National Screening Report

Germany 2022

German Society for Neonatal Screening (DGNS)

Inken Brockow, Oliver Blankenstein, Uta Ceglarek, Regina Ensenauer, Ralph Fingerhut, Gwendolyn Gramer, Friederike Hörster, Ute Holtkamp, Nils Janzen, Jeannette Klein, Erwin Lankes, Martin Lindner, Simona Murko**,** Matthias Nauck, Birgit Odenwald, Jürgen Okun, Melanie Rödel, Sabine Rönicke, Nina Sinemus, Wulf Röschinger, Olaf Sommerburg, Carsten Speckmann, Theresa Winter, Uta Nennstiel

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Corresponding author:

Dr. med. Inken Brockow MPH
Screening Center
Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit
(Bavarian Health and Food Safety Authority)
Veterinärstr. 2
85764 Oberschleissheim
Germany
E-Mail: inken.brockow@lgl.bayern.de

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Abbreviations and Glossary

CACT Deficiency	Carnitine-Acylcarnitine Translocase Deficiency
CAH	Congenital Adrenal Hyperplasia
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
MS/MS	Tandem Mass Spectrometry
MSUD	Maple Syrup Urine Disease
PAP	Pancreatitis-associated Protein
Phe	Phenylalanine
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
SMN Protein	Survival Motor Neuron Protein
VLCAD Deficiency	Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency
WoG	Week of Gestation

Screening Laboratories und Screening Centers

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

(1) Neonatal Screening Lab Berlin
Dr. med. Oliver Blankenstein
Sylter Str. 2, 13353 **Berlin**
030/405 026 391 / Fax: -613
Contact: Dr. Jeannette Klein
Oliver.Blankenstein@charite.de
Jeannette.Klein@charite.de
https://screening.charite.de/

(3/10) Screening Center Saxony
Prof. Dr. med. Berend Isermann
University Clinic Leipzig

(3) Dresden Center
PO Box 160252, 01288 **Dresden**
0351/458 5230 / 5229
Contact: Dr. med. Melanie Rödel
swscreening@uniklinikum-dresden.de

(10) Leipzig Center
Paul-List-Str. 13-15, 04103 **Leipzig**
0341/9722222 (Control Center ILM)
Contact: Prof. Dr. Uta Ceglarek
uta.ceglarek@medizin.uni-leipzig.de
https://www.screeningzentrum-sachsen.de

(5) Screening Center Hessen
PD Dr. med. Martin Lindner
Theodor-Stern-Kai 7, 60596 **Frankfurt**
069/6301 4594
martin.lindner@ukffm.de
https://www.screeningzentrum-hessen.de

(6) Neonatal Screening Centre Mecklenburg-Western Pomerania
Prof. Dr. med. Matthias Nauck
Ferdinand-Sauerbruch-Str., 17475 **Greifswald**
Tel. 03834/865501
Contact: Dr. Theresa Winter
matthias.nauck@med.uni-greifswald.de
theresa.winter@med.uni-greifswald.de
https://www.medizin.uni-greifswald.de/klinchem/

(7) Screening Lab, University Children's Hospital
Prof. Dr. med. Gwendolyn Gramer
Martinistr. 52, 20246 **Hamburg**
040/7410 57037
Contact: Dr. Simona Murko
gramer@uke.de
s.murko@uke.de

(8) Screening Lab Hannover
Dr. med. Dr. rer. nat. Nils Janzen
PO Box 911009, 30430 **Hannover**
05108/92163 0
Contact: Dr. Ute Holtkamp
n.janzen@metabscreen.de
u.holtkamp@metabscreen.de
https://www.metabscreen.de

(9) Neonatal Screening Heidelberg
Prof. Dr. med. G.F. Hoffmann
Im Neuenheimer Feld 669, 69120 **Heidelberg**
06221/56 8278 / Fax -4069
Contact: PD Dr. med. Friederike Hörster
friederike.hoerster@med.uni-heidelberg.de
juergen.guenther.okun@med.uni-heidelberg.de
https://www.neugeborenenscreening.uni-hd.de

(11) Screening Center Saxony Anhalt
University Clinic Magdeburg
Institute for Clinical Chemistry and Pathobiochemistry
Sr. Physician Dr. med. Katrin Borucki
PO Box 140274, 39043 **Magdeburg**
0391/6713986
Contact: Dr. Anja Menzel
anja.menzel@med.ovgu.de
https://stwz.med.ovgu.de/

(12/13) Lab Becker & Colleagues
Neonatal Screening
Prof. Dr. med. Dr. rer. nat. Jürgen Durner
Contact:
Prof. Dr. med. Esther Maier
Ottobrunner Str. 6, 81737 **München**
089/544 654 0
e.maier@labor-becker.de
https://www.labor-becker.de/

(14/15) Screening Labor Synlab, Medical Care Center Weiden
Dr. med. Dr. rer. nat. Wolfgang Schultis
Zur Kesselschmiede 4, 92637 **Weiden**
0961/309 0
Contact: PD Dr. Ralph Fingerhut
wolfgang.schultis@synlab.com
ralph.fingerhut@synlab.com
https://www.synlab.de/lab/weiden

Screening Center Bavaria (12/14)
Bavarian Health and Food Safety Authority
Dr. med. Inken Brockow MPH
Veterinärstr.2
85764 **Oberschleißheim**
09131/6808-5204
screening@lgl.bayern.de
https://www.lgl.bayern.de/gesundheit/praevention/kindergesundheit/neugeborenenscreening/

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 and Food Safety (LGL) on behalf of the German Society for Newborn Screening (DGNS) e.V. together with the German screening laboratories. For the 2022 report, the data collection for confirmation diagnostics was reviewed and simplified by a DGNS working group.

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 parameters, recall rates and confirmed diagnoses for 2022. 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-off value
- 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 time until completion of diagnostics
    - Final diagnosis
- Age at start of therapy

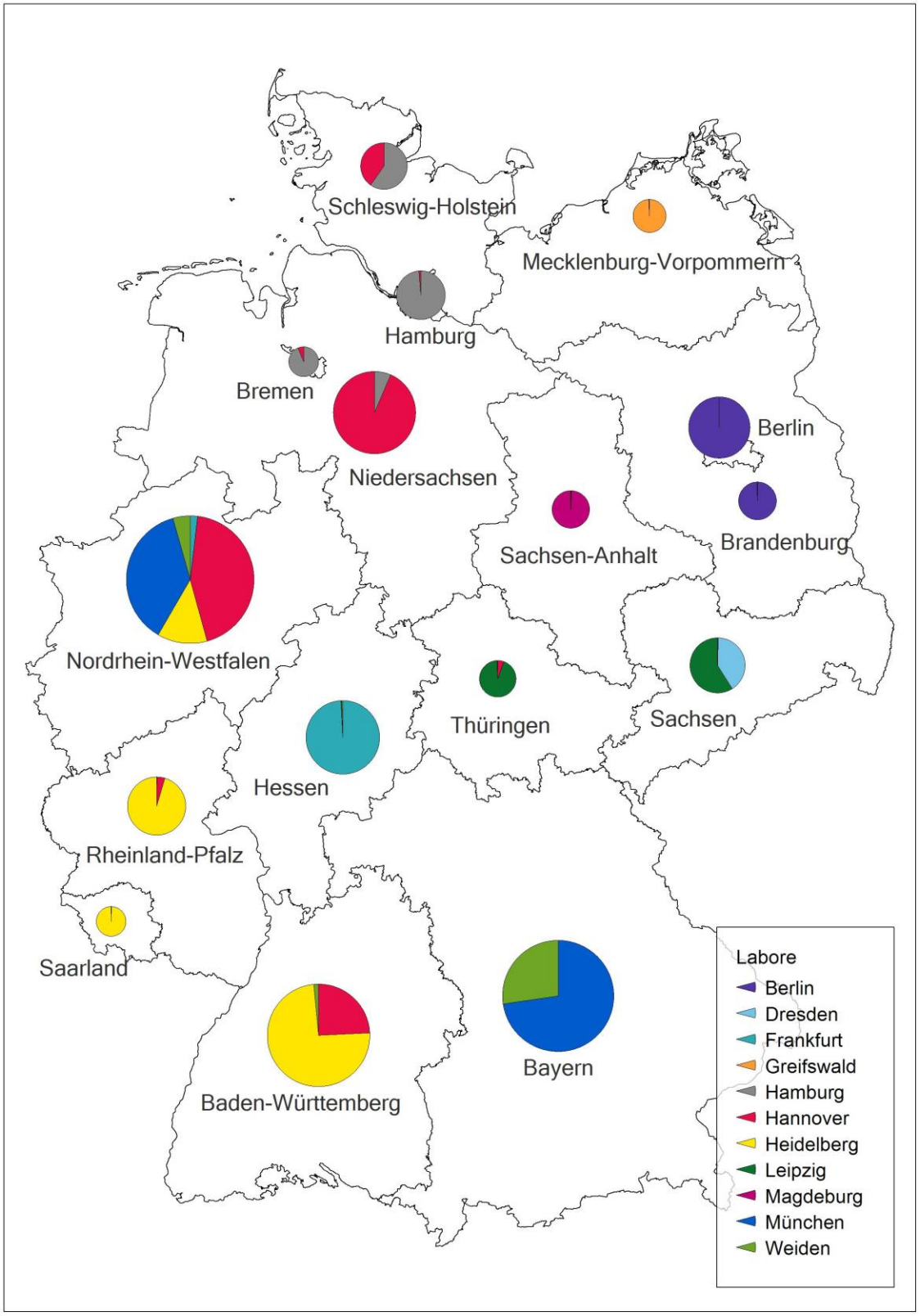
The previous page lists the laboratories that conducted the screening in Germany in 2022 (12 and 13 refer to the same laboratory, once in cooperation with a tracking center and once without; the same is true of 14 and 15). References to paragraphs in the text refer to the Paediatrics Directive from April 1, 2021 [1].

