
# National Screening Report Germany 2018

German Society for Neonatal Screening (DGNS)

Inken Brockow, Oliver Blankenstein, Uta Ceglarek, Regina Ensenauer, Gwendolyn Gramer, Nils Janzen, Jeannette Klein, Erwin Lankes, Martin Lindner, Esther Maier, Richard Mauerer, Peter Mirtschink, Cornelia Müller, Simona Murko, Sabine Rönicke, Wulf Röschinger, Olaf Sommerburg, 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

D-85764 Oberschleißheim

Germany

Email: 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 |
| CPT-I Deficiency | Carnitine Palmitoyl Transferase I Deficiency |
| CPT-II Deficiency | Carnitine Palmitoyl Transferase 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 | Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency |
| MCAD Deficiency | Medium-Chain Acyl-CoA Dehydrogenase Deficiency |
| MSUD | Maple Syrup Urine Disease |
| NBS | Newborn screening |
| PAP | Pancreatitis-associated Protein |
| PKU | Phenylketonuria |
| PPV | Positive Predictive Value |
| Second Tier Method | In case of abnormal finding, second examination of additional parameters or alternative method of analysis with the same test card |
| WoG | Week of Gestation |
| VLCAD Deficiency | Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency |

## Screening Laboratories und Screening Centers

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/

**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. Peter Mirtschink
swscreening@uniklinikum-dresden.de

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

**(5) Screening Center Hessen**
PD Dr. med. Martin Lindner
Theodor-Stern-Kai 7, 60596 **Frankfurt**
069/6301 4594
neugeborenenscreening@kgu.de
www.screening-hessen.de

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

**(7) Screening Lab, University Children's Hospital**
Prof. Dr. med. René Santer
Martinistr. 52, 20246 **Hamburg**
040/7410 57037
Contact: Dr. Simona Murko
r.santer@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: Prof. Dr.med. Gwendolyn Gramer
juergen.guenther.okun@med.uni-heidelberg.de
gwendolyn.gramer@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. rer. nat Sabine Rönicke
sabine.roenicke@med.ovgu.de
www.stwz.ovgu.de

**(12/13) Lab Becker & Colleagues**
Neonatal Screening
Prof. Dr.med. Dr. rer. nat. Jürgen Durner
Contact:
Priv.-Doz. Dr.med. Wulf Röschinger
Ottobrunner Str. 6, 81737 **München**
089/544 654 0
w.roeschinger@labor-becker.de
http://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: Sarah Breuer
wolfgang.schultis@synlab.com
sarah.breuer@synlab.com
https://www.synlab.de/lab/weiden

**Screening Center Bavaria (12/14)**
**Bavarian Health and Food Safety Authority**
Dr. med. Uta Nennstiel MPH
Veterinärstr.2
85764 **Oberschleißheim**
09131/6808-5-204
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 aim of early and complete detection coupled with quality assured therapy for all newborns with treatable endocrine and metabolic diseases and cystic fibrosis.

In the policies for early detection of diseases in children up to 6 years of age, known as the Children's Guideline ("Kinder-Richtlinie"), the regulations for implementing the newborn screening program (NBS) are defined in §13 - §28. The German Society for Neonatal Screening (DGNS e.V.) compiled the 2018 National Screening Report together with the German screening laboratories. The statistical analysis of the screening data was performed in accordance with the guideline and quality criteria of the NBS implementation. This report pertains only to the metabolic and endocrine diseases, as well as cystic fibrosis, which are defined in this guideline. With publication in the Federal Gazette on March 15, 2018, tyrosinemia type 1 was introduced as a new target disease of the NBS.

The report provides a comprehensive statistical summary of disease-related screening figures, recall rates (proportion of abnormal [positive] findings), and confirmed diagnoses for the year 2018. Additionally, the report provides process quality data for all of Germany.

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

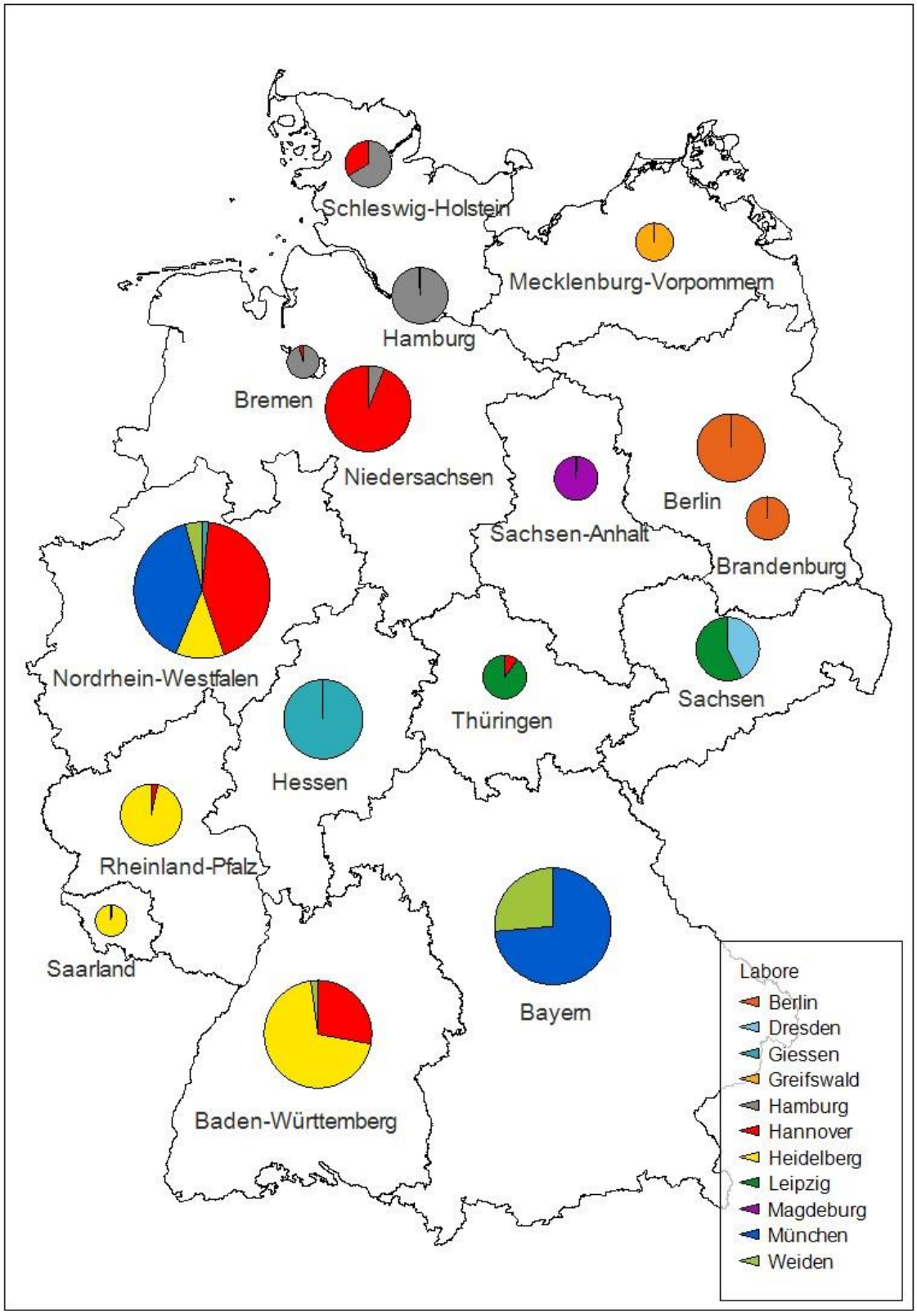
- Total survey of the targeted population
- Completeness of the control (recall) and follow-up examinations
- Recording test parameters and cut-offs
- Specificity and sensitivity of diagnostic tests
- Confirmation diagnostics
    - Type of diagnostics
    - Period of diagnostics
- Final diagnosis
- Start of therapy

The laboratories that conducted the screening in Germany in 2018 are listed on the previous page (12 and 13 refer to the same laboratory, once in cooperation with the screening facility and once without; the same is true of 14 and 15). Mentions of sections and subsections in the text refer to the "Children's Guideline" from November 16, 2019. [1] For convenience, the tables have not been numbered sequentially but rather in accordance with the related chapters.

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

The screening samples from the individual federal states are distributed among the laboratories ("Labore") as illustrated in Figure 1 and Table 2.2.

**Figure 1: Distribution of Screening Samples by State and Laboratory**



## 2 Results

In 2018 a total of 787,523 children were born in Germany according to official statistics. [2] Contrary to previous years, the number of recorded first screenings (784,421) is slightly lower than the number of births. Accordingly, 99.60% of all newborns were screened. A rejection of the examination was documented in only 718 newborns (0.1%).

| | |
|---|---|
| Births: | 787,523 |
| First screenings: | 784,421 |
| Confirmed diagnoses: | 755 |

A reliable statement about the rate of participation in NBS can only be made by reconciling individual data with overall population data. The diseases targeted for the nationwide screening are defined in the “Children’s Guideline”. Other diseases screened in individual laboratories as part of studies or state law requirements are not included in this report.

In one in 1,043 newborns, one of the target diseases defined in the guideline was detected during newborn screening. Table 2.1 shows the prevalence of the target diseases in 2018 in relation to births in Germany.

**Table 2.1: Prevalence of diseases detected in 2018 among 787,523 births**

| Disease | Confirmed cases | Prevalence | |
|---|---|---|---|
| Hypothyroidism | 246 | 1: | 3201 |
| Congenital Adrenal Hyperplasia (CAH) | 58 | 1: | 13578 |
| Biotinidase Deficiency | 23 | 1: | 34240 |
| Galactosemia (classic form) | 11 | 1: | 71593 |
| Phenylketonuria (n=73) / Hyperphenylalaninemia (n=84) | 157 | 1: | 5016 |
| Maple Syrup Urine Disease (MSUD) | 5 | 1: | 157505 |
| Medium-Chain Acyl-CoA Dehydrogenase (MCAD) deficiency | 68 | 1: | 11581 |
| Long-chain 3-Hydroxyacyl-CoA Dehydrogenase (LCHAD) deficiency | 2 | 1: | 393762 |
| Very Long-Chain Acyl-CoA-Dehydrogenase (VLCAD) deficiency | 16 | 1: | 49220 |
| Carnitine Palmitoyl Transferase I deficiency | 1 | 1: | 787523 |
| Carnitine Palmitoyl Transferase II deficiency | 1 | 1: | 787523 |
| Carnitine-Acylcarnitine Translocase deficiency | 0 | | |
| Glutaric Acidemia (GA) Type I | 5 | 1: | 157505 |
| Isovaleric Acidemia (IVA) | 12 | 1: | 65627 |
| Tyrosinemia (Target disease only since 3/2018) | 6 | | |
| Cystic Fibrosis (CF) | 144* | 1: | 5431 |
| **Total** | **755*** | **1:** | **1043** |

*additional CF diagnosis in one child only clinically without CF screening

## 2.1 Total Initial Screening Figures

The proportion of laboratories in the initial screening and the confirmed cases per lab are shown in Table 2.2.

