National Screening Report Germany 2017

German Society for Neonatal Screening (DGNS)

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Abbreviations and Glossary

AGS	Adrenogenital Syndrome
CACT Deficiency	Carnitine-acylcarnitine Translocase Deficiency
CF	Cystic Fibrosis
CF-SPID	Cystic Fibrosis Screen Positive, Inconclusive Diagnosis
CPT-I Deficiency	Carnitine Palmitoyltransferase I Deficiency
CPT-II Deficiency	Carnitine Palmitoyltransferase II Deficiency
DB	Dried Blood
ENS	Established Neonatal Screening
GA I	Glutaric Acidemia Type I
HPA	Hyperphenylalaninemia
IM	Insufficient Material
IRT	Immunoreactive Trypsinogen
IVA	Isovaleric Acidemia
LCHAD Deficiency	Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency
MCAD Deficiency	Medium-Chain Acyl-CoA Dehydrogenase Deficiency
MSUD	Maple Syrup Urine Disease
NBS	Newborn screening
PAP	Pancreatitis-associated Protein
PKU	Phenylketonuria
PPV	Positive Predictive Value
Second tier method	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

Screening Laboratories und Screening Centers

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1 Introduction

The neonatal 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), the regulations for implementing the newborn screening program (NBS) are defined in §13 - §28. The 2017 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, as well as cystic fibrosis, 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 2017. 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 neonatal screening:

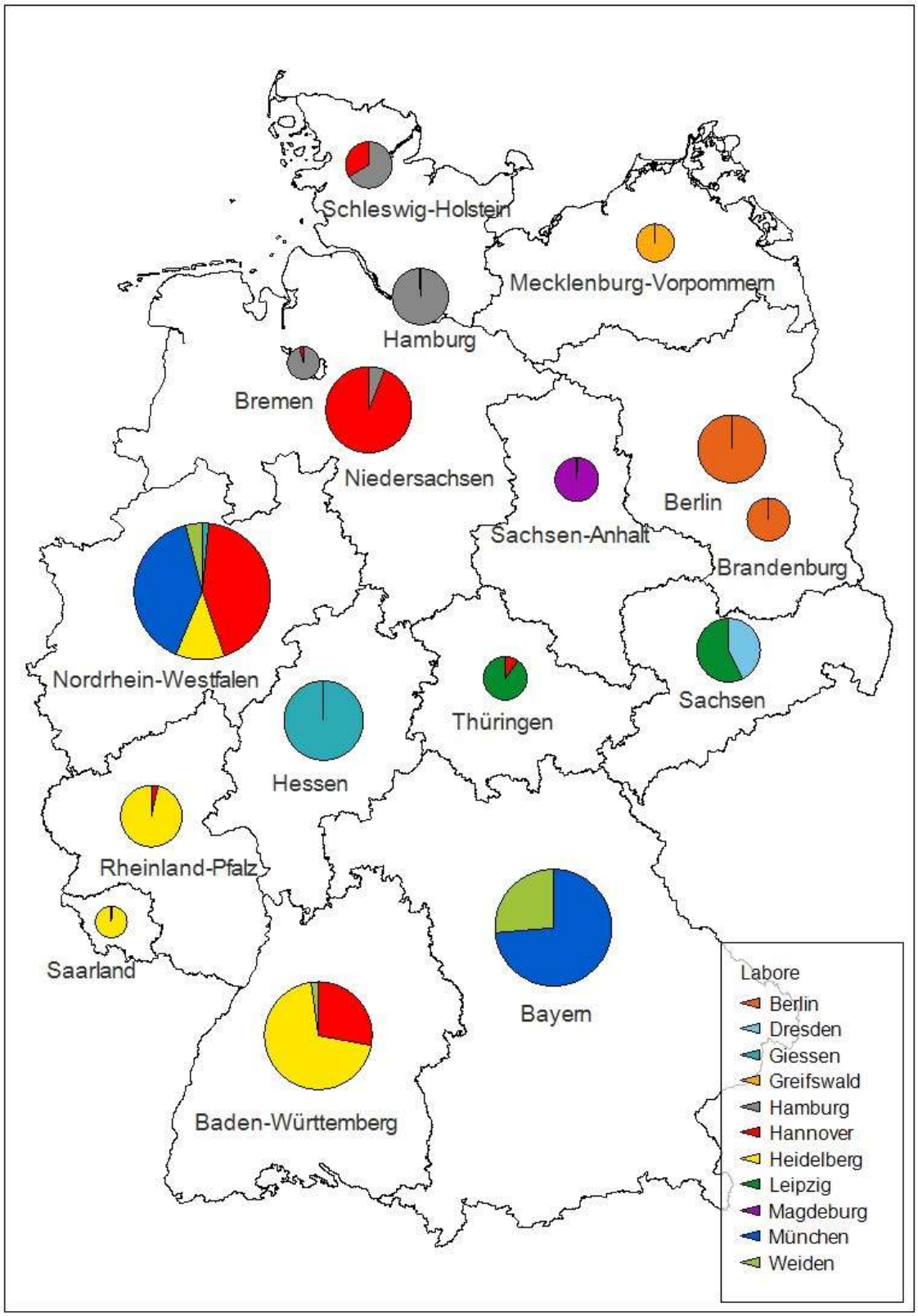
- Total survey of the targeted population
    - Collection method and rate
    - Blank card system
- Completeness of the control (recall) and follow-up examinations
- Recording test parameters and cut-offs
- Stratified recall rates, positive predictive values and prevalence by disease, laboratory, age 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 Germany in 2017 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). Mentions of sections and subsections in the text refer to the "Children's Guidelines" from November 11, 2016. [i] 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 Diagram 1

Figure 1: Distribution of Screening Samples by State and Laboratory



2 Results

In 2019 a total of 784,900 children were born in Germany according to official statistics. [ii] The number of recorded first screenings (786,579) is slightly higher than the number of births.

Reasons for the surplus screening samples could be control cards not declared as such that 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:	784,900
First screenings:	786,579
Confirmed diagnoses:	786

A reliable statement about the rate of participation in NBS can only be made by reconciling individual data with overall population data.

The diseases targeted for the nationwide screening are defined in the “Children’s Guidelines”. In some laboratories, screenings for additional diseases 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 999 newborns. Table 2 shows the prevalence of the targeted diseases in Germany in 2017.

Table 2: Prevalence of diseases detected in 2017

Disease	Confirmed cases	Prevalence
Congenital Hypothyroidism	279	1: 2,813
Adrenogenital Syndrome (AGS)	48	1: 16,352
Biotinidase Deficiency	20	1: 39,245
Galactosemia (classic)	6	1: 130,817
Phenylketonuria (PKU) n=71/ Hyperphenylalaninemia (HPA) n=86	157	1: 4,999
Maple Syrup Urine Disease (MSUD)	6	1: 130,817
Medium-Chain Acyl-CoA Dehydrogenase (MCAD) deficiency	77	1: 10,194
Long-chain 3-Hydroxyacyl-CoA Dehydrogenase (LCHAD) deficiency	11	1: 71,355
(Very) Long-Chain Acyl-CoA-Dehydrogenase (VLCAD) deficiency	11	1: 71,355
Carnitine Palmitoyltransferase I (CPT I) deficiency	0	
Carnitine Palmitoyltransferase II (CPT II) deficiency	1	1: 784,900
Carnitine-Acylcarnitine Translocase (CACT) deficiency	0	
Glutaric Acidemia Type I (GA I)	5	1: 156,980
Isovaleric Acidemia (IVA)	5	1: 156,980
Cystic Fibrosis (CF) n=146 / CFSPID n=14	160	1 4,906
Total	**786**	**1: 999**

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 end of the 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	60079	59001	98.21	518	0.86	560	0.93
3	16088	15854	98.55	109	0.68	125	0.78
5	61212	60075	98.14	486	0.79	651	1.06
6	13279	12882	97.01	222	1.67	175	1.32
7	56344	54732	97.14	764	1.36	848	1.51
8	180129	176366	97.91	1718	0.95	2045	1.14
9	139507	136327	97.72	1293	0.93	1887	1.35
10	37327	36586	98.01	275	0.74	466	1.25
11	17722	17217	97.15	320	1.81	185	1.04
12	93236	91232	97.85	946	1.01	1058	1.13
13	68697	66845	97.30	934	1.36	918	1.34
14	33466	32668	97.62	508	1.52	290	0.87
15	9493	9198	96.89	78	0.82	217	2.29
Total	**786579**	**768983**	**97.76**	**8171**	**1.04**	**9425**	**1.20**