For convenience, the tables have not been numbered sequentially but rather in accordance with the related chapters.

We would like to thank all the laboratories for providing their data. The data have been checked for plausibility. Where inconsistencies remained, 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 2022 a total of 738,819 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 732,791. Cumulatively, 99.2% 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. Refusal of the examination was only documented for 599 newborns (0.08%).

Births:	738,819
First screenings:	732,791
Confirmed diagnoses:	1,004

The diseases targeted for the comprehensive screening are defined in § 17 of the Paediatrics Directive [**Fehler! Textmarke nicht definiert.**]. Other diseases screened in individual laboratories as part of studies or state law requirements are not included in this report. In 1,004 newborns, one of the target diseases defined in the guideline was detected during newborn screening. Table 2.1 shows the confirmed cases and prevalence of the target diseases in 2022 in relation to the number of screened newborns in Germany.

Table 2.1: Prevalence of diseases detected in 2022 among 732,791 initial screenings

Disease	Confirmed cases	Prevalence	
Hypothyroidism	263	1:	2,786
Congenital Adrenal Hyperplasia (CAH)	43	1:	17,042
Biotinidase Deficiency	24	1:	30,533
Galactosemia (classic form)	15	1:	48,853
Hyperphenylalaninemia	148	1:	4,951
of which phenylketonuria (PKU, Phe >10mg/dl) incl. BH4- Cofactor deficiency	57	1:	12,856
Maple Syrup Urine Disease (MSUD)	7	1:	104,684
Medium-Chain Acyl-CoA Dehydrogenase (MCAD) deficiency	65	1:	11,273
Long-chain 3-Hydroxyacyl-CoA Dehydrogenase (LCHAD) / TFP deficiency	5	1:	146,558
Very Long-Chain Acyl-CoA-Dehydrogenase (VLCAD) deficiency	14	1:	52,342
Carnitine Palmitoyl Transferase I (CPT I) deficiency	0		
Carnitine Palmitoyl Transferase II (CPT II) deficiency	2	1:	366,396
Carnitine-Acylcarnitine Translocase (CACT) deficiency	1	1:	732,791
Glutaric Acidemia (GA) Type I	3	1:	244,264
Isovaleric Acidemia (IVA)	6	1:	122,132
Tyrosinemia Type 1 (Target disease starting 03/2018)	1	1:	732,791
Cystic Fibrosis (CF) (starting 09/2016)	153	1:	4,789
Severe Combined Immunodeficiency (SCID / Leaky-SCID / Syndrome, starting 08/2019)	23	1:	31,860
Spinal muscular atrophy (SMA, starting 10/2021)	94	1:	7,796
Sickle Cell Disease (starting 10/2021)	137	1:	5,349
Total	**1,004**	**1:**	**730**

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 screenings. Only "findings reported as positive" are recorded as a 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 weeks' gestation, <36 h) have only been recorded in the follow-up cards since 2021 (see section 2.2) and not as recalls.

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)	Lab share of total initial screening (%)	Number of Recalls (n)	Lab share of initial screening (recall rate%)	Lab share of total recalls (%)	Number of confirmed cases (n)	Lab share of total confirmed cases (%)
1	52,262	7.13	288	0.55	6.82	77	7.67
3	12,392	1.69	55	0.44	1.30	19	1.89
5	57,016	7.78	373	0.65	8.84	71	7.07
6	10,842	1.48	88	0.81	2.09	16	1.59
7	49,235	6.72	610	1.24	14.45	79	7.87
8	171,993	23.47	841	0.49	19.93	253	25.20
09	140,353	19.15	938	0.67	22.23	184	18.33
10	30,582	4.17	126	0.41	2.99	34	3.39
11	13,974	1.91	64	0.46	1.52	13	1.29
12	90,172	12.31	338	0.37	8.01	131	13.05
13	60,874	8.31	278	0.46	6.59	68	6.77
14	33,920	4.63	173	0.51	4.10	50	4.98
15	9,176	1.25	48	0.52	1.14	9	0.90
Total	**732,791**	**100**	**4220**	**0.58**	**100**	**1004**	**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 (range of proportion of recall to initial screening between 0.37 and 1.24). In addition to second-tier procedures, which significantly reduce the recall rate (see e.g. CAH Table 5.2.1, IVA Table 5.12.1), the differences between the laboratories for individual diseases could also be due to different cut-off values. For example, the specified cut-off values and recall rates for Hyperphenylalaninemia and Biotinidase deficiency differ considerably between the laboratories (see Table 5.5.1 and Section 7.3).

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. [1] The following Table 2.1.2 shows the number of initial screening examinations stratified by age and gestational age.

Table 2.1.2: 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	52,262	51,462	98,47	358	0.69	359	0.69	83	0.16
3	12,392	11,939	96,34	334	2.70	111	0.90	8	0.06
5	57,016	56,177	98,53	309	0.54	466	0.82	64	0.11
6	10,842	10,538	97,20	173	1.60	112	1.03	19	0.18
7	49,235	48,083	97,66	523	1.06	579	1.18	50	0.10
8	171,993	168,592	98,02	1,677	0.98	1,606	0.93	118	0.07
9	140,353	137,334	97,85	1,312	0.93	1,557	1.11	150	0.11
10	30,582	30,085	98,37	234	0.77	214	0.70	36	0.12
11	13,974	13,557	97,02	292	2.09	100	0.72	25	0.18
12	90,172	88,008	97,60	1,196	1.33	835	0.93	133	0.15
13	60,874	58,924	96,80	1,057	1.74	847	1.39	46	0.08
14	33,920	33,199	97,87	455	1.34	241	0.71	25	0.07
15	9,176	8,963	97,68	49	0.53	156	1.70	5	0.05
Total	**732,791**	**716,861**	**97,83**	**7,969**	**1.09**	**7,183**	**0.98**	**762**	**0.10**

[a] incl. n= 8,920 initial screenings with missing information about the time or collection or WoG

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

Starting with data collection in 2021, the reason for a necessary reexamination (follow-up card) is recorded again, as was the case until 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 positive results 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 received for around 8% of the requested follow-up cards (Table 2.2.1).

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	1,619	1,498	92.53
3	567	567	100
5	1,327	1,229	92.61
6	390	373	95.64
7 [a]	1,393	1,004	72.07
8	4,354	3,988	91.59
9 [a]	3,675	3,141	85.47
10 [a]	689	643	93.32
11	424	373	87.97
12	2,589	2,555	98.69
13	2,402	2,395	99.71
14	501	494	98.60
15	221	204	92.31
Total	**20,151**	**18,464**	**91.63**

[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	Proportion of received / requested (%)	Follow up card received	Proportion of requested / initial screening (%)
1	52.262	769	1.47	701	91.16
3	12.392	114	0.92	114	100
5	57.016	459	0.81	436	94.99
6	10.842	33	0.30	30	90.91
7	49.235	277	0.56	218	78.70
8	171.993	636	0.37	617	97.01
9	140.353	586	0.42	515	87.88
10	30.582	169	0.55	167	98.82
11	13.974	7	0.05	6	85.71
12	90.172	621	0.69	602	96.94
13	60.874	406	0.67	406	100
14	33.920	35	0.10	35	100
15	9.176	6	0.07	6	100
Total	**732.791**	**4,118**	**0.63**	**3,853**	**93.56**

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

The share of necessary follow-up cards due to poor sample quality still differs significantly between laboratories, although attempts were already made in 2021 to standardize the definition of a quality deficiency (e.g. also strongly scattering IRT values). The percentage ranges from 0.05 % to 2.25 % of all initial screenings in a laboratory. Good quality in the acquisition of the screenings could be achieved through training or regular feedback from the laboratory to the senders.

