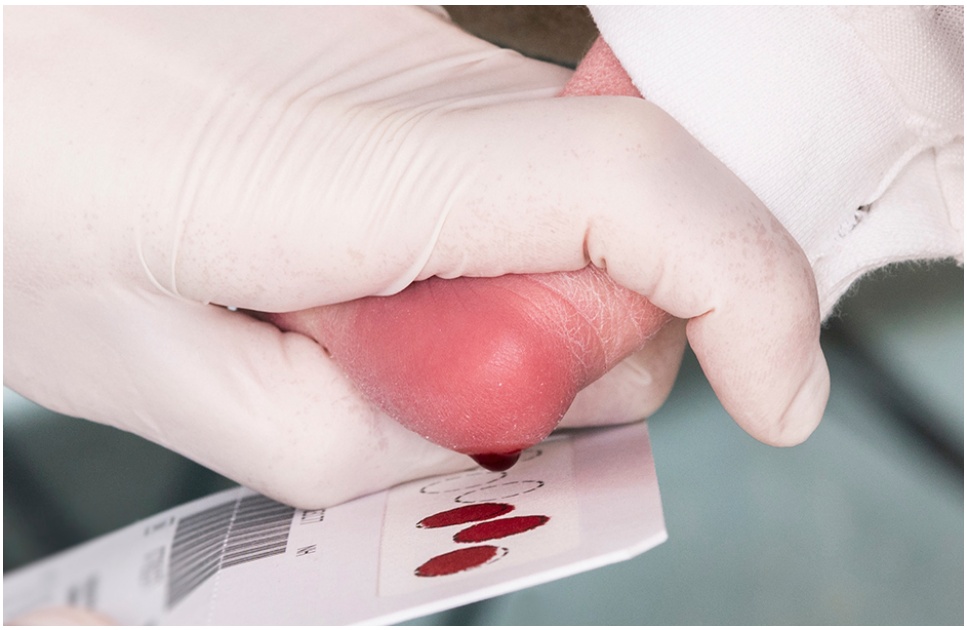
# THE NEWBORN BLOOD SPOT SCREENING IN THE NETHERLANDS

## MONITOR 2022



TNO innovation for life

The aim of the Newborn Blood Spot screening programme (NBS) is the early detection of a number of serious, rare, congenital conditions in newborns. The **target disease** is the variant of the disorder we want to detect with neonatal screening. The screening is designed to preferably detect all children with the target disease and no or as few as possible children with another variant (secondary finding). If these target diseases are detected early, irreversible health damage can be prevented or limited through timely treatment with, for example, medication or diet.

The national monitor with main results of the NBS is carried out annually by TNO at request of the RIVM-CvB. The monitor enables insight into the functioning of all aspects of the NBS as well as insight into a possible need for extra measures to allow for an improvement in functioning of the screening programme. A separate monitor is made about the NBS in the Caribbean Netherlands (in Dutch).

# SUMMARY

**Table 1**
Results of the most important indicators for children born in 2020, 2021 and 2022

| | 2020 | 2021 | 2022 |
|---|---|---|---|
| **Number of screened children (eligible)** | 168,683 (169,734) | 179,095 (180,606) | 167,331 (169,196) |
| **Participation rate** | 99.4% | 99.2% | 98.9% |
| **Number referred (incl. OCTN2) (%)** | 450 (0.27%) | 522 (0.29%) | 482 (0.29%)[4] |
| **Number with target disease (excl. OCTN2)** | 176 | 206 | 233 |
| **Number with still unknown diagnosis** | 15 | 10 | 1 |
| **Detection rate per 1000** | 1.043 | 1.150 | 1.392 |
| **Positive predictive value (PPV, all target diseases combined)** | 42% | 42% | 50% [1] |
| **Sensitivity** | 98% | 99% | 99% [2] |
| **Specificity** | 99.854% | 99.839% | 99.861% |
| **1st heel prick taken within 168 hours** | 98.5% | 98.3% | 98.3% |
| **1st heel prick in recommended period (72-96 hours after birth)** | 40% | 39% | 39% |
| **1st heel prick taken 72-120 hours after birth** | 71% | 70% | 71% |
| **Repeated 1st heel prick (by condition; %)** | 0.04% – 0.26%<br>HbP 0.43% | 0.10 - 0.35 %<br>HbP 0.47% | 0.07 - 0.33 % [3]<br>HbP 0.47% |
| **Timely diagnosis CAH, CH, MD, HbP, CF, SCID and SMA (%)** | 90, 88, 89, 81, 77 % | 73, 80, 88, 82, 72, 90 % | 83, 81, 72, 77, 84, 86, 100% |
| **Costs per child screened** | €113 | € 133 | € 146 |
| **Objection to use of residual blood for scientific research** | 7.1% | 7.9% | 8.9% |

Green: target value met; red: target value not met
[1] In 2022, target values for the positive predictive value of individual diseases are met for all diseases except SCID (7%; target >10%), CF excl. meconium ileus (63%; target > 65%) and the metabolic diseases 3MHM and VLCAD (respectively 20% and 25%; target >30%).
[2] Two children born in 2022 were reported as false-negative (1 for CH, 1 for CF). The target value of 100% for sensitivity of CH and CF was thus not achieved. Furthermore, one child from an earlier birth year was reported as missed. This child was born in 2019 and was diagnosed as having CH.
[3] In 2022, target values for the repeated heel prick rate (≤0.30% for all conditions, except HbP ≤0.50%) were met for all conditions except CF (0.31%), BIO (0.32%), MPS I (0.33%) and SMA (0.32%).
[4] Excluding 3 referrals caused by administrative errors (CAH, and 2x TYR-I).