**Table 2.2: Proportion by lab in initial screening and in confirmed cases**

| Lab | Initial Screening | Proportion of total population (%) | Number of confirmed cases | Proportion of confirmed cases (%) |
|---|---|---|---|---|
| **1** | 59316 | 7.66 | 59 | 7.81 |
| **3** | 15468 | 1.97 | 18 | 2.38 |
| **5** | 62011 | 7.91 | 53 | 7.02 |
| **6** | 13042 | 1.66 | 10 | 1.35 |
| **7** | 54436 | 6.94 | 55 | 7.28 |
| **8** | 179846 | 22.93 | 166 | 21.99 |
| **9** | 140444 | 17.90 | 134 | 17.75 |
| **10** | 36175 | 4.61 | 32 | 4.24 |
| **11** | 16987 | 2.17 | 18 | 2.38 |
| **12/13** | 163472 | 20.84 | 161 | 21.32 |
| **14/15** | 43224 | 5.51 | 49 | 6.49 |
| **Total** | **784421** | 100 | 755 | 100 |

According to the Children's Guideline, every newborn should be screened before discharge from the maternity facility. If the first screening is carried out before 36 hours of life or before 32 weeks of gestation (WoG), a second screening should be carried out.

The following table shows the number of first screening examinations stratified by age and gestational age, defined as follows:

- < 32 WoG: all samples from children born before 32 WoG, regardless of age at the time the sample was collected.
- <36h: all samples in children over 32 WoG taken before 36 hours of life.

**Table 2.3: Age at time of initial screening**

| | | ≥36h and ≥32WoG | | <36h and ≥32WoG | | <32WoG | |
|---|---|---|---|---|---|---|---|
| **Lab** | Total | n | % | n | % | n | % |
| **1** | 59316 | 58291 | 98.27 | 424 | 0.71 | 601 | 1.01 |
| **3** | 15468 | 15202 | 98.28 | 104 | 0.67 | 162 | 1.05 |
| **5** | 62011 | 60932 | 98.26 | 490 | 0.79 | 589 | 0.95 |
| **6** | 13042 | 12623 | 96.79 | 275 | 2.11 | 144 | 1.10 |
| **7** | 54436 | 53092 | 97.53 | 682 | 1.25 | 662 | 1.22 |
| **8** | 179846 | 176465 | 98.12 | 1417 | 0.79 | 1964 | 1.09 |
| **9** | 140444 | 137016 | 97.56 | 1129 | 0.80 | 2299 | 1.64 |
| **10** | 36175 | 35511 | 98.16 | 267 | 0.74 | 397 | 1.10 |
| **11** | 16987 | 16522 | 97.26 | 313 | 1.84 | 152 | 0.89 |
| **12** | 93424 | 91348 | 97.78 | 967 | 1.04 | 1109 | 1.19 |
| **13** | 70048 | 68569 | 97.89 | 863 | 1.23 | 616 | 0.88 |
| **14** | 33703 | 32953 | 97.77 | 449 | 1.33 | 301 | 0.89 |
| **15** | 9521 | 9288 | 97.55 | 48 | 0.50 | 185 | 1.94 |
| **Total** | **784421** | **767812** | **97.88** | **7428** | **0.95** | **9181** | **1.17** |

## 2.2 Ratio of requested and received second screening examinations and stratified recall rates by laboratory

Table 2.4 shows the total second screening examinations requested and carried out. The reason for the request was no longer inquired about in 2018.

Table 2.5 shows the necessary follow-up examinations due to an abnormal initial screening (recall) stratified by laboratory and by age or gestational age.

**Table 2.4: Received second screenings**

| Lab | Second screenings requested | Second screenings received | % |
|---|---|---|---|
| **1** | 2158 | 2008 | 93.05 |
| **3** | 257 | 257 | 100.00 |
| **5** | 1386 | 1179 | 85.06 |
| **6** | 419 | 410 | 97.85 |
| **7** | 1057 | n/a | n/a. |
| **8** | 5182 | 4663 | 89.98 |
| **9** | 4077 | 3068[b] | 75.25 |
| **10** | 954 | 902 | 94.55 |
| **11** | 465 | 428 | 92.04 |
| **12** | 2356 | 2332 | 98.98 |
| **13** | 1786 | 1554 | 87.01 |
| **14** | 865 | 856 | 98.96 |
| **15** | 233 | 207 | 88.84 |
| **Total** | **21195** | **17864** | **88.71[a]** |

[a] Calculation without laboratory 7, as no information was provided.
[b] External findings from other screening laboratories are not recorded

**Table 2.5: Requested repeat examinations due to abnormal findings (recall)[a]**

| | | Recall total | | Recall >=36h[b] | | Recall <36h | | Recall <32 WoG | |
|---|---|---|---|---|---|---|---|---|---|
| **Lab** | Initial Screening | n | % | n | % | n | % | n | % |
| **1** | 59316 | 308 | 0.52 | 253 | 0.43 | 22 | 5.19 | 33 | 5.49 |
| **3** | 15468 | 43 | 0.28 | 40 | 0.26 | 0 | | 3 | 1.85 |
| **5** | 62011 | 309 | 0.50 | 292 | 0.48 | 9 | 1.84 | 8 | 1.36 |
| **6** | 13042 | 113 | 0.87 | 107 | 0.85 | 1 | 0.36 | 5 | 3.47 |
| **7** | 54436 | 805 | 1.48 | 536 | 1.01 | 81 | 11.88 | 188 | 28.40 |
| **8** | 179846 | 1102 | 0.61 | 710 | 0.40 | 273 | 19.27 | 119 | 6.06 |
| **9** | 140444 | 761 | 0.54 | 743 | 0.54 | 3 | 0.27 | 15 | 0.65 |
| **10** | 36175 | 380 | 1.05 | 254 | 0.72 | 88 | 32.96 | 38 | 9.57 |
| **11** | 16987 | 131 | 0.77 | 69 | 0.42 | 46 | 14.70 | 16 | 10.53 |
| **12** | 93424 | 575 | 0.62 | 338 | 0.37 | 179 | 18.51 | 58 | 5.23 |
| **13** | 70048 | 257 | 0.37 | 226 | 0.33 | 5 | 0.58 | 26 | 4.22 |
| **14** | 33703 | 213 | 0.63 | 124 | 0.38 | 58 | 12.92 | 31 | 10.30 |
| **15** | 9521 | 45 | 0.47 | 34 | 0.37 | 5 | 10.42 | 6 | 3.24 |
| **Total** | **784421** | **5042** | **0.64** | **3726** | **0.48** | **770** | **10.37** | **546** | **5.95** |

[a] Excluding recall „MS/ MS abnormal finding for uncertain target disease", as some labs report recalls for projects and the data are not comparable. [b] incl. recall without classification

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

At present, neither of these options is being implemented nationwide in Germany. With the aim of nevertheless monitoring the integrity of the screening, the following regulation was included in the "Children's Guideline":

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

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

**Table 2.6: Blank cards received by the laboratory**

| | | Reason for blank card | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Initial Screening Total | Deceased | Screening refused | Transferred | Early screening rejected | Not differentiable | Total | |
| **Lab** | n | n | n | n | n | n | n | % |
| **1** | 59316 | 347 | 154 | 364 | 2901 | 289 | 4055 | 6.84 |
| **3** | 15468 | 40 | 23 | | | 771 | 834 | 5.39 |
| **5** | 62011 | 38 | 130 | 1345 | 1038 | 440 | 2991 | 4.82 |
| **6** | 13042 | 49 | 26 | 41 | 297 | | 413 | 3.17 |
| **7**[b] | 54436 | | | | | | | |
| **8** | 179846 | | | | | 2979 [a] | 2979 | 1.66 |
| **9** | 140444 | 6 | 311 | 172 | | 677 | 1166 | 0.83 |
| **10** | 36175 | 175 | 60 | | | 1764 | 1999 | 5.53 |
| **11** | 16987 | 59 | 14 | 27 | 194 | 7 | 301 | 1.77 |
| **12** | 93424 | | | 231 | 1002 | 309 | 1542 | 1.65 |
| **13**[b] | 70048 | | | | | | | |
| **14** | 33703 | | | 18 | 85 | 35 | 138 | 0.41 |
| **15**[b] | 9521 | | | | | | | |
| **Total** | **784421** | **714** | **718** | **2198** | **5517** | **7271** | **16418** | **2.09** |

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

**Table 2.7: Secondary screening card due to inferior sample quality**

| Lab | Initial screening | Control requested | Control received | received/ requested (%) | Proportion of samples / Initial screening (%) | IM[b] |
|---|---|---|---|---|---|---|
| **1** | 59316 | 1017 | 949 | 93.31 | 1.71 | 610 |
| **3** | 15468 | 9 | 9 | 100.00 | 0.06 | 23 |
| **5** | 62011 | 326 | 302 | 92.64 | 0.53 | n/a |
| **6** | 13042 | 2 | 2 | 100.00 | 0.02 | 17 |
| **7** | 54436 | 116 | n/a | n/a | 0.21 | n/a |
| **8** | 179846 | 872 | 854 | 97.94 | 0.48 | 72 |
| **9** | 140444 | 117 | 108 | 92.31 | 0.08 | 602 |
| **10** | 36175 | 8 | 8 | 100.00 | 0.02 | 170 |
| **11** | 16987 | 16 | 16 | 100.00 | 0.09 | 5 |
| **12** | 93424 | 562 | 551 | 98.04 | 0.60 | 6 |
| **13** | 70048 | 428 | 408 | 95.33 | 0.61 | n/a |
| **14** | 33703 | 50 | 48 | 96.00 | 0.15 | 1 |
| **15** | 9521 | 21 | 21 | 100.00 | 0.22 | n/a |
| **Total** | **784421** | **3544** | **3276** | **95.57[a]** | **0.45** | **1506** |

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

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

# 3 Process Time

## 3.1 Age at the time of blood sample collection

According to the “Children’s Guideline” (§ 20 paragraph 1) blood samples should be collected between 36 and 72 hours after birth. In 95.2% of cases in which the time of blood sampling was provided, collection took place in the designated time frame, in 3.8% not until after 72 hours and in 1.1% before 36 hours (Table 3.1). The proportion of samples which were collected after 72 hours - i.e. outside the designated time frame - was reduced from 22.3% in 2005 to 3.8% in 2018 (Figure 2).

