NEWBORN SCREENING **ONTARIO**
DÉPISTAGE NÉONATAL **ONTARIO**

Annual Report to the Newborn Screening Ontario Advisory Council – Public Version

Calendar Year 2018

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1. Sample Volumes in 2018

Table 1. Sample volumes from 2016-2018, by sample type.

Indication	Sample Type	2018	2017	2016
Routine screening	Satisfactory	145,724	145,405	145,018
	Unsatisfactory*	1,365	2,248	1,755
Routine Screening – Total		**147,089**	**147,653**	**146,773**
Referred-in screening: full panel	Satisfactory	860	396	410
	Unsatisfactory	13	11	6
Referred-in Screening: – Total		**873**	**407**	**416**
Referred-in screening: AAAC only	Satisfactory	4,028	1,371	410
	Unsatisfactory	<5	0	6
Referred-in Screening: – Total		**4,029**	**1,371**	**416**
Cord Blood	Cord blood - Hemoglobin Screen	503	1,023	914
Post Mortem	Satisfactory	413	357	300
	Unsatisfactory	0	8	-
Diagnostic/Monitoring Bloodspot	Satisfactory	1,460	1,002	669
	Unsatisfactory	0	30	14
Research DBS samples	Satisfactory	108	2,388	1,552
	Unsatisfactory	0	108	40
Non-screening bloodspot samples – Total		**2,484**	**4,916**	**3,489**
Grand Total		**154,475**	**154,347**	**151,094**

*unsatisfactory in this table is defined as samples unable to be tested because of poor sample quality (i.e. laboratory unsats)

1.1 Screening Samples

The overall number of samples received by NSO in 2018 is very similar to 2017. Although there is a lower unsatisfactory rate, the emergency backup coverage for AAAC screening for another province's screening program continued throughout 2018 and will become a contracted service in 2019. The increase in diagnostic and monitoring samples continues, but the number of cord blood samples has reduced. Research samples are expected to increase again in 2019 with further expansion of the Gates project.

1.1.1 Infants Screened

The total number of samples received for newborn screening purposes only is depicted in Figure 1, along with the number of infants screened. The number of infants tested is an estimate which may be impacted by the efficiency of the linking algorithm as well as data quality. The number of infants tested is always lower than the number of samples received due to repeats required for transfusion, prematurity/low birth weight, and laboratory and data unsatisfactory samples.

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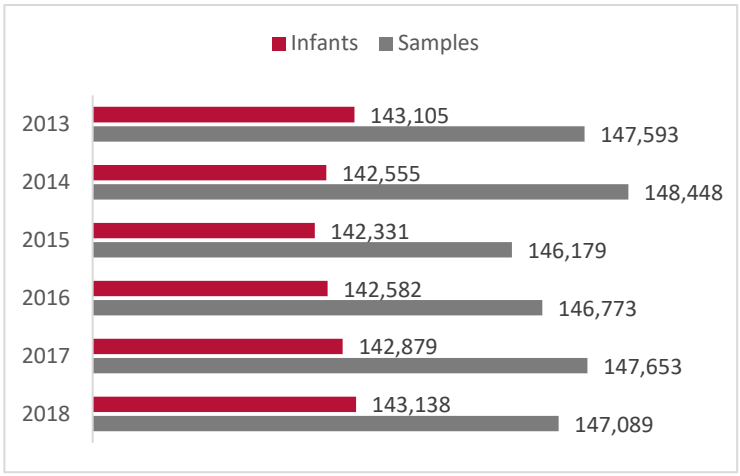

The overall number of infants tested is relatively constant each year with only ~1500 infants difference between the highest and lowest years.

Based on defers/ declines, missed screen alerts and deceased infants from BORN, and newborn screening sample counts, NSO estimates the total number of infants in Ontario as 143, 641, and the rate of screening uptake in 2018 as 99.6% , 0.1% lower than in previous years.

Figure 1: Total number of infants and samples screened from 2013-2018.

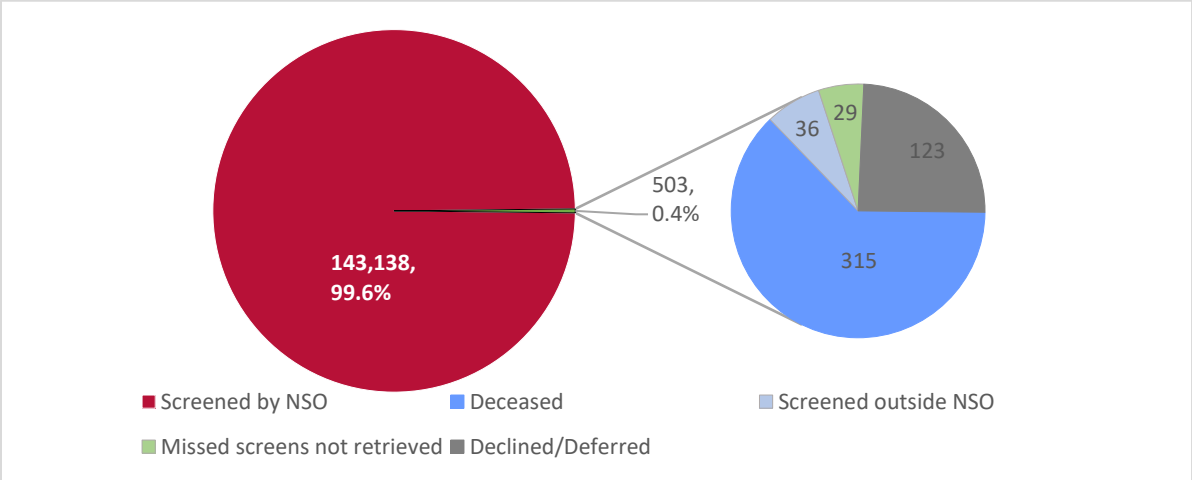

Figure 2. Coverage of screening in Ontario births, 2018.

1.1.2 Declined/Deferred Testing

If parents wished to decline or defer newborn screening, health care providers have the parents sign a decline/defer form included as part of the newborn screening card and submit the card with completed demographic information to NSO. This avoids unnecessary follow up in the case of a decline and allows formal documentation that screening was offered. Upon receipt of the decline form, NSO enters the information and generates a letter to the submitter documenting the receipt of the decline.

Similarly, in the case of a deferral, the information is entered and a letter is sent to the submitter. If a sample is not received by 14 days from the receipt of the deferral notice, NSO sends an additional reminder letter to the family directly.

In 2018, NSO received 603 completed decline/defer forms, a continued increase from previous years. The number of declines documented using this form has increased slightly with 62 declines in 2018 compared with

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50 in 2017. In two cases a decline form was completed but a sample was subsequently received so these have been counted as deferrals. The remaining 541 forms received indicated a parent's desire to defer screening, and samples were eventually received for all but three of these deferred cases. Defer forms were primarily received from nine hospitals, with the top three hospitals contributing 36%, 16% and 12% of the forms respectively. The total number of hospitals and midwifery practice groups using the decline/defer form remains consistent at 22, from 24 in 2017. The use of the decline and defer form continues to increase each year, which is an improvement to documentation and reduces unnecessary follow up.

Table 2. Declined, deferred samples indicated on card between 2018.

Case Type	2018	2017	2016	2015	2014
Declined/deferred form received	603	499	396	234	55
Decline	62	50	28	29	23
Deferral	541	449	368	205	32

An additional 58 declined screens were also identified via missed screen alerts. Although the total number of declines has reduced and remains below 0.1% of the population (table 3), the use of the decline form has increased greatly. This is very helpful in reducing the missed screen alert rate and eliminating additional follow up workload.

Table 3. Overall declined screens from 2014-2018.

Infants with declined newborn screening test				
2018	2017	2016	2015	2014
120	127	116	104	106

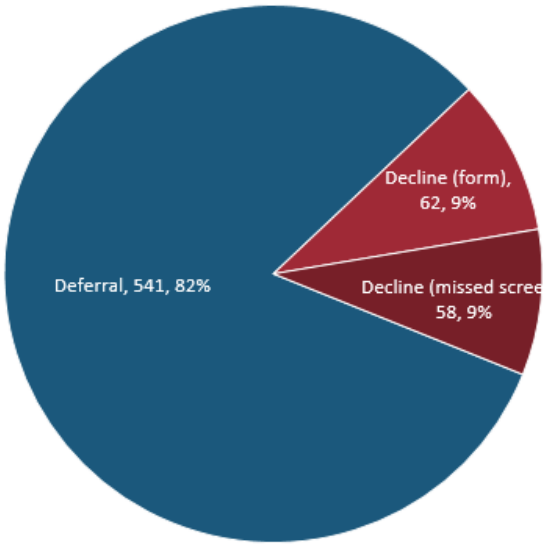

Figure 3. Declines and deferrals in 2018

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1.1.3 Missed Screens

Table 4. Potential missed screen alerts requiring follow-up in 2018, by reason and responsible submitter, and samples received post follow-up.

Category		Total (2018)	Samples received	Percent received	Total (2017)
Other	Deceased/ Palliative	38			35
	Declined	58			83
	Incorrect or incomplete BORN information (ex. infant <8days old, stillborn/TA)	<5			<5
	Incorrect or incomplete information (sample already received)	5			18
	NBS done in other jurisdiction	36			29
	Parents deferred NBS	<5			<5
	Sample received, collected prior to missed screen alert	117			66
Total: Non-Missed Screens		**258**			**237**
True Missed Screens	Home birth/birth centre midwife care	6	<5	17%	11
	Hospital birth midwife care	12	9	75%	39
	Interhospital transfer (between hospitals)	9	9	100%	16
	Intrahospital transfer (between units in same hospital)	9	<5	44%	<5
	Intrahospital/interhospital transfer with midwife involvement	<5	<5	100%	<5
	Sample collected, package lost	64	61	95%	41
	Not taken in error	43	45	105%	62
	Unknown reason hospital birth	25	10	40%	27
Total: True Missed Screens		**169**	**140**	**72%**	**168**
Grand Total		**427**			**439**

In 2018, there were 427 potential missed newborn screen alerts that required follow up by NSO. This is down by 12 alerts from 2017. Hospitals were the responsible facility in 89% of the missed screen alerts and midwives were involved in roughly 11% of the cases. Midwifery involvement has reduced from previous years where there were 158 (36%) cases in 2017 vs. 45 (11%) cases in 2018. Action on the part of NSO resulted in 140 of the 169 (82%) truly missed screens being completed.

Missed Screens and BORN entry

NSO is dependent upon timely data entry into BORN on the part of responsible health care providers for missed screen alerts. The missed screen alert is flagged when the entry is made in BORN if the child is already >8 days of age, therefore NSO is sometimes alerted of a missed screen at a much later age due to late entry into BORN.

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In 2018, true missed screen alert ages ranged from 8 to 98 days at time of alert, 82% of true misses were identified by two weeks of age.

In addition, there were 174 cases in which no alerts were triggered because of late data entry into the BORN system, but samples were received at >8 days of age. This included 58 samples from midwives and 116 from hospitals. Late entry missed screens are also identified by outstanding test requests. Many facilities have a mechanism for flagging pending newborn screening results for samples collected. There were 3 missed screen alerts that were initiated by outstanding report requests because the BORN entry had not yet been completed.

Missed Screens and Declines
In 2018 there were 58 declines identified by the missed screen alert process, compared to the 83 declines identified this way in 2017. Combined with the declines received via the decline form process outlined above, the total number of declines decreased by 7 this year (Table 3). Midwives were the health care provider in 56% (n=68) of declined cases.

