National Screening Report

Germany 2021

German Society for Neonatal Screening (DGNS)

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Abbreviations and Glossary

CAH	Congenital Adrenal Hyperplasia
CACT Deficiency	Carnitine-Acylcarnitine Translocase Deficiency
CF	Cystic Fibrosis (Mucoviscidosis)
CF-SPID	Cystic Fibrosis Screen Positive, Inconclusive Diagnosis
CPTI/II-Deficiency	Carnitine Palmitoyl Transferase I/II Deficiency
DB	Dried Blood
ENS	Extended Neonatal Screening
GA I	Glutaric Acidemia Type I
HPA	Hyperphenylalaninemia
IM	Insufficient Material
IRT	Immunoreactive Trypsinogen
IVA	Isovaleric Acidemia
LCHAD Deficiency / TFP Deficiency	Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency / Mitochondrial Trifunctional Protein Deficiency
MCAD Deficiency	Medium-Chain Acyl-CoA Dehydrogenase Deficiency
MSUD	Maple Syrup Urine Disease
PAP	Pancreatitis-associated Protein
PKU	Phenylketonuria
PPV	Positive Predictive Value
SSD	Sickle Cell Disease
SCID	Severe Combined Immunodeficiency
Second Tier Method	Second examination of additional parameters or alternative method of analysis with the same test card in case of abnormal finding
SMA	Spinal muscular atrophy
WoG	Week of Gestation
VLCAD Deficiency	Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency

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The results for screening centers with multiple locations or laboratories which are affiliated with a screening center are broken down by location / affiliation.

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1 Introduction

The neonatal screening is a medical population-based preventative measure with the goal of complete and early detection of all newborns affected by any of the targeted diseases so that they can receive early treatment

The implementation of the "extended newborn screening" (ENS) is regulated in the guideline on the early detection of diseases in children up to the age of 6 years, known as the “Paediatrics Directive” or (“Kinder-Richtlinie”) in §§13 – 28 [1]. The National Screening Report is compiled at the Bavarian State Office for Health (LGL) on behalf of the German Society for Newborn Screening (DGNS) e.V. together with the German screening laboratories.

For the 2021 report, the contents of the data collection were reviewed and adapted by a DGNS working group. The terms used were clearly defined. For example, “recall” is defined as the request for a control card after a positive (abnormal) screening result. Requests for follow-up cards after early sampling <32 WoG, <36h or due to poor sample quality do not count as a recall. Implausible IRT values in CF screening should be recorded uniformly as follow-up cards for quality deficiencies and not as CF recalls. Further changes in data collection are described in the relevant sections.

The statistical processing of the screening data is based on the quality criteria defined in the guideline for the implementation of ENS in Germany. The report relates exclusively to the target diseases defined in the guideline and presents a comprehensive statistical compilation of the disease-related screening figures, recall rates and confirmed diagnoses for 2021. It also presents data on process quality for the whole 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:

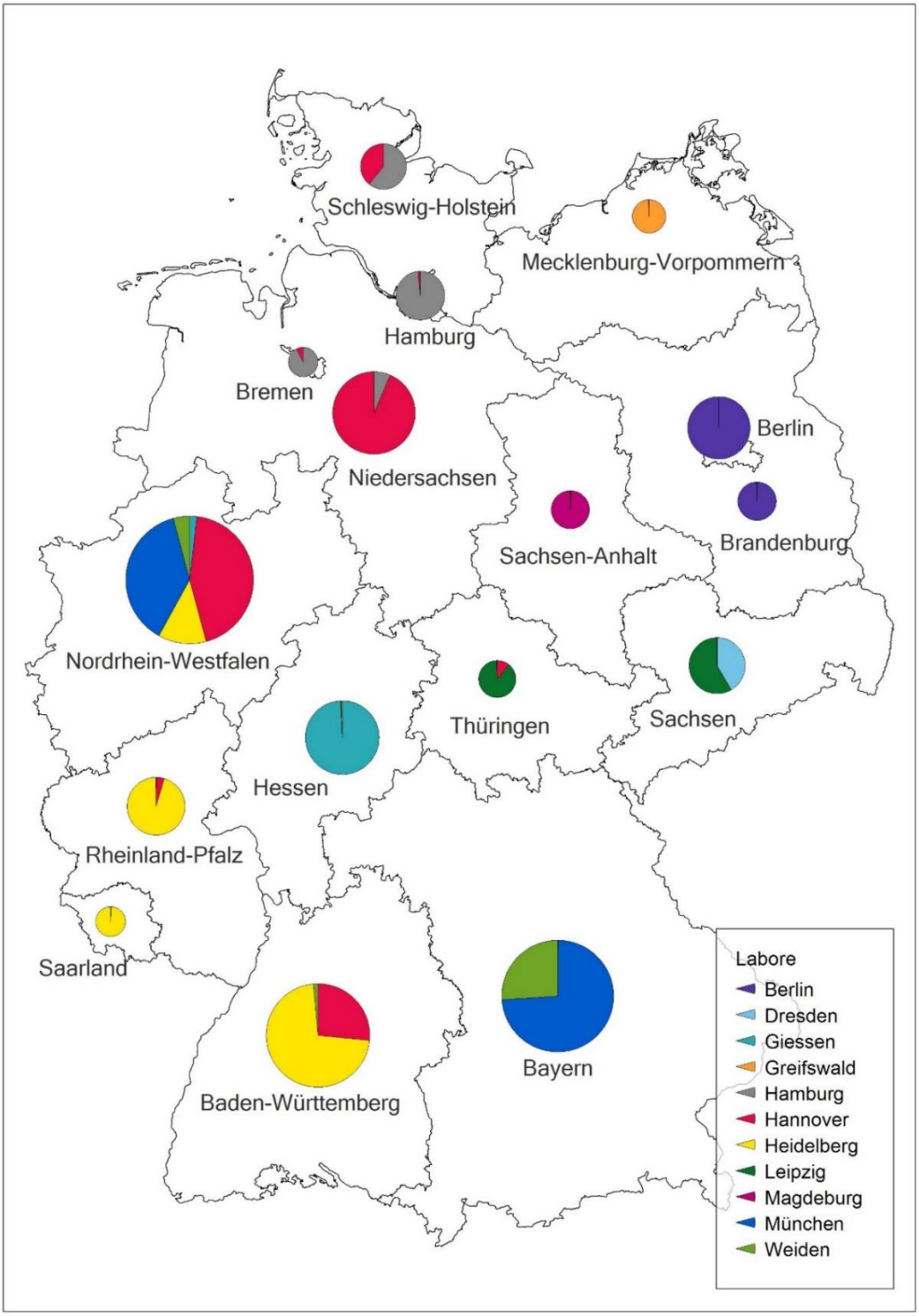
- Total survey of the targeted population
- Completeness of the control and repeat examinations
- Recording test parameters and cut-offs
- Specificity and sensitivity of diagnostic tests
- Age at blood sample collection, time between blood sample collection and receipt at the laboratory and between receipt of the sample and notification of findings.
- Confirmation diagnostics
    - Type and period of diagnostics
    - Final diagnosis
- Age at start of therapy

The previous page lists the laboratories that conducted the screening in Germany in 2021 (12 and 13 refer to the same laboratory, once in cooperation with a tracking center and once without; the same is true of 14 and 15). Paragraphs in the text refer to the Paediatrics Directive from April 4, 2021 [1], in which spinal muscular atrophy and sickle cell disease were defined as new target diseases from October 2021. 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 submitted by the laboratories were used in the tables.

The screening samples from the individual federal states are distributed among the laboratories ("Labore") as illustrated in Figure 1 and Table 2.1.1 The size of the pie charts reflects the number of initial screening examinations.

Figure 1: Distribution of Screening Samples by State and Laboratory



2 Results

In 2021 a total of 795,492 children were born in Germany according to official statistics [2]. As in the previous year, the number of reported initial screening examinations was lower at 789,599. Cumulatively, 99.3% of all newborns were screened. A reliable statement about the rate of participation in ENS can only be made by reconciling individual data with overall population data. A rejection of the examination was documented for only 542 newborns (0.07%).

Births:	795,492
First screenings:	789,599
Confirmed diagnoses:	869

The diseases targeted for the comprehensive screening are defined in § 17 of the Paediatrics Directive. Sickle cell disease and spinal muscular atrophy were newly included from 10/2021. Other diseases screened in individual laboratories as part of studies or state law requirements are not included in this report. One in 915 newborns was diagnosed with one of the target diseases defined in the guideline during newborn screening. Table 2.1 shows the confirmed cases and prevalence of the target diseases in 2021 in relation to births in Germany.