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,c]	Total received	%	Recall requested [c]	Recall received	%
1	1382	1328	96.09	217	216	99.54
3	431	395	91.65	145	145	100
5	1327	1245	94.20	274	274	100
6	448	440	98.21	61	60	98.36
7	2139	n/a		527	n/a	
8	5102	4696	92.04	994	981	98.69
9	3852	2840	73.73	672	537	79.91
10	1092	1039	95.15	262	262	100.00
11	563	547	97.16	70	70	100.00
12	2428	2405	99.05	465	461	99.14
13	2105	1907	90.59	253	251	99.21
14	914	905	99.02	127	127	100.00
15	500	448	89.60	187	187	100.00
Total	**22283**	**18200**	**90.35**[b]	**4254**	**3571**	**95.81**[b]

Lab	<36h requested [c]	<36h received	%	<32WoG requested [c]	<32WoG received	%
1	515	482	93.59	528	528	100.00
3	109	106	97.25	116	116	100.00
5	412	386	93.69	627	574	91.55
6	218	211	96.79	161	161	100.00
7	764	n/a		848	n/a	
8	1716	1448	84.38	1976	1883	95.29
9	1293	838	64.81	1887	1465	77.64
10	275	261	94.91	466	427	91.63
11	319	303	94.98	174	174	100.00
12	937	918	97.97	1026	1026	100.00
13	934	801	85.76	918	855	93.14
14	506	497	98.22	281	281	100.00
15	78	49	62.82	217	195	89.86
Total	**8076**	**6300**	**86.16**[b]	**9225**	**7685**	**91.74**[b]

[a] Including second screenings due to blood transfusions or medicines administered

[b] Calculation excludes laboratories with undifferentiated or implausible results

[c] Deaths not included in the number of requested samples

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 center. 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	60079	346	267	3697	4310
3	16088	53	34	819	906
5	61212	35	135	3215	3385
6	13279	24	20	246	290
7[b]	56344				
8	180129			2846[a]	2846
9	139507	7	253	2356	2616
10	37327	179	60	1860	2099
11	17722	89	10	278	377
12	93236	0	0	1642[a]	1642
13[b]	68697				
14	33466	0	0	177[a]	177
15[b]	9493				
Total	**786579**	**733**	**779**	**17136**	**18648**

[a] Total number, differentiation not possible

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 (%)	IM[b]
1	60079	1027	952	92.70	1.71	596
3	16088	16	16	100.00	0.10	2
5	61212	609	597	98.03	0.99	n/a
6	13279	5	5	100.00	0.04	14
7	56344	119	n/a	.	0.21	n/a
8	180129	901[c]	898	99.67	0.50	262
9	139507	73	59	80.82	0.05	479
10	37327	184	148	80.43	0.49	151
11	17722	13	13	100.00	0.07	8
12	93236	760	752	98.95	0.82	4
13	68697	626	595	95.05	0.91	n/a
14	33466	59	59	100.00	0.18	2
15	9493	32	32	100.00	0.34	n/a
Total	**786579**	**4424**	**4126**	**95.84[a]**	**0.56**	**1518**

[a] Calculation without laboratory 7 due to insufficient data regarding cards with poor sample quality.

[b] IM includes samples for which the number of circles saturated with blood on the screening card was not sufficient to perform the full screening (including samples for which the CF algorithm could not be completely executed).

[C] Contains samples for which insufficient material was available.

3 Process Time

3.1 Age at the time of 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 94.2% of cases in which the time of blood sampling was provided, collection took place in the designated time frame, in 4.7% not until after 72 hours and in 1.1% before 36 hours (Table 3.1). The proportion of samples which were collected after 72 hours - i.e. outside the designated time frame - was reduced from 22.3% in 2005 to 4.7% 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 3.1: Age at blood sample collection - primary screening

	Total	<36h		36h-<48h		48h-<72h		≥72h	
Lab	n	n	%	n	%	n	%	n	%
1[a]	60065	592	0.99	20094	33.45	35901	59.77	3478	5.79
3	16088	132	0.82	4351	27.05	11177	69.47	428	2.66
5[a]	61077	499	0.82	45692	74.81	13189	21.59	1697	2.78
6	13279	240	1.81	5765	43.41	6899	51.95	375	2.82
7	56344	924	1.64	23514	41.73	24610	43.68	7296	12.95
8[a]	179463	1831	1.02	82280	45.85	87026	48.49	8326	4.64
9	139507	1428	1.02	66304	47.53	65565	47.00	6210	4.45
10	37327	327	0.88	12378	33.16	22690	60.79	1932	5.18
11	17722	343	1.94	5993	33.82	10371	58.52	1015	5.73
12[a]	91719	1047	1.14	48359	52.73	39122	42.65	3191	3.48
13	68697	585	0.85	48447	70.52	18091	26.33	1574	2.29
14[a]	32552	529	1.63	15745	48.37	15046	46.22	1232	3.78
15	9493	94	0.99	5054	53.24	4143	43.64	202	2.13
Total	**783333**	**8571**	**1.09**	**383976**	**49.02**	**353830**	**45.17**	**36956**	**4.72**

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.

3.2 Period between sample collection and receipt by the lab

The time interval between taking blood samples and reporting suspicious results should not exceed 72 hours (§ 18 paragraph 3). However, in 28.4% 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% of cases, the time period ranged from 48 to 72 hours. Compared to previous years, there was a significant delay in shipping time for 2017. Efforts should be made to shorten the time span for sending samples, particularly on weekends (table 4.2, fig. 3).

Table 3.2: Period between sample collection and receipt by the lab

	Total	≤24h		>24h-48h		>48h-72h		>72h	
Labor	n	n	%	n	%	n	%	n	%
1[a]	60017	14938	24.89	20836	34.72	12210	20.34	12033	20.05
3[a]	15859	4889	30.83	7197	45.38	2863	18.05	910	5.74
5[a]	61134	2669	4.37	20787	34.00	17485	28.60	20193	33.03
6	13279	2043	15.39	5584	42.05	3046	22.94	2606	19.62
7	56344	10109	17.94	15701	27.87	11167	19.82	19367	34.37
8[a]	179463	15686	8.74	53528	29.83	47589	26.52	62660	34.92
9	139507	8863	6.35	30235	21.67	33716	24.17	66693	47.81
10	37327	4790	12.83	13659	36.59	10263	27.49	8615	23.08
11	17722	2257	12.74	7465	42.12	4725	26.66	3275	18.48
12[a]	92026	30697	33.36	32450	35.26	17246	18.74	11633	12.64
13	68697	19330	28.14	23453	34.14	14849	21.62	11065	16.11
14[a]	33312	20040	60.16	8148	24.46	3464	10.40	1660	4.98
15	9493	1745	18.38	4028	42.43	1949	20.53	1771	18.66
Total	**784180**	**138056**	**17.61**	**243071**	**31.00**	**180572**	**23.03**	**222481**	**28.37**

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.

3.3 Period between receipt by the lab and reporting the results

76% of the results are reported within 24 hours. In the case of marginally elevated findings, the time in the laboratory can be extended due to internal repeat examinations for quality assurance purposes. In comparison to previous years, the proportion of findings that are were not reported until two to three days after receipt by the laboratory has increased. (Table 3.3. Figure 4). This applies primarily to negative results, i.e. results within the normal range.