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

**Table 3.1: Age at blood sample collection - Initial screening**

| | Total | <36h | | 36h-<48h | | 48h-<72h | | ≥72h | |
|---|---|---|---|---|---|---|---|---|---|
| **Lab** | n | n | % | n | % | n | % | n | % |
| **1**[a] | 59299 | 511 | 0.86 | 21359 | 36.02 | 34776 | 58.65 | 2653 | 4.47 |
| **3** | 15468 | 119 | 0.77 | 4305 | 27.83 | 10598 | 68.52 | 446 | 2.88 |
| **5**[a] | 60668 | 490 | 0.81 | 46432 | 76.53 | 12323 | 20.31 | 1423 | 2.35 |
| **6** | 13042 | 294 | 2.25 | 5982 | 45.87 | 6435 | 49.34 | 331 | 2.54 |
| **7** | 54436 | 816 | 1.50 | 25511 | 46.86 | 24772 | 45.51 | 3337 | 6.13 |
| **8**[a] | 179330 | 1622 | 0.90 | 84411 | 47.07 | 85583 | 47.72 | 7714 | 4.30 |
| **9**[a] | 140022 | 1250 | 0.89 | 71540 | 51.09 | 61831 | 44.16 | 5401 | 3.86 |
| **10** | 36175 | 322 | 0.89 | 12563 | 34.73 | 21677 | 59.92 | 1613 | 4.46 |
| **11** | 16987 | 312 | 1.84 | 6200 | 36.50 | 9678 | 56.97 | 797 | 4.69 |
| **12**[a] | 92177 | 1098 | 1.19 | 51632 | 56.01 | 36452 | 39.55 | 2995 | 3.25 |
| **13**[a] | 69489 | 926 | 1.33 | 52929 | 76.17 | 14050 | 20.22 | 1584 | 2.28 |
| **14**[a] | 32875 | 469 | 1.43 | 16858 | 51.28 | 14557 | 44.28 | 991 | 3.01 |
| **15** | 9521 | 56 | 0.59 | 5117 | 53.74 | 4196 | 44.07 | 152 | 1.60 |
| **Total** | **779489** | **8285** | **1.06** | **404839** | **51.94** | **336928** | **43.22** | **29437** | **3.78** |

[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 interval between taking blood samples and reporting abnormal results should not exceed 72 hours (§ 18 paragraph 3). However, in 28.47% of cases in which the shipping times were provided, the sample did not reach the lab until more than 72 hours after the blood sample was taken. In another 22.9% of cases, the time period ranged from 48 to 72 hours.

Compared to prior years, there was a significant delay in dispatch times in 2017, while in 2018 the dispatch times returned those of previous years Overall, together with the senders, efforts must be made to shorten the time span for sending samples, particularly on weekends (Table 3.2. Figure 3).

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

| | Total | ≤24h | | >24h-48h | | >48h-72h | | >72h | |
|---|---|---|---|---|---|---|---|---|---|
| **Lab** | n | n | % | n | % | n | % | n | % |
| **1**[a] | 59248 | 14101 | 23.80 | 21620 | 36.49 | 12093 | 20.41 | 11434 | 19.30 |
| **3**[a] | 15244 | 5069 | 33.25 | 6903 | 45.28 | 2478 | 16.26 | 794 | 5.21 |
| **5**[a] | 60721 | 4308 | 7.09 | 21606 | 35.58 | 16434 | 27.06 | 18373 | 30.26 |
| **6**[a] | 12540 | 2056 | 16.40 | 5286 | 42.15 | 3152 | 25.14 | 2046 | 16.32 |
| **7** | 54436 | 9051 | 16.63 | 15522 | 28.51 | 10903 | 20.03 | 18960 | 34.83 |
| **8**[a] | 179332 | 14734 | 8.22 | 50576 | 28.20 | 48186 | 26.87 | 65836 | 36.71 |
| **9**[a] | 140022 | 9880 | 7.06 | 30348 | 21.67 | 32166 | 22.97 | 67628 | 48.30 |
| **10** | 36175 | 4310 | 11.91 | 14189 | 39.22 | 10230 | 28.28 | 7446 | 20.58 |
| **11** | 16987 | 2052 | 12.08 | 7263 | 42.76 | 4610 | 27.14 | 3062 | 18.03 |
| **12**[a] | 92271 | 30418 | 32.97 | 32903 | 35.66 | 17765 | 19.25 | 11185 | 12.12 |
| **13**[a] | 69489 | 17903 | 25.76 | 23404 | 33.68 | 14840 | 21.36 | 13342 | 19.20 |
| **14**[a] | 33587 | 19981 | 59.49 | 8246 | 24.55 | 3668 | 10.92 | 1692 | 5.04 |
| **15** | 9521 | 1403 | 14.74 | 3922 | 41.19 | 2120 | 22.27 | 2076 | 21.80 |
| **Total** | **779573** | **135266** | **17.35** | **241788** | **31.02** | **178645** | **22.92** | **223874** | **28.72** |

[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

## 3.3 Period between receipt by the lab and reporting the results

75.1% of the results are reported within 24 hours. In the case of marginally elevated findings, the time in the laboratory can be extended due to internal repeat examinations for quality assurance purposes.

From 2016 to 2017 the proportion of findings that were not reported until two to three days after receipt by the laboratory rose and has remained close to that level. This may be related to the new CF screening introduced at the end of 2016. Delays in notification apply primarily to unremarkable findings, as abnormal findings are reported immediately. (Table 3.3, Figure 4).

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

| | Total | ≤24h | | >24h-48h | | >48h-72h | | >72h | |
|---|---|---|---|---|---|---|---|---|---|
| **Lab** | n | n | % | n | % | n | % | n | % |
| **1[a]** | 59309 | 31316 | 52.80 | 22381 | 37.74 | 3321 | 5.60 | 2291 | 3.86 |
| **3** | 15468 | 14211 | 91.87 | 753 | 4.87 | 222 | 1.44 | 282 | 1.82 |
| **5[a]** | 60884 | 43572 | 71.57 | 15387 | 25.27 | 1908 | 3.13 | 17 | 0.03 |
| **6** | 13042 | 8611 | 66.03 | 249 | 1.91 | 1884 | 14.45 | 2298 | 17.62 |
| **7** | 54436 | 19815 | 36.40 | 28742 | 52.80 | 3157 | 5.80 | 2722 | 5.00 |
| **8** | 179846 | 167201 | 92.97 | 10448 | 5.81 | 652 | 0.36 | 1545 | 0.86 |
| **9** | 139870 | 114529 | 81.88 | 21624 | 15.46 | 3189 | 2.28 | 528 | 0.38 |
| **10** | 36175 | 32344 | 89.39 | 3688 | 10.19 | 119 | 0.33 | 24 | .07 |
| **11** | 16987 | 11720 | 68.99 | 4581 | 26.97 | 428 | 2.52 | 258 | 1.52 |
| **12[a]** | 93095 | 66145 | 71.05 | 15860 | 17.04 | 9916 | 10.65 | 1174 | 1.26 |
| **13** | 69489 | 47809 | 68.80 | 14350 | 20.65 | 6842 | 9.85 | 488 | 0.70 |
| **14[a]** | 33588 | 27842 | 82.89 | 3995 | 11.89 | 887 | 2.64 | 864 | 2.57 |
| **15** | 9521 | 2264 | 23.78 | 7149 | 75.09 | 106 | 1.11 | 2 | 0.02 |
| **Total** | **781720** | **587379** | **75.14** | **149207** | **19.09** | **32631** | **4.17** | **12493** | **1.60** |

[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 2005 to 2018**

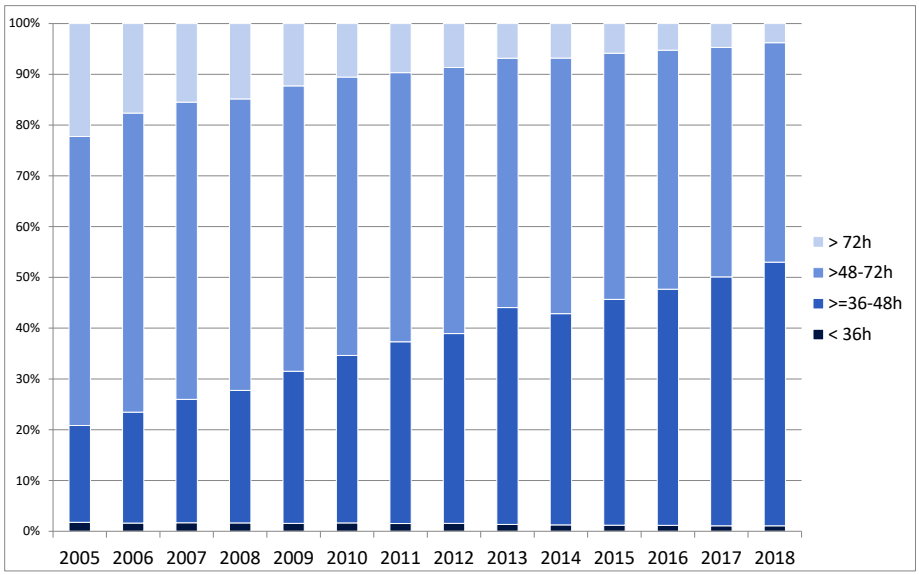



**Figure 3: Time between blood sample collection and receipt by the lab 2005 to 2018**

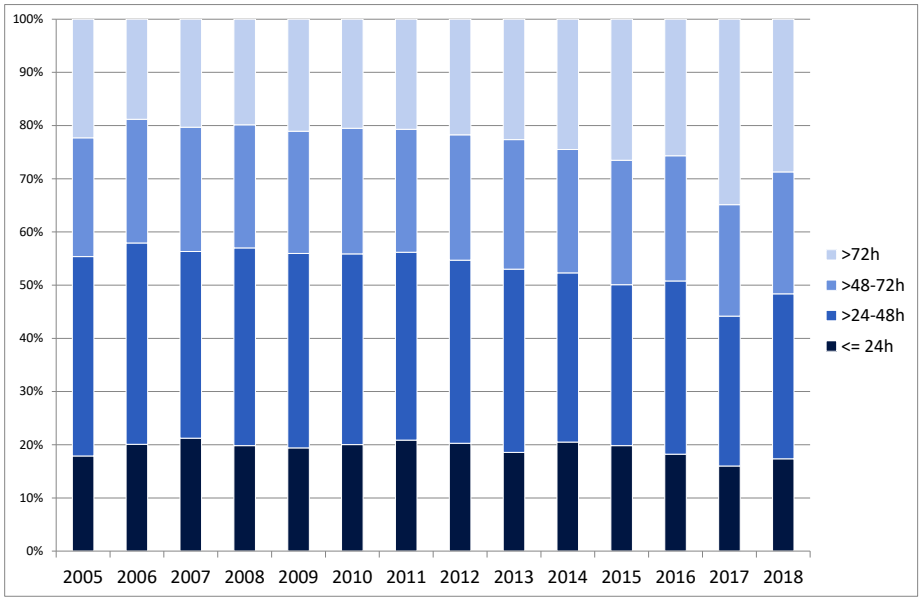
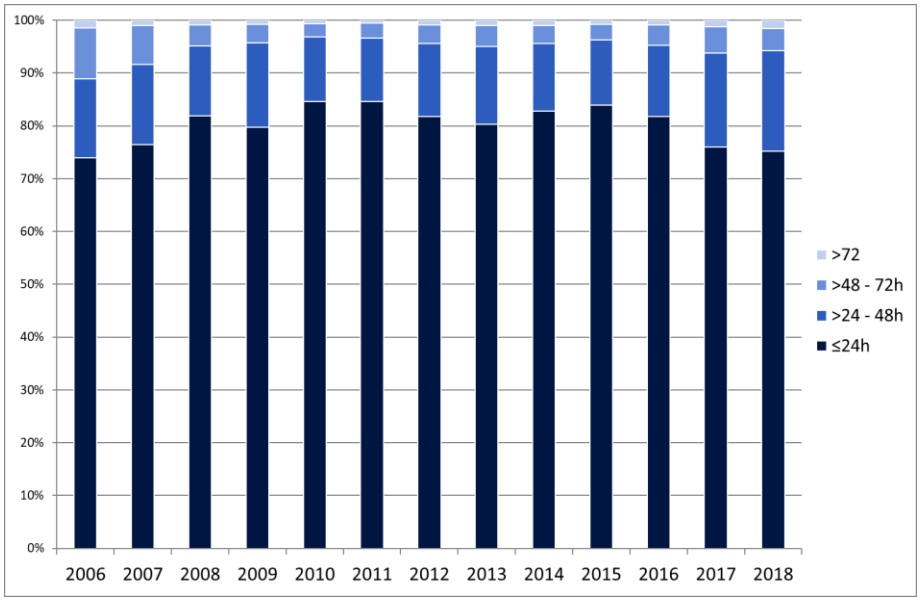