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

	Initial screening < 36 h			Initial screening < 32 WoG			Other		
Lab	requested	received	%	requested	received	%	requested	received	%
1	358	321	89.66	442	427	96.61	50	49	98.00
3	342	342	100	111	111	100			
5	309	270	87.38	532	499	93.80	27	24	88.89
6	236	229	97.03	115	108	93.91	6	6	100
7	574	297	51.74	494	450	91.09	48	39	81.25
8	1,795	1,535	85.52	1,724	1,673	97.04	199	163	81.91
9	1,345	1,118	83.12	1,469	1,268	86.32	275	240	87.27
10	270	240	88.89	250	236	94.40			
11	292	260	89.04	125	107	85.60			
12	1,158	1,144	98.79	810	809	99.88			
13	1,103	1,103	100	893	886	99.22			
14	377	370	98.14	89	89	100			
15	54	45	83.33	161	153	95.03			
Total	**8,213**	**7,247**	**88.57**	**7,215**	**6,816**	**94.47**	**605**	**521**	**86.12**

Follow-up cards, due for example to transfusions and medication (corticosteroid or dopamine therapy), which can lead to falsification of the findings, should be recorded under other reasons. In 2022 the recording of these follow-up cards was only possible in some laboratories.

2.3 Blank card system

Newborn screening as a public health measure should benefit all children born in Germany. This requires tracking for completeness, which can be done for children born in obstetrics departments by checking the consecutive birth book numbers. If legislation of the federal state 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. These options are currently not implemented across the board in Germany.

According to the "Paediatrics Directive" (§ 21 paragraph 6), the completeness of the screening tests should be checked using blank filter paper cards, which are sent to the screening laboratory only if the screening is refused or the newborn dies before the first blood sample is taken. However, blank cards are most frequently submitted due to refused early screening, which is not in accordance with the guidelines. The laboratories receive these blank cards in widely varying numbers, but the percentage of blank cards submitted in relation to the total number of initial screening reports decreased slightly in 2022 compared to 2021.

The blank card system 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 refused	Not differentiable	Total	Proportion of first screening
Lab	n	n	n	n	n	n	%
1	52,262	326	314	3,711	294	4,645	8.89
3	12,392	32	52	525	276	885	7.14
5	57,016	28	974	2,151	284	3,437	6.03
6	10,842	14	16	850	0	880	8.12
7	49,235	0	0	20	472	492	1.00
8 [a]	171,993				4,701	4,701	2.73
9	140,353	2	260	1,957	1,852	4,071	2.90
10	30,582	175	52	405	0	632	2.07
11	13,974	12	48	403	64	527	3.77
12	90,172	0	204	1,946	267	2,417	2.68
13	60,874	24				24	0.04
14	33,920	0	28	185	29	242	0.71
15 [b]	9,176						
Total	**732,791**	**613**	**1,948**	**12,153**	**8,239**	**22,953**	**3.13**

[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 95.5% of cases in which the time of blood sampling was provided, collection took place in the designated time frame, in 3.3% not until after 72 hours and in 1.2% 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 3.3% in 2022 (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.

Table 3.1: Age at blood sample collection - Initial screening

	Total	<36h		36h-<=48h		48h-<=72h		≥72h	
Lab	n	n	%	n	%	n	%	n	%
1	52,261	441	0.84	21,526	41.19	28,332	54.21	1,962	3.75
3	12,392	97	0.78	3,816	30.79	8,186	66.06	293	2.36
5	56,946	309	0.54	44,129	77.49	11,145	19.57	1,363	2.39
6	10,842	192	1.77	5,258	48.50	5,009	46.20	383	3.53
7	49,235	590	1.20	21,231	43.12	24,747	50.26	2,667	5.42
8	170,939	1,795	1.05	91,241	53.38	72,381	42.34	5,522	3.23
9	140,353	1,464	1.04	78,990	56.28	55,230	39.35	4,669	3.33
10	30,582	270	0.88	12,144	39.71	17,310	56.60	858	2.81
11	13,974	319	2.28	6,049	43.29	7,021	50.24	585	4.19
12	89,415	1,353	1.51	61,040	68.27	24,742	27.67	2,280	2.55
13	57,537	1,103	1.92	34,148	59.35	19,452	33.81	2,834	4.93
14	33,917	481	1.42	19,781	58.32	12,992	38.31	663	1.95
15	9,176	55	0.60	5,570	60.70	3,461	37.72	90	0.98
Total	**727,569** [a]	**8,469**	**1.16**	**404,923**	**55.65**	**290,008**	**39.86**	**24,169**	**3.32**

[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 collection of blood sample 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 has been further differentiated since 2021. In 38.7% of cases in which the dispatch times were provided, the sample was not received by the laboratory until more than 72 hours after the blood sample was taken, and in over 14,000 of these it was not even received until a week later (Table 3.2).

The proportion of dispatch times greater than 72 hours varies greatly between the laboratories and has further increased over the years (Figure 3). Urgent efforts must be made to achieve shorter sample delivery times so as not to jeopardize the success of screening for target diseases at risk of early decompensation.

Table 3.2: Time between blood collection and receipt by the laboratory [a]

	≤24h		>24h-48h		>48h-72h		>3d-5d		>5d-7d		>7d	
Lab	n	%	n	%	n	%	n	%	n	%	n	%
1	11,874	22.72	18,620	35.63	9,990	19.12	8,670	16.59	2,312	4.42	795	1.52
3[b]	3,840	30.99	5,271	42.54	2,245	18.12	1,036	8.36				
5	4,768	8.36	19,717	34.59	15,693	27.53	13,139	23.05	2,820	4.95	867	1.52
6	1,444	13.32	3,201	29.52	2,681	24.73	2,677	24.69	680	6.27	159	1.47
7	1,506	3.06	8,582	17.43	13,623	27.67	17,125	34.78	6,430	13.06	1,969	4.00
8	12,409	7.38	41,019	24.39	45,093	26.82	51,672	30.73	16,920	10.06	1,047	0.62
9	7,144	5.09	28,144	20.05	31,788	22.65	45,287	32.27	20,604	14.68	7,386	5.26
10	4,449	14.55	10,621	34.73	8,084	26.43	6,384	20.88	878	2.87	166	0.54
11	2,225	15.92	5,068	36.27	3,949	28.26	2,312	16.55	335	2.40	85	0.61
12	4,718	5.28	28,418	31.77	22,114	24.72	29,661	33.16	3,937	4.40	592	0.66
13	487	0.85	13,626	23.68	14,961	26.00	22,024	38.28	5,368	9.33	1,071	1.86
14	12,309	36.29	12,192	35.95	5,973	17.61	2,986	8.80	352	1.04	105	0.31
15	1,333	14.53	3,205	34.93	2,135	23.27	2,026	22.08	372	4.05	105	1.14
Total	**68,506**	**9.45**	**197,684**	**27.27**	**178,329**	**24.60**	**204,999**	**28.28**	**61,008**	**8.42**	**14,347**	**1.98**

[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 diagnosis

In accordance with the Paediatrics Directive, the findings should be communicated no later than 72 hours after the test card has been taken. It must be ensured (§ 26 paragraph 3) that the tests are carried out and positive findings are reported on the day the sample is received. Based on this wording, the time period up to the notification of findings has been recorded as "days from receipt by the laboratory" since 2021. Previously - as with the sample collection and dispatch time - this time period was always recorded in 24-hour increments. 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.

In 2022 52.1 % and in 2021 a little under half (46.7%) 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 abnormal and normal findings.

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 2nd day after receipt of sample		On 3rd day after receipt of sample		After 3rd day after receipt of sample	
Lab	Total	n	%	n	%	n	%	n	%	n	%
1	52,262	0		39,314	75.22	4,511	8.63	6,759	12.93	1,678	3.21
3	12,392	8,478	68.42	1,824	14.72	1,848	14.91	242	1.95	0	
5	57,016	43,695	76.64	12,181	21.36	983	1.72	153	0.27	4	0.01
6	10,842	0		6,408	59.10	1,043	9.62	1,172	10.81	2,219	20.47
7	49,235	0		44,376	90.13	3,676	7.47	1,114	2.26	69	0.14
8	171,993	158,261	92.02	11,001	6.40	836	0.49	1,056	0.61	839	0.49
9	140,353	108,345	77.19	28,599	20.38	2,910	2.07	340	0.24	159	0.11
10	29,676	22	0.07	28,005	94.37	1,200	4.04	314	1.06	135	0.45
11	13,974	4	0.03	11,178	79.99	2,029	14.52	603	4.32	160	1.14
12	90,172	34,207	37.94	51,210	56.79	1,585	1.76	1,520	1.69	1,650	1.83
13	60,874	23,550	38.69	34,202	56.18	995	1.63	1,304	2.14	823	1.35
14	33,920	2,809	8.28	19,492	57.46	9,169	27.03	1,810	5.34	639	1.88
15	9,176	1,614	17.59	6,312	68.79	1,049	11.43	187	2.04	14	0.15
Total	**731,885[a]**	**380,985**	**52.06**	**294,102**	**40.18**	**31,834**	**4.35**	**16,574**	**2.26**	**8,389**	**1.15**