Table 3.3: Period between receipt by the lab and reporting the results

	Total	≤24h		>24h-48h		>48h-72h		>72h	
Lab	n	n	%	n	%	n	%	n	%
1[a]	59520	32307	54.28	19757	33.19	4488	7.54	2968	4.99
3	16088	15190	94.42	540	3.36	184	1.14	174	1.08
5[a]	61127	44715	73.15	11031	18.05	5338	8.73	43	0.07
6	13279	12739	95.93	398	3.00	92	0.69	50	0.38
7	56344	20503	36.39	29759	52.82	3265	5.79	2817	5.00
8	180129	170702	94.77	8433	4.68	255	0.14	739	0.41
9	139507	109294	78.34	25737	18.45	3860	2.77	616	0.44
10	37327	34097	91.35	3000	8.04	213	0.57	17	0.05
11	17722	11899	67.14	3854	21.75	1396	7.88	573	3.23
12[a]	92861	65897	70.96	14902	16.05	10998	11.84	1064	1.15
13	68697	47990	69.86	11837	17.23	8203	11.94	667	0.97
14[a]	33319	29394	88.22	3250	9.75	434	1.30	241	0.72
15	9493	2091	22.03	7260	76.48	121	1.27	21	0.22
Total	**785413**	**596818**	**75.99**	**139758**	**17.79**	**38847**	**4.95**	**9990**	**1.27**

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 of blood sample collection 2005 to 2017

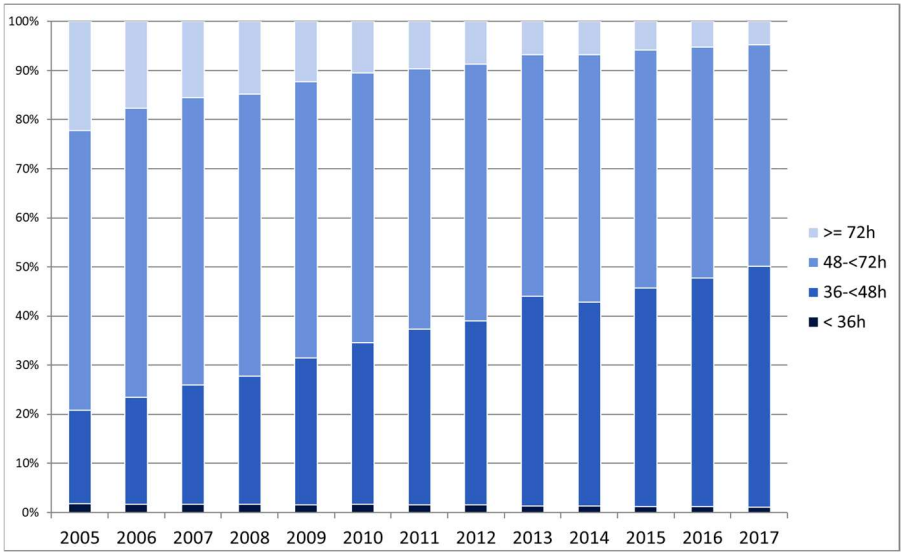


Figure 3: Time between blood sample collection and receipt by the lab 2005 bis 2017

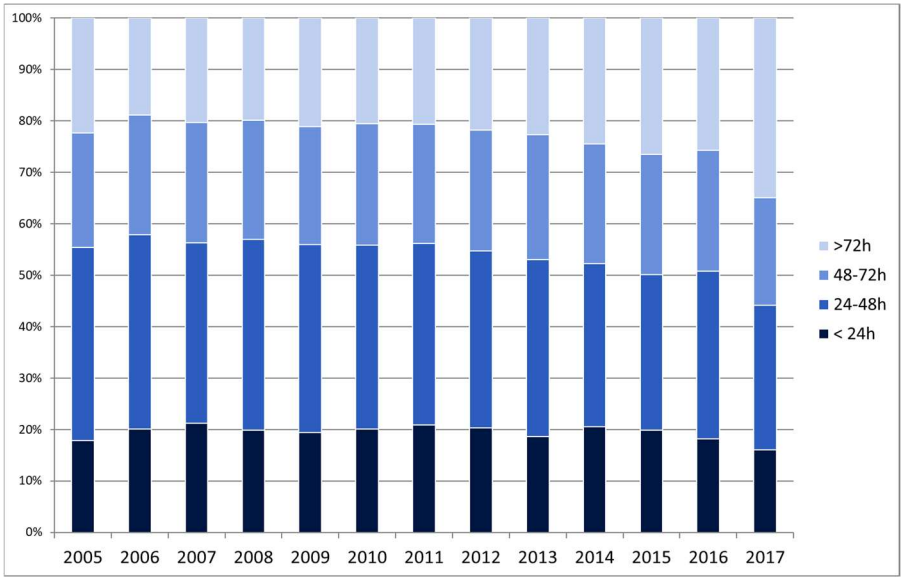
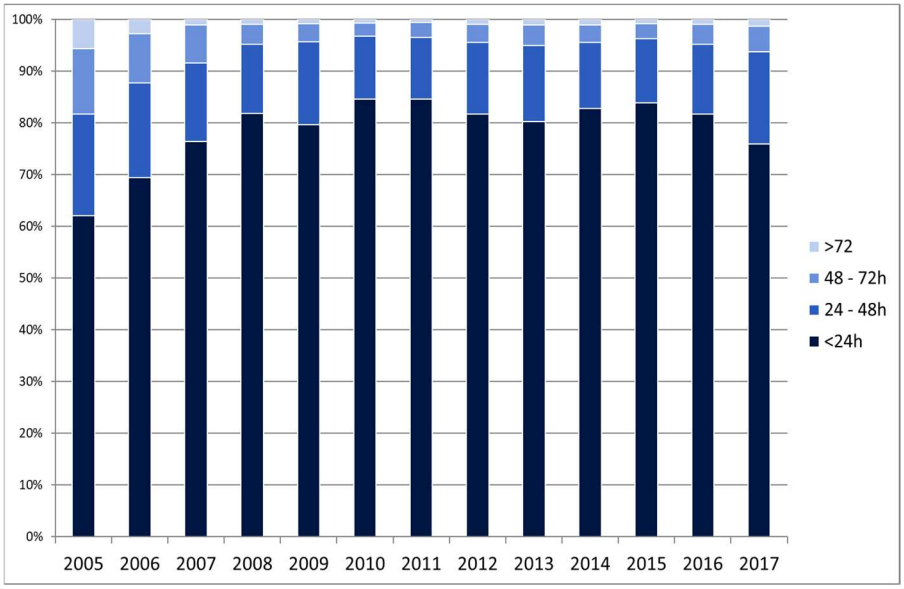


Figure 4: Time between receipt by the lab and reporting the results 2005 bis 2017



4 Quality parameters of screening analysis

The quality of a test procedure is determined by sensitivity, specificity and positive predictive value (PPV). In a screening procedure, the sensitivity (true positive rate, i.e. the percentage of sick people correctly identified as having the condition), but especially the specificity (true negative rate, i.e. the percentage of healthy people correctly identified as not having the condition), 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 positive first screening results, the higher the specificity.

The recall rate for the established newborn screening (ENS) was 0.53% in 2017. In the CF screening, the rate of positive screening results was 0.095%. This means that out of 1,000 screening examinations, approximately 6 results requiring a control examination can be expected. If the blood sample is taken before 36 hours of life or 32 weeks of pregnancy, a second screening must be carried out, irrespective of the result of the analysis. When taking only screening samples into account that were collected after 36 hours of life from babies born at term, the recall rate is 0.37%.

The total specificity was 99.58% for the ENS and 99.93% for the CF screening. The sensitivity cannot be determined, as the number of children missed in the screening has not yet been systematically recorded. Nationwide registers of the diseases included in the screening would be very helpful here.

Table 4: Recall rates and cases found for Germany 2017

Disease	Primary screening	Recall	Recall rate (%)	Confirmed Cases	PPV	Specificity
Congenital Hypothyroidism	786579	996	0.13	279	28.01	99.91
CAH	786579	1881	0.24	48	2.45	99.77
Biotinidase Deficiency	786579	205	0.03	20	9.76	99.98
Galactosemia [a]	786579	168	0.02	6	3.57	99.98
PKU/HPA	786579	374	0.05	157	41.98	99.97
MSUD	786579	50	0.01	6	12.00	99.99
MCAD	786579	154	0.02	77	50.00	99.99
LCHAD	786579	21	0.003	11	52.38	99.99
VLCAD	786579	116	0.01	11	9.48	99.99
CPT-I Deficiency	786579	10	0.001	0		
CPT-II Deficiency	786579	7	0.0009	1	14.28	
CACT Deficiency [b]	786579			0		
GA I	786579	92	0.01	5	5.43	99.99
IVA	786579	68	0.01	5	7.35	99.99
Total ENS	**786579**	**4142**	**0.53**	**626**	**15.11**	**99.55**
CF	**776564**	**735**[c]	**0.095**	**160**	**21.77**	**99.93**

[a] Only classic galactosemia. [b] Recalls for CACT deficiency are listed under CPT-II Deficiency. [C] The cases listed as recalls were either clarified using a specified screening algorithm or because of clinical or anamnestic abnormalities.

