THE NEWBORN BLOOD SPOT SCREENING IN THE NETHERLANDS

MONITOR 2017

TNO innovation for life

The Newborn Blood Spot screening programme (NBS) was introduced in the Netherlands in 1974. The programme is coordinated by the Centre for Population Screening (CvB) of the National Institute for Public Health and the Environment (RIVM). The aim of the NBS is the early detection of certain serious congenital disorders in newborns. Children with these (rare) disorders benefit from early interventions such as medication or a diet, which can prevent or limit irreparable health damage.

The national monitor with main results of the NBS is carried out annually by TNO at the 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 program.

Parties involved in the realization of the NBS are presented in figure 1. The NBS is carried out by a public health care or maternity worker. When the baby is admitted to hospital during the first week after birth, the newborn blot spot is collected by a hospital health care worker.

Figure 1
Parties involved in the execution of the NBS

SUMMARY

- The results of most of the indicators matched the defined target- or signal values and the results of most indicators are in line with the results of previous years.
- NBS **participation rate** was 99.2% in 2017 (n=169,883); 476 children were referred of which 181 had the diagnosis confirmed.
- The **timeliness target value** of the **1st heelprick** was **not reached:** 98.8% was carried out within 168 hours after birth against a target value of 99.0%. The percentage was also below 99% in the years 2011-2016 with the exception of 2013. 38% of the heel pricks was performed in the recommended period of 72-96 hours after birth.
- The total screening programme has a **detection rate** of 1.07 per 1000 screened children in 2017, a **positive predictive value** of 42%, a **sensitivity** of 99% and a **specificity** of 99.850%.
- For **BIO** the number of children referred and the detection rate is remarkably high in 2017. For **CH** the number of children referred strongly rose in 2015, and strongly decreased again in 2016 and 2017.
- The **sensitivity** of screening for CF was 94% (excluding children with meconium ileus (MI) and 96% (including children with MI) in 2017. The sensitivity for CH was 99%. The target values of 100% were therefore not reached in 2017. The other conditions did reach the target value of 100%.
- All conditions reached the target values in terms of **specificity.**
- The target values for **timeliness of diagnostics** were not achieved for CAH (81%), CH (85%), CF (85%) and metabolic diseases (74%) in 2017.
- The target values concerning the percentage of children who needed a **repeat 1st heel-prick** was exceeded in the case of CF (0.52%, target value ≤0.50%). The target value for CH is almost reached (0.503%, target value ≤0.50%).
- The percentage of NBS with **inconclusive CH results** was 0.21% in 2017. This is considerably lower than in 2015 (0.82%) and 2016 (0.53%). The target value (≤0.50%) for this indicator was amply reached in 2017.

- The number of parents who **object** to the storage of bloodremnants for scientific research purposes rose slightly in 2017 to 5.3%.
- In 2017 **screening costs** per child (diagnostic costs excluded), were 94 euro: they show a rising trend since 2012 mainly because of the indexation of the costs for blood collection and laboratory analysis.

RECOMMENDATIONS

New recommendation:
- Improvement of the timeliness of diagnostics in CAH, CH, CF and metabolic diseases.

Existing recommendations that are still valid:
- Continue or intensify measures to improve the **timeliness of the 1st heelprick.**
- Gain more insight into the background of **objections against the NBS.**
- Continue or intensify the measures to reduce the high number of **repeat 1st heelpricks when screening for CH and CF** in so far it concerned an insufficient blood sample.
- Attention to the strong fluctuations in the number of **referrals for CH** over the years.
- Continued attention for timeliness and **clarity of registration** of diagnostic data.

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 NVK (the Dutch Society of Paediatrics) and the RIVM (www.neorah.nl) except for the data on congenital hypothyroidism (CH). The diagnostic CH data are registered by TNO. The NEORAH data related to metabolic disorders have been retrieved from the Dutch Diagnosis Registration Metabolic Diseases (www.ddrmd.nl). Notifications of the Dutch Pediatric Surveillance System (NSCK) have been used to detect possible missed cases. This monitor concerns **children who have been born in 2017** (Praeventis reference date: 16-03-2018, NEORAH: 03-07-2018[1], TNO Database: 11-09-2018).

