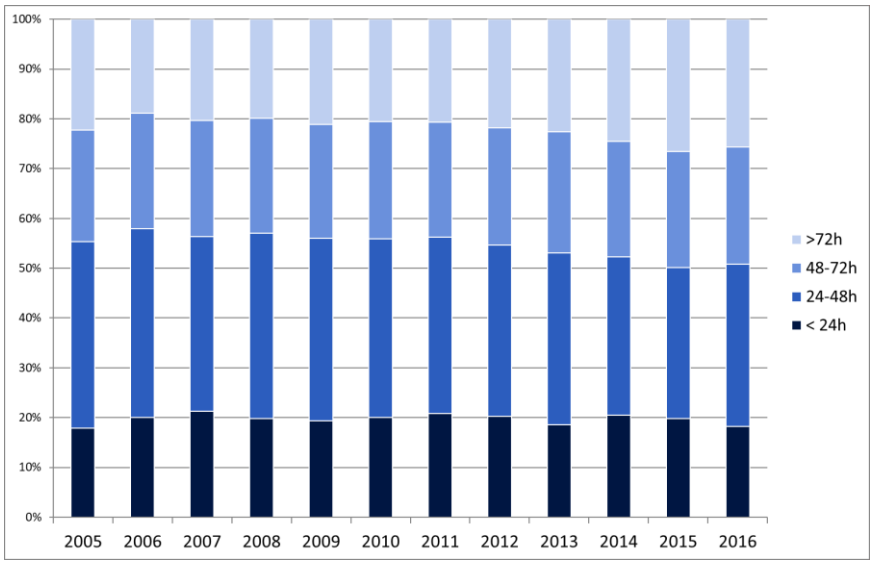
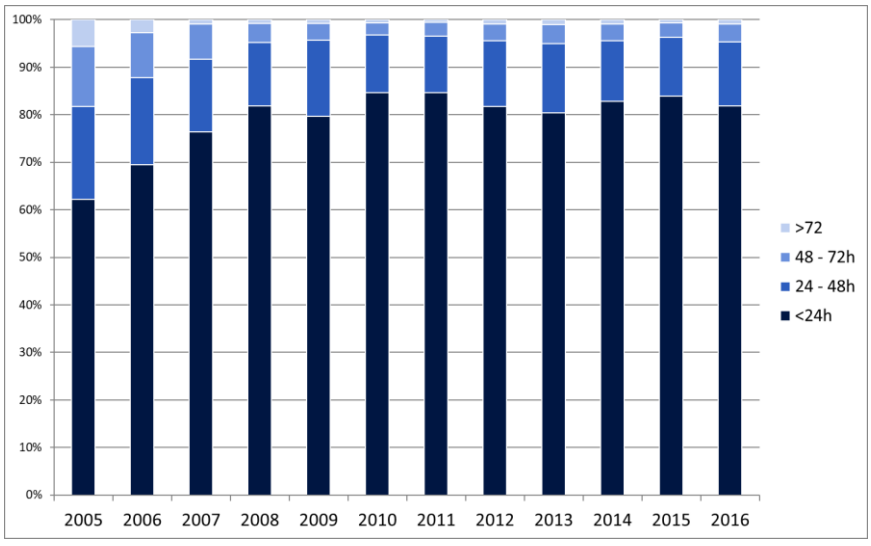


Figure 4: Time between receipt by the lab and report of the results 2005 to 2016



5 Time of screening in confirmed cases

The reliability of the findings and the speed with which confirmatory diagnostics are carried out and therapeutic measures initiated in suspected cases are decisive for the success of the screening. 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, calculated from the number of hours of life. 3% of the affected children were 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[a]	≥36h, time not specified[b]	Not specified[c]	Total
Congenital Hypothyroidism	209	8	1	6	15	1	2	**242**
CAH	41	0	0	7	5	1	0	**54**
Biotinidase	27	0	0	0	0	0	0	**27**
Galactosaemia	12	0	0	2	0	0	0	**14**
PKU/HPA	137	1	2	5	2	1	0	**148**
MSUD	7	0	0	0	0	0	0	**7**
MCAD	67	3	1	3	0	1	1	**76**
LCHAD	8	0	0	0	0	0	0	**8**
VLCAD	8	0	0	0	0	0	0	**8**
CPT I	1	0	0	0	0	0	0	**1**
CPT II	2	0	0	0	0	0	0	**2**
CACT	1	0	0	0	0	0	0	**1**
GA I	5	0	0	0	0	0	0	**5**
IVA	10	1	0	0	0	1	0	**12**
Total	**535**	**13**	**4**	**23**	**22**	**5**	**3**	**605**