Table 2.1: Prevalence of diseases detected in 2021 among 795,492 births

Disease	Confirmed cases	Prevalence
Hypothyroidism	278	1: 2,861
Congenital Adrenal Hyperplasia (CAH)	48	1: 16,573
Biotinidase Deficiency	41	1: 19,402
Galactosemia (classic form)	11	1: 72,317
Hyperphenylalaninemia	120	1: 6,629
Of which classic phenylketonuria (PKU)	49	1: 16,235
Maple Syrup Urine Disease (MSUD)	2	1: 397,746
Medium-Chain Acyl-CoA Dehydrogenase (MCAD) deficiency	75	1: 10,607
Long-chain 3-Hydroxyacyl-CoA Dehydrogenase (LCHAD) / TFP deficiency	3	1: 265,164
Very Long-Chain Acyl-CoA-Dehydrogenase (VLCAD) deficiency	13	1: 61,192
Carnitine Palmitoyl Transferase I (CPT I) deficiency	1	1: 795,492
Carnitine Palmitoyl Transferase II (CPT II) deficiency	3	1: 265,164
Carnitine-Acylcarnitine Translocase (CACT) deficiency	0	
Glutaric Acidemia (GA) Type I	8	1: 99,437
Isovaleric Acidemia (IVA)	9	1: 88,388
Tyrosinemia Type 1 (Target disease starting 03/2018)	2	1: 397,746
Cystic Fibrosis (CF) (starting 09/2016)	164	1: 4,851
Severe Combined Immunodeficiency (SCID / Leaky-SCID / Syndrome, starting 08/2019)	34	1: 23,397
Spinal muscular atrophy (SMA) (starting 10/2021)	29	
Sickle Cell Disease (starting 10/2021)	28	
Total	**869**	**1: 915**

2.1 Total numbers and age at first screening, recall and confirmed cases by laboratory

Table 2.1.1 shows the proportion of initial screening, confirmed diagnoses and recall rates by laboratory. The confirmed cases also include cases with negative (normal) initial screening. For the first time in 2021, it was determined that only positive screening results should be recorded as recall. Abnormal findings that are only checked as part of the repeat examinations provided for in the Paediatrics Directive (e.g. due to early screening <32 WoG, <36h) should only be recorded in the follow-up cards (see section 2.2) and not as a recall.

Table 2.1.1: Distribution of initial screening, requested repeat tests due to abnormal findings (recall)[a] and all confirmed cases among the laboratories

Lab	Initial screenings (n)	Proportion of screening population (%)	Number of Recalls (n)	Proportion of initial screening (%)	Proportion of Recalls (%)	Number of confirmed cases (n)	Proportion of confirmed cases (%)
1	57,593	7.29	288	0.50	7.36	70	8.06
3	13,849	1.75	47	0.34	1.20	15	1.73
5	61,071	7.73	309	0.51	7.89	48	5.52
6	11,841	1.50	108	0.91	2.76	14	1.61
7	51,898	6.57	678	1.31	17.32	63	7.25
8	188,437	23.86	717	0.38	18.32	214	24.63
09	147,549	18.69	768	0.52	19.62	151	17.38
10	32,804	4.15	159	0.48	4.06	36	4.14
11	15,450	1.96	70	0.45	1.79	10	1.15
12	98,903	12.53	321	0.32	8.20	122	14.04
13	65,965	8.35	215	0.33	5.49	77	8.86
14	34,903	4.42	163	0.47	4.16	33	3.80
15	9,336	1.18	71	0.76	1.81	16	1.84
Total	**789,599**	**100**	**3,914**	**0.50**	**100**	**869**	**100**

[a] without recall "MS/MS", as some laboratories also specify recalls of the pilot projects here.

The recall rates differ significantly between the laboratories in some cases (ranging between 0.32 and 1.31). In addition to different definitions of a finding as a recall, which should be less frequent with the new specifications (e.g. strongly scattered IRT values as a quality defect, no recording of abnormal findings as a recall in routine follow-up cards), the differences between the laboratories in the recall rates for individual diseases could also be due to different cut-off values. For example, the specified cut-off values for hyperphenylalaninemia differ considerably between the laboratories (see Table 5.5.1 and Section 7.3). Second-tier methods significantly reduce the recall rate (see e.g. CAH Table 5.2.1, IVA Table 5.12.1).

According to the Paediatrics Directive, screening should be arranged for every newborn before discharge from the maternity facility. If the first screening is carried out before 36 hours of life or before a corrected gestational age of 32 weeks (WoG) a second screening should be carried out in accordance with §20.

The following table shows the number of initial screening examinations stratified by age and gestational age. This is defined as follows:

- **"<32 WoG"**: all samples taken before the child's corrected age of 32 WoG. For the first time in the 2021 report, a distinction is also made for these children between samples taken before or after 36 hours of life.
- **"<36h"**: all samples taken from children before the age of 36 hours.

Table 2.1.3: Age at time of initial screening

		≥36h and ≥32WoG[a]		<36h and ≥32WoG		≥36h and <32WoG		<36h and <32WoG	
Lab	Total	n	%	n	%	n	%	n	%
1	57,593	56,667	98.39	399	0.69	447	0.78	80	0.14
3	13,849	13,218	95.44	396	2.86	213	1.54	22	0.16
5	61,071	60,063	98.35	392	0.64	561	0.92	63	0.10
6	11,841	11,443	96.64	252	2.13	132	1.11	14	0.12
7	51,898	50,715	97.72	533	1.03	602	1.16	48	0.09
8	188,437	184,409	97.86	2.218	1.18	1.643	0.87	167	0.09
9	147,549	144,225	97.75	1.585	1.07	1.602	1.09	137	0.09
10	32,804	32,187	98.12	350	1.07	214	0.65	53	0.16
11	15,450	15,024	97.24	293	1.90	113	0.73	20	0.13
12	98,903	96,413	97.48	1.449	1.47	901	0.91	140	0.14
13	65,965	63,656	96.50	1.281	1.94	989	1.50	39	0.06
14	34,903	33,996	97.40	606	1.74	274	0.79	27	0.08
15	9,336	9,146	97.96	47	0.50	138	1.48	5	0.05
Total	**789,599**	**771,154**	**97.66**	**9.801**	**1.24**	**7.829**	**0.99**	**815**	**0.10**

[a] incl. n= 9,639 initial screenings with missing data

2.2 Requested and received repeat examinations (follow-up cards)

During data collection in 2021, the reason for a necessary repeat screening (follow-up card) was recorded again for the first time since 2017. This may include, for example, the completion of the initial screening <36 hours of life or before a corrected age of 32 weeks' gestation (early screening) as well as a poor quality of the sample. In addition, it was defined that abnormal findings in early screenings that are only checked using a “routine card” as specified in the guideline will only be recorded in the follow-up cards and no longer counted as a recall. Likewise, follow-up cards due to strongly fluctuating IRT values in the context of CF screening should be recorded as poor sample quality and not as CF recall. Overall - with clear differences between the laboratories - no further cards were recorded for around 10% of the requested follow-up cards.

Table 2.2.1: Repeat examinations (follow-up cards) in total by laboratory, excluding control examinations for findings reported as abnormal (recall)

Lab	Follow-up cards requested	Follow-up cards received	%
1	1,766	1,633	92.47
3	631	631	100
5	1,558	1,450	93.07
6	452	412	91.15
7	1,214	841	69.28
8	5,735	5,225	91.11
9 [a]	4,123	3,458	83.87
10 [a]	1,029	915	88.92
11	445	386	86.74
12	3,093	2,985	96.51
13	2,393	2,324	97.12
14	721	688	95.42
15	201	185	92.04
Total	**23,361**	**21,133**	**90.46**

[a] External follow-up cards from other screening laboratories are not recorded

Table 2.2.2: Follow-up cards due to poor sample quality[a]

Lab	Initial screening total	Follow-up card requested	Follow-up card received	Proportion of received / requested (%)	Proportion of requested / initial screening (%)
1	57,593	761	699	91.85	1.32
3	13,849	81	81	100	0.58
5	61,071	559	524	93.74	0.92
6	11,841	41	39	95.12	0.35
7	51,898	379	299	78.89	0.73
8	188,437	836	812	97.13	0.44
9	147,549	720	638	88.61	0.49
10	32,804	308	298	96.75	0.94
11	15,450	16	14	87.50	0.10
12	98,903	736	719	97.69	0.74
13	65,965	439	438	99.77	0.67
14	34,903	46	45	97.83	0.13
15	9,336	10	10	100	0.11
Total	**789,599**	**4,932**	**4,616**	**93.59**	**0.62**

[a] incl. too little material, highly scattered IRT values, EDTA blood

Despite the fact that uniform criteria for determining poor sample quality (e.g. including highly scattered IRT values in CF screening) were established for the 2021 data, there are still significant differences in the proportion of follow-up cards required due to quality issues depending on the laboratory. The proportion ranges from 0.10 % to 1.32 % of all initial screenings in a laboratory. It is possible that the differentiation between recording a test card as poor quality rather than an abnormal finding still varies. The explanation for good quality in the acquisition of the screenings could be training or regular feedback from the laboratory to the senders.

Table 2.2.3: Follow-up cards due to early collection (<36h or <32 weeks' gestation) and other reasons

	Initial screening < 36 h			Initial screening < 32 WoG			Other		
Lab	requested	received	%	requested	received	%	requested	received	%
1	399	363	90.98	526	495	94.11	80	76	95.00
3	418	418	100.00	132	132	100			
5	392	349	89.03	574	544	94.77	33	33	100
6	252	222	88.10	146	138	94.52	13	13	100
7	497	241	48.49	338	301	89.05			
8	2,385	2,072	86.88	1,801	1,696	94.17	713	645	90.46
9	1,589	1,307	82.25	1,504	1,259	83.71	310	254	81.94
10	350	321	91.71	328	296	90.24	43		
11	293	256	87.37	133	116	87.22	3		
12	1,440	1,391	96.60	917	875	95.42			
13	1,328	1,260	94.88	626	626	100			
14	527	515	97.72	148	138	93.24			
15	48	38	79.17	143	137	95.80			
Total	**9,918**	**8,753**	**88.25**	**7,316**	**6,753**	**92.30**	**1,195**	**1,021**	**85.44**

Follow-up cards due to transfusions and medication (corticosteroid or dopamine therapy), which can lead to falsification of the findings, should be recorded under other reasons, for example. The recording of these follow-up cards was only possible in some laboratories for 2021.

2.3 Blank card system

As a public health measure, the newborn screening is intended to benefit all children born in Germany. This requires tracking for completeness. This can be done for children born in obstetrics departments by checking the consecutive birth book numbers. If state legislation permits, a person-specific comparison with the registration records of the residents' registration offices is also possible. A comparison of the screening reports with a unique screening ID assigned to each child at birth or with hearing screening reports is also useful for ensuring completeness.