# RECOMMENDATIONS

Existing recommendations that are still valid:

- Intensify actions to improve **timeliness of the first heel prick**. More attention is needed for the optimal period for the 1st heel prick.
- Improve the **timeliness of diagnostics.**
- Continued attention to **timely and clear registration** of diagnostic data.
- Continued attention to **false-negative results and missed patients:** it remains important to investigate the cause and discuss whether they can be prevented.

New recommendations:

- Continue to monitor that no children with CAH are missed, given the low detection rate for CAH in 2022. [For 2022, this was checked in October 2023, and no children with CAH appear to have been missed].
- In 2022, signal values for the positive predictive value were determined for all metabolic diseases. **For MMA, more clarity on the target disease is needed** so that the PPV for MMA can be assessed. After all, there are many referrals for MMA. Furthermore, for metabolic diseases with a low PPV that is less reliable due to few referrals (GA-1, MSUD, TFP/LCHAD, TYR-1, CPT1, and GALK) it may be beneficial to assess whether the screening is adequate or whether adjustments are needed.

### DATA SOURCES

The screening data in this monitor originate from the Praeventis registration system of the RIVM. Diagnostic data originate from the NEORAH registration system of the RIVM (www.neorah.nl). The NEORAH data related to metabolic diseases have been retrieved from the Dutch Diagnosis Registration Metabolic Diseases (www.ddrmd.nl). Notifications of the Dutch Paediatric Surveillance System (NSCK) have been used to detect possible missed cases until 1st of January 2020. From 1 January 2020, paediatricians report missed patients to RIVM (see 'draaiboek hielprikscreening' (in Dutch)– Kinderarts) because the NSCK has been discontinued. This monitor concerns children who were born in 2022 (Praeventis reference data: 21-3-2023, NEORAH: 17-5-2023 or later).

## READING GUIDE

This monitor differentiates between the first heel prick, a repeat first heel prick, a second heel prick and a repeat second heel prick:

- First heel prick: the first heel prick that has been carried out;
- Repeat first heel prick: the newborn blood spot collection that is repeated because insufficient blood has been collected during the first heel prick in order to carry out the required laboratory analyses ('insufficient filling') or because the material is unreliable (contamination), or because the first heel prick was taken too early (within 48 hours after birth), or because a child received a blood transfusion within 24 hours before the heel prick was carried out. If a blood transfusion with erythrocytes has been carried out, the heel prick needs to be repeated after 91 days to test for haemoglobinopathies (HbP);
- Second heel prick: carried out if the first heel prick gives an inconclusive laboratory result;
- Repeat second heel prick: as in repeat first heel prick.

In this monitor the colours green and red indicate whether the results meet the prior indicated signal- or target values.

- The values which fall within the indicated limits are indicated in green.
- Values outside the formulated limits are indicated in red. If possible, actions can be taken to improve the results or to get the results to fall within the limits of the target value.
- Signal- or target values for trends do not exist. Trends which require vigilance, are indicated in orange. Stable trends are indicated in green.

## WHICH CONDITIONS ARE INCLUDED IN THE SCREENING?[1]

- **Congenital adrenal hyperplasia (CAH)**
- **Cystic fibrosis (CF)**
- **Congenital hypothyroidism (CH)**
- **Severe combined immunodeficiency (SCID)** *(since January 1st, 2021)*
- **Spinal muscular atrophy (SMA)** *(new, since June 1st, 2022)*
- **Hemoglobinopathies (HbP):**
  - Sickle cell disease **(SCD)**
  - HbH-disease **(HbH)**, a form of alpha-thalassemia
  - Beta-thalassemia major **(bTM)**
- **Metabolic diseases (MD):**
  - 3-Methylcrotonyl-CoA carboxylase deficiency **(3-MCC)**[2]
  - Biotinidase deficiency **(BIO)**
  - Carnitine palmitoyltransferase deficiency type 1 **(CPT1)**
  - Galactokinase deficiency **(GALK)**
  - Galactosemia (**GALT**, formerly called GAL)
  - Glutaric acidemia type 1 **(GA-1)**
  - HMG-CoA-lyase deficiency **(HMG)**[2]
  - Isovaleric acidemia **(IVA)**
  - Maple syrup urine disease **(MSUD)**
  - Medium-chain acylCoA dehydrogenase deficiency **(MCADD)**
  - Methylmalonic acidemia **(MMA)**
  - Mucopolysaccharidose type 1 **(MPS I)** *(new, since March 1st, 2021)*
  - Multiple CoA carboxylase deficiency **(MCD)**[2]
  - Phenylketonuria **(PKU)**
  - Propionic Acidemia **(PA)**
  - Trifunctional Protein deficiency/ Long-chain hydroxyacyl-CoA dehydrogenase deficiency **(TFP/LCHAD)**
  - Tyrosinemia type 1 **(TYR-1)**
  - Very-long-chain acylCoA dehydrogenase deficiency **(VLCAD)**