Missed Screens and Screen Positive Results
There were infants identified in missed screen alerts who ultimately screened positive for a disease in 2018. Subsequently these infants were found either to be deceased, not affected, or the DERF was still pending.

Missed Screens and Transportation
In addition to other tracking systems, missed screen alerts help to identify packages delayed or lost in the transportation system. In 2018, 18 packages (64 samples) were identified as delayed or lost via missed screen follow up. Due to the earlier missed screen alert at 8 days of age, 44 of these samples were retrieved quickly and able to be tested. All other samples required repeat sampling due to damaged or lost packages, but submitters were alerted at an earlier age of the need to recall the baby.

1.2 Non-Screening Samples

In addition to routine screening samples, and screening samples referred from other jurisdictions, Newborn Screening Ontario accepts non-screening samples of various types, including post-mortem blood and bile samples from the Ontario Forensic Pathology Service, and cord blood samples from the National Cord Blood Registry. NSO offers diagnostic and monitoring testing for targets of newborn screening, and the biggest volume comes from PKU home monitoring. Samples were received from 91 unique patients in 2018, including 21 patients from other provinces (i.e. NL and NU where contracted services are provided).

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Table 5. Monitoring/Diagnostic Sample volumes from 2014-2018 by sample type.

Indication	Sample Type	2018	2017	2016	2015	2014
Cord Blood	Cord blood - Hemoglobin Screen	503	1,023	914	900	469
Post Mortem	Post Mortem – blood	214	183	152	150	164
	Post Mortem – bile	199	174	148	145	169
	Unsatisfactory	10	8	-	-	-
Diagnostic/Monitoring Bloodspot	Amino acids/Acylcarnitine	7	<5	<5	<5	<5
	CAH Monitoring	<5	<5	<5	<5	0
	Glutaric Aciduria Type 1	16	35	29	45	29
	Tyrosinemia	56	40	23	42	38
	Phenylalanine monitoring	1,222	781	564	407	368
	SCID Diagnostic	72	102	42	24	32
	Identity testing (discrepant results, positives)	<5	<5	<5	<5	5
	CF diagnostic & Other	84	38	<5	<5	<5
	Unsatisfactory	9	30	14	11	<5
Research DBS samples	Gates Cord Satisfactory	314	1,128	168	n/a	n/a
	Gates Heel Satisfactory	152	536	115	n/a	n/a
	Guyana Satisfactory	394	724	1,269	n/a	n/a
	Unsatisfactory	0	108	40	n/a	n/a
Non-screening sample – Total		**3,256**	**4,916**	**3,489**	**1,735**	**1,283**

1.2.1 Congenital Cytomegalovirus Testing

Since its inception in April 2006, NSO has received requests to test stored blood dot samples to assist in the clinical work-up of children suspected to have congenital cytomegalovirus (cCMV).

Table 6. CMV requests from 2014-2018.

	2018		2017	2016	2015	2014
	Diagnostic	Targeted Screening				
Samples tested	259	849	267	189	129	94
Positive CMV results (% of samples tested)	22 (8.5%)	10 (1.2%)	20 (7.5)%	11 (5.8)%	11 (8.5)%	9 (9.6)%

In May 2018 NSO implemented targeted CMV screening for infants referred for audiology assessment through our collaboration with the Ontario Infant Hearing Program (IHP) to screen for risk factors related to permanent hearing loss. The Clinical and Joint IHP/NSO Operations Committees continued to examine key operational issues such as consent, information sharing, the development of referral pathways, and recommendations for follow up of screen positive infants in preparation for universal screening.

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On average for the last 5 years, just under 8% of diagnostic samples tested have been screen positive. For the targeted screening, 1.2% screened positive. The expected CMV positive rate in the NBS population is estimated to be 0.6%, indicating a higher index of suspicion in the requests for testing received by NSO.

1.2.2 Hemoglobin Carrier Requests

Table 7. Hemoglobin carrier requests from 2014-2018.

	2018	2017	2016	2015	2014
Requests from high risk population	46	61	28	34	34
Total Requests	**55**	**69**	**45**	**45**	**53**
Number of carriers	18	18	11	14	13

In 2018, approximately 0.8% of carriers requested their results. The number of hemoglobin carrier requests has decreased over the last year.

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2. Demographics of Screening Samples

2.1 Age at Collection

Table 8. Age at collection for 2018, initial samples only.

Age at Collection	Number of Initial Samples (2018)	% of Initial Samples (2018)	% of Initial Samples (2017)
Less than 24 hours	803	0.56%	0.60%
24-47 hours (1-2 days)	135,948	95.20%	90.86%
48-72 hours (2-3 days)	3,989	2.79%	5.99%
73-168 hours (3-7 days)	1,156	0.81%	2.33%
Greater than 168 hours (7days)	841	0.58%	0.18%
Not specified	28	0.02%	0.04%

The majority of newborn screening samples are collected between 24-48 hours of age. Greater than 95% of samples are collected by 48 hours of age. There has been a positive shift towards samples being collected between 24-48 hours of age following the official change to NSO's recommended age of collection in January 2017.

2.2 Transfusion Status

NSO recommends that a repeat sample be taken 4-6 months after the most recent transfusion, therefore some infants who have had multiple transfusions will be greater than six months old when they are eligible for a repeat newborn screening sample. If a sample is taken prior to the transfusion, even if it is done at <24 hours of age, a repeat sample 4 months later may not be required as the initial sample (even if <24 hours) often allows for appropriate screening of hemoglobinopathies and galactosemia and the post transfusion sample for screening of the remaining conditions. If the submitter has their own tracking system in place, repeat samples are received at NSO between 4-6 months of age and no reminder needs to be issued to the submitter. At 6 months submitters and/or primary health care providers receive a reminder by fax that a repeat screen is required. If no repeat is received by 12 months, the case is closed with a close case letter to the submitter (and HCP if indicated). If NSO is informed by the submitter that the infant is deceased, the case is closed as no repeat sample will be received.

Table 9. Transfusion cases in 2018

Category		Number of Cases
Repeat Not Required		317
Repeat Required		139
Case still open not yet reviewed		17
Grand Total		**473**
Repeat Required	Repeat Received	35
	Repeat Not Received	104
	Case still open	68
	Deceased	19
	Closed case letter sent	10
	Other	7

Table 10. Age at which transfusion repeats were received in 2018

Age	# of samples
4-6 months	7
6-12 months	26
>12 months	<5
Grand Total	**35**

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There were 473 transfusion cases in 2018. For 317 cases (67%) a repeat was not required as a satisfactory pre-transfusion sample was already received. For cases requiring a repeat sample, 35 (25.2%) have been received, the majority of which were received between 6-12 months of age.

2.3 Premature Infants

NSO's extreme premature infant policy indicates that any infant <1500 g or <33 weeks gestation is recommended to have a repeat sample obtained around 21 days of age or sooner if the infant was to be discharged to complete screening for congenital hypothyroidism. In 2018, there were 2238 infants that fit the premature infant policy. Of these, 1572 (70%) had a 3 week (or equivalent) sample obtained.

Table 11. Number of premature samples received per year.

Year	Total # of patients	Number of repeat samples received between 7-31 days of age	Total number of repeat samples received	Percentage of total repeat samples received
2014	2111	1367	1681	79.63%
2015	2058	1420	1678	81.54%
2016	2166	1458	1830	84.49%
2017	2160	1539	1916	88.70%
2018	2238	1572	1944	86.86%

While the number of infants meeting the premature policy has not increased over the past 5 years, the numbers of repeat samples (i.e. those recommended by the policy) received at NSO has increased.

The total number of repeat samples received from premature babies is much higher reflecting those received due to an unsatisfactory initial sample obtained at <7 days of age, and those obtained at >4 months of age in keeping with the NSO transfusion policy.

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3. Unsatisfactory Samples

Table 12. Unsatisfactory samples by reason from 2014-2018.

			2018	2017	2016	2015	2014
SAMPLES	Satisfactory Samples		145,045	144,717	144,359	144,074	144,099
	Unsatisfactory Samples		2,044	2,936	2,414	2,105	4,349
	Unsatisfactory Rate		**1.41%**	**1.99%**	**1.64%**	**1.44%**	**2.93%**
	Samples Collected at <24hrs		575	577	518	603	628
	Unsatisfactory Samples excluding <24hr samples		1,469	2,359	1,896	1,502	3,721
	Unsatisfactory Rate excluding <24hr samples		**1.01%**	**1.60%**	**1.30%**	**1.03%**	**2.52%**
REASONS	Lab Unsat Reasons	Quantity of blood insufficient	710	1471	1094	888	1,707
		Blood spots appear scratched or abraded	292	531	421	228	1353
		Blood spots are supersaturated	176	185	193	222	1140
		Blood spots appear clotted or layered	403	639	491	299	958
		Blood spots appear diluted	<5	5	17	42	65
		Blood spots exhibits serum rings	168	200	95	32	65
		Blood spots are wet and/or discolored	38	<5	5	<5	16
		EDTA contamination	<5	13	-	-	-
		Other	86	49	35	16	7
	Data Unsat Reasons	Blood dot collection paper is expired	12	77	95	104	120
		Insufficient data provided	11	29	14	22	32
		Damaged or delayed in transit	45	8	<5	0	23
		Delivered to lab > 14 days after collection	8	23	<5	20	30
		Sample collected at <24hrs	575	577	518	603	628
		Other/Mislabel	90	47	46	21	16

There were 457 samples that were deemed unsatisfactory for more than one reason (which results in the discrepancy between the total number of unsatisfactory reasons and number of unsatisfactory samples). In total there were 1998 patients with unsatisfactory samples.

3.1 Sample Quality – Laboratory Unsats

The majority of unsatisfactory samples (excluding <24 hour samples) are related to the quality of the blood sample collection directly, including too little or too much blood, or improper application of the blood on the card.

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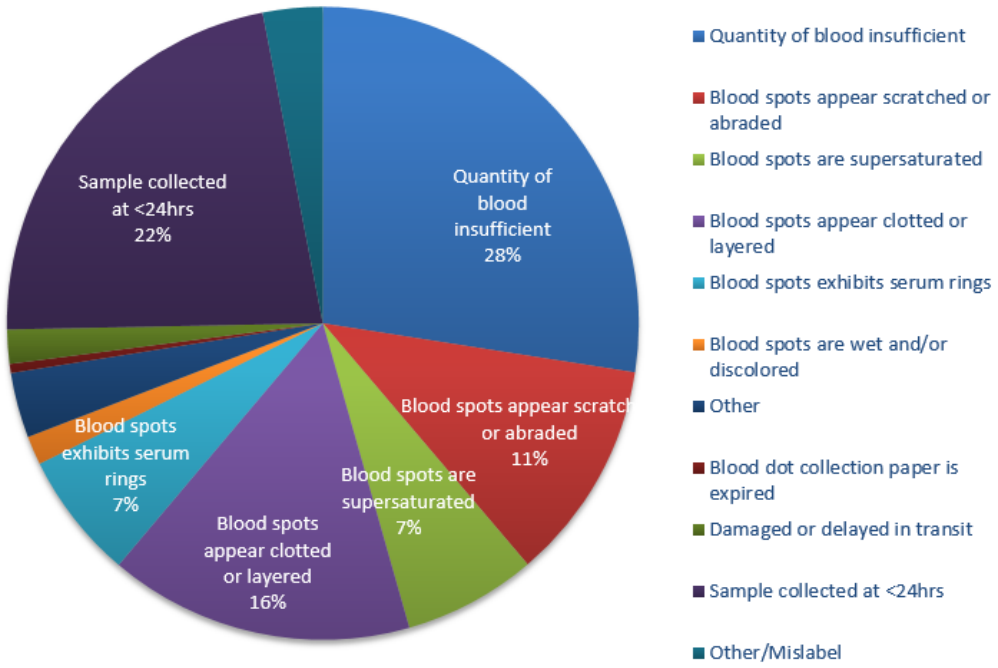

Figure 4. Distribution of unsatisfactory reasons in 2018.