At present these options are not being implemented across the board in Germany. With the aim of nevertheless monitoring the completeness of the screening examinations, in accordance with the Paediatrics Directive (§ 21 Paragraph 6), blank filter paper cards are to be sent to the screening laboratory in the event of refusal of screening or death of the newborn before a possible first blood sample is taken. The laboratories receive these blank cards in widely varying numbers. In addition, blank cards are often sent in for declined early collections. The total number of blank cards sent in 2021 also increased slightly again in relation to the total number of initial screening reports, likely pandemic-related with many outpatient deliveries.

The blank card system appears to be used frequently for rejected early collection, but it is not suitable for ensuring the completeness of the ENS. Based on the data from the perinatal survey, considerably higher numbers would be expected both for children who died before screening and for those who were transferred.

Table 2.3.1: Blank cards received by the laboratory

		Reason for blank card					
	Initial Screening Total	Deceased	Transferred	Early screening rejected	Not differentiable	Total	Proportion of first screening
Lab	n	n	n	n	n	n	%
1	57,593	341	423	5,072	371	6,779	11.77
3	13,849	44	63	629	381	1,117	8.07
5	61,071	24	1,138	2,558	407	4,127	6.76
6	11,841	16	16	896		928	7.84
7	51,898				804 [a]	804	1.55
8	188,437				6,278 [a]	6,278	3.33
9	147,549	8	285	835	2,152	3,280	2.22
10	32,804	176			2,309	2,485	7.58
11	15,450	11	43	441	15	510	3.30
12	98,903		173	2,264	422	2,859	2.89
13	65,965	26				26	0.04
14	34,903		37	225	47	309	0.89
15 [b]	9,336						
Total	**789,599**	**646**	**2,178**	**12,920**	**13,186**	**33,430**	**4.28**

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

3 Processing Time

3.1 Age at the time of blood sample collection

According to the Paediatrics Directive (§ 20 paragraph 1) blood samples should be collected between 36 and 72 hours after birth. In 94.9% of cases in which the time of blood sampling was provided, collection took place in the designated time frame, in 3.7% not until after 72 hours and in 1.3% 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 2006 to 3.7% in 2021 (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. Life-threatening metabolic or electrolyte crises can be avoided through very early diagnosis and initiation of therapy in affected children.

Table 3.1: Age at blood sample collection - Initial screening

	Total	<36h		36h-<=48h		48h-<=72h		≥72h	
Lab	n	n	%	n	%	n	%	n	%
1	57,591	479	0.83	22,816	39.62	31,924	55.43	2,372	4.12
3	13,849	117	0.84	4,393	31.72	9,027	65.18	312	2.25
5	61,070	455	0.75	46,193	75.64	12,739	20.86	1,683	2.76
6	11,841	266	2.25	5,561	46.96	5,598	47.28	416	3.51
7	51,898	618	1.19	22,564	43.48	25,785	49.68	2,931	5.65
8	188,098	2,350	1.25	97,601	51.89	81,388	43.27	6,759	3.59
9	147,549	1,722	1.17	81,483	55.22	58,891	39.91	5,453	3.70
10	32,804	403	1.23	12,972	39.54	18,514	56.44	915	2.79
11	15,450	314	2.03	6,631	42.92	7,775	50.32	730	4.72
12	97,993	1,627	1.66	64,850	66.18	28,698	29.29	2,818	2.88
13	66,855	1,332	1.99	37,870	56.64	22,743	34.02	4,020	6.01
14	34,902	634	1.82	20,217	57.93	13,265	38.01	786	2.25
15	9,336	48	0.51	5,611	60.10	3,542	37.94	135	1.45
Total	**789,236** [a]	**10,365**	**1.31**	**428,762**	**54.33**	**319,889**	**40.53**	**29,330**	**3.72**

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

3.2 Period between sample collection and receipt by the lab

The time between taking blood samples and reporting abnormal results should not exceed 72 hours (§ 18 paragraph 3). As the dispatch times have increased continuously over the years, the dispatch time of more than 3 days was further differentiated in 2021. In 36.4% of cases in which the shipping times were provided, the sample was not received by the laboratory until more than 72 hours after the blood sample was taken, and in almost 15,000 of these cases it was only received after a week.

The proportion of dispatch times greater than 72 hours varies greatly between the laboratories and has continually increased over the years. Urgent efforts must be made to work with the submitting parties to achieve shorter sample delivery times, particularly on weekends, so as not to jeopardize the success of screening for target diseases at risk of early decompensation. (Table 3.2, Figure 3).

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

	≤24h		>24h-48h		>48h-72h		>3d-5d		>5d-7d		>7d	
Lab	n	%	n	%	n	%	n	%	n	%	n	%
1	13,323	23.15	21,683	37.68	11,395	19.80	8,559	14.87	1,865	3.24	723	1.26
3[b]	4,313	31.14	5,919	42.74	2,668	19.26	949	6.85				
5[b]	5,568	9.12	20,184	33.05	16,520	27.05	18,791	30.77				
6	1,377	11.63	3,508	29.63	3,185	26.90	2,962	25.01	673	5.68	136	1.15
7	2,097	4.04	9,339	17.99	14,003	26.98	16,887	32.54	6,761	13.03	2.811	5.42
8	14,431	7.67	45,865	24.38	49,649	26.40	54,853	29.16	19,338	10.28	3.962	2.11
9	9,350	6.34	33,649	22.81	33,932	23.00	45,945	31.14	18,857	12.78	5.816	3.94
10	4,384	13.36	12,051	36.74	9,058	27.61	6,407	19.53	809	2.47	95	0.29
11	2,206	14.28	5,102	33.02	4,610	29.84	2,940	19.03	490	3.17	102	0.66
12	7,204	7.35	34,586	35.29	25,140	25.66	27,389	27.95	3,198	3.26	475	0.48
13	563	0.85	18,953	28.73	18,719	28.38	22,864	34.66	4,291	6.50	575	0.87
14	13,048	37.38	13,021	37.31	5,815	16.66	2,705	7.75	234	0.67	79	0.23
15	893	9.57	3,628	38.86	2,223	23.81	2,021	21.65	475	5.09	96	1.03
Total	**78,757**	**10.04**	**227,488**	**29.01**	**196,917**	**25.11**	**213,272**	**27.20**	**56,991**	**7.27**	**14,870**	**1.90**

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

[b] Dispatch times >3d were not further differentiated

3.3 Period between receipt by the lab and reporting the results

In accordance with the Paediatrics Directive (§ 26 Paragraph 3), examinations must be performed and pathological findings reported on the day the specimen is received.

Based on this wording, the time period up to the notification of findings was recorded for the first time in 2021 as "days from receipt of the laboratory". Previously this time period was always recorded in 24-hour increments - as with the sample collection and dispatch time. This new recording method leads to longer times, especially for laboratories that receive samples in the afternoon, since, for example, a notification of findings sent the next morning is still within 24 hours but is not on the day the sample was received.

58.7 % of the findings were reported on the day the laboratory received the sample, while in 2020 73.7 % of the findings were reported within 24 hours (Table 3.3), whereby no distinction is made between pathological and normal findings. In the case of marginally elevated findings, the time in the laboratory may be extended due to internal repeat examinations. Later reporting of findings primarily occurs with unremarkable findings, as highly suspicious results are usually reported immediately.

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

		Notification of findings									
		on the day the sample was received		on the following day		on the 2nd day after receipt of the sample		on the 3rd day after receipt of the sample		after the 3rd day after sample receipt	
Lab	Total	n	%	n	%	n	%	n	%	n	%
1	57,558	3	0.01	42,476	73.80	5,490	9.54	7,131	12.39	2,458	4.27
3 [b]	13,849	8,466	61.13	2,936	21.20	2,040	14.73	407	2.94		
5	61,070	50,414	82.55	10,609	17.37	36	0.06	11	0.02	0	
6	11,841	0		6,169	52.10	1,329	11.22	1,540	13.01	2,803	23.67
7	51,898	94	0.18	44,290	85.34	5,772	11.12	1,729	3.33	13	0.03
8	188,437	173,748	92.20	11,831	6.28	950	0.50	1,003	0.53	905	0.48
9	147,549	87,019	58.98	55,047	37.31	3,968	2.69	1,285	0.87	230	0.16
10[c]	32,804	28,360	86.45	4,108	12.52	258	0.79	58	0.18	20	0.06
11	15,450	3	0.02	12,140	78.58	2,112	13.67	947	6.13	248	1.61
12	98,903	9,056	9.16	73,518	74.33	5,400	5.46	9,576	9.68	1,353	1.37
13	66,323	5,084	7.67	49,733	74.99	3,996	6.03	6,044	9.11	1,108	1.67
14	34,903	2,852	8.17	21,361	61.20	8,686	24.89	1,319	3.78	685	1.96
15	9,336	3,731	39.96	5,482	58.72	73	0.78	2	0.02	48	0.51
Total	**789,921**[a]	**368,830**	**46.69**	**339,700**	**43.00**	**40,110**	**5.08**	**31,052**	**3.93**	**9,871**	**1.25**

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

[b] The time span was not further differentiated from the 3rd day onwards

[c] Times were calculated and reported according to the previous categories (≤24h, >24h-48h, >48h-72h, >72h)