More information about these conditions can be found on the RIVM website:
https://www.pns.nl/hielprik

[1] OCTN2 deficiency and SCD carrier status are not part of the screening program; they are secondary findings. The C0 level for OCTN2 is determined in every child, because a possible deficiency makes the acylcarnitine profile unreliable. This may cause children with the metabolic disorders MCADD, VLCAD, TFP/LCHAD, IVA, GA-1 and 3-MHM to be missed. The results will be reported back to parents (the SCD carrier status will be reported back only if there is no objection from parents).
[2] These three conditions are reported combined under one name, 3-MHM, since they have the same screening marker.

## PARTICIPATION

In 2022 169,196 children were eligible to participate in the NBS. This is more than 10,000 fewer children than in 2021, and similar to the years before. A heel prick was performed on 167,331 children. This means that the participation rate in 2022 is 98.9%, which for the first time is lower than the signal value of 99.0%. There has been a downward trend since 2020 (Figure 1).

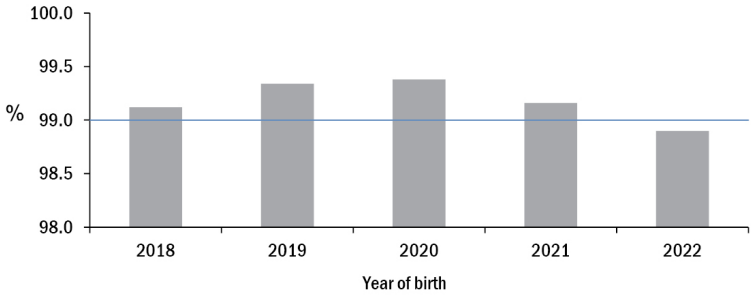



**Figure 1**
Participation rate of the neonatal screening programme by year of birth (2018-2022); to support readability the y-axis starts at 98%; the blue line indicates the target value.

Figure 2 shows that parents more often object to participate than in previous years (0.82% in 2022 versus 0.61% in 2021 and 0.42% in 2020). 'Tested elsewhere', such as a heel prick abroad, is in 2022 (0.20%) similar to 2021 (0.19%), and smaller than the years before (0.23% in 2019 and 0.27% in 2018). The reasons 'left' (e.g. left the country, or child untraceable) and 'unknown' are rare (respectively 0.03% and 0.04% in 2022).

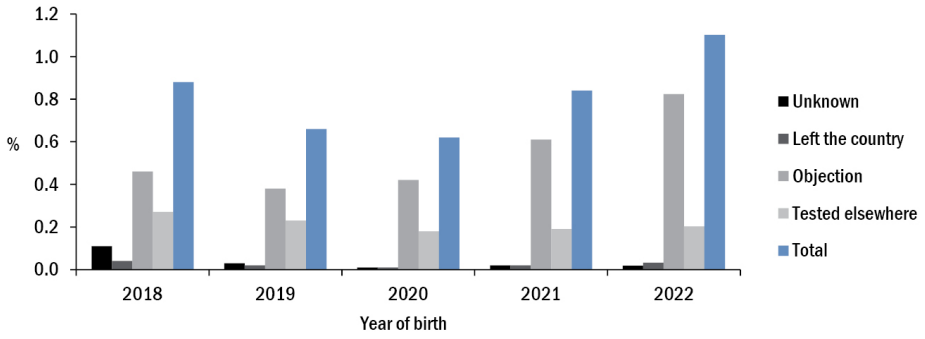



**Figure 2**
Reasons for non-participation in the neonatal screening programme by year of birth (2018-2022)

## TIMELINESS OF BLOOD COLLECTION

The heel prick should be carried out between 72 and 168 hours after birth, but ideally as soon as possible after 72 hours (or after 96 hours in the case of simultaneous neonatal hearing screening). In 2022 the percentage of first heel pricks carried out within 168 hours after birth is 98.3% (excluding children born abroad). This is the same as in 2021, and lower than in the years before that (98.5% in 2020, figure 3). The target value of at least 99.0% still has not been achieved. Late birth registration and weekend days complicate timely screening.

In 38.5% of children, newborn blood spots were collected in the recommended period between 72 and 96 hours after birth (table 1). This seems to be a good outcome in the current situation, as we know from the hearing screening monitors that circa 79% of the heel pricks is combined with the hearing screening, with the latter to be performed from 96 hours after birth. In 70.5% of children, the heel prick was performed 72-120 hours after birth (target value since 2022: ≥ 80%).