READING GUIDE

This monitor differentiates between the 1st heelprick, a repeat 1st heelprick, a 2nd heelprick and a repeat 2nd heelprick.
- 1st heelprick: the first newborn blood spot collection that has been carried out.
- Repeat 1st heelprick: the newborn blood spot collection that is repeated when insufficient blood has been collected during the 1st heelprick in order to carry out the required laboratory analyses or when a child received a blood transfusion within 24 hrs before the heelprick was carried out. If a blood transfusion with erythrocytes has been carried out, the heelprick needs to be repeated after 91 days to exclude haemoglobinopathies (HbP).
- 2nd heelprick: carried out if the 1st heelprick gives an inconclusive laboratory result.
- Repeat 2nd heelprick: as in repeat 1st heelprick.

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.

[1] For CAH, CF and HbP data from NEORAH were extracted on another date, respectively on 03-09-2018, 20-09-2018 and 11-09-2018.

DIFFERENCE COMPARED TO PREVIOUS MONITORS

Since 2017, not only sickle cell disease but also two other types of hemoglobinopathy (HbP), namely HbH disease and beta-thalassemia major, belong to the target group diseases of screening. Previously, these two diseases were considered as incidental findings from the screening for sickle cell disease.

WHICH CONDITIONS ARE INCLUDED IN THE SCREENING?

- Congenital adrenal hyperplasia **(CAH)**
- Cystic fibrosis **(CF)**
- Congenital hypothyroidism **(CH)**
- Hemoglobinopathies **(HbP)**:
  - Sickle cell disease **(SCD)**
  - HbH-disease **(HbH)**, a form of alpha-thalassemia
  - Beta-thalassemia major **(bTM)**
- Metabolic disorders **(MD)**:
  - 3-Methylcrotonyl-CoA carboxylase deficiency **(3-MCC)**[1]
  - Biotinidase deficiency **(BIO)**
  - Galactosemia **(GAL)**
  - Glutaric acidemia type 1 **(GA-1)**
  - HMG-CoA lyase deficiency **(HMG)**[1]
  - Isovaleric acidemia **(IVA)**
  - Maple syrup urine disease **(MSUD)**
  - Medium-chain acylCoA dehydrogenase deficiency **(MCAD)**
  - Multiple CoA carboxylase deficiency **(MCD)**[1]
  - Phenylketonuria **(PKU)**
  - Trifunctional Protein deficiency/ Long-chain hydroxyacyl-CoA dehydrogenase deficiency **(TFP/LCHAD)**
  - Tyrosinemia type 1 **(TYR-1)**
  - Very-long-chain acyl-CoA dehydrogenase deficiency **(VLCAD)**
  - Carnitine transporter (OCTN2) deficiency **(OCTN2)**[2]

[1] These three conditions are reported altogether under one name: 3-MHM, since they have the same marker.
[2] OCTN2-deficiency is not part of the NBS: it is considered an incidental finding.

PARTICIPATION

In 2017 171,225 children were eligible to participate in the NBS. Newborn blood was collected in 169,883 children. This means that the participation rate is 99.2%, which is higher than the target percentage of 99.0% (figure 2).

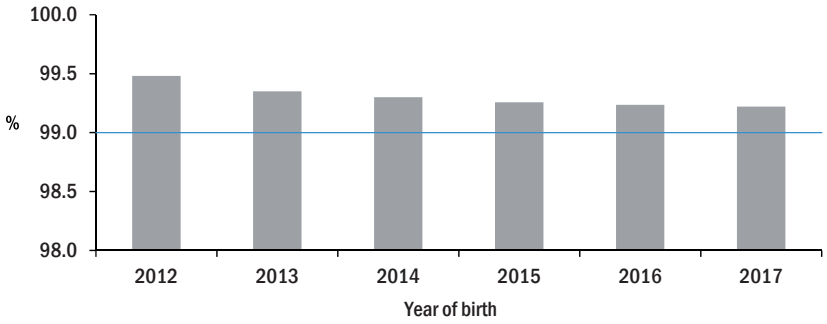

Figure 2
Participation rate of the neonatal screening programme by year of birth (2012-2017); to support readability the y-axis starts at 98%

Participation is slightly declining since 2012. The decrease from 2012 to 2013 (0.13%) can largely be explained by an improved registration of reasons for non-participation (before 2013 some children who did not participate were registered as 'missing' and were therefore not included in the calculation). From 2013 to 2017 there was a small decrease from 99.4% to 99.2%. This is mainly explained by an increase in the number of objections by parents to participate in the NBS (figure 3).