4.1 Time of primary screening in confirmed cases

The success of the screening depends on the reliability of the results and the speed with which, in suspected cases, confirmatory diagnostics are carried out and therapeutic measures initiated. According to the guideline, the blood sample should not be taken less than 36 hours before or more than 72 hours after birth except in the case of early discharge. Any delay represents a potential risk for the children concerned.

Table 4.1 shows the age at primary screening for children with one of the targeted diseases. For better clarity ages of more than 72 hours are given in days, calculated from the number of hours of life.

Table 4.1: 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 Hypothyroid-ism	248	9	0	4	17	1	0	**279**
AGS	35	3	0	6	1	0	3	**48**
Biotinidase	19	0	0	1	0	0	0	**20**
Galactosemia	6	0	0	0	0	0	0	**6**
PKU/HPA	140	3	1	3	8	0	2	**157**
MSUD	6	0	0	0	0	0	0	**6**
MCAD	68	5	1	1	1	0	1	**77**
LCHAD	10	0	0	1	0	0	0	**11**
VLCAD	9	1	0	1	0	0	0	**11**
CPT II	1	0	0	0	0	0	0	**1**
GA I	4	0	1	0	0	0	0	**5**
IVA	5	0	0	0	0	0	0	**5**
CF	148	5	2	1	0	1	3	**160**
Total	**699**	**26**	**5**	**18**	**27**	**2**	**9**	**786**

[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.

5 Recall rate, confirmed cases and confirmation stratified by disease

The following chapter presents recall rates and confirmed cases for the target diseases as well as the diagnostic measures taken to confirm the diagnosis, stratified by laboratory.

Diagnostic measures can only be reported if the laboratories are informed of them. Knowledge of the individual results of confirmation diagnostics is important for quality assurance in the laboratory but they are not always communicated to the laboratories by the attending physicians.

The figures were reported as of December 12, 2018. Cases from birth year 2017 which were found at a later date are not included in this report. The plausibility check of the cases reported as confirmed was carried out by Prof. Dr. Regina Ensenauer, Prof. Dr. Martin Lindner and Prof. Dr. Esther Maier for metabolic diseases, by Dr. Oliver Blankenstein and Dr. Erwin Lankes for endocrinological diseases, and by PD Dr. Olaf Sommerburg for cystic fibrosis.

Cases with missing confirmation diagnosis data were excluded from the analysis.

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 the appropriate forms and parental consent.

For cystic fibrosis, so little data was available in n=180 (24.42%) cases that neither the diagnosis "cystic fibrosis" nor the diagnosis "no indication of cystic fibrosis" could be confirmed. In 39 cases (5.86%) there was insufficient data to confirm the diagnosis of ENS diseases (see section 5.4). For 64 cases, no detailed information on confirmation diagnostics was available, but the available data allow the cases to be assessed as plausibly positive.

5.1 Congenital Hypothyroidism

Table 5.1.1: Hypothyroidism confirmed cases / recall rate

		Total			≥ 36h		
Lab	**Primary screening**	Recall (n)	Recall rate (%)	Confirmed cases (n)	Recall (n)	Recall rate (%)	Confirmed cases (n)
1	60079	72	0.12	24	61	0.10	24
3	16088	14	0.09	7	14	0.09	7
5	61212	77	0.13	22	76	0.13	22
6	13279	8	0.06	3	8	0.06	3
7	56344	90	0.16	18	59	0.11	18
8	180129	308	0.17	52	196	0.11	49
9	139507	97	0.07	54	96	0.07	49
10	37327	71	0.19	11	32	0.09	9
11	17722	52	0.29	4	6	0.03	3
12	93236	103	0.11	41	58	0.06	35
13	68697	49	0.07	29	47	0.07	28
14	33466	45	0.13	11	20	0.06	8
15	9493	10	0.11	3	9	0.10	3
Total	**786579**	**996**	**0.13**	**279**	**682**	**0.09**	**258**

		<36h			<32 WoG		
Lab	**Primary screening**	Recall (n)	Recall rate (%)	Confirmed cases (n)	Recall (n)	Recall rate (%)	Confirmed cases (n)
1	60079	8	1.54	0	3	0.54	0
3	16088	0	0.00	0	0	0.00	0
5	61212	0	0.00	0	1	0.15	0
6	13279	0	0.00	0	0	0.00	0
7	56344	24	3.14	0	7	0.83	0
8	180129	103	6.00	1	9	0.44	2
9	139507	0	0.00	1	1	0.05	4
10	37327	36	13.09	0	3	0.64	2
11	17722	46	14.38	1	0	0.00	0
12	93236	33	3.49	0	12	1.13	6
13	68697	1	0.11	0	1	0.11	1
14	33466	21	4.13	1	4	1.38	2
15	9493	0	0.00	0	1	0.46	0
Total	**786579**	**272**	**3.33**	**4**	**42**	**0.45**	**17**

Of the 279 validated congenital hypothyroidism cases, one was unremarkable in the initial screening (blood collection after 52 hours of life, 34th WoG). The second card at the age of 8 days was conspicuous (TSH 19.2 mU/l); confirmation diagnosis: TSH 113 mU/l. fT4 0.74 ng/dl. fT3 2.56 pg/ml, suspected transient synthesis disturbance.

In addition, n= 47 hyperthyrotropinemia and secondary hypothyroidism were reported and validated as confirmed. These were not included in the calculation of prevalence.

Table 5.1.2: Hypothyroidism Confirmation

Lab	Confirmed cases	TSH (Serum)	fT3	fT4	Sonography	SD Antibodies	Confirmed cases without confirmation details
1	24	24	6	23	24	10	
3	7	7	7	7	6	7	
5	22	20	7	18	15	13	1
6	3	2	2	2	1	1	1
7	18						18
8	52	50	43	49	47	37	
9	54	53	40	53	15	1	
10	11	9	8	9	9	7	2
11	4	3	2	3	3	1	1
12	41	41	33	40	31	22	
13	29	29	25	28	1	1	
14	11	11	7	9	9	7	
15	3	3	2	2	1	2	
Total	**279**	**252**	**182**	**243**	**162**	**109**	**23**

5.2 Adrenogenital Syndrome (AGS)

Table 5.2.1: AGS Confirmed cases / Recall rate

		Total			≥ 36h		
Lab	**Primary screening**	Recall (n)	Recall rate (%)	Confirmed cases (n)	Recall (n)	Recall rate (%)	Confirmed cases (n)
1[b]	60079	18	0.03	6	9	0.02	5
3	16088	9	0.06	0	9	0.06	0
5	61212	132	0.22	3	129	0.21	2
6	13279	24	0.18	0	19	0.15	0
7	56344	713	1.27	2	308	0.56	2
8[c]	180129	214	0.12	16	43	0.02	14
9	139507	344	0.25	6	338	0.25	5
10	37327	175	0.47	1	125	0.34	1
11	17722	69	0.39	1	38	0.22	0
12[b]	93236	134	0.14	8	28	0.03	7
13[b]	68697	26	0.04	2	19	0.03	2
14[b]	33466	17	0.05	2	4	0.01	2
15[b]	9493	6	0.06	1	3	0.03	1
Total	**786579**	**1881**	**0.24**	**48**[a]	**1072**	**0.14**	**41**

		<36h			<32 WoG		
Lab	**Primary screening**	Recall (n)	Recall rate (%)	Confirmed cases (n)	Recall (n)	Recall rate (%)	Confirmed cases (n)
1[b]	60079	2	0.39	1	7	1.25	0
3	16088	0	0.00	0	0	0.00	0
5	61212	2	0.41	1	1	0.15	0
6	13279	0	0.00	0	5	2.86	0
7	56344	47	6.15	0	358	42.22	0
8[c]	180129	144	8.38	2	27	1.32	0
9	139507	5	0.39	1	1	0.05	0
10	37327	17	6.18	0	33	7.08	0
11	17722	22	6.88	0	9	4.86	1
12[b]	93236	90	9.51	1	16	1.51	0
13[b]	68697	0	0.00	0	7	0.76	0
14[b]	33466	11	2.17	0	2	0.69	0
15[b]	9493	3	3.85	0	0	0.00	0
Total	**786579**	**343**	**4.20**	**6**	**466**	**4.94**	**1**