3.2 Test Level Unsats

Test Level Unsats (TLU) are samples deemed unsatisfactory for reporting post testing due to poor quality results or insufficient sample to repeat testing. Results are reported out only for those diseases where testing could be completed, and a repeat is requested when necessary. Repeats may not be required if a previous sample allowed for completion of the testing for a disease.

Table 13. Repeat samples for TLU

Time to receipt of TLU repeat sample	Samples (%)
Total Test Level Unsats	**129**
< 3 weeks	80.6%
≥3 weeks < 6 weeks	8.5%
≥ 6 weeks	4.7%
Not received	8.5%

In 2018 there were 129 TLU which required a repeat. Some of the TLUs were also unsatisfactory samples due to collection at <24 hours. Most (80.6%) repeats were received within 3 weeks. In 16 cases an urgent sample was requested. These urgent requests were all fulfilled within 6 days of notification.

3.3 Data Quality and Process Related Unsats

The number of samples ultimately deemed unsatisfactory related to insufficient information remains consistently low, due to the efforts made by NSO to contact submitting providers for missing data fields.

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Expired cards can fluctuate year to year, depending on when the lots of cards expire. There were two lots of cards that expired in 2017, in April and July. NSO sends out bulletin reminders to submitters when an expiry date is approaching, asking them to check and circulate their stock. In addition, NSO has rolled out the shipment tracking system, Track-Kit, which alerts submitters to expired cards in their inventory. These strategies are having a good impact on reducing the number of expired cards received.

Although great improvements have been made to shipping and timeliness in the last 5 years, there is now a better awareness of damage and delays caused by shipping. These are better identified now that most sites are fully using the Track-Kit shipping software.

3.4 Repeat Rates for Unsatisfactory Specimens

The majority (83.5%) of repeat samples are received within 3 weeks of the initial sample. By 6 weeks, 89.8% of unsatisfactory samples have had screening completed via a repeat sample. A further 3.2% (cumulative total of 93%) of repeats are received at or after 6 weeks. Repeat samples have not yet been received for 140 (6.8%) of unsatisfactory samples in 2018.

Table 14. Repeats received on unsatisfactory samples, 2018 data only.

Time to receipt of repeat sample	Samples (%)
Total Unsats 2018	**2,044**
Up to 3 weeks	83.5%
Greater than 3 weeks up to 6 weeks	6.3%
Greater than or equal to 6 weeks	3.2%
Not received	6.8%

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4. Screen Positives

In 2018, there were 1453 screen positive referrals. This represents 1.02% of the total number of infants screened by NSO. There were 1565 laboratory positives, but 33 had an elevated TSH in samples taken at <24 hours and 79 were premature infants who screened positive for SCID so were not referred. One TSH on a < 24 hour sample was referred as the TSH value was >40. In addition, 104 screen negative twin/multiples referrals were made in 2018.

The number of screen positive infants referred in 2018 was similar to 2017 (1453 vs. 1464). This is discussed further in Section 4.2.

4.1 Referrals by Treatment Centre

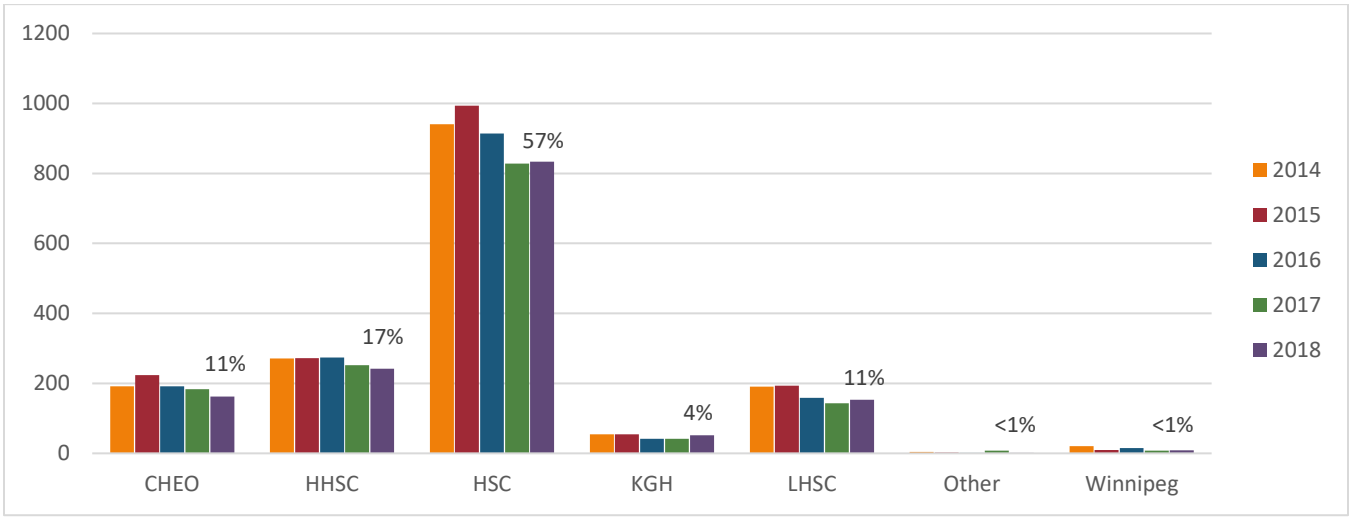

Figure 5. The total number of referrals by treatment centre from 2014-2018

The number of referrals over the last 5 calendar years to the five Ontario treatment centres and the Winnipeg treatment centre are depicted in the graph above. 'Other' represents infants referred to treatment centres outside of Ontario/ Winnipeg, such as Quebec or the USA, or a centre in Ontario that is outside of the standard treatment centres. The proportion of referrals received by each of the five Ontario regional treatment centres remained consistent between 2017 and 2018.

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4.2 Screen Positive Referrals by Disorder Group

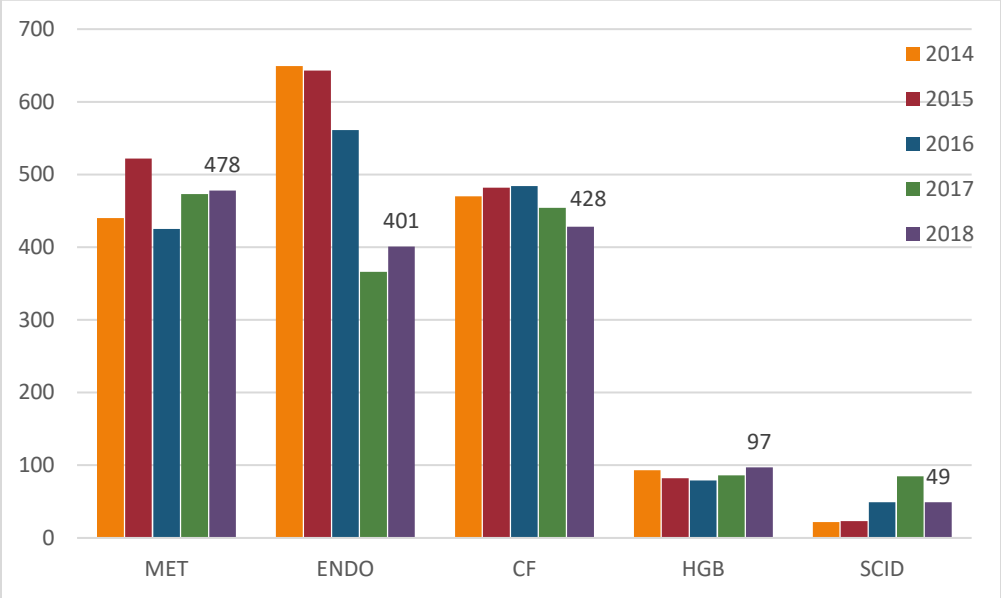

Figure 6. The total number of screen positives by disease grouping from 2014-2018

The number of screen positive referrals per disease grouping increased for endocrine disorders. Numbers remained constant for Hemoglobinopathies and Metabolic disorders, whereas they decreased marginally for Cystic Fibrosis, and decreased significantly for SCID. These details are discussed further in the sub-sections below.

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4.2.1 Percentage of Screen Positive Referrals by Disorder in 2018

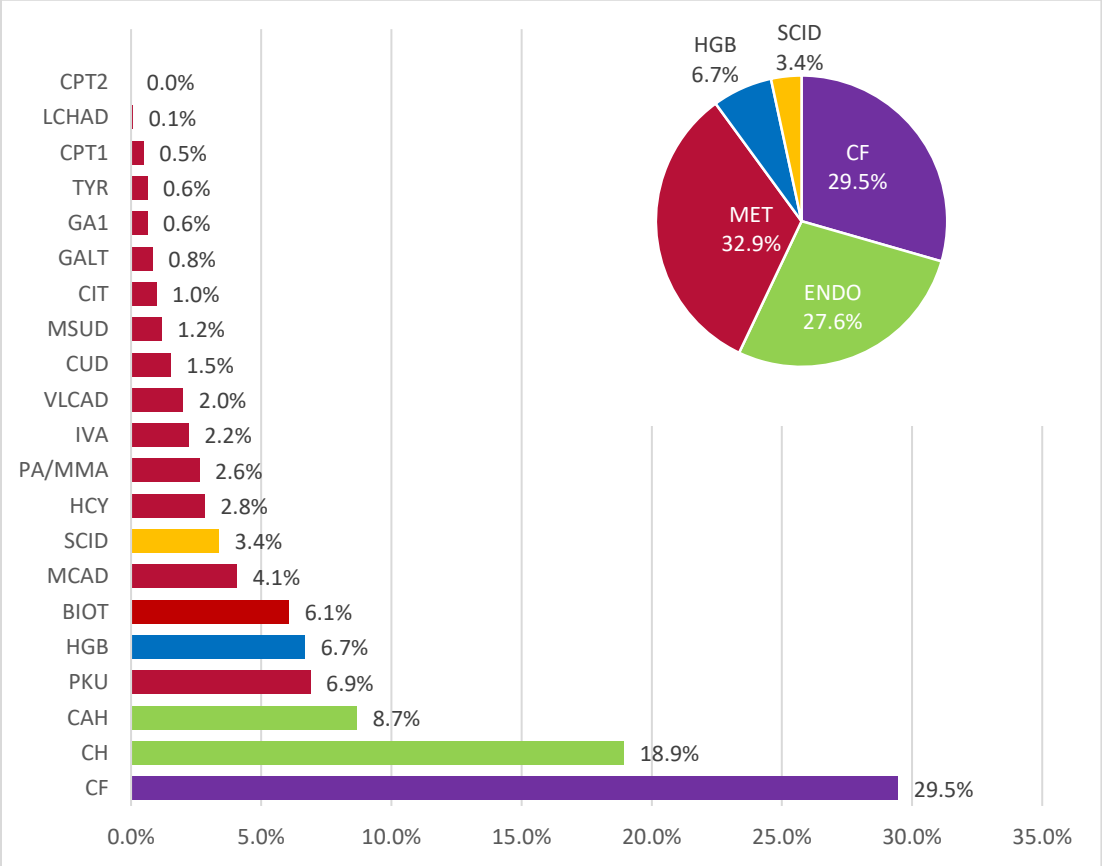

Figure 7. The percentage of screen positive referrals by disorder in 2018.