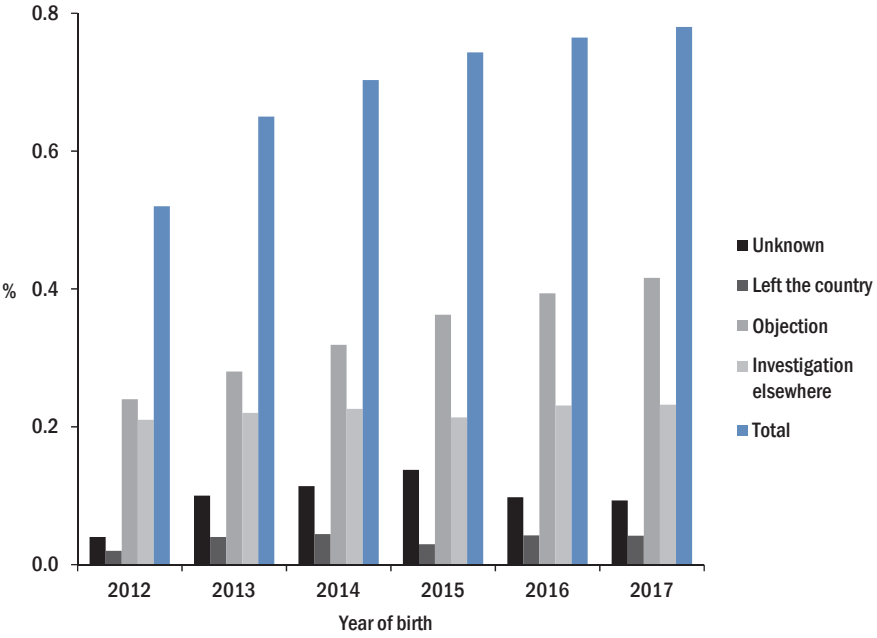

Figure 3
Reasons for non-participation in the neonatal screening programme by year of birth (2012-2017)

TIMELINESS OF BLOOD COLLECTION

Timing of the NBS is crucial. The heelprick should be carried out within 168 hours (7 days) after birth by a screener, but ideally, between 72 and 96 hours. In 2017 the percentage of 1st heelpricks carried out within 168 hours (7 days) after birth is 98.8%. The minimum target of at least 99.0% was therefore not reached. This was also the case in the previous years with the exception of the year 2013 (figure 4). In 38% of children, newborn blood spots were collected in the recommended period between 72-96 hours after birth in 2017.

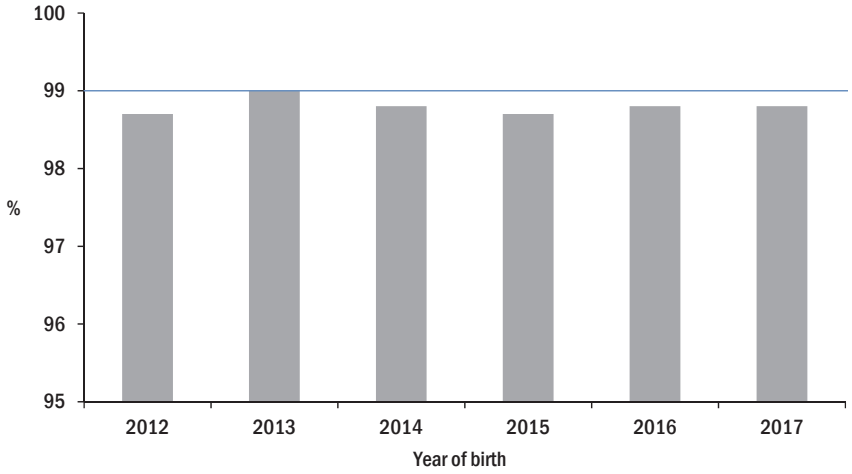

Figure 4
Timeliness of the blood spot collection by year of birth (2012-2017). Children born outside the Netherlands are excluded (the blue line indicates the signal value; to support readability the y-axis starts at 95%)