[a] Confirmed cases including n=1 11ß-Hydroxylase deficiency (11ß-OHlase deficiency)

[b] Lab uses 2nd tier method

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

Table 5.2.2: AGS Confirmation

Lab	Confirmed cases	17-OHP (Serum)	Steroids (Serum/DB)	Urinary steroids	Molecular genetics	Confirmed cases with-out confirma-tion details
1	6	5	6		6	
5	3	2	1	2	1	
7	2					2
8	16	10	15	4	13	
9	6	6	3		5	
10	1	1			1	
11	1	1	1			
12	8	6	6	6	7	
13	2	1			1	1
14	2					2
15	1	1	1	1	1	
Total	**48**	**33**	**33**	**13**	**35**	**5**

5.3 Biotinidase Deficiency

Table 5.3.1: Biotinidase Deficiency - Confirmed cases / Recall rate

Lab	Primary screening	Recall [a]	Recall-rate (%)	Confirmed cases
1	60079	19	0.03	2
3	16088	2	0.01	2
5	61212	5	0.01	0
6	13279	6	0.05	0
7	56344	9	0.02	2
8	180129	72	0.04	5
9	139507	12	0.01	3
10	37327	2	0.01	0
11	17722	5	0.03	0
12	93236	24	0.03	0
13	68697	22	0.03	2
14	33466	9	0.03	1
15	9493	18	0.19	3
Total	**786579**	**205**	**0.03**	**20**

[a] Sum of Recall ≥ 36h, Recall <36h and Recall <32 WoG. The number of cases <36h and <32 WoG was too low to warrant a stratified report.

Of n= 20 confirmed cases with biotinidase deficiency, 11 showed a complete defect or undifferentiated defect. In n=9 cases a partial biotinidase deficiency was diagnosed.

Table 5.3.2: Biotinidase Deficiency Confirmation

Lab	Confirmed cases	Biotinidase (Serum/DB)	Molecular genetics	Confirmed cases without confirmation details
1	2	1		1
3	2	2		
7	2	2	2	
8	5	3		2
9	3	3	2	
13	2	1	1	1
14	1	1		
15	3	2		1
Total	**20**	**15**	**5**	**5**

5.4 Classic Galactosemia

Table 5.4.1: Classic Galactosemia Confirmed cases / Recall rate

Lab	Primary screening	Recall [a]	Recall rate (%)	Confirmed cases
1	60079	16	0.03	0
3	16088	1	0.01	1
5	61212	4	0.01	0
6	13279	4	0.03	0
7	56344	10	0.02	0
8	180129	52	0.03	1
9	139507	24	0.02	1
10	37327	1	0.003	0
11	17722	2	0.01	0
12	93236	47	0.05	1
13	68697	1	0.00	1
14	33466	4	0.01	0
15	9493	2	0.02	1
Total	**786579**	**168**	**0.02**	**6**

[a]Sum of Recall ≥ 36h, Recall <36h and Recall <32 WoG. The number of cases <36h and <32 WoG was too low to warrant a stratified report.

Table 5.4.2: Classic Galactosemia Confirmation

Lab	Confirmed cases	Enzymatics	Galactose, Gal1P	Molecular genetics	Confirmed cases without confirmation details
3	1		1	1	
8	1			1	
9	1		1		
12	1	1	1	1	
13	1		1	1	
15	1	1	1		
Total	**6**	**2**	**5**	**4**	

5.5 Phenylketonuria (PKU) / Hyperphenylalaninemia (HPA)

Table 5.5.1: PKU/HPA Confirmed cases / Recall rate

Lab	Primary screening	Recall [a]	Recall rate (%)	Confirmed cases
1	60079	25	0.04	11
3	16088	3	0.02	3
5	61212	25	0.04	17
6	13279	3	0.02	2
7	56344	139	0.25	19
8	180129	23	0.01	23
9	139507	28	0.02	27
10	37327	17	0.05	7
11	17722	4	0.02	3
12	93236	45	0.05	25
13	68697	33	0.05	12
14	33466	24	0.07	7
15	9493	5	0.05	1
Total	**786579**	**374**	**0.05**	**157**

[a]Sum of Recall ≥ 36h, Recall <36h and Recall <32 WoG. The number of cases <36h and <32 WoG was too low to warrant a stratified report.

Of n=157 confirmed cases, 71 were diagnosed as PKU and 86 as HPA.

Table 5.5.2: PKU/HPA Confirmation

Lab	Confirmed cases	Phe (Serum/DB)	Phe/Tyr	Molecular genetics	Pterins (Urine/DB)	DHPR (DB)	Confirmed cases without confirmation details
1	11	9	7	6	7	9	1
3	3	3	3	2	3	3	
5	17	15	8		15	15	2
6	2	2	2		2	2	
7	19	18	17	5			1
8	23	22	13	5	14	13	1
9	27	21	2	12	26	26	1
10	7	7	7	7	7	7	
11	3	3	2	1	3	3	
12	25	18	16	2	14	14	7
13	12	9	4	3	9	9	3
14	7	6	5	1	6	5	1
15	1	1				1	
Total	**157**	**134**	**86**	**44**	**106**	**107**	**17**

Table 5.5.3: PKU BH4-Test / BH4 Sensitivity

Lab	Confirmed cases	BH4-Test	BH4 sensitive
1	11	6	4
3	3	3	
5	17	1	1
6	2		
7	19		2
8	23	8	2
9	27	10	5
10	7	3	
11	3	3	
12	25	9	3
13	12	4	
14	7	1	
15	1		
Total	**157**	**48**	**17**

5.6 Maple Syrup Urine Disease (MSUD)

Table 5.6.1: MSUD - Confirmed cases / Recall rate

Lab	Primary screening	Recall [a]	Recall rate (%)	Confirmed cases
1	60079	10	0.02	1
3	16088	3	0.02	0
5	61212	3	0.005	3
6	13279	2	0.02	0
7	56344	2	0.004	1
8	180129	3	0.002	0
9	139507	20	0.01	0
10	37327	5	0.01	0
11	17722	0		0
12	93236	1	0.001	0
13	68697	1	0.001	1
14	33466	0		0
15	9493	0		0
Total	786579	50	0.01	6

[a] Sum of Recall ≥ 36h, Recall <36h and Recall <32 WoG. The number of cases <36h and <32 WoG was too low to warrant a stratified report.

Table 5.6.2: MSUD Confirmation

Lab	Confirmed cases	Confirmation (Serum)	Organic acids (urine)	Enzyme activity	Molecular genetics	Confirmed cases without confirmation details
1	1	1	1		1	
5	3	3	3	2	2	
7	1	1	1		1	
13	1	1				
Total	**6**	**6**	**5**	**2**	**4**	

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

Table 5.7.1: MCAD deficiency- Confirmed Cases/Recall rate

Lab	Primary screening	Recall [a]	Recall rate (%)	Confirmed cases
1	60079	8	0.01	5
3	16088	9	0.06	4
5	61212	10	0.02	8
6	13279	4	0.03	2
7	56344	17	0.03	3
8	180129	11	0.01	10
9	139507	43	0.03	16
10	37327	23	0.06	5
11	17722	6	0.03	5
12	93236	16	0.02	16
13	68697	3	0.003	2
14	33466	1	0.003	0
15	9493	3	0.03	1
Total	**786579**	**154**	**0.02**	**77**

[a] Sum of Recall ≥ 36h, Recall <36h and Recall <32 WoG. The number of cases <36h and <32 WoG was too low to warrant a stratified report.

Table 5.7.2: MCAD Deficiency Confirmation

Lab	Confirmed cases	Confirmation (Serum/DB)	Organic Acids (urine)	Enzyme activity	Molecular genetics	Confirmed cases without confirmation details
1	5	5	4	5	5	
3	4	4			4	
5	8	3	3		3	2
6	2	2	2		2	
7	3		2		2	1
8	10	4	4		7	1
9	16	11	7	6	12	1
10	5	4	3		3	
11	5		5		3	
12	16	14	3	2	10	2
13	2	2			2	
15	1		1	1	1	
Total	**77**	**49**	**34**	**14**	**54**	**7**

5.8 Long-Chain-3-Hydroxyacyl-CoA Dehydrogenase (LCHAD) Deficiency

Table 5.8.1: LCHAD Deficiency - Confirmed cases / Recall rate

Lab	Primary screening	Recall [a]	Recall rate (%)	Confirmed cases
1	60079	4	0.01	2
3	16088	0		0
5	61212	3	0.005	0
6	13279	2	0.02	0
7	56344	0		0
8	180129	3	0.002	3
9	139507	1	0.0007	1
10	37327	2	0.01	1
11	17722	2	0.01	1
12	93236	3	0.003	2
13	68697	1	0.001	1
14	33466	0		0
15	9493	0		0
Total	**786579**	21	0.003	11

[a] Sum of Recall ≥ 36h, Recall <36h and Recall <32 WoG. The number of cases <36h and <32 WoG was too low to warrant a stratified report.