Figure 2: Age at the time of blood sample collection 2006 to 2021

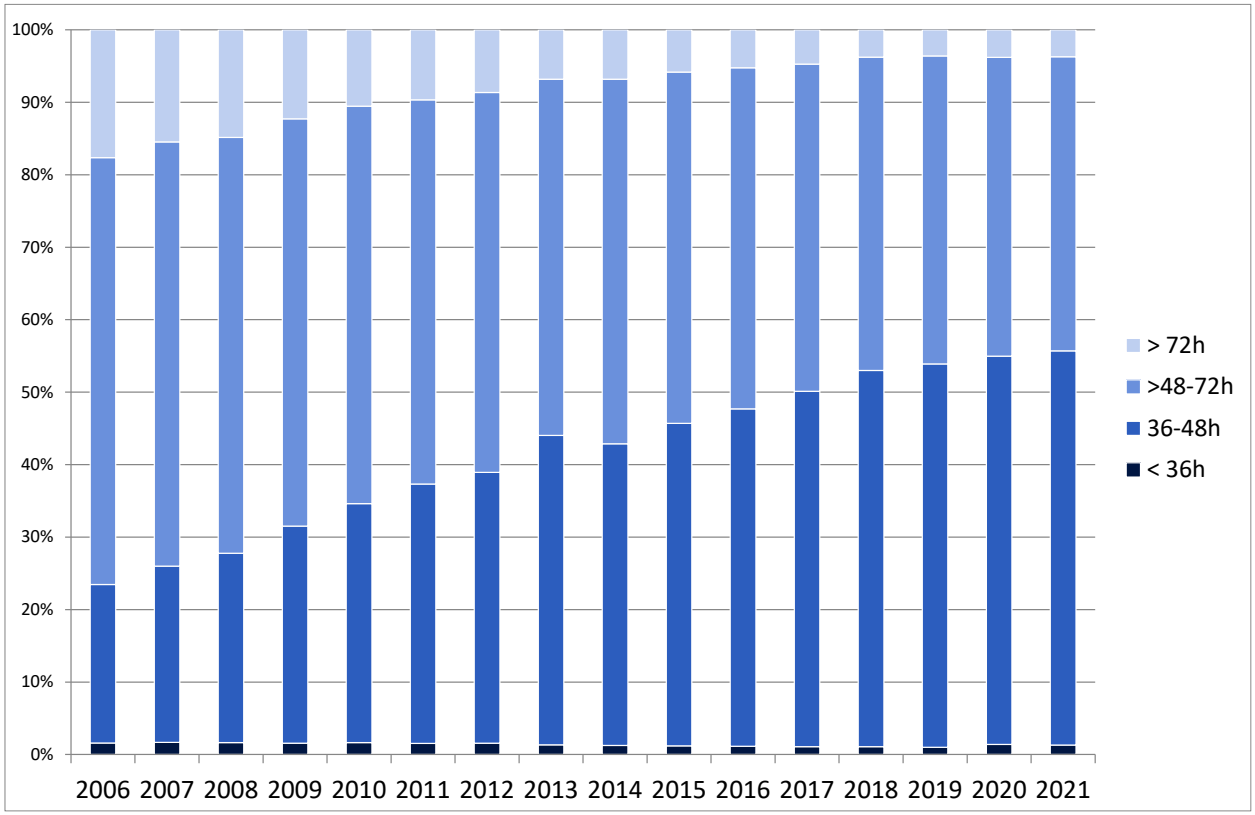
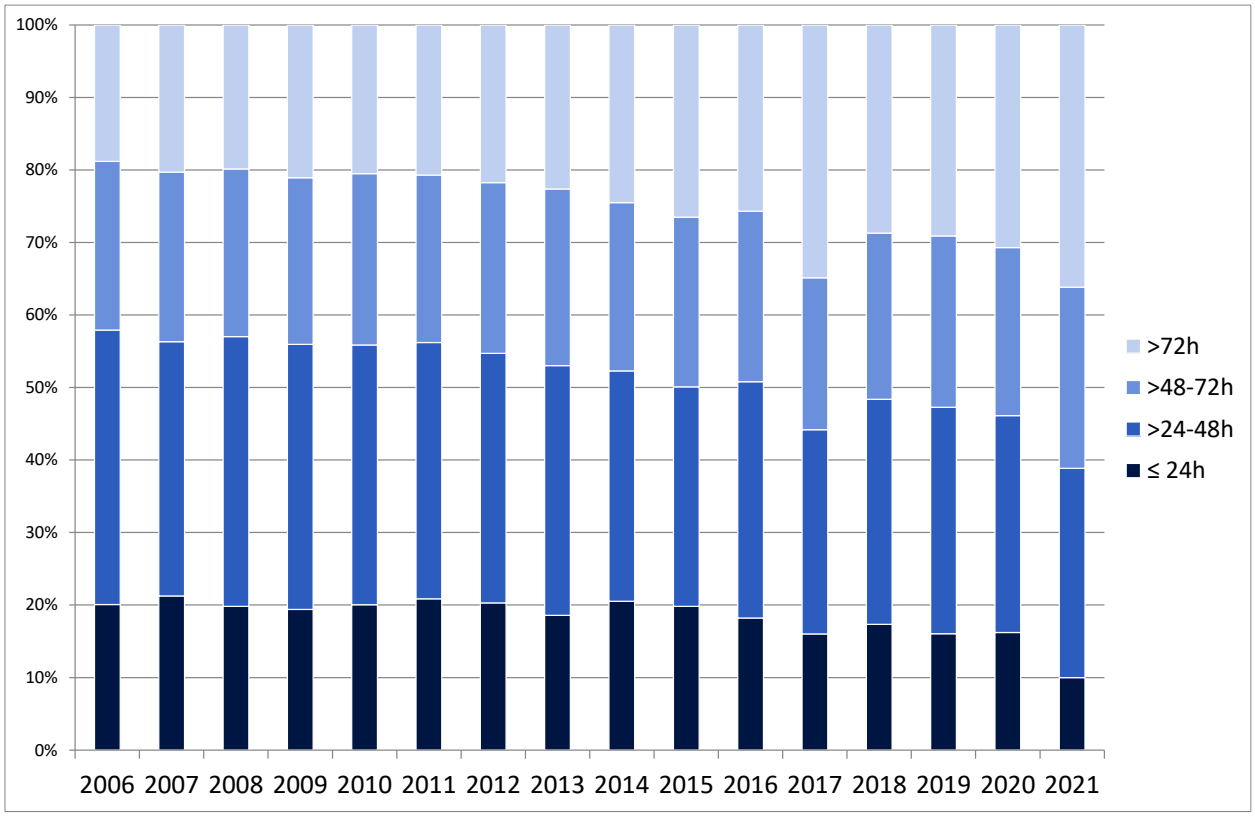


Figure 3: Time between blood sample collection and receipt by the lab 2006 to 2021



4 Quality parameters of screening analysis

4.1 Quality parameters of ENS

The quality of a test procedure is determined by its sensitivity, specificity and positive predictive value (PPV). In a screening procedure, sensitivity and specificity should be high in order to find all those affected on the one hand and to cause as little unnecessary concern and subsequent expense as possible on the other. If a blood sample is taken before 36 hours of life or before a corrected age of 32 weeks of gestation, further screening must be carried out regardless of the result of the analysis. The recall rate in 2021 was 0.5% (see Table 4.1). This means that for every 1,000 screening examinations, approximately 5 findings requiring monitoring are to be expected. When taking only the recall for blood samples taken after 32 weeks' gestation and >36 hours into account, this corresponds to the "recall" rate of 2020. The PPV of the diseases has improved significantly as a result of the new recording method introduced in 2021, especially for hypothyroidism and CAH for which the findings are often positive on early collection. The specificity for newborn screening was 99.6% overall. Sensitivity cannot be specified as the number of children missed in screening is not systematically recorded. Here, registers for the target diseases of the screening would be very helpful, combined with mandatory reporting of cases by the specialized centers.

Table 4.1: Recall rates and cases found through screening for Germany 2021 (Initial screening N= 789,599)

Disease	Recall	Recall rate (%)	Confirmed Cases	PPV	Specificity
Hypothyroidism	758	0,10	274	36.15	99.94
CAH	635	0,08	48	7.56	99.93
Biotinidase Deficiency	217	0,03	41	18.89	99.98
Galactosemia [a]	267	0,03	11	4.12	99.97
PKU/HPA	199	0,03	120	60.30	99.99
MSUD	48	0,006	2	4.17	99.99
MCAD	202	0,03	75	37.13	99.98
LCHAD	26	0,003	3	11.54	100
VLCAD	107	0,01	13	12.15	99.99
CPT-I Deficiency	4	0,002	1	25.00	100
CPT-II Deficiency [d]	13	0,002	3	23.08	100
GA I	146	0,02	8	5.48	99.98
IVA	124	0,02	9	7.26	99.99
Tyrosinemia	25	0,003	2	8.00	100
CF	756	0,10	155	20.5	99.93
SCID [c]	309	0,04	34	11.00	99.97
SMA (from 10/2021)	37		29	78.38	
SSD (from 10/2021)	41		28	68.29	
Total ENS	**3,914**	**0,50**	**856** [b]	**21.87**	**99.62**

[a] Recall also includes variants and other disorders of galactose metabolism, confirmed cases however include only classic galactosemia

[b] excluding 4 hypothyroidism and 8 CF cases with false negative screening and 1 CF case without screening

[c] possibly incl. recall CACT

4.2 Time of Initial 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 4.2 shows the age at Initial 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 4.2: Time of Initial screening in confirmed cases

Disease	36-72h	4-7d	>7d	<36h	<32WoG[a]	Incomplete information [b]	Total
Hypothyroidism	232	5	2	11	24	4	278
CAH	35	2	2	9	0	0	48
Biotinidase Deficiency	36	4	0	0	1	0	41
Galactosemia	11	0	0	0	0	0	11
PKU/HPA	115	2	0	3	0	0	120
MSUD	1	1	0	0	0	0	2
MCAD	69	1	1	3	1	0	75
LCHAD	3	0	0	0	0	0	3
VLCAD	11	0	0	1	0	1	13
CPT I	1	0	0	0	0	0	1
CPT II	3	0	0	0	0	0	3
GA I	8	0	0	0	0	0	8
IVA	9	0	0	0	0	0	9
Tyrosinemia	1	0	0	0	1	0	2
CF	153	4	1	5	0	0	163 [c]
SCID	29	1	0	2	2	0	34
SMA	27	1	0	0	1	0	29
SSD	27	1	0	0	0	0	28
Total	**771**	**22**	**6**	**34**	**30**	**5**	**868** [c]

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

[b] Exact age at the time of blood collection and/or week of gestation not provided

[c] excluding one confirmed CF case without screening

5 Recall rate, confirmed cases and confirmation stratified by disease

In the following chapter, recall rates and confirmed cases as well as the diagnostic measures carried out to confirm the diagnosis for the target diseases are presented stratified by laboratory. This stratified presentation is not used for diseases with a very low overall recall rate. Starting in 2021, only screening results that were reported as positive (abnormal) were recorded as recall. Positive findings in early examinations before a corrected age of 32 weeks' gestation or before 36 hours, which were checked with routine cards provided for in the Paediatrics Directive, should not be recorded as recall.