**Figure 4: Time between receipt by the lab and reporting the results 2005 to 2018**



## 4 Quality parameters of screening analysis

The quality of a test procedure is determined by sensitivity, specificity and positive predictive value (PPV). In a screening procedure, the sensitivity (true positive rate, i.e. the percentage of sick people correctly identified as having the condition), but especially the specificity (true negative rate, i.e. the percentage of healthy people correctly identified as not having the condition), should be high in order to identify all those affected on the one hand and to cause as little unnecessary worry and subsequent expense as possible on the other. The lower the rate of control screening (recall rate) necessitated by positive first screening results, the higher the specificity. The recall rate for the extended newborn screening (ENS) was 0.52% in 2018, In the CF screening, the positivity rate was 0.12%. This means that out of 1.000 screening examinations, approximately 6 results requiring a control examination can be expected. If the blood sample is taken before 36 hours of life or 32 weeks of pregnancy, a second screening must be carried out, irrespective of the result of the analysis. When taking only screening samples into account that were collected after 36 hours of life from babies born at term, the recall rate is 0.48%. The increased recall rate for blood collection <36h or before 32 WoG also has a negative impact on the PPV in CAH and hypothyroidism.

The overall specificity for newborn screening was 99.45%. The sensitivity cannot be determined, as the number of children missed in the screening has not yet been systematically recorded. Nationwide registers of the diseases included in the screening would be very helpful.

**Table 4: Recall rates and cases found through screening for Germany 2018**

| Disease | Initial screening | Recall | Recall rate (%) | Confirmed Cases | PPV | Specificity |
|---|---|---|---|---|---|---|
| **Hypothyroidism** | 784421 | 922 | 0.12 | 245[b] | 26.57 | 99.91 |
| **CAH** | 784421 | 1638 | 0.21 | 57 [b] | 3.47 | 99.80 |
| **Biotinidase Deficiency** | 784421 | 307 | 0.04 | 23 | 7.49 | 99.96 |
| **Galactosemia** [a] | 784421 | 255 | 0.03 | 11 | 4.31 | 99.97 |
| **PKU/HPA** | 784421 | 302 | 0.04 | 157 | 51.99 | 99.98 |
| **MSUD** | 784421 | 50 | 0.01 | 5 | 10.00 | 99.99 |
| **MCAD** | 784421 | 146 | 0.02 | 68 | 46.58 | 99.99 |
| **LCHAD** | 784421 | 13 | 0.002 | 2 | 15.38 | 99.99 |
| **VLCAD** | 784421 | 111 | 0.01 | 16 | 14.41 | 99.99 |
| **CPT-I Deficiency** | 784421 | 8 | 0.001 | 1 | 12.50 | 99.99 |
| **CPT-II Deficiency** | 784421 | 9 | 0.001 | 1 | 50.00 | 99.99 |
| **CACT Deficiency** [d] | 784421 | | | 0 | | |
| **GA I** | 784421 | 73 | 0.01 | 5 | 6.85 | 99.99 |
| **IVA** | 784421 | 109 | 0.01 | 12 | 11.01 | 99.99 |
| **Tyrosinemia** [c] | | 156 | | 6 | 3.21 | |
| **CF** | 777938 | 943 | 0.12 | 133[b] | 14.10 | 99.90 |
| **Total ENS** | **784421** | **5035** | **0.64** | **742** [b] | **14.74** | **99.45** |

[a] Only classic galactosemia [b] Not considered 1 CAH, 1 hypothyroidism and 11 CF cases with unremarkable screening [C] First screening from 3/2018; the PPV was calculated with 5 cases, as the recall for one lab is not known [d] Recalls for CACT deficiency are included under CPT II

## 4.1 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 4.1 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 4.1: Time of Initial screening in confirmed cases**

| Disease | 36-72h | 4-7d | >7d | <36h | <32WoG[a] | ≥36h, time not specified [b] | No information [c] | Total |
|---|---|---|---|---|---|---|---|---|
| **Hypothyroidism** | 197 | 4 | 2 | 9 | 30 | 3 | 1 | 246 |
| **CAH** | 45 | 1 | 0 | 7 | 2 | 2 | 1 | 58 |
| **Biotinidase Deficiency** | 21 | 0 | 0 | 0 | 0 | 0 | 2 | 23 |
| **Galactosemia** | 10 | 1 | 0 | 0 | 0 | 0 | 0 | 11 |
| **PKU/HPA** | 147 | 4 | 0 | 4 | 1 | 0 | 1 | 157 |
| **MSUD** | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 5 |
| **MCAD** | 62 | 1 | 2 | 3 | 0 | 0 | 0 | 68 |
| **LCHAD** | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| **VLCAD** | 13 | 1 | 0 | 2 | 0 | 0 | 0 | 16 |
| **CPT I** | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **CPT II** | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **GA I** | 4 | 1 | 0 | 0 | 0 | 0 | 0 | 5 |
| **IVA** | 9 | 1 | 0 | 1 | 0 | 1 | 0 | 12 |
| **Tyrosinemia** | 2 | 1 | 0 | 2 | 1 | 0 | 0 | 6 |
| **CF** | 130 | 4 | 2 | 3 | 3 | 0 | 2 | 144 |
| **Total** | **656** | **19** | **7** | **31** | **37** | **6** | **8** | **755[d]** |

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

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

[c] Neither gestational age nor age at the time of blood collection is known

[d] Including data on 13 cases with unremarkable screening

# 5 Recall rate, confirmed cases and confirmation stratified by disease

The following chapter presents recall rates and confirmed cases for the target diseases as well as the diagnostic measures taken to confirm the diagnosis, stratified by laboratory. For hypothyroidism and CAH, the recall is also reported separately for recall ≥ 36h, recall <36h and recall <32 WoG. For the other diseases, this stratified presentation was omitted due to the low number of cases <36h and <32 WoG.

Diagnostic measures can only be reported if the laboratories are informed of them. Knowledge of the individual results of confirmation diagnostics is important for quality assurance in the laboratory but they are not always communicated to the laboratories by the attending physicians. In particular, molecular genetic examinations are often only initiated during the course of the disease and are therefore often not included in the findings of the confirmation diagnostics sent to the laboratory. In 2017, for instance, in 180 (24.42%) cases of cystic fibrosis, so little information was available that the diagnosis of "cystic fibrosis" could neither be confirmed nor dismissed. In 2018, all positive CF screening results were no longer requested, but only the confirmed CF cases. The number of non-confirmed abnormal CF screening results is therefore not known from all laboratories. As a rule, it is not possible to draw conclusions from CF screening figures about the probability of a CF diagnosis, unless 2 mutations in the CFTR gene were found in the last step of the screening algorithm (see Fig. 5).

The figures were reported as of March 15, 2020. Cases from birth year 2018 which were found at a later date are not included in this report. Cases reported twice (e.g. from different laboratories) were only considered once. The plausibility check of the cases reported as confirmed was carried out by Prof. Dr. Regina Ensenauer. Prof. Dr. Martin Lindner and Prof. Dr. Esther Maier for metabolic diseases. by Dr. Oliver Blankenstein and Dr. Erwin Lankes for endocrinological diseases, and by PD Dr. Olaf Sommerburg for cystic fibrosis.

Cases with missing information on confirmation diagnostics were only taken into account if the validators judged a diagnosis to be probable based on the screening results. This occurred in a total of 49 cases in 2018 (28 metabolic screening, 16 hypothyroid and 5 CAH). For 36 cases with abnormal ENS, the information on the confirmation diagnostics was not sufficient to confirm the diagnosis (see section 6).

As a result, the true prevalence of some diseases may be higher than reported here. Also, diagnosed cases with unremarkable screening results are not systematically recorded. In 2018, 1 CAH, 1 case of hypothyroidism and 11 CF cases were clinically diagnosed following unremarkable screening and 1 CF case without screening was reported to the laboratories. In the interest of quality assurance of the laboratory analysis and evaluation of the quality of the results, the most comprehensive feedback possible must be sought from the attending physicians. The DGNS provides the appropriate paperwork and parental consent forms.

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

## 5.1 Congenital Hypothyroidism

**Table 5.1.1: Hypothyroidism confirmed cases / recall rate**

| Lab | Initial screening | Total | | | ≥ 36h | | |
|---|---|---|---|---|---|---|---|
| | | Recall (n) | Recall rate (%) | Confirmed cases (n) | Recall (n) | Recall rate (%) | Confirmed cases (n) |
| **1** | 59316 | 65 | 0.11 | 22 | 57 | 0.10 | 21 |
| **3** | 15468 | 14 | 0.09 | 5 | 14 | 0.09 | 5 |
| **5** | 62011 | 55 | 0.09 | 18 | 53 | 0.09 | 16 |
| **6** | 13042 | 10 | 0.08 | 3 | 10 | 0.08 | 3 |
| **7** | 54436 | 55 | 0.10 | 13 | 32 | 0.06 | 10 |
| **8** | 179846 | 241 | 0.13 | 50 | 140 | 0.08 | 42 |
| **9** | 140444 | 78 | 0.06 | 49 | 76 | 0.06 | 40 |
| **10** | 36175 | 76 | 0.21 | 8 | 26 | 0.07 | 8 |
| **11** | 16987 | 47 | 0.28 | 5 | 9 | 0.05 | 4 |
| **12** | 93424 | 151 | 0.16 | 41 | 66 | 0.07 | 32 |
| **13** | 70048 | 42 | 0.06 | 21 | 35 | 0.05 | 18 |
| **14** | 33703 | 73 | 0.22 | 9 | 34 | 0.10 | 5 |
| **15** | 9521 | 15 | 0.16 | 2 | 10 | 0.11 | 2 |
| **Total** | **784421** | **922** | **0.12** | **246** [a] | **562** | **0.07** | **206** |

| Lab | Initial screening | <36h | | | <32 WoG | | |
|---|---|---|---|---|---|---|---|
| | | Recall (n) | Recall rate (%)[b] | Confirmed cases (n) | Recall (n) | Recall rate (%)[b] | Confirmed cases (n) |
| **1** | 59316 | 5 | | 0 | 3 | | 1 |
| **3** | 15468 | 0 | | 0 | 0 | | 0 |
| **5** | 62011 | 1 | | 1 | 1 | | 1 |
| **6** | 13042 | 0 | | 0 | 0 | | 0 |
| **7** | 54436 | 23 | 3.37 | 3 | 0 | | 0 |
| **8** | 179846 | 99 | 6.99 | 2 | 2 | | 6 |
| **9** | 140444 | 0 | | 0 | 2 | | 9 |
| **10** | 36175 | 49 | 18.35 | 0 | 1 | | 0 |
| **11** | 16987 | 36 | 11.50 | 1 | 2 | | 0 |
| **12** | 93424 | 68 | 7.03 | 1 | 17 | 1.53 | 8 |
| **13** | 70048 | 3 | | 0 | 4 | | 2 |
| **14** | 33703 | 30 | 6.68 | 1 | 9 | | 3 |
| **15** | 9521 | 4 | | 0 | 1 | | 0 |
| **Total** | **784421** | **318** | **4.28** | **9** | **42** | **0.46** | **30** |

[a] including 1 case with an unremarkable initial screening and 1 case without indication of the time of the initial screening.