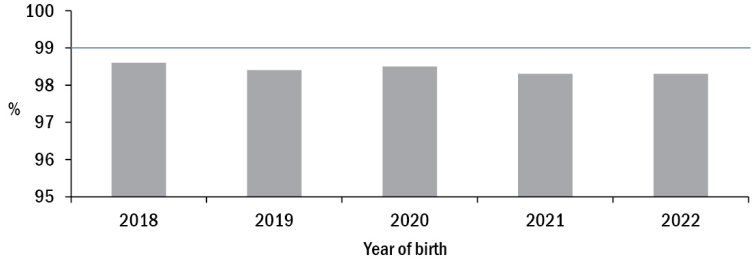



**Figure 3**
Timeliness of the blood spot collection by year of birth (2018-2022). Children born outside the Netherlands are excluded. To support readability the y-axis starts at 95%. The blue line indicates the target value.

## REPEAT FIRST HEEL PRICK

In 2022, 930 children received one or two repeated 1st heel pricks (0.56% of 167,331 participants; 1x in 914, 2x in 16). In 28 of them, the reason was premature 1st collection (not counted in Table 2). From 2018 to 2020, there has been a decreasing trend in the percentage of repeated first heel pricks for all conditions (table 2). In 2021, the rate of repeated heel pricks increased for all conditions. This year (2022), rates continued to increase for a large number of conditions (18). However, for the conditions for which the rate of 1st heel pricks exceeded the target last year, the rate has remained the same (MPS I) or decreased (BIO and SCID). The target rate was exceeded in 2022 for four conditions: CF (0.31%), BIO (0.32%), MPS I (0.33%) and SMA (0.32%). The analyses for MPS I, SMA and SCID are performed last and are therefore more likely to be omitted in the analysis of the first heelprick in case of insufficient blood.
The causes for repeated first heel pricks were further analyzed (results in separate note, in Dutch). The majority (56%) were caused by insufficient blood to perform all analyses.

**Table 2**
Repeated first heel pricks* according to birth year (2018-2022)

| % of repeated first heel prick | | 2018 | 2019 | 2020 | 2021 | 2022 | Number in 2022 | Target value[1] |
|---|---|---|---|---|---|---|---|---|
| **CAH** | | 0.08 | 0.06 | 0.04 | 0.06 | 0.07 | 114 | ≤0.30 |
| **CH** | | 0.42 | 0.27 | 0.22 | 0.27 | 0.29 | 488 | ≤0.30 |
| **CF** | | 0.42 | 0.30 | 0.24 | 0.30 | 0.31 | 526 | ≤0.30 |
| **HbP** | | 0.59 | 0.47 | 0.43 | 0.47 | 0.47 | 789 | ≤0.50 |
| **MD** | 3-MHM | 0.18 | 0.18 | 0.12 | 0.14 | 0.16 | 264 | ≤0.30 |
| | BIO | 0.37 | 0.29 | 0.26 | 0.35 | 0.32 | 528 | ≤0.30 |
| | CPT1 | | 0.15 | 0.12 | 0.14 | 0.16 | 265 | ≤0.30 |
| | GALK | | | 0.10 | 0.14 | 0.17 | 277 | ≤0.30 |
| | GALT | 0.18 | 0.15 | 0.11 | 0.13 | 0.16 | 273 | ≤0.30 |
| | GA-1 | 0.18 | 0.18 | 0.12 | 0.14 | 0.16 | 265 | ≤0.30 |
| | IVA | 0.18 | 0.18 | 0.12 | 0.14 | 0.16 | 265 | ≤0.30 |
| | MSUD | 0.14 | 0.12 | 0.09 | 0.10 | 0.13 | 212 | ≤0.30 |
| | MCADD | 0.18 | 0.18 | 0.12 | 0.14 | 0.16 | 265 | ≤0.30 |
| | MMA | | 0.15 | 0.12 | 0.14 | 0.16 | 269 | ≤0.30 |
| | MPS I | | | | 0.33 | 0.33 | 546 | ≤0.30 |
| | PA | | 0.15 | 0.12 | 0.14 | 0.16 | 269 | ≤0.30 |
| | PKU | 0.14 | 0.12 | 0.09 | 0.10 | 0.13 | 212 | ≤0.30 |
| | TFP/LCHAD | 0.18 | 0.18 | 0.12 | 0.14 | 0.16 | 264 | ≤0.30 |
| | TYR-1 | 0.14 | 0.12 | 0.09 | 0.10 | 0.13 | 212 | ≤0.30 |
| | VLCAD | 0.18 | 0.18 | 0.12 | 0.14 | 0.16 | 265 | ≤0.30 |
| | OCTN2 | 0.14 | 0.12 | 0.10 | 0.10 | 0.13 | 213 | ≤0.30 |
| **SCID** | | | | | 0.31 | 0.30 | 504 | ≤0.30 |
| **SMA** | | | | | | 0.32 | 319 | ≤0.30 |

* Based on 'unclassifiable' result for 1st heel prick, i.e. insufficient/unreliable blood or <24 hours after blood transfusion. Heel pricks that were carried out too early (n=28 in 2022) are not included.
[1] From 2021, the target values have been tightened, from ≤0.50% for all target diseases except HbP (≤0.80%) to ≤0.30% for all target diseases except HbP (≤0.50%).