Diagnostic measures can only be reported if the laboratories are informed of them. Knowledge of the 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. However, the confirmation diagnostics for the 2021 report are known in most cases thanks to subsequent notifications. The figures were reported on 15 March, 2024. Cases from birth year 2021 which were found at a later date are not included in this report. Cases reported twice (e.g. from different laboratories) were only counted once. The plausibility check of the cases reported as confirmed was carried out by Prof. Dr. Regina Ensenauer and PD Dr. Martin Lindner for metabolic diseases, by Dr. Oliver Blankenstein and Erwin Lankes for endocrinological diseases, by PD Dr. Olaf Sommerburg for cystic fibrosis and by PD Dr. Carsten Speckmann for severe combined immunodeficiency.

For the 2021 report, many subsequent notifications could be taken into account, so that the data “only” lacks information on confirmation diagnostics for a total of 58 cases (2020: 81 cases). In 26 cases, the validators assessed a diagnosis as probable based on the screening values, or the dataset indicated only “diagnosis confirmed” (17 metabolic screenings, 8 hypothyroidism, 1 CAH). (see Table 6.1.1.1). In 32 cases with positive ENS, the information on the confirmatory diagnosis was not sufficient to confirm the diagnosis (see section 6.1.2). This applied in particular to 4 cases with positive hypothyroidism screening and 11 cases with positive CF screening. A further 10 cases with positive SCID screening were mostly suspected secondary causes that are not recorded in the DGNS.

Diagnosed cases with negative (normal) screening results are not systematically recorded. In 2021, 4 cases of hypothyroidism and 8 cases of CF were reported to the laboratories after negative screening. In addition, no CF screening was carried out in one further reported CF case. For quality assurance of laboratory analysis and evaluation of the quality of results, the aim should be to provide the treating physicians with the most complete possible feedback on the confirmatory diagnosis and the cases not found in the screening (false negatives).

In the following tables, recall rates <0.01% and for n <5 are not specified, as the random fluctuations have too great an influence for smaller values. No recall rate can be calculated for the target diseases sickle cell disease and SMA, which were newly included in the ENS from October 2021, as the denominator (number of initial screenings in this period) is not known. However, as both diseases have a comparatively high prevalence, the overall recall rate will increase in the future. The PPV is very good for both diseases (see Table 4.1).

5.1 Congenital Hypothyroidism

Table 5.1.1: Hypothyroidism confirmed cases / recall rate

Lab	Initial screening	Recall	Recall-Rate (%)	Confirmed cases
1	57.593	64	0,11	20
3	13.849	16	0,12	8
5	61.071	71	0,12	24
6	11.841	8	0,07	6
7	51.898	38	0,07	9
8	188.437	240	0,13	74
9	147.549	107	0,07	53
10	32.804	37	0,11	12
11	15.450	9	0,06	3
12	98.903	66	0,07	38
13	65.965	51	0,08	19
14	34.903	38	0,11	7
15	9.336	13	0,14	5
Total	**789.599**	**758**	**0,10**	**278** [a]

[a] including 4 cases with unremarkable initial screening

Of the 278 cases of congenital hypothyroidism validated as confirmed, four cases had a negative result in the regular initial screening after 32 weeks' gestation and after 36 hours. One of these children had received catecholamines. No information is available on the possible causes of the false negative screening in the other children. In a further 16 children, the TSH screening was initially negative when the initial screening was taken before 36 hours (n=6) or before a corrected age before 32 weeks' gestation (n=10), but was “correctly” abnormal in the follow-up checks carried out, which underscores the importance of these checks.

In addition, n= 53 hyperthyrotropinemia cases were reported and validated as confirmed. These were not included in the calculation of the prevalence.

Table 5.1.2: Hypothyroidism Confirmation

Lab	Confirmed cases	TSH (Serum)	fT3	fT4	Sonography	SD Antibodies	Confirmed cases without verification details
1	20	20	4	19	19	9	
3	8	8	6	8	8	7	
5	24	23	20	22	18	14	
6	6	6	6	6	6	5	
7	9	7	2	6			2
8	74	72	58	70	59	50	1
9	53	51	33	47	25	23	
10	12	11	9	11	4	7	1
11	3	2	1	2	2	1	1
12	38	38	24	38	4	5	
13	19	19	9	19			
14	7	7	6	7			
15	5	2		1	1		3
Total	**278**	**266**	**178**	**256**	**146**	**121**	**8**

5.2 Congenital Adrenal Hyperplasia (CAH)

Table 5.2.1: CAH Confirmed cases / Recall rate

Labor	Initial screening	Recall	Recall-Rate (%) [b]	Confirmed cases
1 [a]	57,593	14	0.02	2
3	13,849	4		0
5	61,071	106	0.17	2
6	11,841	25	0.21	0
7	51,898	245	0.47	3
8 [a]	188,437	43	0.02	14
9	147,549	111	0.08	7
10 [a]	32,804	23	0.07	2
11	15,450	30	0.19	4
12 [a]	98,903	15	0.02	6
13 [a]	65,965	12	0.02	5
14 [a]	34,903	4		3
15 [a]	9,336	3		0
Total	**789,599**	**635**	**0.08**	**48**

[a] Lab uses 2nd tier method [b] Recall rates only provided if recall rate ≥ 0,01% and n ≥ 5

A second-tier procedure, previously performed in only five laboratories, significantly reduces the recall rate of CAH screening.

Table 5.2.2: CAH Confirmation

Lab	Confirmed cases	17-OHP (Serum)	Steroids (Serum/DB)	Urinary steroids	Molecular genetics	Confirmed cases without confirmation details
1	2	1	2		2	
3	0					
5	2	1	1		2	
6	0					
7	3	2			1	1
8	14	12	8	1	11	
9	7	6	6	1	3	
10	2	2	2	1	1	
11	4	3	3		4	
12	6	5	6	1	5	
13	5	3	2		3	
14	3	2			3	
15						
Total	**48**	**37**	**30**	**4**	**35**	**1**

5.3 Biotinidase Deficiency

Table 5.3.1: Biotinidase Deficiency - Confirmed cases / Recall rate

Lab	Initial screening	Recall	Recall rate (%) [a]	Confirmed cases
1	57,593	21	0.04	4
3	13,849	0		0
5	61,071	2		1
6	11,841	17	0.14	1
7	51,898	57	0.11	9
8	188,437	37	0.02	7
9	147,549	12	0.01	2
10	32,804	1		0
11	15,450	3	0.02	0
12	98,903	30	0.03	5
13	65,965	29	0.04	9
14	34,903	4		1
15	9,336	4		2
Total	**789,599**	**217**	**0.03**	**41**

[a] Recall rates only provided if recall rate ≥ 0,01% and n ≥ 5

Of n= 41 confirmed cases, a partial biotinidase deficiency was diagnosed in n=22 cases.

Table 5.3.2: Biotinidase Deficiency Confirmation

Lab	Confirmed cases	Biotinidase (Serum/TB)	Molecular genetics	Confirmed cases without confirmation details
1	4	3	3	
5	1	1		
6	1	1	1	
7	9	9	8	
8	7	7	3	
9	2	1	1	1
12	5		5	
13	9	7	2	1
14	1	1		
15	2	1		1
Total	**41**	**31**	**23**	**3**

5.4 Classic Galactosemia

Table 5.4.1: Classic Galactosemia Confirmed cases / Recall rate Galactosemia and variants [a]

Lab	Initial screening	Recall [a]	Recall rate (%) [b]	Confirmed cases [a]
1	57,593	34	0.06	1
3	13,849	0		0
5	61,071	6	0.01	0
6	11,841	4		0
7	51,898	73	0.14	0
8	188,437	92	0.05	2
9	147,549	20	0.01	1
10	32,804	7	0.02	2
11	15,450	2		0
12	98,903	19	0.02	1
13	65,965	5	0.01	2
14	34,903	3		2
15	9,336	2		0
Total	**789,599**	**267**	**0.03**	**11**

[a] Recall also includes variants and other disorders of galactose metabolism, whereas confirmed cases only include classic galactosemia

[b] Recall rates only provided if recall rate ≥ 0,01% and n ≥ 5

Table 5.4.2: Classic Galactosemia Confirmation

Labor	Confirmed cases	Enzymatic	Galactose, Gal1P	Molecular genetics
1	1	1	1	1
8	2			2
9	1	1	1	1
10	2	2	2	2
12	1	1	1	1
13	2	2		1
14	2	2	2	1
Total	**11**	**9**	**7**	**9**

For 2021, all confirmed cases (and not just classic galactosemia) should actually be transmitted after a recall, as these cases are otherwise “false positives” and the PPV of the screening is therefore too low. This was only possible for some laboratories and should be re-visited. In addition, “typical” values for a variant often mean that no further diagnostics are performed and kinase and epimerase deficiency are not detected when galactose-1-phosphate uridyltransferase (GALT) is measured alone as a screening parameter. There were n=20 reported cases with a galactosemia variant, n=4 with a kinase deficiency and n=2 with an epimerase deficiency.