OBJECTIONS AGAINST STORAGE OF NEWBORN BLOOD

In 2017 5.3% of parents objected against the storage of the NBS blood remnants for the purpose of (anonymous) scientific research. This percentage shows a rising trend from 4.1% in 2012 to 5.3% in 2017 (figure 5).

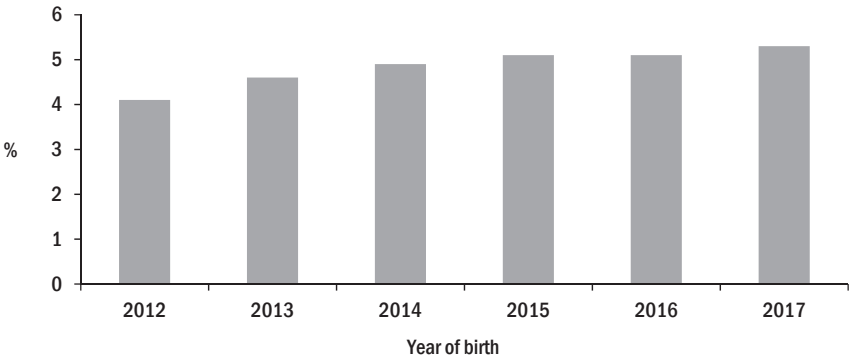

Figure 5
Objection of parents against the storage of NBS remnants for anonymous scientific research, by year of birth (2012-2017)

REPEAT 1ST HEELPRICK

In 2017 some of the blood spot collections needed to be repeated, for example because insufficient blood was collected on the blood spot card. The target values have been exceeded in CH and CF (table 1), but results are closer to the target value than in 2016.

Table 1
Repeat first heelpricks according to year of birth (2012-2017)

% of repeat 1st heelpricks		2012	2013	2014	2015	2016	2017	Number in 2017	Target value
CAH		0.08	0.09	0.10	0.09	0.10	0.09	(145)	≤0.50
CH		0.29	0.29	0.38	0.56	0.55	0.503	(855)	≤0.50
CF		0.34	0.33	0.48	0.58	0.61	0.52	(876)	≤0.50
HbP		0.61	0.58	0.71	0.82	0.82	0.70	(1187)	≤0.80
MD	PKU	0.11	0.11	0.14	0.14	0.18	0.17	(285)	≤0.50
	3-MHM	0.15	0.16	0.17	0.20	0.22	0.20	(339)	≤0.50
	BIO	0.31	0.29	0.42	0.51	0.54	0.46	(779)	≤0.50
	GAL	0.25	0.23	0.31	0.31	0.27	0.23	(384)	≤0.50
	GA-1	0.15	0.16	0.17	0.20	0.22	0.20	(339)	≤0.50
	IVA	0.15	0.16	0.17	0.20	0.22	0.20	(339)	≤0.50
	MSUD	0.11	0.11	0.14	0.18	0.18	0.17	(284)	≤0.50
	MCAD	0.15	0.16	0.17	0.20	0.22	0.20	(339)	≤0.50
	TFP/LCHAD	0.15	0.16	0.17	0.20	0.22	0.20	(339)	≤0.50
	TYR-1	0.11	0.11	0.14	0.18	0.18	0.17	(284)	≤0.50
	VLCAD	0.15	0.14	0.17	0.20	0.22	0.20	(334)	≤0.50
	OCTN2	0.11	0.11	0.14	0.18	0.18	0.17	(283)	≤0.50

SECOND HEELPRICK

In 2017 0.065% of the CAH results indicated the need for a 2nd heelprick. This means that the target value for this indicator (≤0.090%) has been reached (table 2).

In 2017 0.21% of the CH results indicated the need for a 2nd heelprick. The target value for this indicator (≤0.50%) was reached for the first time since 2011.