[a] Data independent of age in days at the time the blood sample was collected

[b] Blood collection ≥36h and ≥ 32 WoG but the exact age at the time of blood collection is not known

[c] 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 2016 no detailed information on confirmation diagnosis is available for 53 of the 605 confirmed cases (8.8%), but the available information allows the case to be assessed 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 15 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 (Serum)	fT3	fT4	Sonogram	SD-Antibodies
1	17	16	1	3	n/a	15
3	3	3	1	3	1	3
5	29	25	n/a	16	1	23
6	2	2	n/a	2	n/a	2
7	18	1	n/a	n/a	n/a	n/a
8	58	58	3	43	2	53
9	41	41	5	32	4	40
10	6	5	n/a	5	n/a	6
11	3	3	n/a	3	n/a	3
12	23	22	n/a	18	n/a	23
13	24	24	n/a	15	n/a	23
14	14	14	n/a	12	n/a	14
15	4	4	n/a	4	n/a	4
Gesamt	**242***	**218**	**10**	**156**	**8**	**209**

* of which n= 19 cases without detailed information on confirmatory diagnostics

6.2 Congenital adrenal hyperplasia (CAH)

Lab	Confirmed cases	17-OHP (Serum)	Steroid (Serum/TB)	Urinary steroids	molecular genetics
1	3	2	3	n/a	3
5	4	3	4	2	2
7	2	2	2	n/a	n/a
8	4	4	3	1	4
9	3	n/a	n/a	n/a	n/a
10	14	11	13	1	13
11	11	11	10	n/a	4
12	3	3	1	n/a	3
13	6	3	4	2	6
14	2	2	n/a	n/a	2
15	2	2	2	n/a	n/a
Total	**54***	**43**	**42**	**6**	**37**

* of which n=3 cases without detailed information about confirmation diagnostics

6.3 Biotinidase deficiency

Lab	Confirmed cases	Biotinidase (Serum/TB)	molecular genetics
1	3	2	1
3	1	n/a	n/a
7	4	4	4
8	7	6	0
9	1	1	n/a
10	1	1	1
11	1	1	n/a
12	3	3	n/a
13	2	n/a	n/a
14	1	n/a	1
15	3	2	n/a
Total	**27***	**20**	**7**

* of which n=6 cases without detailed information about confirmation diagnostics

6.4 Classic Galactosaemia

Lab	Confirmed cases	Enzyme assay	Galactose. Gal1P	molecular genetics
1	1	1	1	1
5	1	1	1	1
7	1	n/a	n/a	1
8	2	2	2	1
9	3	n/a	1	n/a
10	2	2	2	2
12	1	n/a	n/a	1
13	2	n/a	n/a	n/a
14	1	1	1	1
Total	**14***	**7**	**8**	**8**

* of which n=4 cases without detailed information about confirmation diagnostics

Phenylketonuria (PKU) / Hyperphenylalaninemia (HPA)

Lab	Confirmed cases	Phe (Serum/TB)	Phe/Tyr	BH4-Test	BH4 sensitive	molecular genetics	Pterins in Urine/TB	DHPR in dried blood
1	16	16	12	11	4	12	16	16
3	4	4	4	4	n/a	n/a	4	4
5	13	9	1	2	1	n/a	11	11
6	3	3	3	n/a	n/a	n/a	2	2
7	9	0	n/a	1	1	n/a	n/a	n/a
8	26	24	15	12	9	5	18	15
9	21	18	17	8	2	6	14	14
10	10	10	9	2	n/a	8	10	9
11	5	5	1	4	1	1	2	2
12	20	19	19	5	1	8	19	19
13	13	11	10	2	n/a	n/a	8	8
14	7	7	5	3	2	1	6	6
15	1	1	n/a	n/a	n/a	n/a	1	1
Total	**148***	**127**	**96**	**54**	**21**	**41**	**111**	**107**

*of which n= 13 cases without detailed information about confirmation diagnostics

6.5 Maple syrup urine disease (MSUD)

Lab	Confirmed cases	Confirmation Serum	Urinary organic acids	Enzyme activity	molecular genetics
5	2	1	k.A.	k.A.	1
8	4	1	0	0	0
13	1	1	k.A.	k.A.	1
Total	**7***	**3**			**2**