5.5 Phenylketonuria (PKU) / Hyperphenylalaninemia (HPA)

Table 5.5.1: PKU/HPA Confirmed cases / Recall rate

Lab	Initial screening	Recall	Recall rate %) [a]	Confirmed cases
1	57,593	19	0.03	11
3	13,849	4		2
5	61,071	7	0.01	6
6	11,841	5	0.04	4
7	51,898	28	0.05	11
8	188,437	31	0.02	21
9	147,549	31	0.02	24
10	32,804	12	0.04	7
11	15,450	2		1
12	98,903	22	0.02	18
13	65,965	7	0.01	5
14	34,903	23	0.07	8
15	9,336	8	0.09	2
Total	**789,599**	**199**	**0.03**	**120**

[a] Recall rates only provided if recall rate ≥ 0,01% and n ≥ 5

Of n=120 confirmed cases, 49 were diagnosed with PKU and 71 with 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	11	10	10	10	10	
3	2	2	2				
5	6	3	1	4		4	1
6	4	3		2	2	3	1
7	11	10	10	6	8	8	1
8	21	19	12	10	17	17	
9	24	21	17	13	21	21	1
10	7	7	6	6	6	5	
11	1	1	1	1	1	1	
12	18	17	6	7	14	15	1
13	5	5	5	3	4	4	
14	8	7	1	3	7	7	1
15	2	2	1	1	2	2	
Total	**120**	**108**	**72**	**66**	**92**	**97**	**6**

Table 5.5.3: PKU BH4-Test / BH4 Sensitivity

Lab	Confirmed cases	BH4-Test	BH4 sensitive
1	11	4	
3	2		
5	6		
6	4	1	
7	11	1	
8	21	14	7
9	24	8	5
10	7	1	2
11	1	1	
12	18	6	4
13	5		
14	8	1	
15	2		
Total	**120**	**37**	**18**

5.6 Maple Syrup Urine Disease (MSUD)

The overall recall rate is very low at 0.006%.

Table 5.6.1: MSUD - Confirmed cases / Recall rate

Lab	Initial screening	Recall	Confirmed cases
1	57,593	1	0
3	13,849	1	0
5	61,071	0	0
6	11,841	2	0
7	51,898	12	0
8	188,437	0	0
9	147,549	25	1
10	32,804	0	0
11	15,450	0	0
12	98,903	0	0
13	65,965	1	1
14	34,903	2	0
15	9,336	4	0
Total	**789,599**	**48**	**2**

Table 5.6.2: MSUD Confirmation

Labor	Confirmed cases	Confirmation (Serum/DB)	Organic acids (urine)	Enzyme activity	Molecular genetics
9	1		1		
13	1				1
Total	**2**	**0**	**1**	**0**	**1**

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

Table 5.7.1: MCAD deficiency- Confirmed Cases/Recall rate

Lab	Initial screening	Recall	Recall rate (%) [a]	Confirmed cases
1	57,593	11	0.02	7
3	13,849	3		2
5	61,071	3		1
6	11,841	5	0.04	0
7	51,898	43	0.08	3
8	188,437	26	0.01	23
9	147,549	78	0.05	16
10	32,804	6	0.02	1
11	15,450	1		0
12	98,903	12	0.01	11
13	65,965	11	0.02	9
14	34,903	2		1
15	9,336	1		1
Total	**789,599**	**202**	**0.03**	**75**

[a] Recall rates only provided if recall rate ≥ 0,01% and n ≥ 5

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	7		7	6	4	
3	2		1		1	
5	1					1
6	0					
7	3				3	
8	23	6	6	6	15	2
9	16	11	4	11	11	
10	1	1	1	1	1	
11	0					
12	11	2		1	9	2
13	9	7		5	5	1
14	1				1	
15	1					1
Total	**75**	**27**	**19**	**30**	**50**	**7**

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

The overall recall rate is very low at 0.003%. Of the 3 confirmed cases, 2 were classified as mitochondrial trifunctional protein deficiency.

Table 5.8.1: LCHAD Deficiency - Confirmed cases / Recall rate

Lab	Initial screening	Recall	Confirmed cases
1	57,593	0	0
3	13,849	0	0
5	61,071	3	1
6	11,841	2	1
7	51,898	4	0
8	188,437	1	1
9	147,549	14	0
10	32,804	0	0
11	15,450	0	0
12	98,903	1	0
13	65,965	0	0
14	34,903	0	0
15	9,336	1	0
Total	**789,599**	**26**	**3**

Table 5.8.2: LCHAD Deficiency Confirmation

Labor	Confirmed cases	Confirmation (Serum)	Organic Acids (urine)	Enzyme activity	Molecular genetics
5	1				1
6	1	1	1		1
8	1		1	1	1
Total	**3**	**1**	**2**	**1**	**3**

5.9 Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency

Table 5.9.1: VLCAD Deficiency- Confirmed cases / Recall rate

Lab	Initial screening	Recall	Recall rate (%) [a]	Confirmed cases
1	57,593	6	0.01	0
3	13,849	1		1
5	61,071	2		1
6	11,841	2		0
7	51,898	7	0.01	2
8	188,437	8	0.00	4
9	147,549	66	0.04	2
10	32,804	5	0.02	1
11	15,450	2		0
12	98,903	4		0
13	65,965	4		2
14	34,903	0		0
15	9,336	0		0
Total	**789,599**	**107**	**0.01**	**13**

[a] Recall rates only provided if recall rate ≥ 0,01% and n ≥ 5

Table 5.9.2: VLCAD Confirmation

Labor	Confirmed cases	Confirmation (Serum)	Organic Acids (urine)	Enzyme activity	Molecular genetics
3	1	1			
5	1			1	
7	2			2	
8	4	2	2	2	3
9	2			1	2
10	1	1	1	1	1
13	2	1		2	2
Total	**13**	**5**	**3**	**9**	**8**

5.10 CPT I / CPT II / CACT Deficiency

The overall recall rate is very low at 0.002%. Recall CACT deficiency may be recorded in Recall CPT II deficiency.

Table 5.10.1: CPT I / CPT II / Deficiency Recall

	Initial screening	Recall	Confirmed Cases
CPT I Deficiency	789,599	4	1
CPT II Deficiency / CACT Deficiency	789,599	13	3

Table 5.10.2: CPT I Deficiency Confirmation

Lab	Confirmed Cases	Confirmation (Serum/DB)	Enzyme activity	Molecular genetics
8	1	1		
Total	**3**	**3**	**0**	**0**

Table 5.10.3: CPT II Deficiency Confirmation

Lab	Confirmed Cases	Confirmation (Serum/DB)	Enzyme activity	Molecular genetics
7	1			1
13	2	1		2
Total	**3**	**1**	**0**	**3**

5.11 Glutaric Aciduria Type I (GA I)

Table 5.11.1: GA I - Confirmed Cases / Recall rate

Lab	Initial screening	Recall	Recall rate (%) [a]	Confirmed cases
1	57,593	8	0,01	2
3	13,849	0		0
5	61,071	3		0
6	11,841	0		0
7	51,898	13	0.03	1
8	188,437	3		3
9	147,549	111	0.08	
10	32,804	2		1
11	15,450	0		0
12	98,903	2		0
13	65,965	1		1
14	34,903	2		0
15	9,336	1		0
Total	**789,599**	**146**	**0.02**	**8**

[a] Recall rates only provided if recall rate ≥ 0,01% and n ≥ 5

Table 5.11.2: GA I Confirmation

Lab	Confirmed cases	Confirmation (Serum/TB)	Organic Acids (urine)	Enzyme activity	Molecular genetics
1	2	1			2
7	1	1			1
8	3	1	2		2
10	1	1			1
13	1				1
Total	**8**	**4**	**2**		**7**

5.12 Isovaleric Acidemia (IVA)

Table 5.12.1: IVA - Confirmed Cases / Recall rate

Lab	Initial screening	Recall	Recall rate (%)[a]	Confirmed cases
1	57,593	18	0.03	0
3	13,849	2		0
5	61,071	7	0.01	0
6	11,841	11	0.09	0
7	51,898	2		1
8	188,437	3		3
9	147,549	44	0.03	0
10	32,804	4		0
11	15,450	7	0.05	0
12	98,903	2		2
13	65,965	1		1
14	34,903	20	0.06	2
15	9,336	3		0
Total	**789,599**	**124**	**0.02**	**9**

[a] Recall rates only provided if recall rate ≥ 0,01% and n ≥ 5

The recall rate for IVA increased significantly in 2018 compared to 2017 and has remained roughly the same over the years since then. A frequent explanation for this is the administration of pivmecillinam in the case of urinary tract infections in the mother shortly before birth, which leads to false positive screening results. In some laboratories, a second-tier procedure reduces the recall rate due to false positive findings to practically zero.