[b] recall rates only provided if recall rate ≥ 0.01% and n ≥ 5

Of the 246 validated congenital hypothyroidism cases, one was unremarkable in the initial screening (TSH 11 mU/l, normal level <20mU/l, blood collection after 46 hours of life, 41st WoG). Confirmation diagnostics at 31 days of age with clinical abnormalities: TSH 502 mU/l, fT4 <3.9pmol/l.

In addition, n= 28 hyperthyrotropinemia were reported and validated as confirmed. These were not included in the calculation of prevalence.

**Table 5.1.2: Hypothyroidism Confirmation**

| Lab | Confirmed cases | TSH (Serum) | fT3 | fT4 | Sonography | SD Antibodies | Confirmed cases without verification details |
|---|---|---|---|---|---|---|---|
| **1** | 22 | 22 | 3 | 21 | 22 | 6 | |
| **3** | 5 | 5 | 4 | 5 | 4 | 5 | |
| **5** | 18 | 14 | 6 | 13 | 11 | 8 | 3 |
| **6** | 3 | 3 | 3 | 3 | 2 | 2 | |
| **7** | 13 | | | | | | 13 |
| **8** | 50 | 48 | 37 | 48 | 44 | 38 | |
| **9** | 49 | 49 | 32 | 48 | 14 | 1 | |
| **10** | 8 | 8 | 4 | 8 | 7 | 4 | |
| **11** | 5 | 4 | 5 | 5 | 5 | | |
| **12** | 41 | 41 | 34 | 40 | 23 | 23 | |
| **13** | 21 | 21 | 17 | 21 | | | |
| **14** | 9 | 9 | 7 | 9 | 5 | 4 | |
| **15** | 2 | 2 | 2 | 2 | 1 | 1 | |
| **Total** | **246** | **226** | **154** | **223** | **138** | **92** | **16** |

## 5.2 Congenital Adrenal Hyperplasia (CAH)

**Table 5.2.1: CAH Confirmed cases / Recall rate**

| | | Total | | | ≥ 36h | | |
|---|---|---|---|---|---|---|---|
| **Lab** | **Initial screening** | Recall (n) | Recall rate (%)[d] | Confirmed cases (n) | Recall (n) | Recall rate (%)[d] | Confirmed cases (n) |
| **1**[b] | 59316 | 33 | 0.06 | 6 | 12 | 0.02 | 4 |
| **3** | 15468 | 1 | | 1 | 1 | | 1 |
| **5** | 62011 | 150 | 0.24 | 4 | 142 | 0.23 | 4 |
| **6** | 13042 | 34 | 0.26 | 2 | 31 | 0.25 | 2 |
| **7** | 54436 | 449 | 0.82 | 3 | 241 | 0.45 | 2 |
| **8**[c] | 179846 | 193 | 0.11 | 12 | 47 | 0.03 | 11 |
| **9** | 140444 | 307 | 0.22 | 11 | 304 | 0.22 | 10 |
| **10** | 36175 | 192 | 0.53 | 1 | 122 | 0.34 | 1 |
| **11** | 16987 | 46 | 0.27 | 0 | 26 | 0.16 | 0 |
| **12**[b] | 93424 | 174 | 0.19 | 12 | 44 | 0.05 | 9 |
| **13**[b] | 70048 | 36 | 0.05 | 3 | 21 | 0.03 | 2 |
| **14**[b] | 33703 | 20 | 0.06 | 3 | 3 | | 2 |
| **15**[b] | 9521 | 3 | | 0 | 2 | | 0 |
| **Total** | **784421** | **1638** | **0.21** | **58**[a] | **996** | **0.13** | **48** |

| | | <36h | | | <32 WoG | | |
|---|---|---|---|---|---|---|---|
| **Lab** | **Initial screening** | Recall (n) | Recall rate (%)[d] | Confirmed cases (n) | Recall (n) | Recall rate (%)[d] | Confirmed cases (n) |
| **1**[b] | 59316 | 4 | | 2 | 17 | 2.83 | 0 |
| **3** | 15468 | 0 | | 0 | 0 | | 0 |
| **5** | 62011 | 4 | | 0 | 4 | | 0 |
| **6** | 13042 | 0 | | 0 | 3 | | 0 |
| **7** | 54436 | 41 | 6.01 | 1 | 167 | 25.23 | 0 |
| **8**[c] | 179846 | 114 | 8.05 | 0 | 32 | 1.63 | 0 |
| **9** | 140444 | 0 | | 1 | 3 | | 0 |
| **10** | 36175 | 35 | 13.11 | 0 | 35 | 8.82 | 0 |
| **11** | 16987 | 10 | 3.19 | 0 | 10 | 6.58 | 0 |
| **12**[b] | 93424 | 103 | 10.65 | 3 | 27 | 2.43 | 0 |
| **13**[b] | 70048 | 0 | | 0 | 15 | 2.44 | 1 |
| **14**[b] | 33703 | 12 | 2.67 | 0 | 5 | 1.66 | 1 |
| **15**[b] | 9521 | 1 | | 0 | 0 | | 0 |
| **Total** | 784421 | 324 | 4.36 | **7** | 318 | 3.46 | **2** |

[a] including 1 case with an normal initial screening and 1 case without information on the time of the initial screening

[b] Lab uses 2nd tier method

[c] Lab uses 2nd tier method for screening >36h

[d] Recall rates only provided if recall rate ≥ 0.01% and n ≥ 5

**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** | 6 | 5 | 5 | | 4 | 1 |
| **3** | 1 | 1 | 1 | | | |
| **5** | 4 | 3 | 1 | 1 | 2 | 1 |
| **6** | 2 | 2 | 2 | 2 | 2 | |
| **7** | 3 | | | | | 3 |
| **8** | 12 | 5 | 12 | 3 | 12 | |
| **9** | 11 | 9 | 8 | 1 | 5 | |
| **10** | 1 | 1 | 1 | 1 | | |
| **11** | | | | | | |
| **12** | 12 | 12 | 9 | | 11 | |
| **13** | 3 | 2 | | | 1 | |
| **14** | 3 | 2 | 2 | | 3 | |
| **15** | | | | | | |
| **Total** | 58 | 42 | 41 | 8 | 40 | 5 |

Of the 58 confirmed CAH cases, one case was unremarkable in the initial screening with a 17-OHP of 34 nmol/l (normal value<40 nmol/l, recorded at 37h, 37 WoG). Confirmation at the behest of the pediatrician on the 22nd day of life with clitoral hypertrophy and failure to thrive: 17-OHP 322 nmol/l from 2nd test card, 10600 ng/dl in serum, Genetics I172N (c.515T>A) homozygous.

## 5.3 Biotinidase Deficiency

**Table 5.3.1: Biotinidase Deficiency - Confirmed cases / Recall rate**

| Lab | Initial screening | Recall | Recall rate (%)[a] | Confirmed cases |
|---|---|---|---|---|
| **1** | 59316 | 33 | 0.06 | 3 |
| **3** | 15468 | 0 | | 0 |
| **5** | 62011 | 3 | | 1 |
| **6** | 13042 | 16 | 0.12 | 1 |
| **7** | 54436 | 110 | 0.20 | 7 |
| **8** | 179846 | 71 | 0.04 | 5 |
| **9** | 140444 | 15 | 0.01 | 1 |
| **10** | 36175 | 4 | | 1 |
| **11** | 16987 | 6 | 0.04 | 1 |
| **12** | 93424 | 18 | 0.02 | 1 |
| **13** | 70048 | 17 | 0.02 | 1 |
| **14** | 33703 | 9 | 0.03 | 1 |
| **15** | 9521 | 5 | 0.05 | 0 |
| **Total** | **784421** | **307** | **0.04** | **23** |

[a] Recall rates only provided if recall rate ≥ 0.01% and n ≥ 5

Of n= 23 confirmed cases with biotinidase deficiency, 12 showed a complete or undifferentiated defect. In n=11 cases a partial biotinidase deficiency was diagnosed.

**Table 5.3.2: Biotinidase Deficiency Confirmation**

| Lab | Confirmed cases | Biotinidase (Serum/DB) | Molecular genetics | Confirmed cases without confirmation details |
|---|---|---|---|---|
| **1** | 3 | 3 | 2 | |
| **3** | 1 | | | 1 |
| **7** | 1 | 1 | | |
| **8** | 7 | 4 | 4 | 1 |
| **9** | 5 | 4 | | 1 |
| **13** | 1 | 1 | | |
| **14** | 1 | 1 | 1 | |
| **15** | 1 | | | 1 |
| **Total** | 23 | 16 | 7 | 4 |

## 5.4 Classic Galactosemia

**Table 5.4.1: Classic Galactosemia Confirmed cases / Recall rate**

| Lab | Initial screening | Recall | Recall rate (%)[a] | Confirmed cases |
|---|---|---|---|---|
| **1** | 59316 | 33 | 0.06 | 2 |
| **3** | 15468 | 3 | | 0 |
| **5** | 62011 | 1 | | 0 |
| **6** | 13042 | 9 | 0.07 | 0 |
| **7** | 54436 | 25 | 0.05 | 0 |
| **8** | 179846 | 78 | 0.04 | 1 |
| **9** | 140444 | 33 | 0.02 | 3 |
| **10** | 36175 | 5 | 0.01 | 1 |
| **11** | 16987 | 4 | | 1 |
| **12** | 93424 | 57 | 0.06 | 1 |
| **13** | 70048 | 2 | | 0 |
| **14** | 33703 | 5 | 0.01 | 2 |
| **15** | 9521 | 0 | | 0 |
| **Total** | **784421** | **255** | **0.03** | **11** |

[a] Recall rates only provided if recall rate ≥ 0.01% and n ≥ 5

**Table 5.4.2: Classic Galactosemia Confirmation**

| Lab | Confirmed cases | Enzymatics | Galactose. Gal1P | Molecular genetics | Confirmed cases without confirmation details |
|---|---|---|---|---|---|
| **1** | 2 | 2 | 2 | 1 | |
| **8** | 1 | | | 1 | |
| **9** | 3 | | | | 3 |
| **10** | 1 | 1 | 1 | 1 | |
| **11** | 1 | 1 | 1 | 1 | |
| **12** | 1 | | | | 1 |
| **14** | 2 | 2 | 2 | 1 | |
| **Total** | **11** | **6** | **6** | **5** | **4** |

## 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** | 59316 | 21 | 0.04 | 8 |
| **3** | 15468 | 4 | | 4 |
| **5** | 62011 | 34 | 0.05 | 18 |
| **6** | 13042 | 6 | 0.05 | 1 |
| **7** | 54436 | 61 | 0.11 | 11 |
| **8** | 179846 | 41 | 0.02 | 40 |
| **9** | 140444 | 25 | 0.02 | 20 |
| **10** | 36175 | 20 | 0.06 | 8 |
| **11** | 16987 | 6 | 0.04 | 5 |
| **12** | 93424 | 23 | 0.02 | 12 |
| **13** | 70048 | 24 | 0.03 | 18 |
| **14** | 33703 | 31 | 0.09 | 8 |
| **15** | 9521 | 6 | 0.06 | 4 |
| **Total** | **784421** | **302** | **0.04** | **157** |

[a] Recall rates only provided if recall rate ≥ 0.01% and n ≥ 5

Of n=157 confirmed cases, 73 were diagnosed as PKU and 84 as HPA.