Table 5.8.2: LCHAD Deficiency Confirmation

Lab	Confirmed cases	Confirmation (Serum)	Organic Acids (urine)	Enzyme activity	Molecular genetics	Confirmed cases without confirmation details
1	2	2	2		2	0
8	3		2		2	1
9	1	1	1		1	
10	1	1	1		1	
11	1	1	1		1	
12	2					2
13	1				1	
Total	**11**	**5**	**7**		**8**	**3**

5.9 Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency

Table 5.9.1: VLCAD Deficiency- Confirmed cases / Recall rate

Lab	Primary screening	Recall [a]	Recall rate (%)	Confirmed cases
1	60079	19	0.03	2
3	16088	0		0
5	61212	9	0.01	1
6	13279	9	0.07	1
7	56344	12	0.02	3
8	180129	1	0.0006	0
9	139507	39	0.03	1
10	37327	3	0.01	0
11	17722	4	0.02	0
12	93236	3	0.003	1
13	68697	5	0.01	2
14	33466	10	0.03	0
15	9493	2	0.02	0
Total	**786579**	**116**	**0.01**	**11**

[a] Sum of Recall ≥ 36h, Recall <36h and Recall <32 WoG. The number of cases <36h and <32 WoG was too low to warrant a stratified report.

Table 5.9.2: VLCAD Confirmation

Lab	Confirmed cases	Confirmation (Serum)	Organic Acids (urine)	Enzyme activity	Molecular genetics	Confirmed cases without confirmation details
1	2		1	2	2	
5	1			1		
6	1		1	1		
7	3			3		
9	1	1		1	1	
12	1	1				
13	2	2			1	
Total	**11**	**4**	**2**	**8**	**4**	

5.10 CPT I Deficiency

Table 5.10.1: CPT I Deficiency - Recall rate

Lab	Primary screening	Recall[a]	Recall rate (%)	Confirmed cases
1	60079	1	0.001	0
3	16088	0		0
5	61212	0		0
6	13279	4	0.03	0
7	56344	0		0
8	180129	4	0.002	0
9	139507	0		0
10	37327	0		0
11	17722	0		0
12	93236	0		0
13	68697	1	0.001	0
14	33466	0		0
15	9493	0		0
Total	786579	10	0.001	0

[a] Sum of Recall ≥ 36h, Recall <36h and Recall <32 WoG. The number of cases <36h and <32 WoG was too low to warrant a stratified report.

For the year 2017, no confirmed cases of CPTI deficiency were reported.

5.11 CPT II Deficiency / CACT Deficiency

Table 5.11.1: CPT II Deficiency / CACT Deficiency - Confirmed Cases /Recall rate

Lab	Primary screening	Recall [a]	Recall rate (%)	Confirmed cases
1	60079	1	0.002	0
3	16088	0		0
5	61212	0		0
6	13279	0		0
7	56344	0		0
8	180129	0		0
9	139507	1	0.0007	0
10	37327	0		0
11	17722	0		0
12	93236	3	0.003	1[b]
13	68697	1	0.001	0
14	33466	1	0.003	0
15	9493	0		0
Total	**786579**	**7**	**0.0009**	**1[b]**

[a] Sum of Recall ≥ 36h, Recall <36h and Recall <32 WoG. The number of cases <36h and <32 WoG was too low to warrant a stratified report.

[b] CPTII Deficiency was confirmed by the determination of acyl carnitine in the serum and molecular genetics

5.12 Glutaric Aciduria Type I (GA I)

Table 5.12.1: GA I - Confirmed Cases / Recall rate

Lab	Primary screening	Recall [a]	Recall rate (%)	Confirmed cases
1	60079	10	0.02	0
3	16088	0		0
5	61212	2	0.003	0
6	13279	2	0.02	0
7	56344	7	0.01	0
8	180129	3	0.002	1
9	139507	57	0.04	0
10	37327	4	0.01	1
11	17722	2	0.01	0
12	93236	1	0.001	0
13	68697	3	0.004	2
14	33466	0		0
15	9493	1	0.01	1
Total	**786579**	**92**	**0.01**	**5**

[a] Sum of Recall ≥ 36h, Recall <36h and Recall <32 WoG. The number of cases <36h and <32 WoG was too low to warrant a stratified report.

Table 5.12.2: GA I Confirmation

Lab	Confirmed cases	Confirmation (Serum)	Organic Acids (urine)	Enzyme activity	Molecular genetics	Confirmed cases without confirmation details
8	1		1			
10	1	1			1	
13	2	1	1		1	1
15	1	1	1		1	
Total	**5**	**3**	**3**		**3**	**1**

5.13 Isovaleric Acidemia (IVA)

Table 5.13.1: IVA - Confirmed Cases / Recall rate

Lab	Primary screening	Recall [a]	Recall rate (%)	Confirmed cases
1	60079	6	0.01	1
3	16088	1	0.01	0
5	61212	0		0
6	13279	2	0.02	0
7	56344	10	0.02	0
8	180129	10	0.01	1
9	139507	4	0.003	0
10	37327	10	0.03	0
11	17722	5	0.03	0
12	93236	5	0.01	2
13	68697	14	0.02	1
14	33466	1	0.003	0
15	9493	0		0
Total	**786579**	**68**	**0.01**	**5**

[a] Sum of Recall ≥ 36h, Recall <36h and Recall <32 WoG. The number of cases <36h and <32 WoG was too low to warrant a stratified report.

Table 5.13.2: IVA Confirmation

Lab	Confirmed cases	Confirmation (Serum)	Organic Acids (urine)	Enzyme activity	Molecular genetics	Confirmed cases without confirmation details
1	1		1		1	
8	1		1			
12	2	1			1	1
13	1					1
Total	**5**	**1**	**2**		**2**	**2**

5.14 Cystic Fibrosis

Screening for cystic fibrosis is performed in three steps as a serial combination of two biochemical tests, initially for immunoreactive trypsin (IRT). If this is elevated, pancreatitis-associated protein (PAP) is tested. In the case of pathologic PAP, a third molecular genetic screening for the 31 most common pathogenic mutations of the Cystic Fibrosis Transmembrane Regulator gene (CFTR gene) in Germany is carried out (Figure 5).

The screening is found to be conspicuous (positive) if an IRT value above the 99.9th percentile is determined ("Failsafe" method or "Safety Net") or if at least one mutation of the 31 examined mutations of the CFTR gene is detected on at least one allele in the third step.

In all other situations the screening is considered inconspicuous (negative). As a result of this screening algorithm, "failsafe" (IRT >99.9th Percentile) accounts for 77.53% of the positive screening results. This means that almost 80% of the children with positive screening results did not undergo DNA analysis. It can be assumed that only every fourth child with a positive screening result has cystic fibrosis.

The proportion of newborns without a CF screening was 1.27% in 2017 (Table 5.14.1). Depending on the laboratory, this rate ranges from 0.09 to 2.07%.

Table 5.14.1: Number of Cases without CF Screening

Lab	Primary screening ENS	Primary screening CF	Without CF Screening	Proportion without CF Screening (%)
1	60079	58837	1242	2.07
3	16088	16074	14	0.09
5	61212	55930	5282	8.63
6	13279	13176	103	0.78
7	56344	56248	96	0.17
8	180129	179127	1002	0.56
9	139507	139255	252	0.18
10	37327	36892	435	1.17
11	17722	17678	44	0.25
12	93236	92495	741	0.79
13	68697	68077	620	0.90
14	33466	33305	161	0.48
15	9493	9470	23	0.24
Total	**786579**	**776564**	**10015**	**1.27**

Table 5.14.2: CF – Further Diagnostics Necessary / Confirmed cases

Lab	Primary screening	Further diagnostics necessary (sweat test)	Rate (%)	Confirmed cases
1	58837	64	0.11	19
3	16074	15	0.09	3
5	55930	55	0.10	11
6	13176	12	0.09	2
7	56248	65	0.12	1
8	179127	172	0.10	33
9	139255	131	0.09	33
10	36892	49	0.13	10
11	17678	16	0.09	3
12	92495	70	0.08	18
13	68077	52	0.08	12
14	33305	27	0.08	9
15	9470	9	0.10	6
Total	**776564**	**737**	0.09	**160**

Of n=160 confirmed cases, cystic fibrosis was diagnosed in 146 cases and CF-SPID in 14 cases.