[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

Figure 2: Age at the time of blood sample collection 2006 to 2022

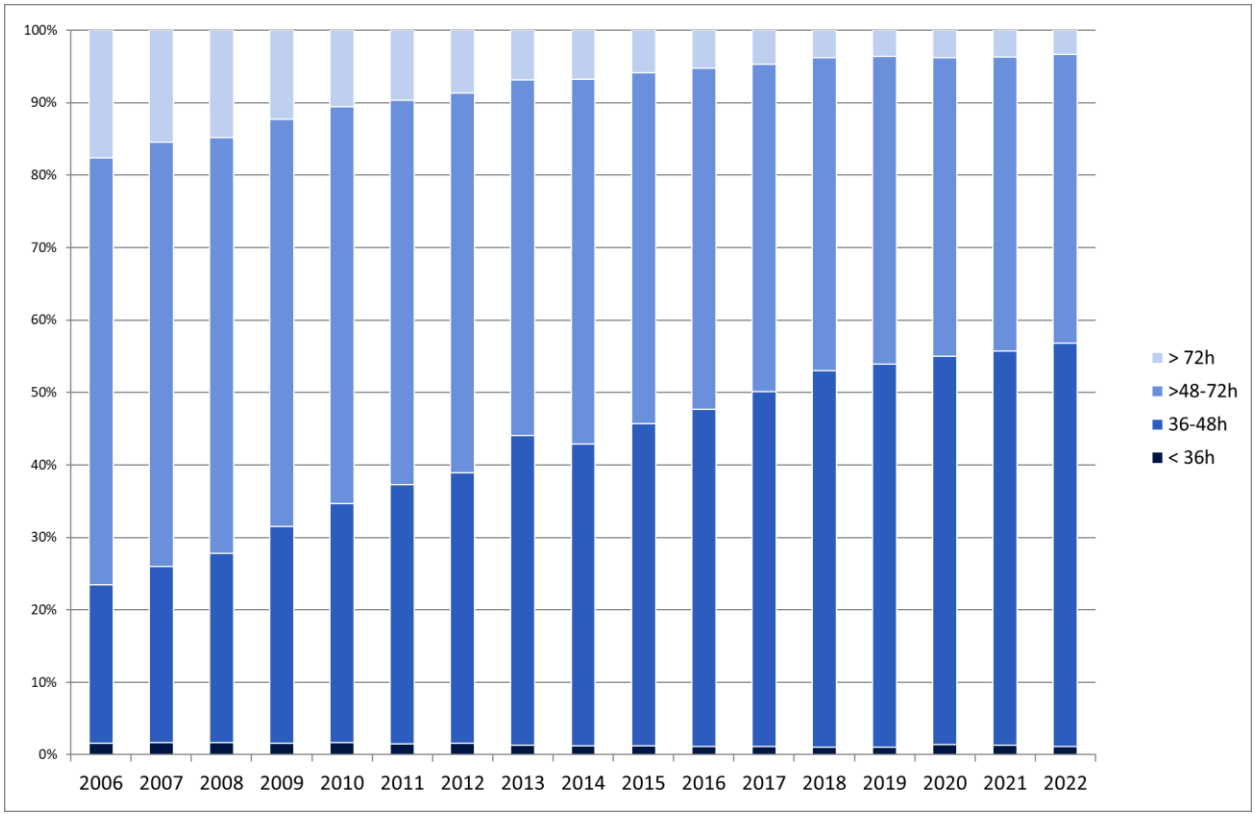
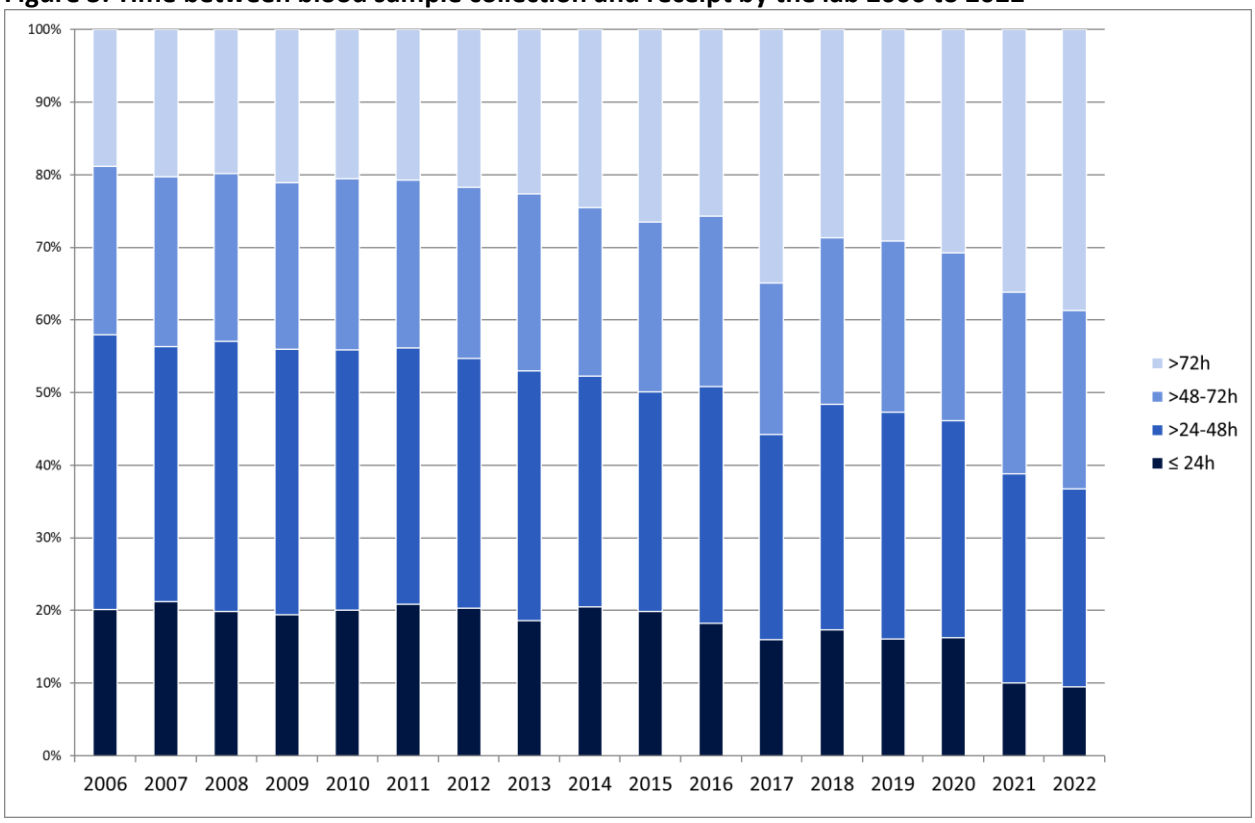


Figure 3: Time between blood sample collection and receipt by the lab 2006 to 2022



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. The recall rate in 2022 was 0.58% (see Table 2.1.1 and Table 4.1), almost 0.1% higher than in 2021, in part due to the new target diseases sickle cell disease and SMA with relatively high prevalence. This means that for every 1,000 screening examinations, approximately six findings requiring monitoring are to be expected. The PPV depends on the disease and is very high for the new target diseases, as there are hardly any false positive findings. For example, the PPV for SMA was 100 % and 82.5 % for sickle cell disease. 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 comprehensive case feedback from the treatment centers to the labs.

Table 4.1: Recall rates and cases found through screening in 2022 (Initial screening n= 732,791)

Disease	Recall	Recall rate (%)	Confirmed Cases	PPV	Specificity
Hypothyroidism	789	0.11	256 [b]	33.33	99.93
CAH	628	0.09	43	6.85	99.92
Biotinidase Deficiency	263	0.04	24	9.13	99.97
Galactosemia [a]	273	0.04	15	5.49	99.96
PKU/HPA	243	0.03	148	60.91	99.99
MSUD	44	0.01	7	15.91	99.99
MCAD	177	0.02	65	36.72	99.98
LCHAD	24	0.003	5	20.83	100
VLCAD	88	0.01	14	15.91	99.99
CPT-I Deficiency	13	0.002	0		99.99
CPT-II Deficiency [b]	5	0.001	2	40.00	99.99
CACT Deficiency	3	0.0004	1	33.33	99.99
GA I	181	0.02	3	1.66	99.98
IVA	148	0.02	6	4.05	99.98
Tyrosinemia	52	0.01	1	1.92	99.99
CF	859	0.12	144 [b]	17.81	99.90
SCID	170	0.02	23	13.53	99.98
SMA (from 10/2021)	94	0.01	94	100	99.99
SSD (from 10/2021)	166	0.02	137	82.53	99.99
Total	**4,220**	**0.58**	**988** [b]	**23.41**	**99.56**

[a] Recall also includes variants and other disorders of galactose metabolism, confirmed cases however include only classic galactosemia; the PPV is therefore not meaningful for classical galactosemia

[b] excluding 7 hypothyroidism and 8 CF cases with false negative screening and 1 CF case without screening

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. While in the case of some target diseases immediate clarification is urgently required if there is a very strong suspicion of the disease (e.g. CAH, classic galactosemia), confirmation diagnostics are less time-critical for other target diseases (e.g. sickle cell disease, CF or partial biotinidase deficiency). In accordance with the guideline, the blood sample should not be taken less than 36 hours or more than 72 hours after birth except in the case of early discharge. Any delay in blood sampling represents a potential risk for the children concerned.