**Table 5.5.2: PKU/HPA Confirmation**

| Lab | Confirmed cases | Phe (Serum/DB) | Phe/Tyr | Molecular genetics | Pterins (Urine/DB) | DHPR (DB) | Confirmed cases without confirmation details |
|---|---|---|---|---|---|---|---|
| **1** | 8 | 8 | 8 | 6 | 7 | 7 | |
| **3** | 4 | 4 | 4 | 1 | | | |
| **5** | 18 | 9 | 1 | 4 | 13 | 13 | 4 |
| **6** | 1 | 1 | | 1 | 1 | 1 | |
| **7** | 11 | 10 | 10 | 5 | 10 | 10 | |
| **8** | 40 | 30 | 14 | 6 | 23 | 24 | 5 |
| **9** | 20 | 17 | 3 | 3 | 19 | 19 | |
| **10** | 8 | 8 | 5 | 5 | 7 | 6 | |
| **11** | 5 | 5 | 4 | 1 | 1 | 1 | |
| **12** | 12 | 9 | 2 | 4 | 5 | 5 | 3 |
| **13** | 18 | 17 | 17 | 1 | 13 | 13 | 1 |
| **14** | 8 | 5 | 4 | | 5 | 5 | 2 |
| **15** | 4 | 4 | 1 | 1 | 3 | 3 | |
| **Total** | **157** | **127** | **73** | **38** | **107** | **107** | **15** |

**Table 5.5.3: PKU BH4-Test / BH4 Sensitivity**

| Lab | Confirmed cases | BH4-Test | BH4 sensitive |
|---|---|---|---|
| **1** | 8 | 5 | 4 |
| **3** | 4 | 4 | 2 |
| **5** | 18 | 3 | 3 |
| **6** | 1 | 1 | |
| **7** | 11 | | |
| **8** | 40 | 13 | 5 |
| **9** | 20 | 5 | 2 |
| **10** | 8 | 2 | 1 |
| **11** | 5 | 1 | |
| **12** | 12 | 2 | |
| **13** | 18 | 7 | |
| **14** | 8 | 2 | 2 |
| **15** | 4 | 1 | |
| **Total** | **157** | **46** | **19** |

## 5.6 Maple Syrup Urine Disease (MSUD)

**Table 5.6.1: MSUD - Confirmed cases / Recall rate**

| Lab | Initial screening | Recall | Confirmed cases |
|---|---|---|---|
| **1** | 59316 | 6 | 0 |
| **3** | 15468 | 1 | 1 |
| **5** | 62011 | 4 | 0 |
| **6** | 13042 | 4 | 0 |
| **7** | 54436 | 8 | 0 |
| **8** | 179846 | 3 | 2 |
| **9** | 140444 | 22 | 1 |
| **10** | 36175 | 2 | 1 |
| **11** | 16987 | 0 | 0 |
| **12** | 93424 | 0 | 0 |
| **13** | 70048 | 0 | 0 |
| **14** | 33703 | 0 | 0 |
| **15** | 9521 | 0 | 0 |
| **Total** | **784421** | **50** | **5** |

Total recall rate: 0.01%

**Table 5.6.2: MSUD Confirmation**

| Lab | Confirmed cases | Confirmation (Serum) | Organic acids (urine) | Enzyme activity | Molecular genetics | Confirmed cases without confirmation details |
|---|---|---|---|---|---|---|
| **3** | 1 | 1 | 1 | | 1 | |
| **8** | 2 | 2 | 2 | | 1 | |
| **9** | 1 | 1 | | | 1 | |
| **10** | 1 | 1 | 1 | 1 | 1 | |
| **Total** | **5** | **5** | **4** | **1** | **4** | 0 |

## 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** | 59316 | 9 | 0.02 | 5 |
| **3** | 15468 | 3 | | 1 |
| **5** | 62011 | 5 | 0.01 | 2 |
| **6** | 13042 | 5 | 0.04 | 0 |
| **7** | 54436 | 12 | 0.02 | 6 |
| **8** | 179846 | 22 | 0.01 | 17 |
| **9** | 140444 | 38 | 0.03 | 11 |
| **10** | 36175 | 22 | 0.06 | 2 |
| **11** | 16987 | 2 | 0.01 | 2 |
| **12** | 93424 | 10 | 0.01 | 10 |
| **13** | 70048 | 8 | 0.01 | 6 |
| **14** | 33703 | 9 | 0.03 | 5 |
| **15** | 9521 | 1 | | 1 |
| **Total** | **784421** | **146** | **0.02** | **68** |

[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** | 5 | 1 | 5 | 3 | 5 | |
| **3** | 1 | | | | 1 | |
| **5** | 2 | 1 | 2 | | | |
| **7** | 6 | | 1 | | 6 | |
| **8** | 17 | 7 | 7 | 1 | 13 | 2 |
| **9** | 11 | 7 | 5 | 2 | 5 | |
| **10** | 2 | 2 | 2 | 1 | 2 | |
| **11** | 2 | 2 | 2 | 2 | 2 | |
| **12** | 10 | 7 | | 2 | 8 | |
| **13** | 6 | 6 | 1 | | 4 | |
| **14** | 5 | 3 | | 2 | 3 | |
| **15** | 1 | 1 | | | 1 | |
| **Total** | **68** | **37** | **25** | **13** | **50** | **2** |

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

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

| Lab | Initial screening | Recall | Confirmed cases |
|---|---|---|---|
| **1** | 59316 | 1 | 0 |
| **3** | 15468 | 0 | 0 |
| **5** | 62011 | 3 | 0 |
| **6** | 13042 | 3 | 0 |
| **7** | 54436 | 0 | 0 |
| **8** | 179846 | 0 | 0 |
| **9** | 140444 | 4 | 1 |
| **10** | 36175 | 0 | 0 |
| **11** | 16987 | 0 | 0 |
| **12** | 93424 | 0 | 0 |
| **13** | 70048 | 1 | 1 |
| **14** | 33703 | 1 | 0 |
| **15** | 9521 | 0 | 0 |
| **Total** | **784421** | **13** | **2** |

**Table 5.8.2: LCHAD Deficiency Confirmation**

| Lab | Confirmed cases | Confirmation (Serum) | Organic Acids (urine) | Enzyme activity | Molecular genetics | Confirmed cases without confirmation details |
|---|---|---|---|---|---|---|
| **9** | 1 | | | | 1 | |
| **13** | 1 | 1 | 1 | | 1 | |
| **Total** | **2** | **1** | **1** | | **2** | **0** |

## 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** | 59316 | 12 | 0.02 | 0 |
| **3** | 15468 | 0 | | 0 |
| **5** | 62011 | 7 | 0.01 | 2 |
| **6** | 13042 | 2 | | 0 |
| **7** | 54436 | 16 | 0.03 | 2 |
| **8** | 179846 | 4 | | 2 |
| **9** | 140444 | 52 | 0.04 | 8 |
| **10** | 36175 | 1 | | 0 |
| **11** | 16987 | 4 | | 1 |
| **12** | 93424 | 5 | 0.01 | 0 |
| **13** | 70048 | 1 | | 1 |
| **14** | 33703 | 4 | | 0 |
| **15** | 9521 | 3 | | 0 |
| **Total** | **784421** | **111** | **0.01** | **16** |

[a] Recall rates only provided if recall rate ≥ 0.01% and n ≥ 5

**Table 5.9.2: VLCAD Confirmation**

| Lab | Confirmed cases | Confirmation (Serum) | Organic Acids (urine) | Enzyme activity | Molecular genetics | Confirmed cases without confirmation details |
|---|---|---|---|---|---|---|
| **5** | 2 | | 1 | 2 | | |
| **7** | 2 | | | 2 | 2 | |
| **8** | 2 | 1 | 1 | | 2 | |
| **9** | 8 | 2 | | 7 | 3 | |
| **11** | 1 | 1 | 1 | 1 | 1 | |
| **13** | 1 | 1 | | | 1 | |
| **Total** | **16** | **5** | **3** | **12** | **9** | **0** |

## 5.10 CPT I / CPT II / CACT Deficiency

**Table 5.10.1: CPT I /II / CACT Deficiency Recall**

| | Recall | Confirmed Cases |
|---|---|---|
| CPT I Deficiency | 8 | 1 |
| CPT II Deficiency | 2 | 1 |
| CACT Deficiency | 7 | 0 |

**Table 5.10.2: CPT I / II Deficiency Confirmation**

| | Lab | Confirmed Cases | Confirmation (Serum/TB) | Enzyme activity | Molecular genetics | Confirmed cases without details of confirmation |
|---|---|---|---|---|---|---|
| CPT I Deficiency | 8 | 1 | 1 | | | |
| CPT II Deficiency | 1 | 1 | | 1 | 1 | 0 |

## 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** | 59316 | 11 | 0.02 | 1 |
| **3** | 15468 | 0 | | 0 |
| **5** | 62011 | 6 | 0.01 | 0 |
| **6** | 13042 | 0 | | 0 |
| **7** | 54436 | 5 | 0.01 | 0 |
| **8** | 179846 | 2 | | 1 |
| **9** | 140444 | 47 | 0.03 | 2 |
| **10** | 36175 | 0 | | 0 |
| **11** | 16987 | 0 | | 0 |
| **12** | 93424 | 1 | | 1 |
| **13** | 70048 | 1 | | 0 |
| **14** | 33703 | 0 | | 0 |
| **15** | 9521 | 0 | | 0 |
| **Total** | **784421** | **73** | **0.01** | **5** |

[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 | Confirmed cases without confirmation details |
|---|---|---|---|---|---|---|
| **1** | 1 | 1 | 1 | | | |
| **8** | 1 | 1 | 1 | | 1 | |
| **9** | 2 | 2 | 1 | | 2 | |
| **12** | 1 | 1 | 1 | | 1 | |
| **Total** | **5** | **5** | **4** | | **4** | **0** |

## 5.12 Isovaleric Acidemia (IVA)

**Table 5.13.1: IVA - Confirmed Cases / Recall rate**

| Lab | Initial screening | Recall | Recall rate (%)[a] | Confirmed cases |
|---|---|---|---|---|
| **1** | 59316 | 8 | 0.01 | 0 |
| **3** | 15468 | 3 | | 1 |
| **5** | 62011 | 1 | | 1 |
| **6** | 13042 | 4 | | 1 |
| **7** | 54436 | 14 | 0.03 | 1 |
| **8** | 179846 | 15 | 0.01 | 2 |
| **9** | 140444 | 8 | 0.01 | 1 |
| **10** | 36175 | 6 | 0.02 | 2 |
| **11** | 16987 | 7 | 0.04 | 0 |
| **12** | 93424 | 15 | 0.02 | 1 |
| **13** | 70048 | 22 | 0.03 | 2 |
| **14** | 33703 | 4 | | 0 |
| **15** | 9521 | 2 | | 0 |
| **Total** | **784421** | **109** | **0.01** | **12** |

[a] Recall rates only provided if recall rate ≥ 0.01% and n ≥ 5

The recall rate has increased significantly in comparison with the previous year (n=68). A frequent explanation is the administration of Pivmecillinam for urinary tract infections in the mother shortly before birth, which leads to false positive screening results.