Table 5.12.2: IVA Confirmation

Lab	Confirmed cases	Confirmation (Serum)	Organic Acids (urine)	Enzyme activity	Molecular genetics
7	1		1		1
8	3	3	3		3
12	2		2		2
13	1				1
14	2	1	2		2
Total	**9**	**4**	**8**		**9**

5.13 Tyrosinemia

The overall recall rate is very low at 0.003%.

Table 5.13.1: Tyrosinemia – Confirmed Cases

Lab	Initial Screening	Recall	Confirmed Cases
1	57,593	6	0
3	13,849	0	0
5	61,071	0	0
6	11,841	0	0
7	51,898	0	0
8	188,437	5	0
9	147,549	7	0
10	32,804	3	0
11	15,450	1	0
12	98,903	0	0
13	65,965	0	0
14	34,903	1	0
15	9,336	2	2
Total	**789,599**	**25**	**2**

Table 5.13.2: Tyrosinemia Confirmation

Lab	Confirmed Cases	Confirmation (Serum/TB)	Confirmation Organic Acids	Enzyme activity	Molecular genetics	Confirmed cases without confirmation information
15	2				1	1
Total	**2**				**1**	**1**

5.14 Severe Combined Immunodeficiency (SCID)

Table 5.14.1: SCID - Confirmed Cases / Recall rate

Labor	Initial Screening	Recall	Recall rate (%) [a]	Confirmed cases
1	57,593	15	0.03	7
3	13,849	9	0.06	0
5	61,071	12	0.02	3
6	11,841	9	0.08	0
7	51,898	99	0.19	5
8	188,437	46	0.02	7
9	147,549	24	0.02	4
10	32,804	23	0.07	1
11	15,450	0		0
12	98,903	18	0.02	1
13	65,965	16	0.02	4
14	34,903	29	0.08	1
15	9,336	9	0.10	1
Total	**789,599**	**309**	**0.04**	**34**

[a] Recall rates only provided if recall rate ≥ 0,01% and n ≥ 5

Table 5.14.2: SCID Confirmed Cases

Lab	Confirmed cases	Genetics	Cytology
1	7	5	7
5	3	2	3
7	5	5	2
8	7	6	4
9	4	4	4
10	1	1	1
12	1	1	1
13	4	1	4
14	1	1	1
15	1	1	1
Total	**34**	**27**	**28**

Of the n = 34 cases, n= 14 were validated as SCID, n=18 as syndromes and n=2 as idiopathic T-cell lymphopenia.

5.15 Spinal Muscular atrophy (SMA)

Table 5.15.1: SMA – Confirmed cases / Recall

Lab	Recall	Confirmed cases
1	1	0
3	0	0
5	2	1
6	1	1
7	11	6
8	6	6
9	5	5
10	0	0
11	1	0
12	6	6
13	3	3
14	1	1
15	0	0
Total	**37**	**29**

SMA was included in the ENS as a new target disease on 01.10.2021. It is not possible to calculate the recall rate due to the unknown denominator.

5.16 Sickle cell disease (SCD)

Table 5.16.1: SCD – Confirmed cases / Recall

Lab	Recall	Confirmed cases
1	2	2
3	0	0
5	1	0
6	0	0
7	6	6
8	6	6
9	4	4
10	2	2
11	0	0
12	3	3
13	5	4
14	12	1
15	0	0
Total	**41**	**28**

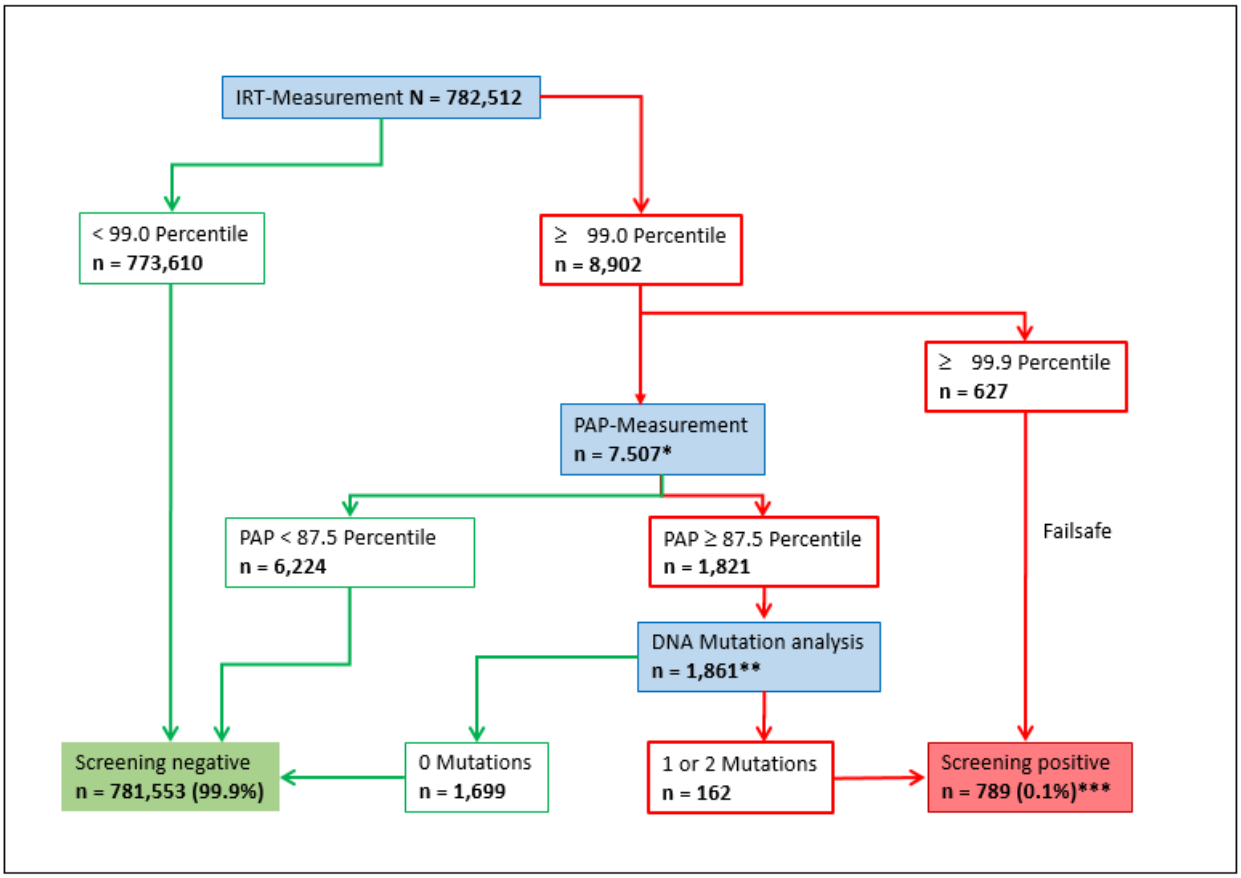
Sickle cell disease was included in the ENS as a new target disease as of 01.10.2021. It is not possible to calculate the recall rate due to the unknown denominator.

5.17 Cystic Fibrosis (CF)

Since September 2016, screening for cystic fibrosis has been performed in three stages as a serial combination of two biochemical tests. First, the concentration of immunoreactive trypsin (IRT) is determined, and in the case of elevated values, the concentration of pancreatitis-associated protein (PAP) is measured as a second step. In the case of pathological PAP, a molecular genetic examination is performed in a third step. Here, the 31 most common pathogenic mutations of the cystic fibrosis transmembrane regulator gene (CFTR gene) in Germany are searched for (see Figure 4). The screening is considered positive (abnormal) if an IRT value is above the 99.9th percentile ("failsafe" method or "safety net") or if one of the 31 examined mutations of the CFTR gene is detected on at least one allele in the third stage. In all other constellations, the screening is considered negative (normal). For data reporting in 2021, it was determined that highly scattered IRT values should not be recorded as recall but as poor quality. The variance in the recording method was previously one of the reasons for the different CF recall rates of the laboratories.

This screening algorithm results in "failsafe" (IRT >99.9th percentile) conditions in 627 (79.5%) of the 789 positive screening results (see Figure 4). The diagnosis of CF was only confirmed in 155 children (19.6 %); in addition, cystic fibrosis was diagnosed in 8 children after a false negative CF screening and one child without a CF screening.

Figure 4: Screening algorithm for Cystic Fibrosis in Germany 2021



* PAP measurement was not performed for all abnormal IRT values >99.0 % but for <99.9 % (no failsafe), as some were early samples or not enough material was available for the examination.
** Mutation analysis also in children with product IRT and PAP value above internal laboratory cut-off
*** The information differs from Table 5.17.2 as it is based on different data sources.

According to the Paediatrics Directive, CF screening requires both a separate declaration of consent and a consultation with a physician; screening cannot be performed by a midwife alone with the option to consult with a physician, as is the case with ENS in exceptional cases. The proportion of newborns without CF screening was around 1% in 2020 (Table 5.17.1).