Table 4.2 shows the age at initial screening and confirmation diagnosis for children confirmed to have one of the target diseases. In 4 cases with hypothyroidism, the time of initial screening is unknown and in a total of 115 cases the day of confirmation diagnosis is not known.

Table 4.2: Time of Initial screening and confirmation of confirmed cases

	Time of initial screening (n) [a]			Time of confirmation (n) [a]			
Disease	<36h	36-72h	>72h	<7d	7-14d	>14d	Confirmed cases
Hypothyroidism	13	244	2	108	112	35	263
CAH	5	37	1	22	19	0	43
Biotinidase Deficiency	0	24	0	0	4	18	24
Galactosemia	1	14	0	6	7	1	15
PKU/HPA	6	138	4	41	63	37	148
MSUD	0	7	0	3	1	0	7
MCAD	6	57	2	14	34	8	65
LCHAD	1	4	0	3	1	0	5
VLCAD	0	14	0	7	3	1	14
CPT II	0	2	0	2	0	0	2
CACT Deficiency	0	1	0				1
GA I	0	3	0	1	1	1	3
IVA	1	5	0	3	2	0	6
Tyrosinemia	0	1	0	1	0	0	1
CF	8	141	3	0	10	123	152 [b]
SCID	1	22	0	4	11	2	23
SMA	1	90	3	17	65	1	94
SSD	1	135	1	0	13	83	137
Total	**44**	**939**	**16**	**232**	**346**	**310**	**1003** [b]

[a] Excluding cases for which the time is unknown

[b] Excluding one case of CF confirmed without screening

5 Recall rate, confirmed cases and confirmation stratified by disease

The following chapter presents recall rates and confirmed cases for the individual target diseases as well as the diagnostic measures performed to confirm the diagnosis, stratified by laboratory. This stratified presentation is not used for diseases with a very low overall recall rate.

The recording of confirmatory diagnostics for 2022 for confirmed cases was simplified by the DGNS working group data, in which, as a rule, only the diagnostic measures for the diagnosis were recorded rather than individual laboratory values (e.g. molecular genetics, organic acids in urine). The figures were reported on 15 March, 2024. Cases reported twice (e.g. from different laboratories) were only counted once and attributed to the lab of the initial screening. 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 PD Dr. Olaf Sommerburg for cystic fibrosis, by Dr. Oliver Blankenstein and Erwin Lankes for endocrinological diseases, and by PD Dr. Carsten Speckmann for severe combined immunodeficiency.

For the 2022 report, information on the confirmatory diagnosis was missing in a total of 92 cases. In 43 cases, the validators assessed a diagnosis as probable based on the screening values, or the dataset indicated only “diagnosis confirmed” (19 metabolic screenings, 4 hypothyroidism, 1 CAH, 1 SCID, 18 sickle cell disease) (see Table 6.1.1.1). In 49 cases with positive ENS, the information on the confirmatory diagnosis was not sufficient to validate the diagnosis (see Table 6.1.2). This applied in particular to hypothyroidism and CF with 7 and 21 positive screenings respectively without sufficient data for validation of the confirmation diagnostics.

Diagnosed cases for which the screening results were negative (normal) are not systematically recorded. In 2022, 7 cases of hypothyroidism and 8 cases of CF were reported to the laboratories after a 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. (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	52,262	65	0.12	23
3	12,392	10	0.08	6
5	57,016	64	0.11	22
6	10,842	9	0.08	7
7	49,235	41	0.08	14
8	171,993	320	0.19	72
9	140,353	104	0.07	45
10	30,582	17	0.06	5
11	13,974	8	0.06	1
12	90,172	68	0.08	34
13	60,874	39	0.06	17
14	33,920	32	0.09	13
15	9,176	12	0.13	4
Total	**732,791**	**789**	**0.11**	**263[a]**

[a] including 7 cases with negative initial screening

Of the 263 cases of congenital hypothyroidism validated as confirmed, seven cases had a negative result in the regular initial screening (n= 5) or for the control screening (n= 2) after 32 weeks' gestation and after 36 hours. Three of these children had received catecholamines. No information is available on the possible causes of the false negative screening in the other children. In 20 other children, who all had an initial screening before a corrected age before 32 weeks' gestation, of whom (n= 6) also had an early screening before 36 h, the TSH screening was initially negative, but became "correctly" positive in the follow-up test carried out, which underlines the importance of these follow-ups after early screenings.

In addition to the 263 cases of congenital hypothyroidism, n= 38 hyperthyrotropinemia cases were reported and validated. These were not included in the calculation of the prevalence.

Table 5.1.2: Hypothyroidism confirmation

Lab	Confirmed cases	TSH (Serum)	fT4	Sonography	Thyroid Antibodies	Confirmed cases without verification details
1	23	23	21	21	1	
3	6	6	6	6		
5	22	19	20	17		1
6	7	6	6	6		
7	14	13	13	1		1
8	72	70	64	62	4	1
9	45	44	44	14	1	
10	5	4	4	2		1
11	1			1		
12	34	32	33	4		
13	17	17	16			
14	13	13	13	1		
15	4	4	4	2		
Total	**263**	**251**	**244**	**137**	**6**	**4**

5.2 Congenital Adrenal Hyperplasia (CAH)

Table 5.2.1: CAH confirmed cases / recall rate

Lab	Initial screening	Recall	Recall-Rate (%) [b]	Confirmed cases
1 [a]	52,262	19	0.04	6
3	12,392	2		1
5	57,016	141	0.25	1
6	10,842	18	0.17	0
7	49,235	203	0.41	1
8 [a]	171,993	31	0.02	10
9 [a]	140,353	141	0.10	10
10 [a]	30,582	21	0.07	1
11	13,974	21	0.15	0
12 [a]	90,172	13	0.01	7
13 [a]	60,874	10	0.02	3
14 [a]	33,920	4		2
15 [a]	9,176	4		1
Total	**732,791**	**628**	**0.09**	**43**

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

A second-tier procedure carried out in six laboratories to date, has significantly reduced the recall rate of CAH screening.

Table 5.2.2: CAH Confirmation

Lab	Confirmed cases	With spectrometric steroid measurement	Without spectrometric steroid measurement	Molecular genetics	Confirmed cases without confirmation details
1	6	6		6	
3	1		1	1	
5	1	1			
7	1		1	1	
8	10	7	2	5	
9	10	9		2	
10	1				1
12	7		5	7	
13	3			3	
14	2	1		2	
15	1	1			
Total	**43**	**25**	**9**	**27**	**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	52,262	40	0.08	2
3	12,392	1		1
5	57,016	9	0.02	1
6	10,842	7	0.06	0
7	49,235	65	0.13	7
8	171,993	67	0.04	5
9	140,353	13	0.01	1
10	30,582	0		0
11	13,974	3		0
12	90,172	26	0.03	4
13	60,874	32	0.05	3
14	33,920	0		0
15	9,176	0		0
Total	**732,791**	**263**	**0.04**	**24**

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

Of n= 24 confirmed cases, a partial biotinidase deficiency was diagnosed in n= 15 cases.

Table 5.3.2: Biotinidase Deficiency Confirmation

Lab	Confirmed cases	Biotinidase (Serum/TB)	Molecular genetics	Without confirmation details
1	2	1	2	
3	1			1
5	1	1		
7	7	7	6	
8	5	4		1
9	1	1		
12	4	2	2	
13	3	1		2
Total	**24**	**17**	**10**	**4**

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		36	0.07	3
3	12,392	1		0
5	57,016	14	0.02	0
6	10,842	4		0
7	49,235	76	0.15	2
8	171,993	85	0.05	3
9	140,353	17	0.01	1
10	30,582	1		1
11	13,974	0		0
12	90,172	20	0.02	4
13	60,874	0		0
14	33,920	14	0.04	1
15	9,176	5	0.05	0
Total	**732,791**	**273**	**0.04**	**15**

[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

Lab	Confirmed cases	Enzymatic	Molecular genetics	Confirmed cases without confirmation details
1	3	3	3	
8	2		2	
9	3		3	
10	1	1		
12	1		1	
13	4		2	2
14	1		1	
Total	**15**	**4**	**12**	**2**

In 2022, all confirmed cases (and not just classic galactosemia) were to be reported after a positive recall, as these cases would otherwise be “false positives” and the PPV of the screening would therefore be too low. This was only possible for some laboratories. 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. In addition to classic galactosemia, n= 35 reported cases with a galactosemia variant and n= 5 with a kinase deficiency were reported.