Not all of the confirmed diagnoses were found using the specified screening algorithm for cystic fibrosis. Seven of the 160 confirmed cases were negative in the screening.

These children were further diagnosed in 6 cases due to clinical abnormalities (meconium ileus, failure to thrive). In one case of normal PAP, the product of IRT*PAP was suspicious (see Table 7.1). It is not known whether additional children with cystic fibrosis were not detected in the screening.

Table 5.14.3: Confirmed Cases CF - Confirmation

Lab	Confirmed cases	Sweat Test				Genetics	Other [a]
		Simple chloride measurement	Double chloride measurement	Chloride and conductivity	Conductivity only		
	n	n	n	n	n	n	n
1	19	12	2	0	0	15	7
3	3	0	0	3	0	3	0
5	11	6	4	0	0	5	2
6	2	0	2	0	0	2	0
7	1	0	0	0	0	1	0
8	33	8	16	4	0	29	3
9	33	8	8	7	4	21	7
10	10	5	0	3	1	4	1
11	3	2	0	0	0	2	1
12	18	3	3	8	0	5	3
13	12	6	3	0	0	3	1
14	9	5	1	3	0	1	1
15	6	2	2	0	0	5	3
Total	**160[b]**	**57**	**41**	**28**	**5**	**96**	**29**

[a] Meconium ileus. Elastase

[b] in one confirmed case, no confirmatory diagnostic information is available.

Of 160 confirmed diagnoses, no sweat test was carried out in 26 cases. In three further cases, the result of the sweat test was not available. The confirmation diagnosis of these cases is shown in Table 5.14.4.

Table 5.14.4: Confirmed Cases without Sweat Test

Methods / Clinical Symptoms	**Count (n)**
Molecular genetics only	11
Molecular genetics and Meconium Ileus	12
Molecular genetics and Elastase	2
Meconium Ileus and Elastase	1
Molecular genetics, Meconium Ileus and Elastase	2
Total	**29**

Table 5.14.5: No indication of cystic fibrosis – Confirmation

	No Indication of CF	Sweat test	Conductivity only	Molecular genetics	Other
Lab	n	n	n	n	n
1	43	41		13	1
3	11	11		4	
5	32	29			
6	10	10	1		
7	n/a	n/a	n/a	n/a	n/a
8	119	114	2	22	2
9	66	64	12		
10	n/a	n/a	n/a	n/a	n/a
11	12	11		4	3
12	51	50	1	7	
13	36	34	0	5	0
14	17	17	0	2	0
15	n/a	n/a	n/a	n/a	n/a
Total	**397[a]**	**381**	**16**	**57**	**6**

[a] Only cases that were submitted individually could be processed. Cumulative notifications were not taken into account.

6 Lost to follow-up

In total, no information is available on the further analysis of 966 positive screening results (lost to follow-up = 17.08%). In 683 anomalous findings, there was definitely no control screening or it is unclear whether a control card was sent in (Table 2.2).

Of 103 children with positive screening results in the ENS, it is not known whether the confirmatory diagnosis took place or was completed. In 64 of these children however (Table 6.1.1), the findings from the screening were so unambiguous that they were included in the prevalence calculation; for 39 children this was not possible (Table 6.1.1.2).

Of the 737 cases with suspicious results in the CF screening, in n=180 cases (24.42%) it is not known whether the finding was ever clarified or whether the result was reported to the laboratory (lost to follow-up).

6.1 Cases without confirmation details

Cases for which no confirmation information was available but with unambiguous screening results were validated on the basis of the screening results as 'probable cases'. These cases were included in the prevalence calculation despite the lack of confirmation data.

6.1.1 Confirmed cases without confirmation

Table 6.1.1.1: Confirmed Cases without Confirmation

		Reason no confirmation provided			
Disease	Confirmed cases without confirmation	No feedback from clinic / pediatrician	No parental consent	unclear	Clinic did not request confirmation
Hypothyroidism	23	12		11	
AGS	5	2		3	
Biotinidase Deficiency	5	3		2	
PKU/HPA	17	10	2	5	
MCAD	7	5			2
LCHAD	3	3			
GA I	1		1		
IVA	2	2			
Cystic Fibrosis*	1*				
Total	**64**	**37**	**3**	**21**	**2**

* only 2 mutations from screening, no further information about confirmation

6.1.2 Unconfirmed cases from the ENS (lost to follow up)

Table 6.1.2.1: Cases with implausible or missing confirmation information

Disease	Number of Cases n
Congenital Hypothyroidism	20
AGS	7
Biotinidase Deficiency	1
Classic Galactosemia	2
MSUD	1
MCAD	3
VLCAD	2
CPT I Deficiency	1
CPT II Deficiency	1
IVA	1
Total	**39**

Table 6.1.2.2: Proportion of cases by laboratory identified as unclear/open

Lab	Proportion screening of total population (%)	Number of cases identified as unclear/open [a]	Proportion of reported cases (%)
1	7.6	1	1.72
5	7.8	4	5.97
7	7.2	7	11.11
8	22.9	7	4.43
9	17.7	2	1.61
10	4.8	7	20.59
12	11.9	1	0.93
13	8.7	6	9.52
14	4.3	2	8.00
15	1.2	2	14.29

[a] Total number of cases identified as unclear/open n=39

Of the 39 cases that were considered unclear/open, no confirmation data were available in 23 cases. Possible reasons for unavailable information are listed in Table 6.1.2.3.

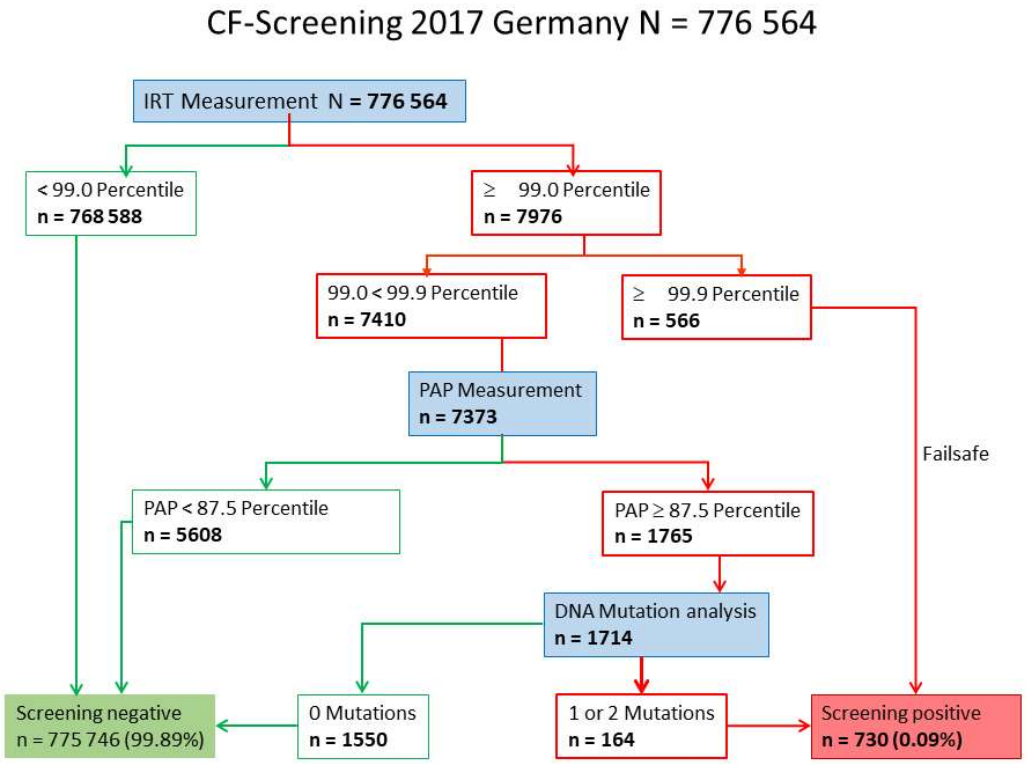
Table 6.1.2.3: Unconfirmed cases without confirmation details (n=23)

