NEWBORN SCREENING ONTARIO
DÉPISTAGE NÉONATAL ONTARIO

Annual Report

Calendar Year 2015

Contents

1. Sample Volumes in 2015

Table 1. Sample volumes between 2015-2011 by sample type.

Indication	Sample Type	2015	2014	2013	2012	2011
Routine screening	Satisfactory	144,074	144,099	144,402	143,979	142,993
	Unsatisfactory	2,105	4,349	3,191	3,826	2,912
Routine Screening – Total		**146,179**	**148,448**	**147,593**	**147,805**	**145,905**
Referred in sample: full panel	Satisfactory	400	192	8	17	49
	Unsatisfactory	22	5	0	0	0
Referred-in screening: Full panel – Total		**422**	**197**	**8**	**17**	**49**
Non-screening sample – Total		**1,724**	**1,283**	**907**	**523**	**299**
Grand Total		**148,325**	**149,928**	**148,508**	**148,345**	**146,253**

1.1 Screening samples

There was a modest reduction in the overall number of samples received in 2015 as compared to 2014, primarily due to a reduction in unsatisfactory samples. As described in section 3 below, in response to a notable increase in unsats in 2014, NSO revised the review procedure to more clearly describe the sample requirements. This has resulted in over 2000 fewer infants being called back in for repeat samples, and therefore quicker turnaround times and a much better patient experience.

The number of referred-in screening samples has doubled in the last year as NSO has provided screening services for infants from Nunavut through a service contract with Dynacare Laboratories.

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.

The overall number of infants tested is relatively constant each year with only ~1500 infants difference between the highest and lowest years. In 2015, the number of infants screened is the lowest in 5 years and continues a decreasing trend since 2012 in the number of infants screened. Due to a strong matching with records in the BORN Registry, missed screen alerts, and improved documentation of declined samples, NSO does not interpret this trend as a decrease

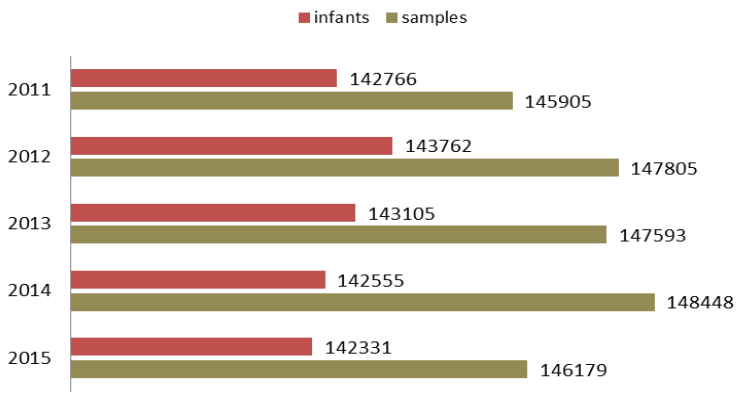


Figure 1. The total number of infants and samples screened between 2011-2015.

in uptake of screening in Ontario. This trend is more likely related to better data quality and linkage since the development of the BORN Registry. Based on defers/ declines, missed screen alerts, and newborn screening sample counts, NSO estimates the total number of infants in Ontario as 142,807, and the rate of screening uptake in 2014 as 99.7%, the same rate of uptake as in 2014.