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	Of which PKU (Phe>10mg/dl)
1	52,262	16	0.03	9	5
3	12,392	6	0.05	4	0
5	57,016	19	0.03	14	6
6	10,842	9	0.08	5	1
7	49,235	37	0.08	7	4
8	171,993	48	0.03	45	16
9	140,353	36	0.03	28	9
10	30,582	10	0.03	5	2
11	13,974	4		3	1
12	90,172	17	0.02	12	7
13	60,874	11	0.02	7	4
14	33,920	24	0.07	8	2
15	9,176	6	0.07	1	0
Total	**732,791**	**243**	**0.03**	**148**	**57**

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

Of the n= 147 confirmed cases, 57 were diagnosed with PKU, including 2 with BH4 cofactor deficiency, and 91 cases were diagnosed with HPA.

Table 5.5.2: PKU/HPA confirmation

Lab	Confirmed cases	Phenylalanin (Serum/TB)	Molecular genetics	Pterin/ DHPR	Amino acids in Plasma/ Serum	Confirmed cases without confirmation details
1	9	9	9	9	9	
3	4	1			3	1
5	14	10	5	11	7	1
6	5	4	5			
7	7	7	2	3	7	
8	45	39	22	29	36	1
9	28	14	17	24	11	1
10	5	4	3	5	4	
11	3	3	1	3	3	
12	12	12	9		12	
13	7	5	5	5	5	
14	8	8	1		8	
15	1	1		1		
Total	**148**	**117**	**79**	**90**	**105**	**4**

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	52,262	2	2
3	12,392	1	0
5	57,016	2	0
6	10,842	1	0
7	49,235	11	0
8	171,993	2	2
9	140,353	21	3
10	30,582	0	0
11	13,974	0	0
12	90,172	0	0
13	60,874	0	0
14	33,920	2	0
15	9,176	2	0
Total	**732,791**	**44**	**7**

Table 5.6.2: MSUD confirmation

Labor	Confirmed cases	Amino acids in plasma / serum	Organic acids in urine)	Alloisoleucine test	Molecular genetics
1	2	2	2	2	2
8	2	2	2	2	2
9	3	2	1	1	1
Total	**7**	**6**	**5**	**5**	**5**

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	52,262	12	0.02	7
3	12,392	5	0.04	2
5	57,016	3	0.01	3
6	10,842	5	0.05	0
7	49,235	46	0.09	6
8	171,993	17	0.01	17
9	140,353	53	0.04	8
10	30,582	6	0.02	0
11	13,974	1	0.01	1
12	90,172	16	0.02	15
13	60,874	8	0.01	4
14	33,920	3	0.01	1
15	9,176	2	0.02	1
Total	**732,791**	**177**	**0.02**	**65**

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

Table 5.7.2: MCAD Deficiency Confirmation

Lab	Confirmed cases	Acylcarnitine profile	Enzyme activity	Molecular genetics	Confirmed cases without confirmation details
1	7	7	7	7	
3	2	2		2	
5	3	1	1		2
7	6	1	3	2	1
8	17	11	3	13	
9	8	4	5	5	
11	1	1	1		
12	15	15	1	14	
13	4	2		2	
14	1	1	1		
15	1			1	
Total	**65**	**45**	**22**	**46**	**3**

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

The overall recall rate is very low at 0.003%. Of the 5 confirmed cases, 2 were classified as mitochondrial trifunctional protein deficiency (TFP).

Table 5.8.1: LCHAD / TFP Deficiency - Confirmed cases / Recall rate

Lab	Initial screening	Recall	Confirmed cases
1	52,262	2	2
3	12,392	1	0
5	57,016	1	0
6	10,842	1	0
7	49,235	0	0
8	171,993	1	1
9	140,353	16	0
10	30,582	0	0
11	13,974	0	0
12	90,172	2	2
13	60,874	0	0
14	33,920	0	0
15	9,176	0	0
Total	**732,791**	**24**	**5**

Table 5.8.2: LCHAD Deficiency Confirmation

Labor	Confirmed cases	Acylcarnitine profile	Enzyme activity	Molecular genetics
1	2	2	0	1
8	1	1	0	1
12	2	1	0	2
Total	**5**	**4**	**0**	**4**

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	52,262	0		0
3	12,392	2		0
5	57,016	5	0.01	1
6	10,842	5	0.05	1
7	49,235	17	0.03	1
8	171,993	2		2
9	140,353	49	0.03	5
10	30,582	0		0
11	13,974	1		1
12	90,172	3		1
13	60,874	0		0
14	33,920	4		2
15	9,176	0		0
Total	**732,791**	**88**	**0.01**	**14**

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

Table 5.9.2: VLCAD Confirmation

Labor	Confirmed cases	Acylcarnitine profile	Enzyme activity	Molecular genetics
5	1		1	1
6	1	1	1	1
7	1		1	1
8	2	2	1	1
9	5		5	4
11	1	1	1	
12	1	1		1
14	2	2	1	
Total	**14**	**7**	**11**	**9**

5.10 CPT I / CPT II / CACT Deficiency

The overall recall rate is very low at 0.002%. The recall CACT deficiency is recorded in Recall CPT II deficiency, as the two are biochemically indistinguishable.

Table 5.10.1: CPT I / CPT II / Deficiency Recall

	Initial screening	Recall	Confirmed Cases
CPT I Deficiency	732,791	13	0
CPT II Deficiency / CACT Deficiency	732,791	8	3

Table 5.10.2: CPT I Deficiency Confirmation

Lab	Confirmed Cases	Acylcarnitine profile	Enzyme activity	Molecular genetics
5	1			1
10	1			1
12	1			1
Total	**3**	**0**	**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	52,262	3		0
3	12,392	1		0
5	57,016	2		0
6	10,842	0		0
7	49,235	25	0.05	0
8	171,993	2		2
9	140,353	144	0.10	0
10	30,582	0		0
11	13,974	0		0
12	90,172	0		0
13	60,874	0		0
14	33,920	4		1
15	9,176	0		0
Total	**732,791**	**181**	**0.02**	**3**

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

Table 5.11.2: GA I confirmation

Lab	Confirmed cases	3 OH-glutaric acid in urine/plasma	Enzyme activity	Molecular genetics
8	2	2		2
14	**3**	**3**	**0**	**3**
Total	2	2		2

5.12 Isovaleric Acidemia (IVA)

Table 5.12.1: IVA - confirmed cases / recall rate

Lab	Initial screening	Recall	Recall rate (%)[a]	Confirmed cases
1	52,262	16	0.03	0
3	12,392	4		0
5	57,016	3		0
6	10,842	5	0.05	0
7[b]	49,235	12	0.02	1
8[b]	171,993	1		1
9	140,353	67	0.05	2
10	30,582	10	0.03	0
11	13,974	11	0.08	1
12[b]	90,172	1		0
13[b]	60,874	0		0
14[b]	33,920	17	0.05	1
15[b]	9,176	1		0
Total	**732,791**	**148**	**0.02**	**6**

[a] Recall rates only provided if recall rate ≥ 0,01% and n ≥ 5
[b] Laboratory carries out second-tier procedures, laboratory 14/15 since 10/2022

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. For differentiation, it is helpful for the sender to also indicate the mother's therapy on the test card. A second-tier procedure, which was carried out in four laboratories in 2022 ([b] lab 14/15 since 10/2022), made it possible to avoid a total of over 300 recalls due to false positive results when administering pivmecillinam. Without these second-tier procedures, the recall rate for IVA would be 0.06%!

Table 5.12.2: IVA Confirmation

Lab	Confirmed cases	Organic Acids (urine)	Enzyme activity	Molecular genetics
7	1	1		1
8	1	1		1
9	2	2		
11	1	1		1
14	1			
Total	**6**	**5**		**3**

5.13 Tyrosinemia Type I

Table 5.13.1: Tyrosinemia – confirmed cases / recall rate

Lab	Initial Screening	Recall	Recall-Rate (%) [a]	Confirmed Cases
1	52,262	5	0.01	0
3	12,392	1		0
5	57,016	0		0
6	10,842	0		0
7	49,235	0		0
8	171,993	10	0.01	0
9	140,353	26	0.02	1
10	30,582	3		0
11	13,974	1		0
12	90,172	0		0
13	60,874	0		0
14	33,920	5	0.01	0
15	9,176	1		0
Total	**732,791**	**52**	**0.01**	**1**

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

Table 5.13.2: Tyrosinemia confirmation

Lab	Confirmed Cases	Succinylacetone in urine	Succinylacetone in plasma	Molecular genetics
9	1			1
Total	**1**	**0**	**0**	**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	52,262	14	0.03	4
3	12,392	2		0
5	57,016	12	0.02	0
6	10,842	2		0
7	49,235	12	0.02	2
8	171,993	26	0.02	6
9	140,353	20	0.01	3
10	30,582	25	0.08	3
11	13,974	1		1
12	90,172	22	0.02	1
13	60,874	20	0.03	2
14	33,920	12	0.04	1
15	9,176	2		0
Total	**732,791**	**170**	**0.02**	**23**

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

Table 5.14.2: SCID confirmed cases

Lab	Confirmed cases	Genetics	Flow rate Cytometry
1	4	3	4
7	2	2	1
8	6	6	5
9	3	2	2
10	3		2
11	1		1
12	1	1	1
13	2	1	1
14	1	1	1
Total	**23**	**16**	**18**

Of the 23 cases, n= 8 were validated as SCID, n= 3 as Leaky SCID / Omenn and n= 12 as syndromes.