**Table 5.12.2: IVA Confirmation**

| Lab | Confirmed cases | Confirmation (Serum) | Organic Acids (urine) | Enzyme activity | Molecular genetics | Confirmed cases without confirmation details |
|---|---|---|---|---|---|---|
| **3** | 1 | | 1 | | 1 | |
| **5** | 1 | | | | | 1 |
| **6** | 1 | | 1 | | 1 | |
| **7** | 1 | | 1 | | 1 | |
| **8** | 2 | 1 | 1 | | 2 | |
| **9** | 1 | 1 | 1 | | 1 | |
| **10** | 2 | 2 | 2 | | 2 | |
| **12** | 1 | | | | | 1 |
| **13** | 2 | | 2 | | 2 | |
| **Total** | **12** | **4** | **9** | | **10** | **2** |

## 5.13 Tyrosinemia

Tyrosinemia was added to the ENS as a new target disease in 3/2018. Since the number of initial screenings per laboratory is only known for the whole year of 2018, no recall rate can be calculated for tyrosinemia 2018.

**Table 5.13.1: Tyrosinemia – Confirmed Cases**

| Lab | Recall | Confirmed Cases |
|---|---|---|
| **1** | 5 | 1 |
| **3** | 0 | 0 |
| **5** | k. A. | 1 |
| **6** | 2 | 0 |
| **7** | 1 | 1 |
| **8** | 69 | 0 |
| **9** | 6 | 1 |
| **10** | 16 | 0 |
| **11** | 1 | 1 |
| **12** | 27 | 0 |
| **13** | 28 | 1 |
| **14** | 1 | 0 |
| **15** | 0 | 0 |
| **Total** | **156** | **6** |

**Table 5.13.2: Tyrosinemia Confirmation**

| Lab | Confirmed Cases | Confirmation (Serum/TB) | Confirmation Organic Acids | Enzyme activity | Molecular genetics | Confirmed cases without confirmation information |
|---|---|---|---|---|---|---|
| **1** | 1 | 1 | 1 | | | |
| **5** | 1 | | 1 | | 1 | |
| **7** | 1 | 1 | 1 | | 1 | |
| **9** | 1 | 1 | 1 | | 1 | |
| **11** | 1 | 1 | 1 | | 1 | |
| **13** | 1 | | | | | 1 |
| **Total** | **6** | **4** | **5** | | **4** | **1** |

## 5.14 Cystic Fibrosis (CF)

Since September 2016, screening for cystic fibrosis has been performed in three steps as a serial combination of two biochemical tests, initially for immunoreactive trypsin (IRT). If this is elevated, the algorithm is continued in a second step for pancreatitis-associated protein (PAP). In the case of pathologic PAP, a third molecular genetic screening for the 31 most common pathogenic mutations of the Cystic Fibrosis Transmembrane Regulator gene (CFTR gene) in Germany is carried out (Figure 5).

The screening is considered remarkable (positive) if an IRT value above the 99.9th percentile is determined ("failsafe" method or "safety net") or if in the third step at least one of the 31 examined mutations of the CFTR gene is detected on at least one allele. In all other circumstances, the screening is considered unremarkable (negative).

This screening algorithm results in "failsafe" (IRT >99.9th percentile) accounting for 81.01% of the 795 positive screening findings (see Fig. 5). The diagnosis of CF was confirmed in only 133 children (16.73%), of whom 103 (15.99%) were confirmed after positive screening by failsafe and 30 (19.87%) upon detection of one or two of the 31 mutations. In addition, 11 children were diagnosed with CF after unremarkable CF screening (Table 5.14.4) and one child without CF screening.

According to the Children's Guideline, a separate declaration of consent is required for CF screening, and screening cannot be performed by a midwife acting alone in consultation with a physician in exceptional cases, as is the case with ENS. The percentage of newborns without CF screening was 0.89% in 2018 (Table 5.14.1).

**Table 5.14.1: Number of Cases without CF Screening**

| Lab | Initial screening ENS | Without CF Screening | Proportion without CF Screening (%) |
|---|---|---|---|
| **1** | 59316 | 851 | 1.43 |
| **3** | 15468 | 6 | 0.04 |
| **5** | 62011 | 2251[a] | 3.63 |
| **6** | 13042 | 27 | 0.21 |
| **7** | 54436 | n/a. | k. A. |
| **8** | 179846 | 1694 | 0.94 |
| **9** | 140444 | 223 | 0.16 |
| **10** | 36175 | 410 | 1.13 |
| **11** | 16987 | 55 | 0.32 |
| **12** | 93424 | 778 | 0.83 |
| **13** | 70048 | 51 | 0.07 |
| **14** | 33703 | 103 | 0.31 |
| **15** | 9521 | 34 | 0.36 |
| **Total** | **784415** | **6483** | **0.89[b]** |

[a] Refers to initial screening only [b] Calculated without laboratory 7

**Table 5.14.2: CF – Confirmed cases / Recall Rate**

| Lab | Initial screening with CF Screening | Recall | Recall Rate (%) | Confirmed cases[a] |
|---|---|---|---|---|
| **1** | 58465 | 69 | 0.12 | 10 |
| **3** | 15462 | 14 | 0.09 | 5 |
| **5** | 59760 | 48 | 0.08 | 6 |
| **6** | 13015 | 17 | 0.13 | 2 |
| **7** | 54436 | 49 | 0.09 | 11 |
| **8** | 178152 | 362 | 0.20 | 33 |
| **9** | 140221 | 118 | 0.08 | 25 |
| **10** | 35765 | 36 | 0.10 | 8 |
| **11** | 16932 | 8 | 0.05 | 2 |
| **12** | 92646 | 92 | 0.10 | 10 |
| **13** | 69997 | 73 | 0.10 | 18 |
| **14** | 33600 | 56 | 0.17 | 12 |
| **15** | 9487 | 10 | 0.11 | 2 |
| **Total** | **777938** | **943** | **0.12** | **144** |

[a] of which 11 cases with unremarkable CF screening

**Table 5.14.3: CF – Validation of confirmed cases**

| Lab | Confirmed Cases | One Sweat Test | Two Sweat Tests | Conductivity | 2 Mutations in confirmation or screening | Meconium ileus |
|---|---|---|---|---|---|---|
| **1** | 10 | 7 | 2 | | 3 | 1 |
| **3** | 5 | | 5 | 4 | 5 | 1 |
| **5** | 6 | 3 | 1 | | 3 | 2 |
| **6** | 2 | | 1 | | 2 | |
| **7** | 11 | 5 | 5 | | 7 | 1 |
| **8** | 33 | 9 | 19 | 1 | 33 | 2 |
| **9** | 25 | 10 | 8 | 10 | 16 | 3 |
| **10** | 8 | 5 | 1 | 5 | 4 | 1 |
| **11** | 2 | | 2 | | 2 | |
| **12** | 10 | 6 | 3 | 5 | 6 | 3 |
| **13** | 18 | 9 | 3 | 1 | 12 | 3 |
| **14** | 12 | 10 | 2 | 7 | 3 | 2 |
| **15** | 2 | 2 | | | 1 | |
| **Total** | **144** | **66** | **52** | **33** | **96** | **19** |

In 8 cases reported by the laboratories, the information was not sufficient to confirm the diagnosis. Out of n=144 confirmed cases, 140 were diagnosed with cystic fibrosis and 4 with Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID). Screening via failsafe was positive in 71.5% of the cases, one or 2 mutations from the panel were detected in 20.8% of them, and the CF screening was unremarkable in 7.6% of the cases.

In n=100 of the confirmed cases, genetic data from screening or confirmation were available. Two mutations from the panel of 31 were present in 76 cases, one mutation in 23 cases, and only 1 child had 2 other mutations. This child had an abnormal screening result via failsafe but also had meconium ileus and severe asphyxia at birth. In total, 19 children were reported to have meconium ileus. Information on one sweat test (n=67) or two sweat tests (n=52) was available in 119 cases. Information on 2 existing mutations was available in only 22 cases, and 3 cases were validated as probable based solely on conductivity.

11 of the confirmed diagnoses were not found via the predefined screening algorithm for cystic fibrosis and were unremarkable in the screening. 4 of these children were diagnosed due to meconium ileus, 1 child was diagnosed based on failure to thrive. In 2 children, the diagnosis of CF was already made prenatally due to family history, but these children would have been missed in the screening. In 4 children, no information is available as to why the evaluation took place (see Table 5.14.4). In addition to these 11 cases, after the CF screening was deliberately not performed one child was diagnosed with cystic fibrosis at 7 months of age. It is not known whether other children with cystic fibrosis missed during screening.

**Table 5.14.4: Confirmed Cases with unremarkable CF Screening**

| Screening Parameter | Found via | Count (n) |
|---|---|---|
| IRT unremarkable | Meconium ileus (n=2)<br>Failure to thrive (n=1)<br>n/a (n=2) | **5** |
| PAP unremarkable | Meconium ileus (n=1)<br>Prenatally diagnosed due to family history (n=2)<br>n/a (n=1) | **4** |
| None of the 31 Mutations | Meconium ileus and family history (n=1)<br>n/a (n=1) | **2** |

# 6 Lost to follow-up

Of a total of 21,195 second cards requested, 17,864 (88.71%) were sent in, meaning that no further information on a clarification was available for 11.29% of the cards requested (Table 2.3). The breakdown of the response rate according to the reasons for requesting the duplicate card (recall/early collection) was not requested in 2018.

## 6.1 Cases without confirmation data

Of 85 children with positive screening results in the ENS, it is not known whether the confirmatory diagnosis took place or was completed. 49 of these cases, for which no confirmation information was available but with unambiguous screening results, were validated as 'probable cases' on the basis of the screening results (Table 6.1.1.1) and included in the calculation of prevalence. This was not possible for 36 children (Tab. 6.1.2.1).