Table 2
Second heelprick according to birth year (2012-2017)

		2012	2013	2014	2015	2016	2017	Number in 2017	Target value
CAH	% of 2nd heelpricks	0.083	0.096	0.070	0.079	0.078	0.065	(110)	≤0.09
CH	% of 2nd heelpricks	0.53	0.55	0.74	0.82	0.53	0.21	(351)	≤0.50

REFERRALS

In 2017 the NBS resulted in 491 referrals (table 3). This gives a referral rate of 0.29% of the total number of screened children in 2017. This is a lower percentage when compared to previous years.

The referral rate for BIO is high in 2017 compared to previous years. The number of referrals for CH strongly fluctuates.

Table 3
Referrals according to birth year (2012-2017)

% referrals		2012	2013	2014	2015	2016	2017	Number in 2017	Trend
CAH		0.014	0.024	0.014	0.015	0.015	0.016	(27)[1]	stable
CH		0.20	0.19	0.22	0.31[2]	0.21	0.13	(229)	fluctuates
CF		0.027	0.023	0.019	0.020[3]	0.026[4]	0.016	(28)	fluctuates
HbP	Total	0.042	0.041	0.040	0.027	0.035	0.024	(40)	stable
	SCD[5]						0.015	(25)	
	HbH[5]						0.005	(8)	
	bTM[5]						0.004	(7)	
MD	PKU	0.009	0.009	0.011	0.012	0.012	0.008[6]	(13)	stable
	3-MHM	0.008	0.003	0.004	0.004	0.003	0.005	(9)	stable
	BIO	0.011	0.006	0.007	0.011	0.010	0.018[7]	(30)	2017 high
	GAL	0.029	0.032	0.035	0.041	0.019	0.021	(35)	reduction[8]
	GA-1	0.004	0.002	0.001	0.001[9]	0.001	0.001	(1)	stable
	IVA	0.002	0.001	0.002	0.001	0.004	0.002	(4)	stable
	MSUD	0.003	0.005	0.005	0.007[10]	0.012	0.010	(17)	stable
	MCAD	0.014	0.013	0.012	0.011	0.012	0.011	(19)	stable
	TFP/LCHAD	0.003	0.001	0.001	0.001	0	0.001	(2)	stable
	TYR-1	0	0.001	0.001	0.002	0.002	0.002	(4)	stable
	VLCAD	0.002	0.009	0.003	0.011[11]	0.005	0.011	(18)	fluctuates
	OCTN2[12]	0.009	0.008	0.006	0.005	0.012	0.009	(15)	fluctuates
Total referral rate		0.38	0.37	0.38	0.48	0.37	0.29	(491)	

[1] CAH: Excluding 1 child who was wrongly registered as deceased before the heelprick was carried out. And excluding 1 child who was incorrectly referred due to a registration error.
[2] CH: Includes a child who needed a 2nd heelprick ≥ 60 days after birth. TSH was not abnormal, however criteria belonging to a heelprick carried out <60 days after birth were used, leading to an 'abnormal' result.
[3] Excluding a child with an abnormal result, who died before referral (on day 3 after birth).
[4] Probably as a result of adapted reference values for CF per 01-07-2016 (resulting in more DNA testing and subsequently more referrals).
[5] HbP: until and including 2016: Concerns HPLC patterns appropriate to sickle cell disease, and incidental findings of alpha-thalassemia and beta-thalassemia. From 1-1-2017, HbH disease and beta-thalassemia major also belong to the target group diseases of screening and are reported accordingly.
[6] PKU: excluding a child who was not referred, because he/she died shortly after the heelprick was carried out.
[7] BIO: excluding a child who was not referred, because he/she died shortly after the heelprick was carried out.
[8] GAL: Possibly as a result of adapted reference values for GALT per 01-07-2015.
[9] GA-1: Excluding a child with an abnormal result which died before referral (on day 1 after birth).
[10] MSUD: Excluding a child with an abnormal result who died (date unknown) and was not referred.
[11] Results for VLCAD vary by year. Excluding a child with abnormal results who died before referral (3.5 weeks after birth). First heelprick was not classifyable, repeat first heelprick arrived in the laboratory three days before the child's death.
[12] OCTN2: is not part of the screening program, but is included in the calculation of the total referral rate.