Metabolics, Cystic Fibrosis, and Endocrinopathies represent 32.9%, 29.5%, and 27.6% of screen positives respectively. SCID screen positive referrals decreased in 2018 and now represent only 3.4% of total screen positive referrals. Hemoglobinopathies represent approximately 6.7% of screen positive referrals.

4.2.2 Hemoglobinopathies

The number of screen positives in 2018 remained about the same as 2017, with an increase of only 11 referrals.

4.2.3 Cystic Fibrosis

The number of screen positives in 2018 decreased slightly as compared to 2017, with a difference of 26 referrals noted.

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4.2.4 Endocrinopathies

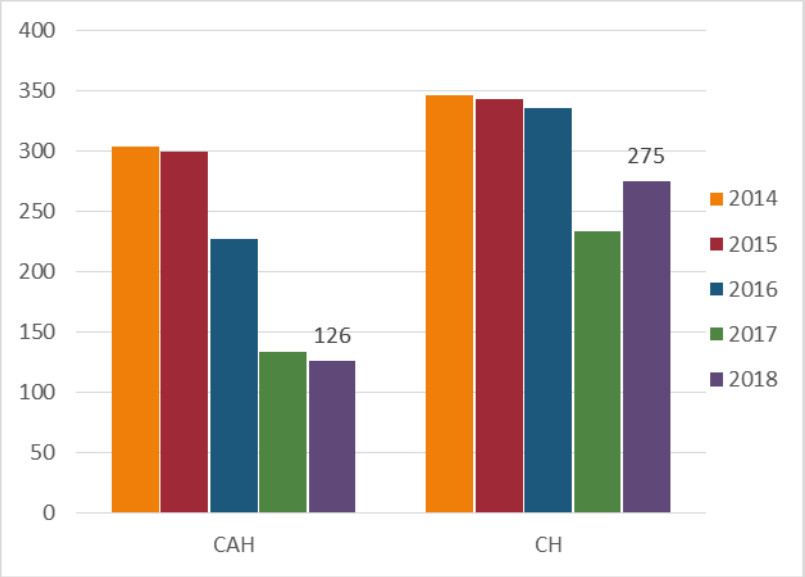

Figure 8. The total number of congenital adrenal hyperplasia and congenital hypothyroidism screen positives from 2014-2018

The number of screen positives for CAH remained consistent between 2017 and 2018. NSO has maintained the disorder logic that includes both birth weight and gestational age and continues not to refer extremely premature infants on their repeat sample if their initial sample was screen negative; 86 samples fell into this category.

The number of screen positives for CH increased in 2018, both in the number of laboratory positives and screen positive referrals (increase of ~40 referrals). While the number of 2018 referrals is still lower than the years of 2014-2016, there was an increase compared to 2017. In June 2018 there was an instrument change. An equivalent threshold for TSH was utilized. In the first 5.5 months of 2018, there were 110 screen positive CH referrals (~20/month). In the last 6.5 months of 2018, there were 165 referrals (~25/month).

The CH PPVs prior to June 12, 2018 were 32.9% for primary targets and 40% for primary and variant primary targets (1.9% of DERFs [52 of 2735] pending). The PPVs as of June 12, 2018 to December 31, 2018 were 21% for primary targets and 26.6% for primary and variant primary targets (13.3% of DERFs [22 of 165] pending).

4.2.5 Metabolics

There was an increase in the number of biotinidase deficiency referrals in 2018. The increase in biotinidase referrals coincided with the introduction of new screening cards. The newer cards interfered with the biotinidase enzyme activity. The PPV for 2017 and 2018 have decreased compared to previous years with the exception of 2014 when there was a disorder logic change and a similar number of referrals.

There was a slight increase in the amino acidemia referrals with the exception of MSUD. The disorder logic for these conditions has not changed and the fluctuation in referral numbers is unknown.

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Figure 9. The number of metabolic screen positives from 2014-2018 by disease

The number of organic acidemia referrals decreased in 2018 for all 3 conditions screened. With the exception of MCADD, the remainder of the FAODs had similar rates of referrals as in previous years.

In 2018, the number of Medium Chain Acyl coA Dehydrogenase Deficiency (MCADD) referrals was the highest since screening began in 2006. The number of premature babies screening positive steadily increased between 2014 and 2017 but did not further increase in 2018. However, the number of infants screening positive who were born at ≥33 weeks gestational age increased ~65% from 26 to 43 in 2018. Within this group the number of infants who screened positive between 33-<37 weeks gestation remained the same. The increase in numbers was in the referral of term infants. The majority of screen positive MCADD cases were collected between 24-47 hours of age (41 of 59; 69%) compared to 57% in 2017 (26 of 46). There was also an increase in the number of exclusively breastfed infants (n=35) compared to 2017 (n=26); however the percentage of MCADD screen positive infants who were exclusively breastfed were similar (57% in 2017 compared to 59% in 2018). There was no submitter that had an excess of MCADD positives.

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NSO reviewed data related to MCADD screening from 2015-2018. In that time there has not been an increase of the mean C8 acylcarnitine in all samples submitted from screening (0.08uM), nor of the coefficient of variance of this analyte. QC material near the decision limit did not show any upward shift in results, nor any increased variation. The outcome of all screen positive cases was also reviewed and there was no increase in the number of true positive cases; i.e. all additional referrals appear to be of children who were not affected.

4.2.6 Severe Combined Immune Deficiency

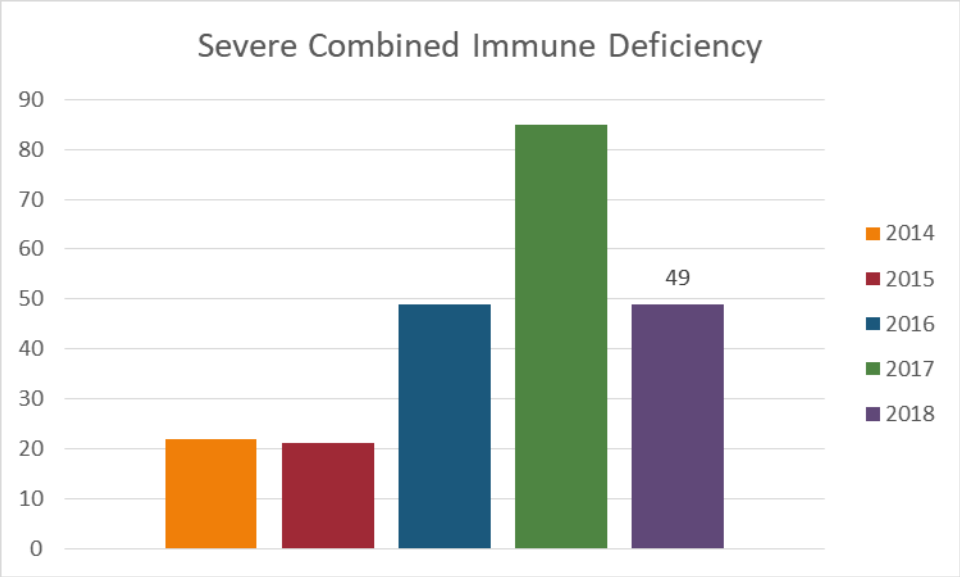

Figure 10. The number of SCID screen positives from 2014-2018.

The overall number of screen positive results for SCID decreased significantly in 2018. This is attributable to not reporting screen positive cases where a previous sample was screen negative (29 cases were not referred in 2018). Starting in September 2018, TBX1 was no longer tested and reported.

4.2.7 Screen Positive by Sample Type for Premature Infants

In 2018 there were 218 premature infants who screened positive: 158 infants who were screen positive on their initial sample only, 44 infants who only screened positive on their repeat samples (indicated in blue), and 16 infants who screened positive for the same condition on both their initial and repeat samples (indicated in yellow).

Although the policy for CAH screen positive premature infants is to not refer in a case where an initial sample is negative and the repeat sample is positive, there were 2 CAH cases that were referred that were positive on their second samples only. In the first case the infant had a significantly elevated 17-OHP value. In the second case the infant's initial sample was unsatisfactory as it was collected at <24 hours of age.

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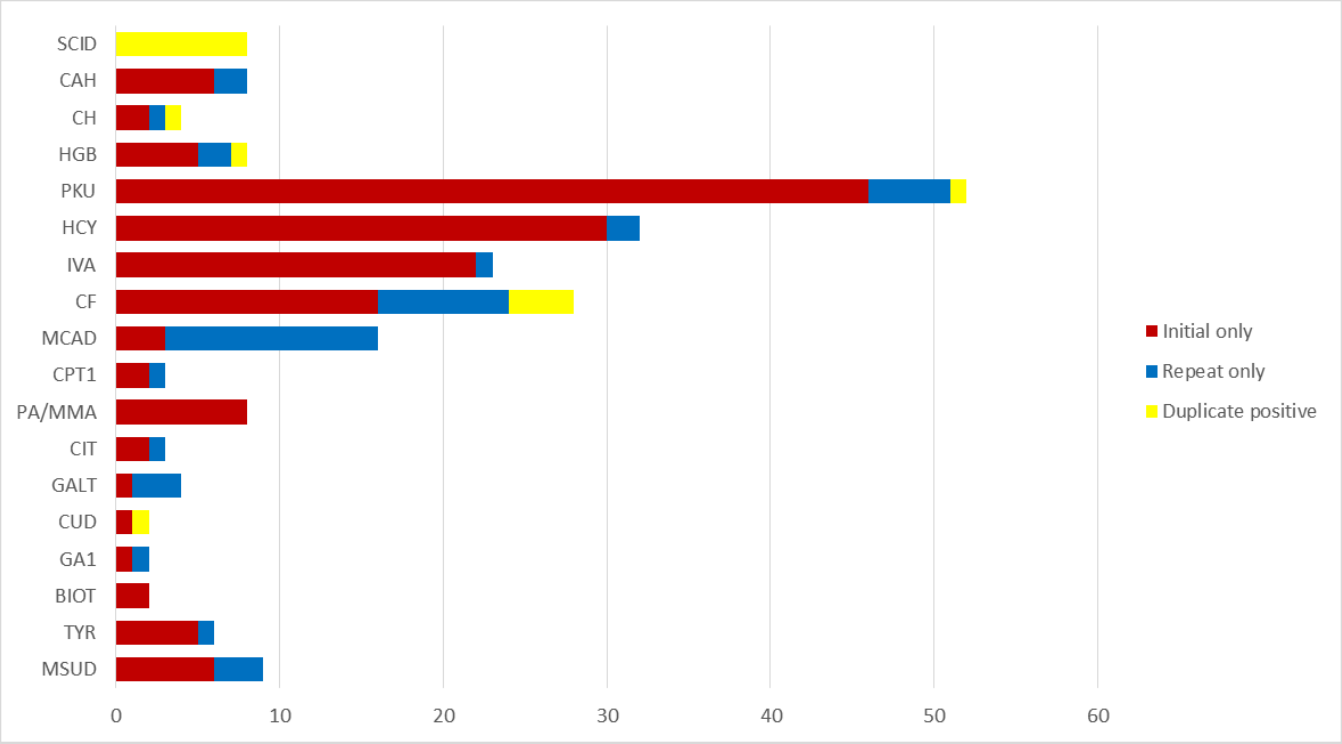

Figure 11. The number of screen positives by disease for extremely premature infants (<33 weeks gestation and/or <1500g): red is initial sample positive only; blue is repeat sample positive only; yellow is two samples for the same infant positive for the same condition.