5.15 Spinal Muscular atrophy (SMA)

Table 5.15.1: SMA – confirmed cases / recall

Lab	Initial Screening	Recall	Recall Rate (%) [a]	Confirmed cases
1	52,262	6	0.01	6
3	12,392	0		0
5	57,016	5	0.01	5
6	10,842	2		2
7	49,235	9	0.02	9
8	171,993	25	0.01	25
9	140,353	19	0.01	19
10	30,582	6	0.02	6
11	13,974	0		0
12	90,172	11	0.01	11
13	60,874	6	0.01	6
14	33,920	5	0.01	5
15	9,176	0		0
Total	**732,791**	**94**	**0.01**	**94**

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

5q-associated SMA was added to the ENS as a new target disease on October 1, 2021. In most cases, the cause is a mutation of the SMN 1 (survival of motoneuron) gene. The screening is carried out as a genetic screening using PCR to detect a homozygous SMN 1 gene deletion; compound heterozygous mutations are not detected. There were no false positive cases in the screening, so the PPV is 100%. Whether cases were overlooked is not systematically recorded by the DGNS. The median of the confirmation diagnosis (n= 83) was 8 days of life (range 2-15d), 19 children (20.2 %) already had clinical symptoms at the time of presentation for confirmation diagnosis. The number of SMN2 copies present is decisive for the prognosis.

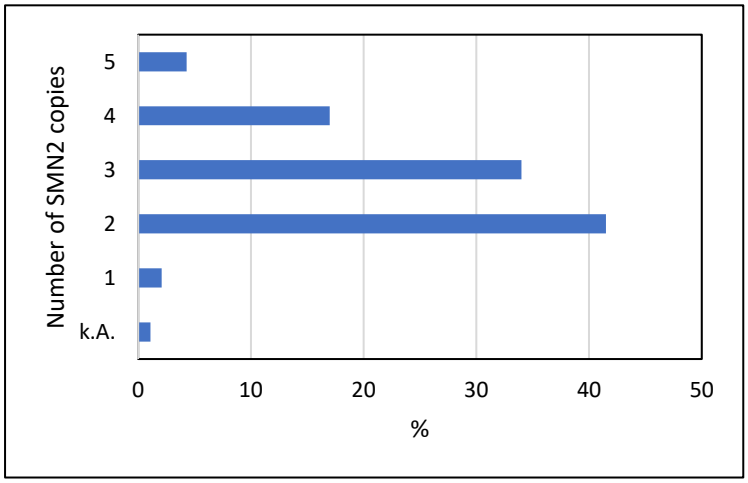


Figure 4: Number of SMN2 copies in children with SMA (n= 94
Note: k.A. = n/a

5.16 Sickle cell disease (SCD)

Table 5.16.1: SCD – confirmed cases / recall

Lab	Initial screening	Recall	Recall-Rate (%) [a]	Confirmed cases
1	52.262	8	0.02	7
3	12.392	0		0
5	57.016	9	0.02	9
6	10.842	0		0
7	49.235	19	0.04	19
8	171.993	42	0.02	32
9	140.353	36	0.03	34
10	30.582	2		1
11	13.974	1		1
12	90.172	12	0.01	11
13	60.874	22	0.04	16
14	33.920	10	0.03	5
15	9.176	5	0.05	2
Total	**732.791**	**166**	**0.02**	**137**

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

Table 5.16.2: SCD - confirmation

Lab	Confirmed cases	Hemoglobin-electrophoresis	Molecular-genetics	Confirmed cases without confirmation details
1	7	6	7	
5	9	7	8	
7	19	15	7	4
8	32	29	21	
9	34	16	20	14
10	1	0	1	
11	1	1	1	
12	11	10	9	
13	16	16	16	
14	5	5	4	
15	2	2	2	
Total	**137**	**107**	**96**	**18**

Sickle cell disease was included in the ENS as a new target disease as of 01.10.2021. The prevalence of 1 in around 5,500 newborns is high compared to other target diseases and roughly corresponds to the prevalence of hyperphenylalaninemia and CF. The PPV is 82.5 %, whereby hardly any false positive screening findings were actually expected. The DGNS working group data should be used to discuss whether other hemoglobinopathies, such as thalassemia, which were found in the screening, should also be counted as cases (analogous to SCID screening). Similarly, some recalls due to transfusions may have been counted.

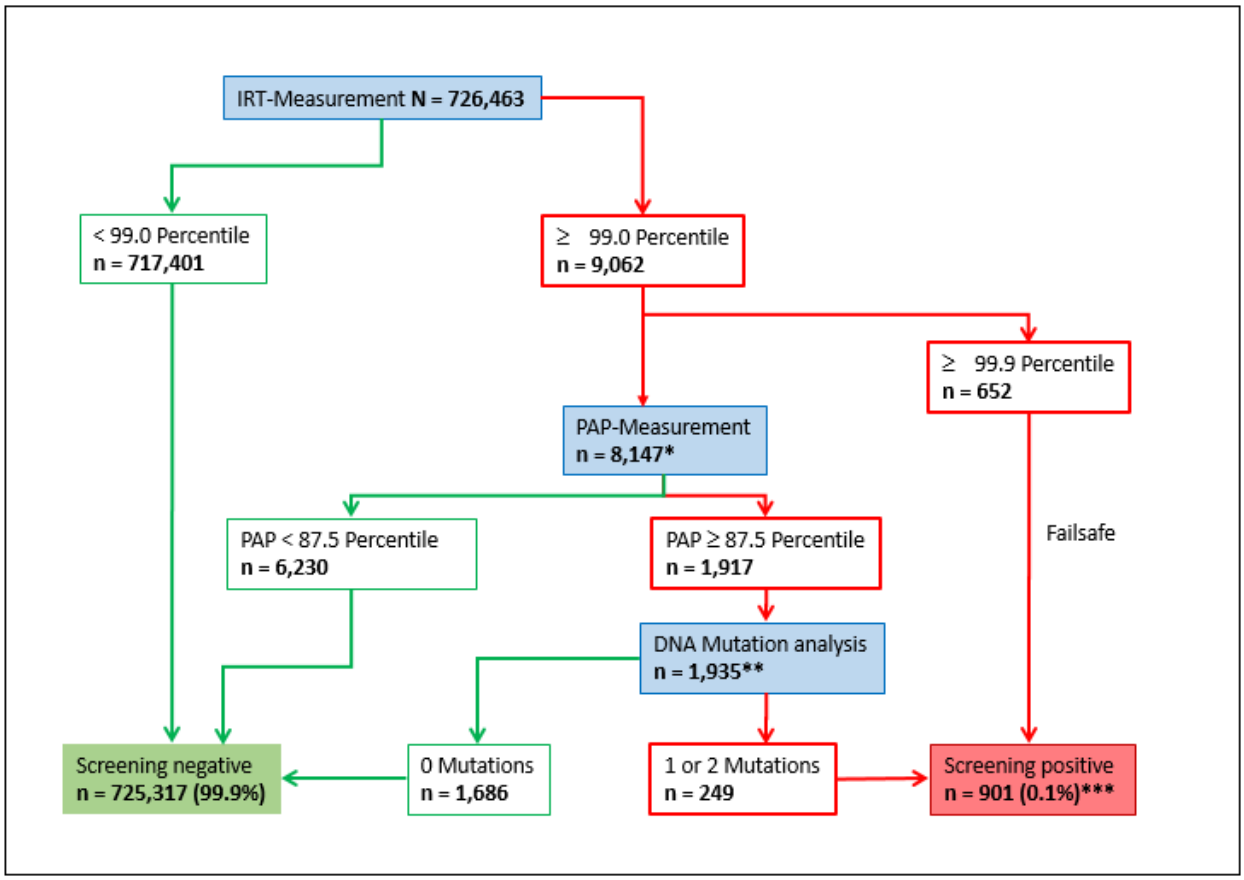
The most common type reported was SCD-S/S at 68.6 %, with SCD-S/C present in 20 %.

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 5). 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).

This screening algorithm results in "failsafe" (IRT >99.9th percentile) conditions in 652 (72.4%) of the 901 positive screening results (see Figure 5). The diagnosis of CF was only confirmed in 144 children (15.9 %); in addition, cystic fibrosis was diagnosed in 8 children after a false negative CF screening and one child without a CF screening.