## SECOND HEEL PRICK

In 2022 0.32% of the CH results of the first heel prick indicated the need for a second heel prick. For OCTN2, SCID and SMA this was 0.031%, 0.026%, and 0.001% respectively. The target values for this indicator were reached for all conditions (table 3). For CAH, 2nd heel pricks were no longer required in 2022: they have been replaced by an additional analysis on the blood from the 1st heel prick since October 1, 2021.

**Table 3**
Percentage second heel prick according to birth year (2018-2022)

| | 2018 | 2019 | 2020 | 2021 | 2022 | Number in 2022 | Target value |
|---|---|---|---|---|---|---|---|
| **CAH** | 0.072 | 0.042 | 0.049 | 0.044 | - | 0 | ≤0.09 |
| **CH** | 0.36 | 0.36 | 0.28 | 0.28 | 0.32 | 529 | ≤0.40 |
| **OCTN2[1]** | 0.045 | 0.054 | 0.027 | 0.036 | 0.031 | 52 | ≤0.04 |
| **SCID** | | | | 0.052 | 0.026 | 43 | ≤0.06 |
| **SMA** | | | | | 0.001 | 1 | ≤0.02 |

[1] OCTN2 is an incidental finding. In the event of an inconclusive result for OCTN2, a second heel prick is performed. If both results are inconclusive, the child will be referred. In that case, other metabolic disorders with a screening based on acylcarnitines are unclassifiable and are further examined in the hospital. In 2018 no target value was used for OCTN2.

## REFERRALS

In 2022, a total of 482 referrals were made as a result of the heel prick (table 4). This includes 15 referrals for the incidental finding OCTN2. This gives a total referral rate of 0.29% of the number of screened children in 2022. This is comparable to previous years.

The referral rates for individual conditions are similar to previous years. Only for CAH the referral rate in 2022 (0.004%) is much lower than in previous years (0.012-0.016% in 2018-2021). This is expected to be due to the addition of a second tier (i.e. a follow-up test with blood from the same heel prick) in CAH screening since October 1, 2021. Finally, also for SCID, the referral rate in 2022 (0.008%) is lower than in 2021 (0.016%). This is due to variation between kit lots, with some lot numbers in 2021 that on average yielded lower TREC values and thus more (false positive) referrals.

**Table 4**
Referrals according to birth year (2018-2022)

| % referrals | | 2018 | 2019 | 2020 | 2021 | 2022 | Number in 2022 | Trend |
|---|---|---|---|---|---|---|---|---|
| **CAH** | | 0.016 | 0.012 | 0.012[1] | 0.012 | 0.004 | 6 | 2022: decrease |
| **CH** | | 0.147 | 0.148 | 0.135[1] | 0.135[1] | 0.139[1] | 233[1] | stable |
| **CF** | | 0.021 | 0.022 | 0.016 | 0.022 | 0.020 | 34 | fluctuates |
| **HbP** | *subtotal* | *0.032* | *0.032* | *0.022* | *0.025* | *0.029* | *49* | |
| | SCD | 0.018 | 0.024 | 0.014 | 0.017 | 0.019 | 31 | fluctuates |
| | HbH | 0.007 | 0.006 | 0.004 | 0.005 | 0.003 | 5 | stable |
| | bTM | 0.007 | 0.002 | 0.004 | 0.003 | 0.008 | 13 | stable |
| **MD** | *subtotal* | *0.095* | *0.079* | *0.081* | *0.081* | *0.081* | *136* | |
| | 3-MHM | 0.009 | 0.006 | 0.007 | 0.006 | 0.009 | 15 | stable |
| | BIO | 0.013 | 0.010 | 0.005[3] | 0.005 | 0.005 | 9 | stable since 2020 |
| | CPT1 | | 0.002[2] | 0.001 | 0.002 | 0.002 | 4 | stable |
| | GALK | | | 0.002[2] | 0.001 | 0.001 | 1 | stable |
| | GALT | 0.025 | 0.004[4] | 0.006 | 0.006 | 0.005 | 8 | stable since 2019 |
| | GA-1 | 0 | 0.002 | 0.001 | 0.001[1] | 0.001 | 1 | stable |
| | IVA | 0.002 | 0.002 | 0.004 | 0.003 | 0.003 | 5 | stable |
| | MSUD | 0.002 | 0.003 | 0.002 | 0.001[1] | 0.001 | 1 | stable |
| | MCADD | 0.012 | 0.013 | 0.013[1] | 0.009 | 0.012 | 20 | stable |
| | MMA | | 0.013[2] | 0.014 | 0.016 | 0.011 | 18 | stable |
| | MPS I | | | | 0.003[2] | 0.002 | 3 | stable |
| | PA | | 0.007[2] | 0.001 | 0.002 | 0.001 | 2 | stable |
| | PKU | 0.010 | 0.008 | 0.007 | 0.007[1] | 0.011 | 19 | stable |
| | TFP/LCHAD | 0.001 | 0.002 | 0.001 | 0.001 | 0.001 | 2 | stable |
| | TYR-1 | 0.001 | 0.002[5] | 0.005[5] | 0.004 | 0.001 | 1 | stable |
| | VLCAD | 0.008 | 0.007 | 0.007 | 0.006 | 0.007 | 12 | stable |
| | OCTN2 | 0.011 | 0.014 | 0.008 | 0.010 | 0.009 | 15 | stable |
| **SCID** | | | | | 0.016 | 0.008[1] | 14[1] | 2022: decrease |
| **SMA** | | | | | | 0.010[2] | 10 | - |
| **Total referral rate** | | 0.31 | 0.29 | 0.27 | 0.29 | 0.29 | 482 | stable |