Table 5.17.1: Number of CF Screenings

Lab	Initial screening ENS	CF Screening	Proportion of CF Screening (%)
1	57,593	56,926	99.70
3	13,849	13,808	97.79
5	61,071	59,719	99.95
6	11,841	11,835	95.95
7	51,898	49,798	99.57
8	188,437	187,624	99.91
9	147,549	147,423	98.23
10	32,804	32,225	99.73
11	15,450	15,409	99.33
12	98,903	98,238	99.28
13	65,965	65,492	99.41
14	34,903	34,697	99.81
15	9,336	9,318	99.10
Total	**789,599**	**782,512**	**99.10**

Table 5.17.2: CF – Confirmed cases and abnormal screening findings

Lab	Initial screening with CF Screening	Recall	Recall Rate (%)	Confirmed cases
1	56,926	68	0.12	14
3	13,808	7	0.05	2
5	59,719	82	0.13	8
6	11,835	13	0.11	1
7	49,798	37	0.07	6
8	187,624	169	0.09	42
9	147,423	106	0.07	32
10	32,225	33	0.10	7
11	15,409	12	0.08	2
12	98,238	121	0.12	31
13	65,492	67	0.10	10
14	34,697	22	0.06	6
15	9,318	19	0.20	3
Total	**782,512**	**756**	**0.10**	**164[a]**

[a] of which 8 cases with negative CF screening and 1 case without CF screening

Table 5.17.3: CF – Validation of confirmed cases

Lab	Confirmed Cases	One Sweat Test	Two Sweat Tests	Conductivity	2 Mutations in confirmation or screening	Meconium ileus	without confirmation details
1	14	11	1		5		
3	2		2	2	2		
5	8	3	3		1		4
6	1				1		
7	6	3	2		3		
8	42	16	18	1	33	3	
9	32	7	16	9	21	4	4
10	7	6		1	7		
11	2	2			2	1	
12	31	12	15	16	22	2	
13	10	6	2		8		
14	6	5		3	3		
15	3				2		2
Total	**164**	**71**	**59**	**32**	**110**	**10**	**10**

In 11 reported cases, the information was not sufficient to confirm the diagnosis. Of n=164 confirmed cases, 151 cases were diagnosed with Cystic Fibrosis and 13 cases were diagnosed with Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID).

Screening was positive in 111 (67.7%) of CF cases via fail safe, 44 (26.8%) cases had one or 2 mutations detected from the screening panel (31 mutations), and 8 children (4.9%) had an negative CF screening.

Genetic information from screening or confirmation was available for n=119 of the confirmed cases. Accordingly, 84 cases had two mutations and 35 cases had one mutation from the panel of 31. A total of 10 children were reported to have meconium ileus.

For confirmation diagnostics, information on one (n=59) or two (n=71) sweat tests was available for 130 cases; in 10 cases only the comment "diagnosis confirmed" was provided.

Of the confirmed CF cases, eight were not found using the specified screening algorithm and were false negative in the screening. Four children each had an IRT value and four children had a PAP value below the laboratory cut-off. Two of these children had meconium ileus. It is not known whether other children with cystic fibrosis were not found in the screening, as these are not systematically recorded.

6 Lost to follow-up

Of a total of 23,361 follow-up cards requested, 21,133 (90.46%) were sent in, meaning that no further information was available for just under 10% of the cards requested (Table 2.2.1).

6.1 Cases without confirmation data

Of 58 children with positive screening results, it is not known whether confirmation diagnostics took place or were completed. 26 of these cases, for which no information on confirmation was available but for which there were clearly pathological screening values or the remark "diagnosis confirmed", were validated as "probable case" (Table 6.1.1.1) and included in the calculation of prevalence.

This was not possible for 32 children, who often had an abnormal SCID screening with a suspected secondary cause of T-cell lymphopenia, which is not recorded in the DGNS, or CF. (Table 6.1.2.1).

6.1.1 Confirmed cases without information about validation diagnostics

26 cases were validated as probable cases without confirmation information.

Table 6.1.1.1: Confirmed Cases without information about validation

		Reason for no confirmation given		
Disease	Confirmed cases without validation	Clinic did not request confirmation	Only the remark "diagnosis confirmed"	Unclear
Hypothyroidism	8	1	4	3
CAH	1		1	
Biotinidase Deficiency	3			3
PKU/HPA	6		4	2
MCAD	7		4	3
Tyrosinemia	1		1	
Total	**26**	**1**	**14**	**11**

6.1.2 Non-assessable cases of ENS after abnormal screening findings (lost to follow-up)

Table 6.1.2.1: Cases with implausible or missing confirmation information

	Number of Cases
Disease	n
Congenital Hypothyroidism	4
CAH	1
Galactosemia	2
HPA/PKU	1
MCAD	1
MSUD	1
VLCAD	1
CF	11
SCID	10
Total	**32**

7 Methods and Cutoff-Values used in Screening

Table 7.1.: Methods and cut-off 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 µU/ ml	GSP
8	TSH	15 mU/l (≤ 8 days of life) 10 mU/l (>8 days of life)	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	AutoDELFIA
14 /15	TSH	<20 mU/l (1st day of life) <15 mU/l (2nd-4th day of life) <10 mU/l (> 5th day of life)	AutoDELFIA

Table 7.2: Methods Congenital Adrenal Hyperplasia (CAH)

Lab	Parameter	Second-tier method (steroid profile using LC-MS/MS)	Method
1	17 OHP	ja	AutoDELFIA
3	17 OHP		AutoDELFIA Kit B024
5	17 OHP		AutoDELFIA
6	17 OHP		DELFIA
7	17 OHP		GSP
8	17 OHP	ja	DELFIA
9	17 OHP		GSP
10	17 OHP	ja	AutoDELFIA
11	17 OHP		DELFIA
12/13	17 OHP	ja	AutoDELFIA
14/15	17 OHP	ja	AutoDELFIA

Table 7.3: Cut-off Hyperphenylalaninemia und Quotient Phe/Tyr

Lab	Parameter	Cut off	Comment
1	Phenylalanin Phe/Tyr	113 µmol/l 2	Percentile 99,9 %
3	Phenylalanin Phe/Tyr	99,67 µmol/l 2,5	Percentile 99,9 % Percentile 99,9 %
5	Phenylalanin Phe/Tyr	150 µmol/l 2,4	 Percentile 99,9 %
6	Phenylalanin Phe/Tyr	120 µmol/l 2,5	Percentile 99,9 % Percentile 99,9 %
7	Phenylalanin Phe/Tyr	118 µmol/l 2,84	
8	Phenylalanin Phe/Tyr	150 µmol/l 1,5	
9	Phenylalanin Phe/Tyr	123 µmol/l 1,5	Cut-off >99,9 % Cut-off 99,0- 99,5 %
10	Phenylalanin Phe/Tyr	101 µmol/l 110µmol/l 2,52 3,02	Cut-off change from 26 April 2021 Percentile 99,5 % Percentile 99,5 %
11	Phenylalanin Tyrosin Phe/Tyr	118 µmol/l 39µmol/l 1,7	Percentile 99,9 % Percentile 0,1 % Percentile 99,9 %
12/13	Phenylalanin Phe/Tyr	120 µmol/l 2	
14/15	Phenylalanin Phe/Tyr	105 µmol/l 1,8	Consideration of pre-series (2000 children)

Table 7.4: Methods and cut-off Biotinidase Deficiency

Lab	Parameter	Cutoff	Methods
1	Biotinidase	30% Mean value MTP	Qualitative colorimetry
3	Biotinidase	30% daily median	Qualitative colorimetry
5	Biotinidase	<30%	Qualitative colorimetry
6	Biotinidase	55 U	Fluorometry (PE)
7	Biotinidase	85,7 U/g Hb	GSP
8	Biotinidase	<30% daily mean	Quantitative colorimetry
9	Biotinidase	< 0.2	Qualitative colorimetry
10	Biotinidase	<30%	Qualitative colorimetry
11	Biotinidase	<30%	Quantitative colorimetry
12/13	Biotinidase	<30%	Quantitative fluorometry
14/15	Biotinidase	>50U	Quantitative colorimetry

Table 7.5: Methods and cut-off Galactosemia

Lab	Parameter	Cut-off	Methods
1	GALT Galactose	>3.5 U/g Hb <13 mg/dl	Fluorometry (PE)
3	GALT Galactose	>3.5 U/g Hb <15 mg/dl	Fluorometry (PE)
5	GALT Galactose	>3.5 U/g Hb <15 mg/dl	Fluorometry (PE)
6	GALT	3.5 U/g Hb	Fluorometry (PE)
7	GALT	3.9 U/dl	GSP
8	GALT Galactose	<20% daily mean 30 mg/dl (until 28th day of life, after that 18mg/dl)	Quantitative fluorometry Quantitative colorimetry
9	GALT Galactose	5.3 U/g Hb 20 mg/dl	DELFIA
10	GALT Galactose	>3.5 U/gHb >461µmol/l	Fluorometry (PE)
11	GALT	3.5 U/g Hb	Fluorometry (PE)
12/13	GALT Galactose	>20% < 30 mg/dl	Colorimetry non-kit Quant. fluoro, (non-kit)
14/15	GALT Galactose	<3,0U/g Hb <7,4 mg/dl	Quantitative colorimetry

Table 7.6: Tandem mass spectrometry (MS/MS)

Lab	Method
1	non-derivatized PE kit
3	non-derivat. Chromsystems kit
5	non-derivatized PE kit
6	non-derivatized PE kit
7	non-derivatized PE kit
8	non-derivitized non Kit
9	non-derivatized Chromsystems kit
10	deriv. Chromsystems Kit (until 25 April) / non derivat. Chromsystems Kit (from 26 April)
11	non-derivat. Chromsystems Kit
12/13	derivatized non-kit
14/15	non-derivat. Chromsystems Kit

8 Literature

1) Paediatrics Directive Effective: 01 April, 2021 of the Federal Joint Committee on the Early Detection of Diseases in Children (Paediatrics Directive – "Kinder-Richtlinie); https://www.g-ba.de/downloads/62-492-2432/Kinder-RL_2020-12-17_iK-2021-04-01.pdf

2) Paediatrics Directive Effective: 01 April, 2021 of the Federal Joint Committee on the Early Detection of Diseases in Children (Paediatrics Directive – "Kinder-Richtlinie); https://www.g-ba.de/downloads/62-492-2432/Kinder-RL_2020-12-17_iK-2021-04-01.pdf (accessed 3 March, 2024)