Figure 5: Screening algorithm for Cystic Fibrosis in Germany 2022***



* 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 and unlike ENS, screening cannot be performed by a midwife alone in exceptional cases with the option of consulting a physician. The proportion of newborns without CF screening was around 1% in 2022 (Table 5.17.1).

Table 5.17.1: Number of CF screenings

Lab	Initial screening ENS	CF Screening	Proportion of CF Screening (%)
1	52,262	51,619	98.77
3	12,392	12,380	99.90
5	57,016	56,064	98.33
6	10,842	10,832	99.91
7	49,235	47,506	96.49
8	171,993	170,884	99.36
9	140,353	140,220	99.91
10	30,582	30,050	98.26
11	13,974	13,971	99.98
12	90,172	89,618	99.39
13	60,874	60,486	99.36
14	33,920	33,638	99.17
15	9,176	9,161	99.84
Total	**732,791**	**726,429**	**99.13**

Table 5.17.2: CF – confirmed cases and abnormal screening findings (recall rate)

Lab	Initial screening with CF Screening	Recall	Recall Rate (%)	Confirmed cases
1	51,619	41	0.08	6
3	12,380	18	0.15	5
5	56,064	83	0.15	14
6	10,832	17	0.16	1
7	47,506	37	0.08	10
8	170,884	159	0.09	30
9	140,220	168	0.12	24
10	30,050	24	0.08	11
11	13,971	12	0.09	4
12	89,618	126	0.14	28
13	60,486	130	0.21	10
14	33,638	37	0.11	10
15	9,161	7	0.08	0
Total	**726,429**	**859**	**0.12**	**153[a]**

[a] including 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	6	5	1				
3	5	3	2	5	5		
5	14	5	6		8	2	
6	1		1				
7	10	3	4	1	4	1	2
8	30	12	13	4	25	6	
9	24	12	7	8	14	3	
10	11	8	1	5	9	2	
11	4	2	2		3		
12	28	18	6	18	19	4	
13	10	8	1		6	1	
14	10	7	1	3	4	10	
15	0						
Total	**153**	**83**	**45**	**44**	**97**	**29**	**2**

In 21 reported cases, the information was not sufficient to confirm the diagnosis. Of n= 153 confirmed cases, 146 cases were diagnosed with Cystic Fibrosis and five with Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID). In two additional cases, the genetic information was missing, so that a distinction between CF and CFSPID was not possible.

The screening was positive in 107 (69.9%) of the CF cases via fail safe, one or two mutations from the screening panel (31 mutations) were detected in 437 (24.2%) cases, and eight children (5.2%) had a negative CF screening.

Genetic information from screening or confirmation was available for n= 105 of the confirmed cases. Based on this, 75 cases had two mutations and 29 cases had one mutation from the panel of 31. In one child, none of the mutations from the panel were detected. A total of 29 children were reported to have meconium ileus.

For confirmation diagnostics, information on one (n= 83) or two (n= 45) sweat tests was available for 128 cases; in 97 cases, two mutations were detected in the screening or confirmation diagnostics.

Of the confirmed CF cases, eight were not found using the specified screening algorithm and were negative in the screening. Six children had an IRT value below the lab cut-off and two children had a PAP value below the lab cut-off. Three of these children had meconium ileus; one had small intestine atresia. It is not known whether other children with cystic fibrosis were not found in the screening, as these are not systematically recorded.

6 Cases without confirmation data

For 92 children with abnormal screening results, it is not known whether confirmatory diagnostics were performed or completed. 43 of these cases, for which no information on the confirmatory diagnostics performed was available, but for which the screening values were clearly pathological or the laboratory made the comment "diagnosis confirmed", were validated as "probable cases" (Table 6.1.1) and included in the calculation of the prevalence. This applied to 18 sickle cell cases alone. For 49 children, most of whom had an abnormal CF screening, this was not possible (Table 6.1.2).

6.1 Confirmed cases without information about confirmation diagnostics performed

43 cases were validated as probable cases without confirmation information.

Table 6.1: Confirmed Cases without information about confirmation diagnostics

		Reason no confirmation given	
Disease	Number of cases	Only the remark "diagnosis confirmed"	Unclear
Hypothyroidism	4	4	
CAH	1	1	
Biotinidase Deficiency	4		4
Galaktosämie	7	2	5
PKU/HPA	4	3	1
MCAD	3	2	1
IVA	1	1	
SCID	1	1	
Sickle Cell Disease	18	15	3
Total	**43**	**29**	**14**

6.2 Non-assessable cases of ENS after positive screening findings (lost to follow-up)

Table 6.1.2: Cases with implausible or missing confirmation information

Disease	Number of cases n
Congenital Hypothyroidism	7
CAH	2
MCAD	7
VLCAD	8
CF	21
SCID	2
Sickle Cell Disease	2
Total	**49**

7 Methods and cut-off-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	yes	AutoDELFIA
3	17 OHP		AutoDELFIA Kit B024
5	17 OHP		AutoDELFIA
6	17 OHP		DELFIA
7	17 OHP		GSP
8	17 OHP	yes	DELFIA
9	17 OHP		GSP
10	17 OHP	yes	AutoDELFIA
11	17 OHP		DELFIA
12/13	17 OHP	yes	AutoDELFIA
14/15	17 OHP	yes	AutoDELFIA

Table 7.3: Cut-off Hyperphenylalaninemia und Quotient Phe/Tyr as well as recall rate

Lab	Parameter	Cut off	Comment	Recall Rate
1	Phenylalanin Phe/Tyr	113 µmol/l 2		0.03
3	Phenylalanin Phe/Tyr	99.67 µmol/l 2.5		0.05
5	Phenylalanin Phe/Tyr	150 µmol/l 2.4	 Percentile 99.9 %	0.03
6	Phenylalanin Phe/Tyr	120 µmol/l 2.5	Percentile 99.9 % Percentile 99.9 %	0.08
7	Phenylalanin Phe/Tyr	118 µmol/l 2.84		0.08
8	Phenylalanin Phe/Tyr	150 µmol/l 1.5		0.03
9	Phenylalanin Phe/Tyr	123 µmol/l 1.5	Cut-off >99.9 % Cut-off 99.0- 99.5 %	0.03
10	Phenylalanin Phe/Tyr	101 µmol/l 110µmol/l 2.52 3.02	Percentile 99.5 % Percentile 99.5 %	0.03
11	Phenylalanin Tyrosin Phe/Tyr	118 µmol/l 39µmol/l 1.7	Percentile 99.9 % Percentile 0.1 % Percentile 99.9 %	0.03
12/13	Phenylalanin Phe/Tyr	120 µmol/l 2		0.02
14/15	Phenylalanin Phe/Tyr	105 µmol/l 1.8	Consideration of pre-series (2000 children)	0.07

Table 7.4: Methods and cut-off biotinidase deficiency and recall rate (biotinidase parameter)

Lab	Cutoff	Methods	Recall Rate
1	30 % Mean value MTP	Non-Kit colorimetry	0.08
3	30 % daily median	Qualitative colorimetry	0.01
5	60 U	Fluorometry (PE)	0.02
6	55 U	Fluorometry (PE)	0.06
7	85,7 U/g Hb	GSP	0.13
8	<30 % daily mean	Quantitative colorimetry	0.04
9		Qualitative colorimetry	0.01
10	<30 %	Qualitative colorimetry	0
11	<30 %	Quantitative colorimetry	0.02
12/13	<30 %	Quantitative fluorometry	0.04
14/15	>50 U	Quantitative colorimetry	0

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) Quantitative colorimetry
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			Total galactose photometric
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	Non-Kit Fluorometry Photometry
14/15	GALT Galactose	<3.0U/g Hb <7.4 mg/dl	Quantitative fluorometry Quantitative colorimetry

Table 7.6: Methods, cut-off and recall rate tyrosinemia (parameter: succinylacetone)

Lab	Cut-off	Methode	Recall-Rate
1	0.65 µmol/l	non-derivatized PE kit	0.010
3	1.12 µmol/l	non-derivatized chromium systems	0.008
5	1 µmol/l	non-derivatized PE kit	
6	0.81 µmol/l	Perkin Elmer	
7	1.6 µmol/l	LC-MS/MS	
8	1.5 µmol/l	not derivative non kit	0.006
9	n/a		0.019
10	1.0 µmol/l	non-derivatized chromium systems	0.010
11	1.08 µmol/l	non-derivatized chromium systems	0.007
12/13	3.0 µmol/l	Tandem MS	
14/15	1.5µmol/l	non-derivatized chromium systems	0.014

Table 7.7: Method 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	non derivat. Chromsystems Kit
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) Destatis, Federal Statistical Office, Births 2022 2022 https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Bevoelkerung/Geburten/Publikationen/Downloads-Geburten/statistischer-bericht-geburten-5126104217005.html (accessed 10 March, 2024)