*davon n= 3 Fälle ohne detaillierte Angaben zur Konfirmationsdiagnostik

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

Lab	Confirmed cases	Confirmation Serum/TB	Urinary organic acids	Enzyme activity	Molecular genetics
1	4	4	4	4	4
3	4	n/a	n/a	n/a	4
5	1	n/a	n/a	n/a	n/a
6	1	1	1	n/a	n/a
7	3	n/a	n/a	n/a	2
8	20	8	10	1	15
9	13	11	11	3	6
10	5	5	5	3	5
11	2	1	2	n/a	n/a
12	14	13	1	n/a	11
13	5	3	1	n/a	4
14	3	2	n/a	1	3
15	1	1	1	n/a	1
Total	**76***	**49**	**36**	**12**	**55**

* of which n=3 cases without detailed information about confirmation diagnostics

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

Lab	Confirmed cases	Confirmation Serum/TB	Urinary organic acids	Enzyme activity	Molecular genetics
5	2	n/a	n/a	n/a	2
7	1	n/a	n/a	n/a	1
8	2	1	1	0	2
9	1	1	n/a	n/a	1
10	1	1	1	n/a	1
13	1	1	1	n/a	1
Total	**8**	**4**	**3**	**n/a**	**8**

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

Lab	Confirmed cases	Confirmation Serum/TB	Urinary organic acids	Enzyme activity	Molecular genetics
1	1	1	1	1	1
7	1	n/a	n/a	1	n/a
8	4	2	1	1	4
9	1	n/a	n/a	1	1
12	1	1	1	1	1
Total	**8**	**4**	**3**	**5**	**7**

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

Lab	Diagnosis	Confirmed cases	Confirmation Serum	Enzyme activity	Molecular genetics
8	CPT I	1	1	0	1
9	CPT II	2	1	1	2
5	CACT	1	1	n/a	1
Total		**4**	**3**	**1**	**4**

6.10 Glutaric aciduria Type I (GA I)

Lab	Confirmed cases	Confirmation Serum/TB	Urinary organic acids	Enzyme activity	Molecular genetics
1	1	1	1	n/a	1
8	2	2	2	n/a	n/a
13	2	n/a	n/a	n/a	n/a
Total	**5***	**3**	**3**	**n/a**	**1**

* of which n=2 cases without detailed information about confirmation diagnostics

6.11 Isovalerianacidaemia (IVA)

Lab	Confirmed cases	Confirmation Serum	Urinary organic acids	Enzyme activity	Molecular genetics
1	4	2	4	n/a	3
5	1	n/a	1	n/a	n/a
8	4	2	4	0	2
9	1	1	n/a	n/a	1
10	1	1	1	n/a	1
13	1	1	n/a	n/a	n/a
Gesamt	**12**	**7**	**10**	**n/a**	**7**

7 Methods and Cutoffs used in Screening

7.1 Filter paper

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)
12/13	Munktell
14/15	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 mol/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 Kit B024
5	17 OHP	AutoDELFIA
6	17 OHP	DELFIA
7	17 OHP	AutoDELFIA
8*	17 OHP	DELFIA
9	17 OHP	GSP
10	17 OHP	AutoDELFIA
11	17 OHP	DELFIA
12/13*	17 OHP	AutoDELFIA
3	17 OHP	AutoDELFIA Kit B024

* 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	Extinction < 0.2	Qualitative colorimetry
10	Biotinidase	30%	Qualitative colorimetry
11	Biotinidase	30%	Quantitative colorimetry
12/13	Biotinidase	30%	Quantitative fluorometry
14/15	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	Quantitative colorimetry
9	GALT	<5.3 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)
12/13	GALT	>20%	Colorimetry (not-kit) /. Fluorometry (non-kit)
	Galactose	< 15 mg/dl	
14/15	GALT	<2.3 U/g Hb	Quantitative fluorometry
	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
12/13	derivatized non Kit
14/15	derivatized non Kit

Literature

1) Decision on an amendment to the guidelines of the Federal Committee of Physicians and Health Insurance Companies (Bundesausschuss der Ärzte und Krankenkassen) 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

2) Statistical Yearbook 2016. Publisher: Federal Statistical Office, Wiesbaden www.destatis.de

3) Information provided orally by the Federal Statistical Office (May 29, 2018)

4) IQTIG: Federal evaluation for the registration year 2016 Obstetrics Quality Indicators https://iqtig.org/downloads/auswertung/2016/16n1gebh/QSKH_16n1-GEBH_2016_BUAW_V02_2017-07-12.pdf

5) Quality report on behalf of the Society for Quality in Outpatient Obstetrics (Gesellschaft für Qualität in der außerklinischen Geburtshilfe e.V.) Non-clinical obstetrics in Germany http://www.quag.de/downloads/QUAG_bericht2016.pdf