4.3 Diagnostic Feedback

Due to sustained efforts in 2018 to complete outstanding DERFs (Diagnostic Evaluation Report Forms) approximately 18% (261 cases) of feedback information remains pending for referrals made in 2018 as of April 1, 2019. This is higher than in 2017 (12.7%). Many of the outstanding DERFs from previous years have been completed.

4.4 Classification of True/False Positives

NSO has developed a classification system for true positives to take into account the variability of definitive diagnoses and the impact of variant conditions and incidental findings. The definitions are as follows:

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Table 15. Definitions of the classification of true positive.

True Positive?	Definition	Example
Yes	confirmed diagnosis of a targeted condition	Classical PKU
No	confirmed to be NOT affected by a target or related disease	Not Affected
Other	lost to follow up; family refused follow up; infant deceased prior to completion of diagnostic evaluation	Deceased
Variant	confirmed diagnosis of a variant of the targeted condition	CF indeterminate or gray zone
Incidental	not affected by target or variant disease but not unaffected; affected with secondary target or other condition; carriers; reason intrinsic to baby or mother that caused the baby to screen positive	Vitamin B12 deficient (PA/MMA screen positive), maternal Grave's disease (CH screen positive)

The category of incidental is a large group – consisting of reasons due to mom and baby. Now that the DERF information is captured in BORN, we have added additional classifications to allow for more useful data extractions in the future.

Table 16. True positive categories.

True Positive Categories	
Generic	Detailed
No	Not Affected
Yes	Primary Target – Classic
Variant	Primary Target – Variant or Indeterminate
Incidental	Secondary Target – Classic
	Secondary Target – Variant or Indeterminate
	Untargeted Disease
	Persistent Laboratory Abnormalities
	Carrier
	Maternal Disease
	Maternal Persistent Laboratory Abnormalities
Other	Lost to Follow Up
	Deceased
	Other
Twin	Twin (Screen Negative)

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4.5 Definitive Diagnosis Data and Positive Predictive Values

The current PPVs are for current disorder logics. The PPV for yes is calculated using our classification of 'yes' in the numerator and the sum of 'yes', 'variant', 'incidental' and 'no' in the denominator. 'Other' is excluded as follow up data is not known. The PPV including yes plus variant is calculated with the addition of 'variant' in the numerator.

Variant is particularly important in CF = indeterminate or gray zone where there are borderline sweat results and 1 or more CFTR mutations identified, biotinidase deficiency (partial deficiency), PKU variant = mild hyperphe (Phe = 120-359), and CPT1 deficiency with the Inuit common mutation (which is questionable as to whether or not it is associated with disease). Therefore, our PPVs are higher when these primary disease variants are taken into account.

The data below includes all follow-up information received prior to April 1, 2019.

Table 17. The PPV calculations for each disease screened by NSO.

Disease		Additional information	PPV (Yes)	PPV (Yes + Variant)	PPV (Yes + Variant + Secondary)	DERFs Pending	Total No. Screen Positive
Endocrinopathies	Congenital Hypothyroidism	Past (until Jun 11, 2018)	32.9%	40.0%	40.0%	52	2735
		Current (Jun 12, 2018 - Dec 31, 2018)	21.0%	26.6%	26.6%	22	165
	Congenital Adrenal Hyperplasia	Past (Sept 2, 2016 - Jun 22, 2018)	5.9%	5.9%	5.9%	13	235
		Current (Jun 12, 2018 - Dec 31, 2018)	**0.0%**	**0.0%**	**0.0%**	**8**	**61**
Hemoglobinopathies		Past (Nov 1, 2010 - July 31, 2015)	64.8%	65.7%	83.7%	6	373
		Current (Aug 1, 2015 - Dec 31, 2018)	**60.6%**	**61.4%**	**86.7%**	**41**	**300**
Cystic Fibrosis		Category A	98.9%	100.0%	100.0%	11	273
		Category B	2.1%	5.7%	5.7%	55	3527
		Category C	0.3%	0.7%	0.7%	26	1059
		All	**7.2%**	**10.0%**	**10.0%**	**92**	**4859**
Severe Combined Immune Deficiency		Past (Jan 4, 2018 - Sept 19, 2018)	6.3%	6.3%	9.4%	7	43
		Current (Sept 20, 2018 - Dec 31, 2018)	**0.0%**	**0.0%**	**0.0%**	**4**	**6**
Organic Acidemia	Glutaric Aciduria type 1		**7.6%**	**7.6%**	**25.7%**	**4**	**160**
	Isovaleric Acidemia		**2.1%**	**3.7%**	**3.7%**	**9**	**349**
	PA/MMA	Past (Feb 16, 2010 - Apr 21, 2013)	3.7%	3.7%	8.3%	2	219
		Current (Apr 22, 2013 - Dec 31, 2018)	**4.7%**	**4.7%**	**8.9%**	**23**	**218**
Fatty Acid Oxidation Defects	CPTI		**5.3%**	**61.1%**	**61.1%**	**2**	**117**
	CPTII		**14.7%**	**14.7%**	**14.7%**	**0**	**34**
	LCHAD		**78.6%**	**78.6%**	**92.9%**	**0**	**14**
	VLCAD		**8.8%**	**13.9%**	**15.4%**	**11**	**292**
	CUD	Past (until Mar 4, 2014)	5.5%	5.5%	5.5%	1	300
		Current (Mar 5, 2014 - Dec 31, 2018)	**3.1%**	**3.1%**	**3.1%**	**10**	**110**
	MCAD	Past (until Aug 30, 2016)	31.3%	37.0%	39.1%	0	311
		Current (Sept 1, 2016 - Dec 31, 2018)	**16.0%**	**17.0%**	**17.0%**	**20**	**123**
Amino Acidopathies	Citrullinemia		**19.4%**	**22.2%**	**22.2%**	**2**	**153**
	Homocystinuria		**0.5%**	**0.5%**	**3.9%**	**9**	**265**
	Phenylketonuria		**13.6%**	**26.7%**	**27.9%**	**23**	**888**
	MSUD	Past (until Nov 14, 2011)	3.8%	3.8%	3.8%	0	90
		Current (Nov 15, 2011 - Dec 31, 2018)	**7.5%**	**8.8%**	**8.8%**	**4**	**86**
	Tyrosinemia	Past (Sep 14, 2009 - Sep 19, 2011)	1.4%	1.4%	1.4%	0	70
		Current (Sep 20, 2011 - Dec 31, 2018)	**12.0%**	**12.0%**	**16.0%**	**3**	**56**
Other Metabolic Diseases	Galactosemia	Past (until Jan 12, 2014)	35.7%	41.4%	41.4%	1	72
		Current (Jan 13, 2014 - Dec 31, 2018)	**12.9%**	**24.3%**	**24.3%**	**4**	**75**
	Biotinidase Deficiency	Past (Jan 13, 2014 - Jul 2, 2014)	2.1%	37.5%	37.5%	1	49
		Current (Jul 3, 2014 - Dec 31, 2018)	**4.4%**	**34.7%**	**34.7%**	**22**	**274**

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5. Screening Timeliness

The purpose of the benchmarks was to establish days of age at which samples should be received, analyzed and resulted by the screening program, and screen positive infants should be referred, retrieved, have an initial and full diagnosis established. Each disease group developed clinically meaningful benchmarks and aggressive diseases were assigned alert and non-alert benchmarks. The goal would be to have 90% of the screened population meet the benchmarks.

5.1 Initial Samples

Table 18: The Benchmarks and Percentages of Initial Samples at Age of Receipt by NSO, and availability of Initial and Final Results, 2017 and 2018

	1. Screening (Initial Samples) 2017 ONLY			2. Screening (Initial Samples) 2018 ONLY		
Category	**Age at receipt**	**Age at Initial Results**	**Age at Final Results**	**Age at receipt**	**Age at Initial Results**	**Age at Final Results**
Benchmark (days)	**4**	**5**	**7**	**4**	**5**	**7**
Cit, FAOD, GA1, HCY, PKU, IVA, LCHAD, MCAD, MSUD, PA/MMA, PKU, Tyr, VLCAD	**72%**	**70%**	**96%**	**79%**	**75%**	**98%**
Biotinidase Deficiency	**72%**	**70%**	**96%**	**79%**	**75%**	**98%**
Galactosemia	**72%**	**71%**	**97%**	**79%**	**77%**	**97%**
Congenital Adrenal Hyperplasia	**72%**	**70%**	**97%**	**79%**	**77%**	**98%**
Congenital Hypothyroidism	**72%**	**70%**	**97%**	**79%**	**77%**	**98%**
Cystic Fibrosis	**72%**	**67%**	**92%**	**78%**	**75%**	**93%**
Hemoglobinopathies	**72%**	**51%**	**91%**	**79%**	**54%**	**91%**
Severe Combined Immune Deficiency	**72%**	**40%**	**86%**	**79%**	**32%**	**84%**

Cells highlighted in green met the benchmarks. Cells highlighted in yellow had 70-89% of infants achieving benchmarks. Cells highlighted in red had benchmarks <70%. Between 2017 and 2018, the general trend is an overall improvement in age at receipt of samples at NSO, and in turn, improvements regarding age at availability of both initial and final results can be appreciated as well. The majority of newborn screening samples are collected between 24-48 hours of age.

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Table 19: Median and 90th centile values for age of receipt of initial samples, and availability of initial and final results, 2017 and 2018

	2. Screening (Initial Samples) 2017 ONLY							2. Screening (Initial Samples) 2018 ONLY						
Category	**Age at Receipt**		**Age at Initial Results**		**Age at Final Results**			**Age at Receipt**		**Age at Initial Results**		**Age at Final Results**		
	Median	**90th Centile**	**Median**	**90th Centile**	**n**	**Median**	**90th Centile**	**Median**	**90th Centile**	**Median**	**90th Centile**	**n**	**Median**	**90th Centile**
C5OH-Related Disorders, Cit, FAOD, GA1, HCY, IVA, LCHAD, MCAD, MSUD, PA/MMA, PKU, Tyr, VLCAD	4	6	5	7	1,078	6	8	3	5	4	6	1,086	6	8
Biotinidase Deficiency					1,457	6	8					722	6	8
Galactosemia					333	7	11					340	6	9
Congenital Adrenal Hyperplasia					628	6	8					580	6	8
Congenital Hypothyroidism					1,097	6	7					1,739	6	7
Cystic Fibrosis					6,281	9	12					6,325	9	12
Hemoglobinopathies					104	8	10			5	7	102	7	8
Severe Combined Immune Deficiency			6	8	1,099	9	12			6	8	796	9	12

The age at receipt has decreased by one day, resulting in a comparable decrease at the time of initial results. Age at final result refers to any screening sample that requires confirmatory testing prior to being reported as a screen positive or screen negative result. Most times have remained consistent between 2017. There has been a decrease in the age at final report for hemoglobinopathies due to a change in the timing of review.

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5.2 Screen Positive Infants

Table 20. The benchmarks and percentage of infants achieving benchmarks for all screen positive infants for the 5 year period of 2014-2018.