### 6.1.1 Confirmed cases without information about validation diagnostics

**Table 6.1.1.1: Confirmed Cases without information about validation**

| | | Reason no confirmation provided | | | |
|---|---|---|---|---|---|
| **Disease** | Confirmed cases without confirmation | No feedback from clinic / pediatrician | Clinic did not request confirmation | Only diagnosis with no information on the diagnostics performed | unclear |
| **Hypothyroidism** | 16 | 3 | | | 13 |
| **CAH** | 5 | 1 | | | 4 |
| **Biotinidase Deficiency** | 4 | 1 | | | 3 |
| **Galactosemia** | 4 | 1 | | 1 | 2 |
| **PKU/HPA** | 15 | 3 | 1 | 4 | 7 |
| **MCAD** | 2 | 1 | | | 1 |
| **IVA** | 2 | | 1 | 1 | |
| **Tyrosinemia** | 1 | | 1 | | |
| **Total** | **49** | **10** | **3** | **6** | **30** |

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

**Table 6.1.2.1: Cases with implausible or missing confirmation information**

| Disease | Number of Cases |
|---|---|
| | n |
| **Congenital Hypothyroidism** | 15 |
| **CAH** | 6 |
| **Biotinidase Deficiency** | 2 |
| **Classic Galactosemia** | 3 |
| **PKU / HPA** | 2 |
| **MCAD** | 3 |
| **VLCAD** | 2 |
| **GA I Deficiency** | 1 |
| **IVA** | 1 |
| **Tyrosinemia** | 1 |
| **Total** | **36** |

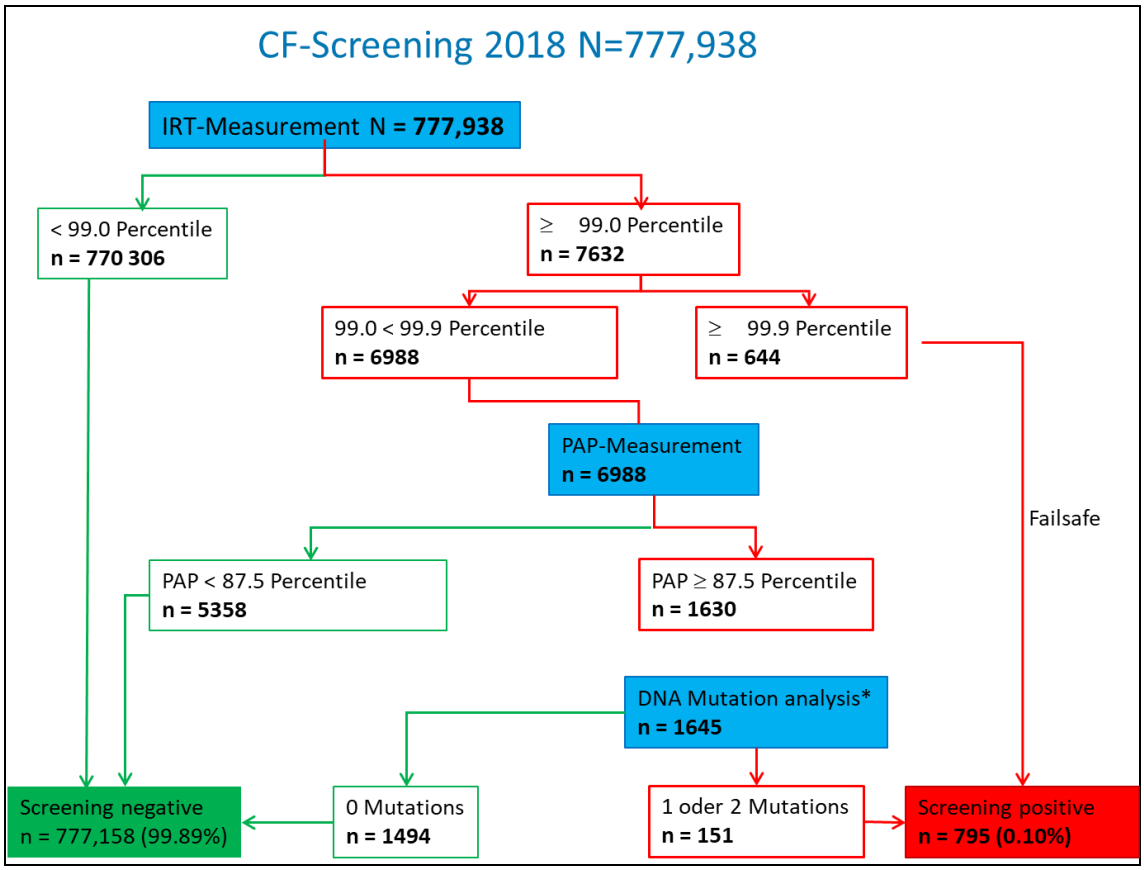
**Table 6.1.2.2: Proportion of cases by lab identified as unclear/open (n=36)**

| Lab | Number of confirmed cases (n=755) | Number of cases identified as unclear/open | Proportion of reported cases (%) |
|---|---|---|---|
| **1** | 59 | 2 | 3.92 |
| **3** | 18 | 0 | 0 |
| **5** | 53 | 4 | 7.84 |
| **6** | 10 | 1 | 11.11 |
| **7** | 55 | 10 | 18.51 |
| **8** | 166 | 7 | 0.05 |
| **9** | 134 | 3 | 2.67 |
| **10** | 32 | 3 | 11.11 |
| **11** | 18 | 0 | 0 |
| **12** | 89 | 2 | 2.47 |
| **13** | 72 | 3 | 5.26 |
| **14** | 40 | 1 | 3.44 |
| **15** | 9 | 0 | 0 |

# 7 Screening Algorithm Cystic Fibrosis (CF)

## 7.1 Screening Algorithm Germany

**Figure 5: Screening Algorithm Cystic Fibrosis Germany**




* Due to an abnormal product of PAP × IRT or for other reasons (e.g., small premature infants), DNA mutation analysis was performed for 15 children, deviating from the standard screening algorithm

An additional 11 children with a confirmed diagnosis had an unremarkable screening result, i.e. these children were not detected by the screening algorithm (see Table 5.14.4).

# 8 Methods and Cutoffs used in Screening

**Table 8.1: Filter paper**

| Lab | Filter paper |
|---|---|
| **1** | ID Biological (Ahlstrom 226) |
| **3** | ID Biological (Ahlstrom 226) |
| **5** | Munktell |
| **6** | ID Biological (Ahlstrom 226) |
| **7** | ID Biological (Ahlstrom 226) |
| **8** | Ahlstrom Munksjö |
| **9** | ID Biological (Ahlstrom 226) |
| **10** | ID Biological (Ahlstrom 226) |
| **11** | ID Biological (Ahlstrom 226) |
| **12/13** | ID Biological (Ahlstrom 226) |
| **14/15** | ID Biological (Ahlstrom 226) |

**Table 8.2 Hypothyroidism**

| Lab | Parameter | Cutoff | Method |
|---|---|---|---|
| **1** | TSH | 15 mU/l | AutoDELFIA |
| **3** | TSH | 15 mU/l | AutoDELFIA |
| **5** | TSH | 15 mU/l | AutoDELFIA |
| **6** | TSH | 15 mU/l | DELFIA |
| **7** | TSH | 15 mU/l | GSP |
| **8** | TSH | 15 mU/l (≤ 7 days)<br>10 mU/l (>7 days) | DELFIA |
| **9** | TSH | 15 µU/ml | GSP |
| **10** | TSH | 15 mU/l | AutoDELFIA |
| **11** | TSH | 15 mU/l | DELFIA |
| **12 /13** | TSH | 20 mU/l (1 day)<br>15 mU/l (2-4 days)<br>10 mU/l (≥ 5 days) | AutoDELFIA |
| **14 /15** | TSH | 20 mU/l (1 day)<br>15 mU/l (2-4 days)<br>10 mU/l (≥ 5 days) | AutoDELFIA |

**Table 8.3: Congenital Adrenal Hyperplasia (CAH)**

| Lab | Parameter | Method |
|---|---|---|
| **1*** | 17 OHP | AutoDELFIA |
| **3** | 17 OHP | AutoDELFIA Kit B024 |
| **5** | 17 OHP | AutoDELFIA |
| **6** | 17 OHP | DELFIA |
| **7** | 17 OHP | AutoDELFIA |
| **8*** | 17 OHP | DELFIA |
| **9** | 17 OHP | GSP |
| **10** | 17 OHP | AutoDELFIA |
| **11** | 17 OHP | DELFIA |
| **12/13*** | 17 OHP | AutoDELFIA |
| **14/15*** | 17 OHP | AutoDELFIA |

*Lab uses 2nd tier method

**Table 8.4: Biotinidase Deficiency**

| Lab | Parameter | Cutoff | Methods |
|---|---|---|---|
| **1** | Biotinidase | 30% | Qualitative colorimetry |
| **3** | Biotinidase | 30% | Qualitative colorimetry |
| **5** | Biotinidase | 30% of panel mean | Qualitative colorimetry |
| **6** | Biotinidase | 55 U | Fluorometry (PE) |
| **7** | Biotinidase | 2.7 U/g Hb<br>85.7 U/g Hb | Until 31 May 2018: Quantitative colorimetry<br>From 1 June 2018: GSP |
| **8** | Biotinidase | 30% daily mean | Quantitative colorimetry |
| **9** | Biotinidase | Extinction < 0.2 | Qualitative colorimetry |
| **10** | Biotinidase | 30% | Qualitative colorimetry |
| **11** | Biotinidase | 30% | Quantitative colorimetry |
| **12/13** | Biotinidase | 30% | Quantitative fluorometry |
| **14/15** | Biotinidase | 30% | Quantitative colorimetry |

**Table 8.5: Galactosemia**

| Lab | Parameter | Normal range | Method |
|---|---|---|---|
| **1** | GALT | >3.5 U/g Hb | Quantitative fluorometry |
| | Galactose | <20 mg/dl | BIORAD Quantase |
| **3** | GALT | >2.3 U/g Hb | Fluorometry (PE) |
| | Galactose | <15 mg/dl | |
| **5** | GALT | >3.5 U/g Hb | Quantitative fluorometry |
| | Galactose | 20 mg/dl | Quantitative colorimetry |
| **6** | GALT | >3.5 U/g Hb | Fluorometry (PE) |
| **7** | GALT | >3.5 U/g Hb | Quantitative fluorometry |
| **8** | GALT | >20% daily mean | Quantitative fluorometry |
| | Galactose | <30 mg/dl | Quantitative colorimetry |
| **9** | GALT | >5.3 U/g Hb | Fluorometry (PE) |
| | Galactose | <20 mg/dl | BIORAD Quantase |
| **10** | GALT | >3.5 U/gHb | Fluorometry (PE) |
| | Galactose | 1111 µmol/l | BIORAD Quantase |
| **11** | GALT | >3.5 U/g Hb | Fluorometry (PE) |
| **12/13** | GALT | >20% | Colorimetry non-kit / Quant. fluoro. |
| | Galactose | < 15 mg/dl | (non-kit) |
| **14/15** | GALT | >3.5 U/g Hb | Quantitative fluorometry |
| | Galactose | <15 mg/dl | BIORAD Quantase |

**Table 8.6: Tandem mass spectrometry (MS/MS)**

| Lab | Method |
|---|---|
| **1** | non-derivat. Chromsystems Kit |
| **3** | non-derivat.. Chromsystems |
| **5** | non-derivatized Kit |
| **6** | non-derivatized PE kit |
| **7** | derivatized PE kit |
| **8** | 2018 switched from derivatized to non-derivitized Kit |
| **9** | derivatized non-kit |
| **10** | deriv. Chromsystems Kit |
| **11** | non-derivat. Chromsystems Kit |
| **12/13** | derivatized non-kit |
| **14/15** | derivatized non-kit |

# 9 Literature

[1] Children's Guideline Status: May 14, 2020 of the Federal Joint Committee on the Early Detection of Diseases in Children (Children's Guideline – "Kinder-Richtlinie); https://www.g-ba.de/downloads/62-492-2156/Kinder-RL_2020-05-14_iK-2020-03-25.pdf

[2] Destatis, Federal Statistical Office, Births 2018 https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Bevoelkerung/Geburten/_inhalt.html (accessed 6/18/2020)