		Reason no confirmation provided			
Lab	Unconfirmed Cases	No feedback from clinic / pediatrician	No parental consent	Confirmation not requested	Unclear
5	3	1			2
7	8	3			5
8	2	1		1	
10	6	2			4
13	3	2	1		
15	1	1			
Total	**23**	**10**	**1**	**1**	**11**

7 Screening Algorithm Cystic Fibrosis (CF)

7.1 Screening Algorithm Germany

Figure 5: Screening Algorithm Cystic Fibrosis Germany



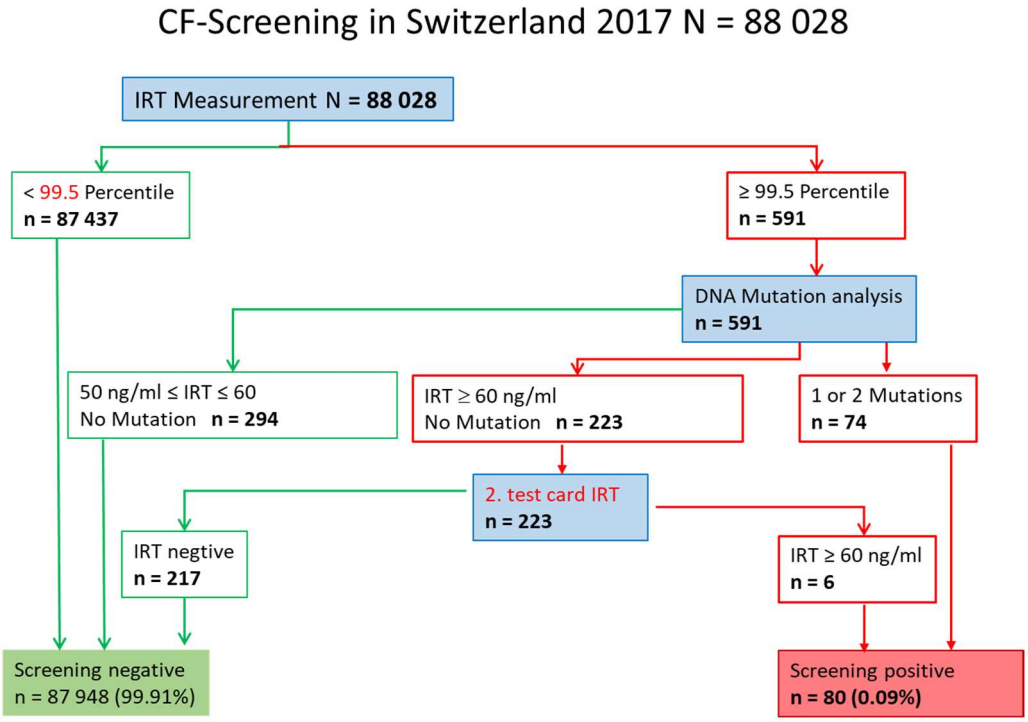
Seven children with confirmed diagnosis had a false negative screening result, i.e. these children were not found using the screening algorithm see Table 7.1.

Table 7.1. Cases with False Negative Screening for CF

Screening Parameter	Found via	Number (n)
IRT negative	Meconium ileus	**1**
PAP negative	Meconium ileus (n=3) Product IRT*PAP positive (n=1) Failure to thrive at 7 months (n=1)	**5**
IRT < 99.9th percentile, mutations (screening) negative	Meconium ileus	**1**

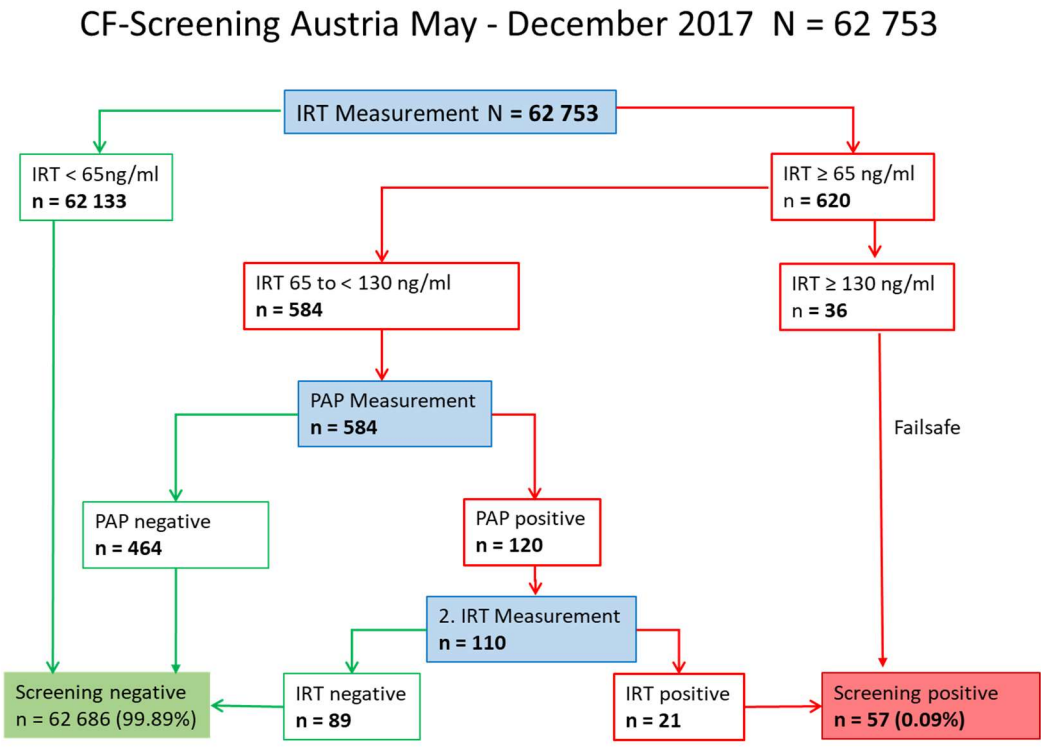
7.2 Screening Algorithm Switzerland

Figure 6: Screening Algorithm Cystic Fibrosis Switzerland



7.3 Screening Algorithm Austria

Figure 7: Screening Algorithm Cystic Fibrosis Austria



8 Methods and Cutoffs used in Screening

Table 8.1: Filter paper

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

Table 8.2 Hypothyroidism

Lab	Parameter	Cutoff	Method
1	TSH	15 mU/l	AutoDELFIA
3	TSH	15 mU/l	AutoDELFIA
5	TSH	15 mU/l	AutoDELFIA
6	TSH	15 mU/l	DELFIA
7	TSH	15 mU/l	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

Table 8.3: Adrenogenital Syndrome (AGS)

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
14/15*	17 OHP	AutoDELFIA

*Lab uses 2nd tier method

Table 8.4: Biotinidase Deficiency

Lab	Parameter	Cutoff	Methods
1	Biotinidase	30%	Qualitative colorimetry
3	Biotinidase	30%	Qualitative colorimetry
5	Biotinidase	30% of panel mean	Qualitative colorimetry
6	Biotinidase	60 U	Fluorometry (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

Table 8.5: Galactosemia

Lab	Parameter	Normal range	Methode
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 non-kit /
	Galactose	< 15 mg/dl	Quant. fluoro. (non-kit)
14/15	GALT	>3.5 U/g Hb	Quantitative fluorometry
	Galactose	<15 mg/dl	BIORAD Quantase

Table 8.6: MS/MS

Lab	Method
1	non-derivat. Chromsystems Kit
3	non-derivat.. Chromsystems
5	derivatized non-kit
6	non-derivatized PE kit
7	derivatized PE kit
8	derivatized non-kit
9	derivatized non-kit
10	deriv. Chromsystems Kit
11	non-derivat. Chromsystems Kit
12/13	derivatized non-kit
14/15	derivatized non-kit

9 Literature

[i] 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

[ii] https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Bevoelkerung/Geburten/_inhalt.html (Zugriff am 17.5.2019)