Category	ACMG Code	Age at receipt	Age at Sreening Results		Age (days) at retrieval		Age (days) at Definitive	
			ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert
Benchmark (days)		4	5	7	5	8	90	
Congenital Adrenal Hyperplasia	CAH	61% 656 / 1,080	49% 34 / 69	80% 811 / 1,011	39% 23 / 59	85% 807 / 951	98% 58 / 59	95% 911 / 957
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, CIT, MSUD, TYR1	62% 318 / 510	49% 23 / 47	69% 318 / 463	50% 20 / 40	77% 305 / 398	90% 36 / 40	87% 354 / 408
Galactosemia	GALT	25% 18 / 73	17% 8 / 46	30% 8 / 27	17% 7 / 41	44% 11 / 25	93% 38 / 41	84% 21 / 25
Benchmark (days)		4	5	7	5	8	90	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	54% 191 / 356	55% 23 / 42	63% 199 / 315	37% 11 / 30	71% 190 / 268	93% 28 / 30	89% 243 / 272
Benchmark (days)		4	N/A	7	N/A	8	90	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	55% 96 / 174	-	60% 105 / 174	-	65% 94 / 145	-	83% 122 / 147
Benchmark (days)		4	N/A	10	N/A	12	90	
Organic and Amino Acidemias	GA1, HCY, PKU	69% 494 / 721	-	93% 670 / 721	-	93% 517 / 557	-	97% 558 / 575
Biotinidase Deficiency	BIOT	67% 217 / 322	-	96% 309 / 322	-	93% 266 / 287	-	86% 248 / 287
Congenital Hypothyroidism	CH	76% 1,145 / 1,512	-	98% 1,476 / 1,512	-	97% 1,374 / 1,421	-	97% 1,390 / 1,430
Benchmark (days)		4	N/A	14	N/A	21	90	
Cystic Fibrosis	CF	70% 1,629 / 2,311	-	90% 2,090 / 2,311	-	64% 1,336 / 2,091	-	93% 1,961 / 2,118
Severe Combined Immune Deficiencies	SCID	52% 116 / 224	-	70% 156 / 224	-	81% 146 / 181	-	76% 127 / 167
Benchmark (days)		4	N/A	14	N/A	30	90	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	69% 286 / 414	-	88% 365 / 414	-	50% 152 / 305	-	63% 193 / 307

Each cell contains the percentage of infants meeting benchmarks, the number of infants meeting benchmarks as well as the total number of infants in each category. Cells highlighted in green met the benchmarks. Cells highlighted in yellow had 70-89% of infants achieving benchmarks. Cells highlighted in red had benchmarks <70%.

C5OH related targets have been removed from the table as NSO is no longer screening for this group of disorders. The benchmark for age at definitive diagnosis was changed from 60 to 90 days of age for the hemoglobinopathy group at the request of the DSWG to better align the benchmark with literature and clinical care guidelines.

Compared to data from 2013-2017, there continue to be improvements in the percentages of infants achieving benchmarks for all screen positive infants throughout the screening experience. Improvements related to Age at Receipt and Age at Screening Results are likely attributed to a combination of factors including earlier age at collection, improved shipping times, and NSO expanding operations to include weekend reporting. However, despite these enhancements, challenges persist regarding the timely receipt of samples at NSO and this in turn ultimately influences the remainder of the screening process and ability to meet downstream benchmarks related to result availability. The percentage of infants meeting the benchmark regarding Age at Retrieval has remained relatively stable with small improvements noted year over year. Regional variation in triage practices and certain clinical criteria/eligibility to pursue diagnostic investigations (e.g. GA and weight requirements for sweat chloride testing) may be influencing the disease categories where a lower % of infants are meeting this benchmark.

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Table 21. The benchmarks and percentage of infants achieving benchmarks for all screen positive infants, 2018 data only (cells with only percentages had numbers <5).

Category	ACMG Code	Age at receipt	Age at Sreening Results		Age (days) at retrieval		Age (days) at Definitive	
			ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert
Benchmark (days)		4	5	7	5	8	90	
Congenital Adrenal Hyperplasia	CAH	70% 88 / 125	50%	76% 94 / 123	-	90% 100 / 111	-	97% 114 / 117
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, CIT, MSUD, TYR1	66% 71 / 107	70% 7 / 10	73% 71 / 97	71% 5 / 7	74% 51 / 69	100% 7 / 7	93% 69 / 74
Galactosemia	GALT	33%	20%	43%	33%	50%	100%	100% 6 / 6
Benchmark (days)		4	5	7	5	8	90	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	56% 49 / 87	43%	69% 55 / 80	33%	80% 45 / 56	100%	95% 57 / 60
Benchmark (days)		4	N/A	7	N/A	8	90	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	66% 19 / 29	-	66% 19 / 29	-	69% 11 / 16	-	92% 12 / 13
Benchmark (days)		4	N/A	10	N/A	12	90	
Organic and Amino Acidemias	GA1, HCY, PKU	72% 108 / 150	-	91% 136 / 150	-	89% 85 / 95	-	99% 112 / 113
Biotinidase Deficiency	BIOT	66% 57 / 87	-	98% 85 / 87	-	90% 60 / 67	-	96% 65 / 68
Congenital Hypothyroidism	CH	80% 214 / 269	-	98% 264 / 269	-	98% 238 / 242	-	99% 248 / 251
Benchmark (days)		4	N/A	14	N/A	21	90	
Cystic Fibrosis	CF	77% 327 / 427	-	94% 401 / 427	-	78% 263 / 339	-	94% 343 / 366
Severe Combined Immune Deficiencies	SCID	53% 26 / 49	-	71% 35 / 49	-	84% 31 / 37	-	72% 26 / 36
Benchmark (days)		4	N/A	14	N/A	30	90	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	71% 66 / 93	-	92% 86 / 93	-	57% 33 / 58	-	87% 52 / 60

5.3 True Positive Infants

Table 22. The benchmarks and percentage of infants achieving benchmarks for all true positive infants with classic disease for 2014 – 2018 (cells with only percentages had numbers <5).

Category	ACMG Code	Age at receipt	Age at Sreening Results		Age (days) at retrieval		Age (days) at Initial Diagnosis		Age (days) at Definitive	
			ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert
Benchmark (days)		4	5	7	5	8	6	10	90	
Congenital Adrenal Hyperplasia	CAH	69% 11 / 16	71%	89% 8 / 9	60%	83% 5 / 6	60%	67%	100% 5 / 5	100% 6 / 6
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, CIT, MSUD, TYR1	67% 10 / 15	64% 9 / 14	100%	64% 9 / 14	100%	64% 9 / 14	0%	93% 13 / 14	100%
Galactosemia	GALT	86% 6 / 7	67%	100%	67%	100%	83% 5 / 6	100%	83% 5 / 6	100%
Benchmark (days)		4	5	7	5	8	8	10	90	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	73% 43 / 59	69% 22 / 32	78% 21 / 27	44% 11 / 25	86% 19 / 22	68% 17 / 25	57% 13 / 23	92% 23 / 25	91% 21 / 23
Benchmark (days)		4	N/A	7	N/A	8	N/A	14	90	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	56% 5 / 9	-	78% 7 / 9	-	40%	-	40%	-	100% 5 / 5
Benchmark (days)		4	N/A	10	N/A	12	N/A	14	90	
Organic and Amino Acidemias	GA1, HCY, PKU	68% 30 / 44	-	95% 42 / 44	-	97% 34 / 35	-	83% 29 / 35	-	100% 35 / 35
Biotinidase Deficiency	BIOT	73% 8 / 11	-	91% 10 / 11	-	100% 9 / 9	-	78% 7 / 9	-	89% 8 / 9
Congenital Hypothyroidism	CH	67% 218 / 327	-	94% 307 / 327	-	94% 287 / 304	-	81% 248 / 307	-	98% 302 / 307
Benchmark (days)		4	N/A	14	N/A	21	N/A	30	90	
Cystic Fibrosis	CF	65% 106 / 163	-	93% 151 / 163	-	91% 128 / 140	-	77% 108 / 141	-	91% 128 / 141
Severe Combined Immune Deficiencies	SCID	40%	-	80% 8 / 10	-	100% 9 / 9	-	89% 8 / 9	-	100% 9 / 9
Benchmark (days)		4	N/A	14	N/A	30	N/A	60	90	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	66% 140 / 213	-	92% 195 / 213	-	54% 100 / 186	-	39% 74 / 189	-	70% 133 / 189

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Overall, many factors within a screening system can impact timeliness benchmarks, and comparing and contrasting benchmarks from all screen positives alongside true positives can illuminate some of these issues. There are external and other circumstances that can increase the screen positive rate of a disorder and thus screening timeliness benchmarks as well (for example, consider delayed transit times for Galactosemia). However, when the true positive data for Galactosemia is examined the percentage meeting benchmarks improves dramatically.

5.4 Treatment Centre Deltas

To review the days from referral to different time points (which eliminates the downstream effects of age at collection, receipt and referral) screening timeliness data was reviewed looking at just treatment centre metrics. As in other analyses, DERFs that were pending and infants diagnosed prior to retrieval were excluded from the analysis. This table also includes columns for primary and variant targets to have initial diagnoses. In these columns places were N/A is included means that the variant targets included diseases that were not typically treated (i.e. CPT1 Inuit Variant, CF indeterminate, etc.). The time from referral to retrieval was green or yellow in the majority of disease groups indicating quick action on the part of the treatment centres. The majority of disease groups were meeting benchmarks for age at definitive diagnosis. However, time to initial diagnosis did not improve with this analysis with only alert Galactosemia infants being diagnosed by 1 day after referral.

Table 23. Screening timeliness data for the treatment centres from time of referral to various endpoints (cells with only percentages had numbers <5).

Category	ACMG Code	Time from referral to retrieval (% meeting benchmark)		Time from referral to Diagnostic Investigations (% meeting benchmark)		Time from referral to Initial Diagnosis Classical Disease [1] (% meeting benchmark)		Time from referral to Initial Diagnosis Primary and Variant Targets (% meeting benchmark)		Time from referral to Definitive Diagnosis and Disposition [2] (% meeting benchmark)	
		ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert
Benchmark (days)		1	3	1	3	1	4	1	4	85	
Congenital Adrenal Hyperplasia	CAH	95% 58 / 61	99% 940 / 954	44% 26 / 59	65% 621 / 953	86% 6 / 7	50%	86% 6 / 7	44%	97% 59 / 61	97% 938 / 963
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, CIT, MSUD, TYR1	95% 36 / 38	98% 400 / 408	78% 29 / 37	84% 333 / 396	71% 10 / 14	0%	76% 13 / 17	0%	90% 36 / 40	89% 370 / 416
Galactosemia	GALT	100% 40 / 40	96% 24 / 25	88% 35 / 40	63% 15 / 24	100% 6 / 6	0%	N/A	N/A	93% 39 / 42	100% 25 / 25
Benchmark (days)		1	3	1	3	1	4	1	4	85	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	89% 32 / 36	99% 273 / 275	82% 28 / 34	83% 221 / 265	59% 17 / 29	59% 13 / 22	60% 18 / 30	48% 14 / 29	91% 31 / 34	91% 256 / 281
Benchmark (days)		N/A	3	N/A	3	N/A	4	N/A	4	85	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	-	97% 147 / 152	-	78% 103 / 132	-	44%	-	N/A	-	92% 140 / 153
Benchmark (days)		N/A	3	N/A	3	N/A	4	N/A	4	85	
Organic and Amino Acidemias	GA1, HCY, PKU	-	97% 568 / 584	-	82% 452 / 548	-	73% 32 / 44	-	55% 48 / 87	-	96% 573 / 600
Biotinidase Deficiency	BIOT	-	89% 266 / 298	-	68% 196 / 287	-	55% 6 / 11	-	N/A	-	86% 260 / 302
Congenital Hypothyroidism	CH	-	91% 1,321 / 1,453	-	81% 1,152 / 1,417	-	80% 260 / 324	-	66% 294 / 448	-	97% 1,425 / 1,467
Benchmark (days)		N/A	7	N/A	14	N/A	16	N/A	16	85	
Cystic Fibrosis	CF	-	56% 1,202 / 2,147	-	58% 1,202 / 2,088	-	73% 116 / 158	-	N/A	-	93% 2,010 / 2,170
Severe Combined Immune Deficiencies	SCID	-	88% 164 / 186	-	82% 145 / 176	-	89% 8 / 9	-	62% 8 / 13	-	79% 137 / 173
Benchmark (days)		N/A	16	N/A	35	N/A	55	N/A	55	85	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	-	44% 154 / 353	-	65% 216 / 332	-	42% 90 / 213	-	42% 91 / 215	-	68% 244 / 360

In future years, at the suggestion of the Advisory Council, the screening timeliness data will be analyzed by year and by treatment centre.