[1] Excluding children who died before a referral could be made. In 2022, 6 for CH, 1 for SCID.
[2] Figure applies to only a part of the year: PA, MMA and CPT1 added to the screening programme per 1-10-2019, GALK per 1-10-2020, MPS I per 1-3-2021, SMA per 1-6-2022.
[3] BIO: possibly as a result of adapted reference values for BIO per 27-1-2020.
[4] GALT: possibly as a result of adapted reference values for GALT per 1-1-2019.
[5] TYR-1: possibly as a result of adapted reference values per 1-4-2019.

## DIAGNOSTIC RESULTS

In 2022, 467 children (excluding OCTN2) were referred for a target disease of the screening programme. In 233 (50%) cases one of the conditions was confirmed (table 5). This percentage is higher than in 2021 (41%). Children with a referral for OCTN2 deficiency (15 referrals, of which none were diagnosed with OCTN2) are not included in these numbers, because this condition is not a target condition of the screening programme, but an incidental finding. For 1 of the 467 referred children, no diagnosis was yet known at the time of writing this monitor.

Of the children born in 2022, one child was reported with a false-negative result for CH, and one child was reported with a false-negative result for CF.

**Table 5**
Diagnostic results of referred children born in 2022 (excl. OCTN2)

| 2022 | | Referred | Diagnosis confirmed | No target disease | Diagnosis (still) unknown | False-negative (test wrongly indicates no need for referral)[1] | Missed/ other[1] |
|---|---|---|---|---|---|---|---|
| **CAH** | | 6 | 4[2] | 2 | 0 | 0 | 1 |
| **CH** | | 233 | 100 | 132 | 1 | 1 | 0 |
| **CF** | | 34 | 22[3] | 12 | 0 | 1 | 0 |
| **HbP** | SCD | 31 | 30 | 1 | 0 | 0 | 0 |
| | HbH | 5 | 2 | 3[4] | 0 | 0 | 0 |
| | bTM | 13 | 5 | 8 | 0 | 0 | 0 |
| **MD** | 3-MHM | 15 | 3 | 12 | 0 | 0 | 0 |
| | BIO | 9 | 4 | 5 | 0 | 0 | 0 |
| | CPT1 | 4 | 0 | 4 | 0 | 0 | 0 |
| | GALK | 1 | 0 | 1 | 0 | 0 | 0 |
| | GALT | 8 | 4 | 4 | 0 | 0 | 1 |
| | GA-1 | 1 | 0 | 1 | 0 | 0 | 0 |
| | IVA | 5 | 2 | 3 | 0 | 0 | 0 |
| | MSUD | 1 | 1 | 0 | 0 | 0 | 0 |
| | MCADD | 20 | 19 | 1 | 0 | 0 | 0 |
| | MMA[5] | 18 | 1 | 17 | 0 | 0 | 0 |
| | MPS I | 3 | 2 | 1 | 0 | 0 | 0 |
| | PA | 2 | 2 | 0 | 0 | 0 | 0 |
| | PKU | 19 | 17 | 2 | 0 | 0 | 0 |
| | TFP/LCHAD | 2 | 1 | 1 | 0 | 0 | 0 |
| | TYR-1 | 1 | 0 | 1 | 0 | 0 | 0 |
| | VLCAD | 12 | 3 | 9 | 0 | 0 | 0 |
| **SCID** | | 14 | 1 | 13 | 0 | 0 | 0 |
| **SMA**[6] | | 10 | 10 | 0 | 0 | 0 | 0 |
| **Total** | | **467** | **233** | **233** | **1** | **2** | **2** |

[1] 'False-negative (test wrongly indicates no need for referral)' refers specifically to children who have not been detected by the screening test. Missed patients for other reasons (e.g. administrative) fall under the indicator 'Missed/other'.
[2] CAH: all 4 had classic salt-wasting CAH.
[3] CF: including 2 children with meconium ileus (MI).
[4] HbH: including 2 children with a mild form of alpha-thalassaemia.
[5] MMA: the definition of target disease is still under review: the diagnostic results may change. Four of the 17 children without MMA had maternal B12 deficiency.
[6] SMA was added to the screening programme per June 1st, 2022.

## DETECTION RATES AND VALIDITY

Table 6 shows the detection rates (per 1000 screened children), the positive predictive value (PPV), the sensitivity (Sens) and specificity (Spec) of the programme.

The detection rates of 2022 are comparable to those of previous years for most conditions (stable since 2018). The detection rate of CAH is lower compared to the years 2018-2021 (4 children with CAH in 2022, compared to 9-12 children in 2018-2021). The detection rate of CH was higher in 2022 compared to previous years (100 children with CH compared to 64-82 in 2018-2021).