DIAGNOSTIC RESULTS

In 2017, 476 children were referred for a condition that is part of the screening program. In 181 (38%) cases the condition was confirmed (table 4). For 40 children the diagnosis is (still) unknown.

Children with a referral for OCTN2-deficiency (n=15) are not included in these numbers, because this condition is not a target disease of the screening program, but an incidental finding.

In 2017 two children had a false-negative test result: 1 with CF and 1 with CH. The NBS results of these children were not abnormal, although they were diagnosed with one of the conditions from the screening programme at a later stage.

Table 4
Diagnostic results of referred children born in 2017[1]

2017		Referred	Diagnosis confirmed	No target disease	(Still) unknown	False negative	Missed
CAH		27	12	12[2]	3	0	0
CH		229	70	139	20[3]	1	0
CF[4]		28	23[4]	4	1	1	0
HbP[5]	SCD	25	17	1[6]	7	0	0
	HbH	8	3	2	3	0	0
	bTM	7	4[7]	1[8]	2	0	0
MD	PKU	13	12	0	1	0	0
	3-MHM	9	3	4	2	0	0
	BIO	30	9	21	0	0	0
	GAL	35	0	35	0	0	0
	GA-1	1	0	1	0	0	0
	IVA	4	3	1	0	0	0
	MSUD	17	0	17	0	0	0
	MCAD	19	18	1	0	0	0
	TFP/LCHAD	2	1	1	0	0	0
	TYR-1	4	2	2	0	0	0
	VLCAD	18	4	13	1	0	0
Total		476	181	255	40	2	0

[1] This table does not include 15 referrals for OCTN2-defciency (all without OCTN2).
[2] CAH: Of which four children with a classic non-salt-wasting form of CAH. For these four children referral is considered useful. Eight children do not have CAH.
[3] CH: Includes 7 children in which a conclusion with regard to the diagnosis is not yet possible and 13 children whose diagnosis is unknown (including 4 deceased children).
[4] CF: Including 6 children with meconium ileus.
[5] Since 1-1-2017 the screening has been extended with HbH-disease and beta-thalassemia major.
[6] Carrier of mild alpha-thalassemia.
[7] bTM: 2 of which have a confirmed bTM (beta-0 / beta-0), but in 2 other children it is not certain whether it is beta-thalassemia major or a milder variant of beta-thalassemia.
[8] bTM: this child has a mild form of beta-thalassemia (HBEE) and does not belong to the target group of the screening.

DETECTION RATES AND VALIDITY

Table 5 shows the detection rates (per 1000 screened children), the positive predictive value (PPV), the sensitivity (Sens) and Specificity (Spec) of the program, based on the numbers of 2017.

The detection rates are comparable to that of previous years since 2012 (stable) in most cases. In case of CAH and BIO, the detection rate is higher in 2017 when compared to previous years. The detection rate for BIO gradually decreased in previous years due to a change in diagnostic criteria. In 2017 there is a large increase in the number of children with BIO: instead of 1 child in 2016, 9 children with BIO have now been detected. The reason for this change is unknown. The detection rate for SCD decreased between 2012 and 2017.

The PPV target values have been reached for CAH (>15%), CH (>15%), SCD (>90%), PKU (>75%) and MCAD (>60%).

The target value for sensitivity is 100% for all conditions. In 2017 this target value for CH and CF has not been reached. For all other conditions the target value was reached.

The target values for specificity have been reached for all conditions in 2017.