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6. CCHD Screening

6.1 CCHD cards received

Submitters submit their Critical Congenital Heart Disease (CCHD) screen results to NSO via a tear off sheet on the standard NSO dried blood spot card. These may come with the dried blood spot, or separately, depending on hospital process. The total number of CCHD cards registered at NSO in 2018 is 136,596 representing 134,944 infants. Full implementation at all sites was achieved in May 2018.

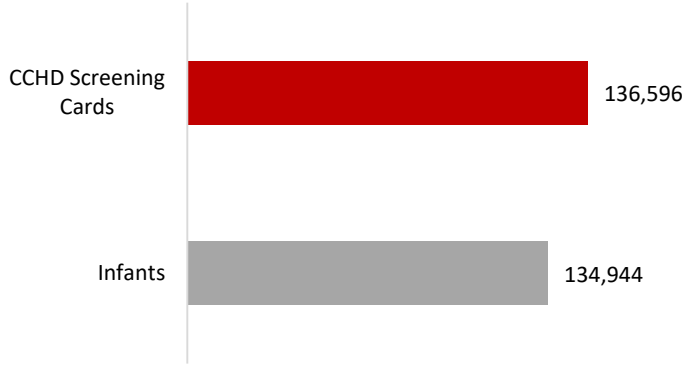

Figure 12. CCHD Cards and Infants, 2018

Table 24. CCHD cards received.

CCHD Cards received	2018	2017
Screen Completed	132,134	41,847
Screen Not Done	4,462	1,074
	136,596	**42,921**

6.2 Screens Completed

The NSO CCHD algorithm allows for up to 3 repeat tests done one hour apart prior to making a referral. In the cards where screening was done, 98.3% of the screens were resolved after just one test (most often this would be a pass, but this could also be an immediate referral). Only 1.5% required a second test and 0.2% required three tests to complete the screen.

Table 25. Tests required to complete screen

Tests Done	2018		2017	
1 Test	129,967	98.3%	40,984	97.9%
2 Tests	1,948	1.5%	766	1.8%
3 Tests	219	0.2%	97	0.2%
	132,134		**41,847**	

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6.3 Screens Not Done

In 2018, CCHD screens were not done on 3.3% of the cards received. The most common reason for CCHD screen not done is because the infant is expected to be in the NICU for > 7 days.

Table 26. Reasons for CCHD Screen not done, 2017 and 2018.

	2018	2017
'Screen Not Done' cards submitted	4,462	1074
Decline/deferred (back page of form not completed)	1.7%	1.6%
Declined	0.6%	0.5%
Deferred	10.1%	5.2%
Infant diagnosed prenatally with heart defect	1.3%	1.9%
Infant diagnosed with heart defect by physical exam	0.9%	1.1%
Infant is not appropriate for screening (e.g. NICU > 7 days, on oxygen, IV in right hand, limb anomaly, etc.)	83.2%	81.6%
Already done	0.2%	2.2%
Echocardiogram or cardiology investigations already done	0.4%	0.8%
Insufficient information provided	0.4%	2.8%
Early discharge	0.3%	0.9%
Hospital transfer	0.5%	0.9%
Other	0.4%	0.5%

6.4 Age at time of CCHD Screen

The recommended age for CCHD screening is 24-48 hours of age, with an optimal window between 24 and 36 hours. The majority (87.8%) of screening in 2018 was done in the recommended range.

Table 27. Age at time of CCHD Screen, 2017and 2018

Age at time of screen	2018	2017
	% of CCHD screens done	% of CCHD screens done
Less than 24 hours	4.5	1.65
24-48 hours (1-2 days)	87.8	76.8
>48-72 hours (2-3 days)	2.4	14.2
>72-168 hours (3-7 days)	0.9	1.8
Greater than 168 hours (> 7 days)	0.2	0.4
Not specified	4.2	5.2

The percentage of screens done at less than 24 hours is increasing as compared with preliminary 2017 numbers, with 4.5% of tests done too early. Midwives are testing later than hospitals, with 5.7% of their testing being done after 48 hours, compared to 3.3% in hospitals.

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6.5 Unsatisfactory CCHD Screens

Upon entry into the NSO database, unsatisfactory CCHD screens are identified when there has been a misinterpretation of the screening algorithm, the algorithm was not followed, or where the outcome is not adequately documented. This includes cases where the result should have been 'REFER' but a 'PASS' result was documented, and cases where the result should have been 'REPEAT' but a 'PASS' result was documented. NSO contacts the submitter who performed the screen to clarify the information provided and inform them of the unsatisfactory screen. If required the submitter will contact the family to bring the infant back to complete their CCHD screen.

The number of unsatisfactory screens done in 2018 was 616, which is 0.45% of the total screens done. The most frequent error is incomplete documentation of a repeat test done after 1 hour (Table 28). On average the number of unsatisfactory screens has decreased over 2018 as submitters became more familiar with the algorithm (Figure 13).

Table 28. Reasons for Unsatisfactory CCHD Screen

	2018	2017
Satisfactory Screens	**135,980**	**42,689**
Unsatisfactory Screens	**616**	**232**
Referral not documented	6.4%	19.8%
Repeat not documented	51.3%	63.8%
Incomplete	31.3%	14.2%
Other	10.9%	2.2%
Total Screening Forms Submitted	**136,596**	**42,921**
Unsatisfactory Rate	**0.45%**	**0.54%**

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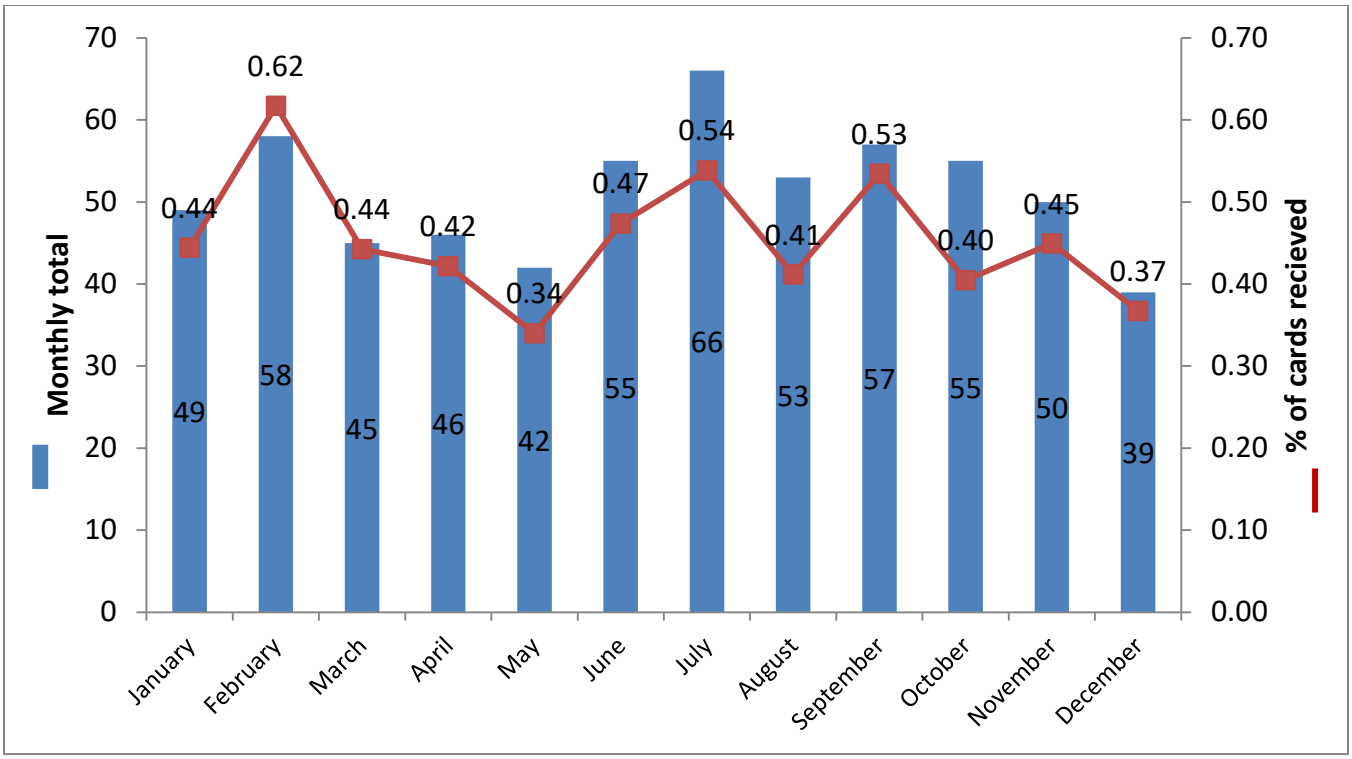

Figure 13. Total number and percentage of unsatisfactory CCHD Screens requiring follow up

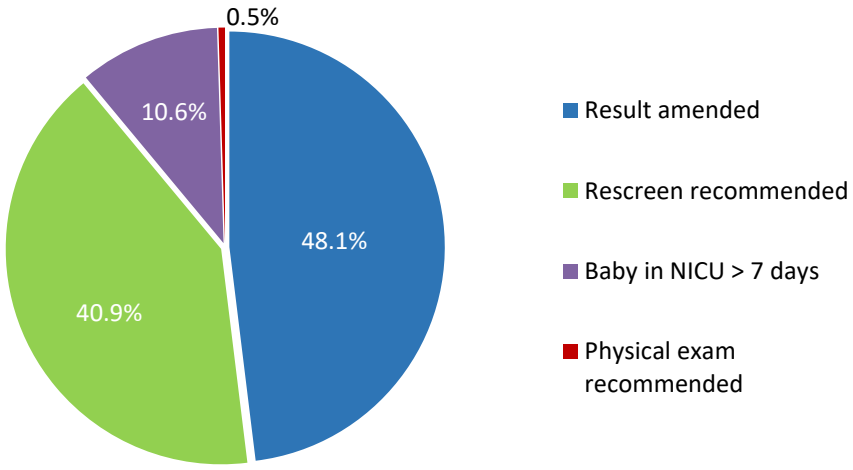

Figure 14. Actions taken on Unsatisfactory CCHD Screens

NSO performed follow-up on the 616 unsatisfactory screens, and in 48.1% of follow-up cases the result was amended by the submitter due to incorrect completion of the form. In 40.9% of cases a re-screen was recommended. In 591 (96%) cases NSO performed a same-day telephone call and follow-up. 41% of unsats were followed up by 3 days of age and 83% by 5 days of age.