In 2022, almost all target values of the positive predictive value (PPV) have been reached: CAH (>60%), CH (>30%), CF incl. MI (>65%), SCD (>90%), PKU (>60%), MCADD (>70%), MPS I (>50%) and SMA (>95%). Only for SCID (>10%) and CF excl. MI (>65%) target values were not met, and the signal value of >30% for the other MD with at least 5 referrals (introduced in this monitor) was not achieved for 3-MHM, VLCAD and MMA. For MMA, the target disease has not yet been clearly defined. The overall PPV (50%) is slightly higher than the 2018-2022 average (46%).

In 2022, the target values for sensitivity were not achieved for CH and CF due to false-negative results for CH and CF. The target values for specificity were met for all conditions.

**Table 6**
Detection rate, positive predictive value (PPV), sensitivity (Sens) and specificity (Spec) in children born in 2022 and the period 2018-2022 (excl. OCTN2)[1]

| | | 2022 | | | | 2018-2022[1,2] | | | | Trend detection rate 2018-2022 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Detection rate (per 1000) | PPV[3] (%) | Sens (%) | Spec (%) | Detection rate (per 1000) | PPV[3] (%) | Sens (%) | Spec (%) | |
| **CAH** | | 0.024 | 67 | 100 | 99.999 | 0.054 | 51 | 97.9 | 99.995 | low in 2022 |
| **CH** | | 0.598 | 43 | 99.0 | 99.921 | 0.457 | 33 | 98.2 | 99.908 | high in 2022 |
| **CF** incl. MI | | 0.131 | 65 | 95.7 | 99.993 | 0.142 | 71 | 95.3 | 99.994 | fluctuates |
| excl. MI | | 0.120 | 63 | 95.2 | 99.993 | 0.124 | 68 | 94.6 | 99.994 | fluctuates |
| **HbP** | SCD | 0.179 | 97 | 100 | 99.999 | 0.179 | 99 | 100 | 99.999 | fluctuates |
| | HbH | 0.012 | 40 | 100 | 99.998 | 0.020 | 40 | 100 | 99.997 | stable |
| | bTM | 0.030 | 38 | 100 | 99.995 | 0.022 | 49 | 100 | 99.998 | stable |
| **MD** | 3-MHM | 0.018 | 20 | 100 | 99.993 | 0.027 | 37 | 100 | 99.995 | stable |
| | BIO | 0.024 | 44 | 100 | 99.997 | 0.019 | 25[3] | 100 | 99.994 | stable |
| | CPT1[2] | 0 | | - | 99.998 | *0.002* | *9* | *100* | *99.998* | - |
| | GALK[2] | 0 | | - | 99.999 | *0* | *0* | - | *99.999* | - |
| | GALT | 0.024 | 50 | 100 | 99.998 | 0.019 | 21[3] | 100 | 99.993 | stable |
| | GA-1 | 0 | | - | 99.999 | 0 | 0 | - | 99.999 | stable |
| | IVA | 0.012 | 40 | 100 | 99.998 | 0.012 | 42 | 100 | 99.998 | stable |
| | MSUD | 0.006 | | 100 | 100 | 0.004 | 21 | 100 | 99.999 | stable |
| | MCADD | 0.114 | 95 | 100 | 99.999 | 0.109 | 92 | 100 | 99.999 | stable |
| | MMA[2] | 0.006 | 6 | 100 | 99.990 | *0.011* | *8* | *100* | *99.988* | - |
| | MPS I[2] | 0.012 | 63 | 100 | 99.999 | *0.016* | *63* | *100* | *99.999* | - |
| | PA[2] | 0.012 | | 100 | 100 | *0.009* | *50* | *100* | *99.999* | - |
| | PKU | 0.102 | 89 | 100 | 99.999 | 0.078 | 92 | 100 | 99.999 | stable |
| | TFP/LCHAD | 0.006 | | 100 | 99.999 | 0.002 | 20 | 100 | 99.999 | stable |
| | TYR-1 | 0 | | - | 99.999 | 0.002 | 9 | 100 | 99.998 | stable |
| | VLCAD | 0.018 | 25 | 100 | 99.995 | 0.025 | 35 | 95.5 | 99.995 | stable |
| **SCID[2]** | | 0.006 | 7 | 100 | 99.992 | *0.006* | *5* | *100* | *99.988* | - |
| **SMA** | | 0.100 | 100 | 100 | 100 | - | - | - | - | - |
| **Total[2]** | | **1.392** | **50** | **99.1** | **99.861** | **1.170** | **46** | **98.5** | **99.860** | |

[1] The PPV, Sens and Spec of five years combined are calculated because for some conditions only few children are referred per year. For these conditions a calculation over several years gives a more stable outcome.
[2] The total at the bottom of the table excludes conditions added to the heel prick screening less than 5 years ago. The total is thus without CPT1, MMA and PA (added per 1-10-2019, although the average over 3 years based on 11, 75 and 10 referrals, respectively, is shown in italics), and without GALK (per 1-10-2020), SCID (per 1-1-2021), MPS I (per 1-3-2021) and SMA (per 1-6-2022). The definition of target disease MMA is still under review: the diagnostic results may change.
[3] The PPV for 2022 is shown for conditions with 5 or more referrals. For the 5-year average, for the MD with 50 or more referrals, the PPV below the signal values are shown on a red background, while the unmet signal values with less than 50 referrals are shown in red numbers. The PPV for BIO is 35% since adjustment of the cutoff value for referral in 2020, and for GALT the PPV is 36% since adjustment in 2019 (signal values achieved).