Table 5
Detection rate, positive predictive value (PPV), sensitivity (Sens) and specificity (Spec) in children born in 2017[1,2]

2017		Detection rate (per 1000)	Trend detection rate 2012-2017[3]	PVW[4] (%)	Sens (%)	Spec (%)
CAH		0.071	2017 high	50	100	99.993
CH		0.412	stable	33	99	99.918
CF excl. MI		0.100	stable	81	94	99.998
incl. MI[5]		0.135	stable	85	96	99.998
HbP	SCD	0.10	reduction	94	100	99.999
	HbH	0.018	-		100	99.999
	bTM	0.024	-		100	99.999
MD	PKU	0.071	stable	100	100	100
	3-MHM	0.018	stable		100	99.998
	BIO	0.053	2017 high		100	99.988
	GAL	0	stable		-	99.979
	GA-1	0	stable		-	99.999
	IVA	0.018	stable		100	99.999
	MSUD	0	stable		-	99.999
	MCAD	0.106	stable	95	100	99.999
	TFP/LCHAD	0.006	stable		100	99.999
	TYR-1	0.012	stable		100	99.999
	VLCAD	0.024	stable		100	99.992
Total[4]		1.066		42	99	99.850

[1] In an extended evaluation report the PPV, Sens and Spec of several years combined are calculated. For some disorders, only few children are found per year. For these disorders a calculation over several years gives a more stable outcome.
[2] OCTN2 is not included in this table.
[3] Data not shown.
[4] Only a few children per year are referred for HbH, bTM and for many of the various metabolic diseases. There are therefore no target values for the PPV of these diseases. Due to the small numbers, the PPV is omitted.
[5] Includes children with CF with meconium ileus.

TIMELINESS OF DIAGNOSTICS

From 2017 onwards, the timeliness of diagnostics will be calculated in the total population of children that have been referred to paediatricians for all diseases. Until 2016, only children with the condition were included in the calculation for CAH, CH and CF.

The target values for the conditions CAH, CH, CF and MD were not achieved in 2017 (Table 6).

Table 6
Timeliness of diagnostic results in children born in 2017[1]

Screening	% diagnosed in time	Target value
CAH	81	≥90%<15 days
CH	85	≥90%<15 days
CF all referrals	85	≥90%<30 days
excl. MI[2]	86	≥90%<30 days
HbP[3]	97	≥90%<12 weeks[4]
MD[5]	74	≥90%<10 days

[1] Calculated over all children that were referred.
[2] Calculated over all children referred for CF excluding children with meconium ileus.
[3] All children referred for HPLC patterns matching with sickle cell disease, HbH-disease and beta-thalassemia.
[4] 38% of children were seen <28 dagen after birth.
[5] OCTN2 excluded.

COSTS

The costs of the screening programme (excluding diagnostics) were about 16.2 million euro in 2017 (Source: Final bill NBS, RIVM-CvB). Screening costs per child are 94 euro. Since 2012, screening costs per child have been rising with an average of 3.5% each year, caused partly by the indexation of the costs for blood collection, the heel prick set and laboratory analysis.

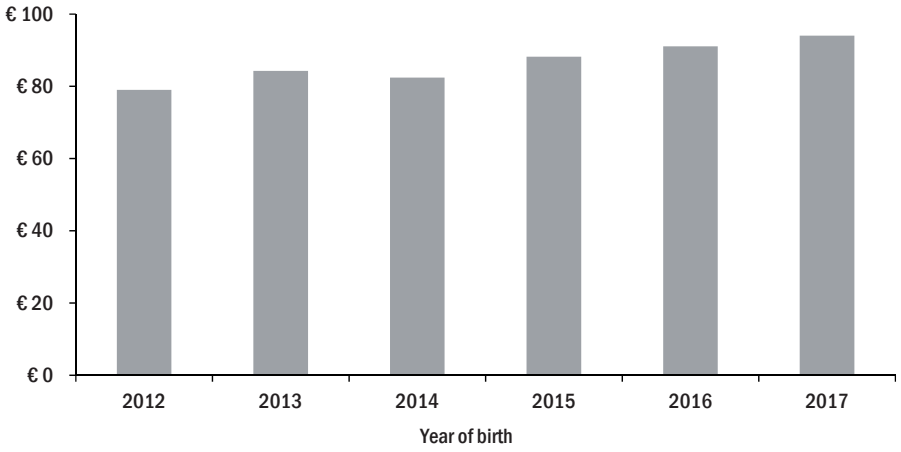

Figure 6
Costs of the screening programme per screened child according to year of birth (2012-2017)

December 2018

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PROJECT NUMBER
060.32378

REPORT NUMBER
TNO 2018 R11681

COMMISSIONED BY
RIVM

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