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6.6 CCHD Screen Positives – 2018 data

There were 189 CCHD screen positives in 2018, most (94%) of which were screened within 24-48 hours. 83% of infants referred in 2018 had diagnosis within 24 hours of the screen, and a further 4% before 72 hours.

Of the 189 screen positives received in 2018, 9 were diagnosed with a critical congenital heart defect; this includes cases of true positives that were either initially identified to be not affected or were not given a definitive diagnosis when screen positive follow-up occurred). Ninety six (96) screen positive cases had a secondary CHD target or were diagnosed with an incidental finding such as pulmonary disease or infection, and 84 were found to be not affected.

Table 29. Reason for referral by definitive diagnosis, 2018 data*

Reason for referral	Primary target	Incidental	Not affected	Total No.
Saturation under 90 %	<5	49	35	89
3 tests and no pass result	<5	24	30	55
2 tests and no pass result			<5	<5
Clinical judgement	<5	14	7	23
Not specified		9	10	19
Grand Total	**7**	**96**	**85**	**188**

*Excludes cases with DERF information pending.

6.7 CCHD Definitive Diagnosis Data and Positive Predictive Values

Cumulatively, the Positive Predictive Value (PPV) for CCHD screening is 4.4% for primary targets only, and 27.5% for primary and classical secondary target diseases (Table 30). Of the 273 screen positives since the initiation of CCHD screening, 142 (52%) have been determined to be not affected after diagnostic follow up.

Table 30. PPV calculations for CCHD Screen Positives (cumulative).

Disease	PPV		Total No. Screen Positive	Outcome Classification			
				Yes	Incidental		No
	PPV (Yes)	PPV (Yes + Classic Secondary)			Classic Secondary Targets	All Other Incidentals	
Critical Congenital Heart Disease (CCHD)	4.7%	29.1%	189	9	46	49	84

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Table 31. Definitive diagnosis for CCHD Screen Positives (cumulative)

Definitive Diagnosis Categorization	Total No.
Primary target	**12**
Tetralogy of Fallot	5
Total anomalous pulmonary venous return	<5
Transposition of the great arteries	<5
Tricuspid atresia	<5
Truncus arteriosus	<5
Secondary target- Classic	**63**
Coarctation of the aorta	<5
Ebstein anomaly	<5
Infection	12
Persistent fetal circulation	19
Pulmonary disease	30
Secondary target- Untargeted disease	**55**
CHD *arrhythmia*	5
CHD *structural*	14
CHD *Other*	<5
Other	11
No disease, no definitive diagnosis	22
Not affected	**142**
Grand Total	**272**

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7. Appendix A: Detailed Screening Timeliness Data

Table 1A: Median, 70th and 90th Centile for All Screen Positive Samples by Disease Category, 2014-2018

					Alert Confirmation				Routine Confirmation				ALERT				Non-Alert				ALERT				Non-Alert			
Category	ACMG Code	Age at Receipt			Age at Referral				Age At Referral				Age at retrieval (contact with family)								Age at Definitive Diagnosis and Disposition [2]							
		Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile
Benchmark (days of age)		4			5				7				5				8				90							
Congenital Adrenal Hyperplasia	CAH	4	5	21	69	6	6	10	1,011	6	7	23	59	6	7	15	951	6	7	21	59	20	30	71	957	19	30	67
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, CIT, MSUD, TYR1	4	5	10	47	5	7	10	463	7	8	13	40	5	7	16	398	7	8	13	40	17	29	76	408	27	38	103
Galactosemia	GALT	7	22	33	46	9	14	28	27	8	26	55	41	9	14	27	25	9	28	55	41	35	47	79	25	61	74	106
Benchmark (days of age)		4			5				7				5				8				90							
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	4	6	22	42	5	6	7	315	7	8	25	30	6	7	8	268	7	8	25	30	26	35	80	272	37	52	93
Benchmark (days of age)		4							7								8				90							
Fatty Acid Oxidation Diseases	CUD, CPT1 CPT2	4	6	24	No Type 1				174	7	9	27	No Type 1				145	7	10	26	No Type 1				147	25	36	108
Benchmark (days of age)		4							10								12				90							
Organic and Amino Acidemias	GA1 HCY, PKU	4	5	6	No Type 1				721	6	7	10	No Type 1				557	7	7	10	No Type 1				575	26	31	61
Biotinidase Deficiency	BIOT	4	5	6	No Type 1				322	7	7	9	No Type 1				287	7	9	12	No Type 1				287	27	47	108
Congenital Hypothyroidism	CH	3	4	5	No Type 1				1512	6	7	8	No Type 1				1421	7	8	10	No Type 1				1430	12	19	48
Benchmark (days of age)		4							14								21				90							
Cystic Fibrosis	CF	4	4	6	No Type 1				2311	10	12	14	No Type 1				2091	18	23	32	No Type 1				2118	31	41	78
Severe Combined Immune Deficiencies	SCID	4	7	24	No Type 1				224	11	15	29	No Type 1				181	13	17	32	No Type 1				167	41	79	164
Benchmark (days of age)		4							14								30				90							
Hemoglobinopathies	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	4	5	6	No Type 1				414	9	11	15	No Type 1				305	29	39	51	No Type 1				307	75	98	160

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Table 2A: Median, 70th, 90th Centile for All Screen Positive samples by Disease Category, 2018 only

2.a) ALL SCREEN POSITIVE SAMPLES

		Alert Confirmation							Routine Confirmation				ALERT				Non-Alert				ALERT				Non-Alert			
Category	ACMG Code	Age at Receipt			Age at Alert Screening Result				Age At Screening Result				Age at retrieval (contact with family)								Age at Definitive Diagnosis and Disposition [2]							
		Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile
Benchmark (days of age)		**4**			**5**				**7**				**5**				**8**				**90**							
Congenital Adrenal Hyperplasia	CAH	4	4	6	<5	5	N/A	N/A	123	7	7	8	0	N/A	N/A	N/A	111	7	7	8	0	N/A	N/A	N/A	117	15	18	49
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, CIT, MSUD, TYR1	4	5	13	10	4	5	7	97	7	7	20	7	4	N/A	N/A	69	7	8	20	7	17	N/A	N/A	74	26	33	66
Galactosemia	GALT	8	20	24	5	6	N/A	N/A	7	15	N/A	N/A	<5	7	N/A	N/A	6	11	N/A	N/A	<5	45	N/A	N/A	6	33	N/A	N/A
Benchmark (days of age)		**4**			**5**				**7**				**5**				**8**				**90**							
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	4	6	13	7	6	N/A	N/A	80	7	8	16	<5	6	N/A	N/A	56	7	8	19	<5	7	N/A	N/A	60	30	47	69
Benchmark (days of age)		**4**							**7**								**8**				**90**							
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	4	5	22	No Type 1				29	7	8	25	No Type 1				16	7	9	16	No Type 1				13	19	27	38
Benchmark (days of age)		**4**							**10**								**12**				**90**							
Organic and Amino Acidemias	GA1, HCY, PKU	4	4	7	No Type 1				150	6	7	10	No Type 1				95	6	7	17	No Type 1				113	26	29	39
Biotinidase Deficiency	BIOT	4	5	6	No Type 1				87	7	7	8	No Type 1				67	8	9	14	No Type 1				68	24	29	60
Congenital Hypothyroidism	CH	3	4	5	No Type 1				269	6	7	8	No Type 1				242	6	7	9	No Type 1				251	12	21	46
Benchmark (days of age)		**4**							**14**								**21**				**90**							
Cystic Fibrosis	CF	3	4	6	No Type 1				427	10	11	14	No Type 1				339	16	20	30	No Type 1				366	28	35	63
Severe Combined Immune Deficiencies	SCID	4	7	25	No Type 1				49	12	13	30	No Type 1				37	14	15	31	No Type 1				36	40	86	152
Benchmark (days of age)		**4**							**14**								**30**				**90**							
Hemoglobinopathies	Hb SS, Hb S/βTh, Hb SC, Hb S/HPFH	3	4	6	No Type 1				93	8	10	13	No Type 1				58	24	39	51	No Type 1				60	56	68	95

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Table 3A: Median, 70th and 90th Centile for all True Positive Samples by Disease Category, 2014-2018

3.a) ALL TRUE POSITIVE SAMPLES

Category	ACMG Code	Age at Receipt			Alert Confirmation				Routine Confirmation				ALERT				Non-Alert				ALERT				Non-Alert				ALERT				Non-Alert			
		Age at Receipt			Age at Alert Screening Result				Age At Screening Result				Age at retrieval (contact with family)								Age at Initial Diagnosis Classical Disease [1]								Age at Definitive Diagnosis and Disposition [2]							
		Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile
Benchmark (days of age)		4			5				7				5				8				6				10				90							
Congenital Adrenal Hyperplasia	CAH	3	4	6	7	4	N/A	N/A	9	6	N/A	N/A	5	4	N/A	N/A	6	6	N/A	N/A	5	5	N/A	N/A	6	9	N/A	N/A	5	5	N/A	N/A	6	11	N/A	N/A
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, C3T, MSUD, TYR1	4	5	5	14	5	6	7	<5	4	N/A	N/A	14	5	6	7	1	4	N/A	N/A	14	6	8	17	<5	10	N/A	N/A	14	8	20	42	<5	53	N/A	N/A
Galactosemia	GALT	4	N/A	N/A	6	5	N/A	N/A	<5	4	N/A	N/A	6	5	N/A	N/A	<5	4	N/A	N/A	6	5	N/A	N/A	<5	9	N/A	N/A	6	33	N/A	N/A	<5	22	N/A	N/A
Benchmark (days of age)		4			5				7				5				8				8				10				90							
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	4	4	7	32	5	6	8	27	6	7	10	25	5	6	8	22	6	7	9	25	7	9	30	23	9	10	52	25	28	35	84	23	33	56	88
Benchmark (days of age)		4							7								8								14				90							
Fatty Acid Oxidation Diseases	CUD, CPT1 CPT2	4	N/A	N/A	No Type 1				9	6	N/A	N/A	No Type 1				5	7	N/A	N/A	No Type 1				5	10	N/A	N/A	No Type 1				5	25	N/A	N/A
Benchmark (days of age)		4							10								12								14				90							
Organic and Amino Acidemias	GAL HCY, PKU	4	5	6	No Type 1				44	6	7	8	No Type 1				35	6	7	8	No Type 1				35	8	10	25	No Type 1				35	9	35	60
Biotinidase Deficiency	BIOT	3	4	7	No Type 1				11	8	9	9	No Type 1				9	8	N/A	N/A	No Type 1				9	13	N/A	N/A	No Type 1				9	27	N/A	N/A
Congenital Hypothyroidism	CH	4	5	6	No Type 1				327	7	7	9	No Type 1				304	7	8	10	No Type 1				307	8	10	27	No Type 1				307	9	11	33
Benchmark (days of age)		4							14								21								30				90							
Cystic Fibrosis	CF	4	5	6	No Type 1				183	10	11	14	No Type 1				140	12	14	19	No Type 1				141	18	26	54	No Type 1				141	32	45	113
Severe Combined Immune Deficiencies	SCID	5	8	11	No Type 1				10	10	12	15	No Type 1				9	10	N/A	N/A	No Type 1				9	16	N/A	N/A	No Type 1				9	20	N/A	N/A
Benchmark (days of age)		4							14								30								60				90							
Hemoglobinopathies	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	4	5	6	No Type 1				213	9	11	14	No Type 1				186	27	36	45	No Type 1				189	89	96	140	No Type 1				189	68	89	128

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