## TIMELINESS OF DIAGNOSTICS

The timeliness of diagnostics is calculated based on data from all referred children. In 2022, only the target value for SMA was met (table 7).

**Table 7**
Timeliness of diagnostics among children born in 2018-2022

| Screening | 2018 | 2019 | 2020 | 2021 | 2022 | Targett value |
|---|---|---|---|---|---|---|
| **CAH** | 77 | 86 | 90 | 73 | 83 | ≥90%<15 days |
| **CH** | 84 | 86 | 88 | 80 | 81 | ≥90%<15 days |
| **CF all referrals** | 77 | 58 | 77 | 72 | 72 | ≥90%<30 days |
| **excl. MI** | 74 | 53 | 74 | 70 | 70 | ≥90%<30 days |
| **HbP**[1] | 91 | 100 | 81 | 82 | 77 | ≥90%≤6,0 weeks[2] |
| **MD** (excl. OCTN2) | 76 | 91 | 89 | 88 | 84 | ≥90%<10 days (most MD), <14 d (PA/MMA) or <30 d (MPS I) |
| **SCID** | | | | 90 | 86 | ≥90% < 15 days if TREC ≤2; <30 days if TREC >2 - ≤10; <15 days from aterme date for preterm childrenr |
| **SMA** | | | | | 100 | ≥90% < 15 days |

[1] All children referred for HPLC patterns matching with sickle cell disease, HbH-disease and beta-thalassemia.
[2] The target value has been changed to ≥90% ≤6.0 weeks since 1-1-2020 (this was ≥90% ≤12.0 weeks).

## COSTS

The costs of the screening programme (excluding diagnostics) were about 24.5 million euro in 2022 (source: Final bill NBS, RIVM-CvB, excluding the costs for Caribbean Netherlands). Screening costs per child are approximately 146 euro. Compared to last year, there is a cost increase of approximately 10% per child screened (figure 4). This increase is explained by an increase in fees for blood collection and laboratory analyses, the expansion of heel prick screening to include SMA and increased organizational costs, combined with a lower number of births in 2022 compared to 2021. Total costs increased less (3% relative to 23.8 million in 2021) due to this decrease in the number of births. In 2021 -presumably due to the COVID-19 lockdowns- many more children were born. In 2022, the number was again similar to 2020. Over the past 5 years, screening costs have increased by almost 50%.

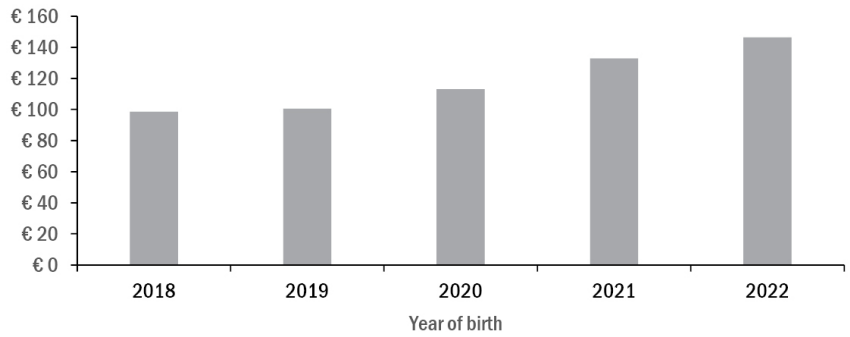



**Figure 4**
Costs of the screening programme per screened child according to year of birth (2018-2022)

## OBJECTIONS AGAINST STORAGE OF NEWBORN BLOOD

In 2022 8.9% of parents objected against the storage of the NBS blood residuals for the purpose of (non-identifiable) scientific research. This percentage shows an upward trend over time (figure 5).

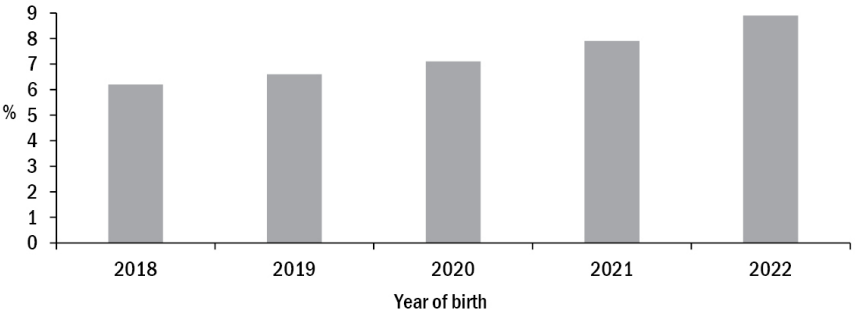



**Figure 5**
Objection of parents against the storage of NBS remnants for anonymous scientific research, by year of birth (2018-2022)

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