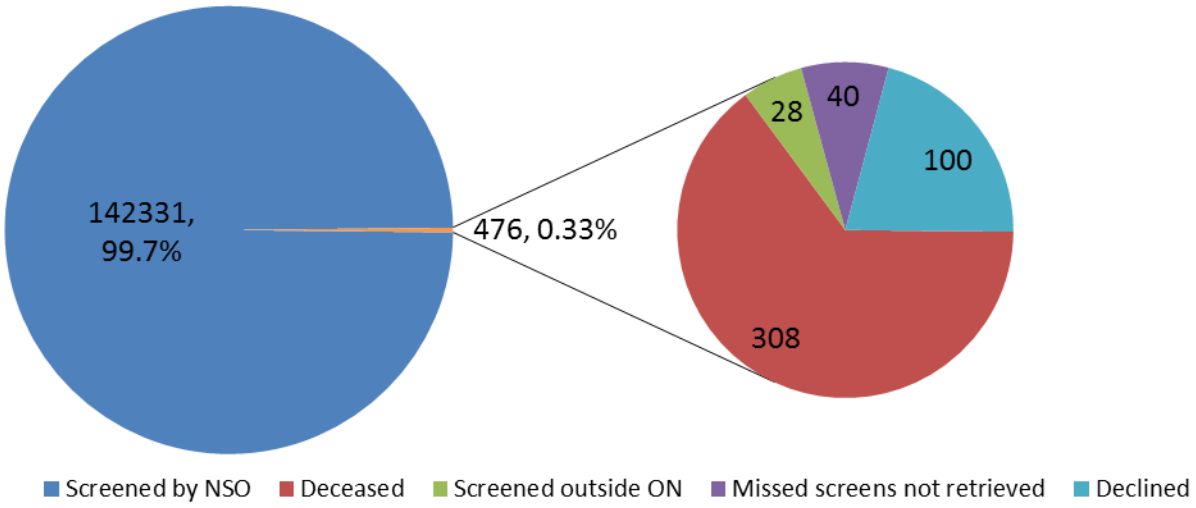


Figure 2. Coverage of screening in Ontario births.

1.1.2 Declined/Deferred Testing

If parents wished to decline or defer newborn screening, health care providers had 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. In the case of a decline, it avoided unnecessary follow up when a missed screen alert was received and it allowed formal documentation on the part of the health care provider that they offered NBS. Upon receipt of the decline form, NSO entered the information into their system and generated a letter to the submitter documenting the receipt of the decline.
In the case of a deferral, the family once again signed the NBS card and the submitter sent it to NSO. Similar to the decline process, the information was entered and a letter generated to the submitter. If a NBS sample was not received by 14 days from the receipt of the deferral notice, NSO would generate an additional letter that would be sent to the family directly.

In 2015, there were 29 declines identified using this form. Some of these were declines of repeat samples. The remaining 205 forms received indicated a parent's desire to defer screening, and samples were eventually received for all but one of these deferred cases.

Table 2. Declined, deferred samples and potential missed screens between 2015 – 2011.

Case Type	2015	2014	2013	2012	2011
Declined/deferred form received	234	54	<5	N/A	N/A
Potential missed newborn screen	390	454	558	212	0

1.1.3 Missed Screens

In 2015, there were 390 potential missed newborn screen alerts that required follow up by NSO. This is down by approximately 60 cases from 2014. Hospitals were the responsible facility in 61% of the missed screen alerts and midwives were involved in roughly 32% of the cases. Other (representing 7% of alerts) includes birth centres, out of province hospitals, or nursing stations involved in follow up care post discharge. There were 61 different midwifery practices involved in the alerts and 70 different hospitals. Action on the part of NSO resulted in 123 of the 166 (74%) truly missed screens being completed.

Table 3. Potential missed screen alerts requiring follow-up in 2015, by reason and responsible submitter, and samples received post follow-up.

	2015	**% received**	2014
Incomplete or incorrect information	224	n/a	293
True missed screens	166	74%	163

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. Of the missed screen alerts, 214 (79 true misses) were received at >14 days of age and the age at which true missed screen alerts were received ranged from 15 to 426 days of age. In addition, there were 83 cases in which no alerts were triggered because of late data entry into the BORN system, but samples were received at ≥14 days of age. This included 32 samples from midwives, 2 from doctor's offices, and 49 from hospitals. While ideally BORN data entry would allow for more timely alerting of missed screens in all cases, the total number of late entry missed screens has decreased by 50% since 2014, and NSO sees this as a positive trend.

Missed Screens and Declines

In 2015 there were 75 declines identified in the missed screen alerts, compared to the 83 declines in 2014. Including the 25 (4 declines were duplicated in the missed screen and decline flows) declines from the decline process outlined above, the total number of declines only decreased by 6 from 2014. Midwives were the health care provider in 75% (n=75) of declined cases.

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.

In 2013, NSO began accepting cord blood samples for hemoglobin screening to support the national cord blood registry. Cord blood samples have been submitted from Ontario since 2013, Alberta and British Columbia were included in 2014. The number of cord blood samples being screened at NSO has doubled from 2014 to 2015, as the two new collection sites in Edmonton and Vancouver have increased to full volumes.

Since 2010, NSO has had an agreement with the Ontario Forensic Pathology Service to provide postmortem dried blood spot and dried bile spot sample analysis for all unexplained deaths of children under two years of age. These sample volumes have been steadily increasing each year, likely due to coroner awareness and compliance. Although a blood and bile sample is requested for each case, both sample types may not always be retrievable. NSO received 150 blood samples and 145 bile samples in 2015.

NSO offers diagnostic and monitoring testing for targets of newborn screening, and volumes are relatively steady from 2013, with the biggest volume being from PKU home monitoring.

2. Demographics of Screening Samples

2.1 Age at Collection

Table 7. Age at collection for 2015 initial samples only.

Age at Collection	Number of Initial Samples	% of Initial Samples (2015)	% of Initial Samples (2014)
Less than 24 hours	778	0.55%	0.55%
24-47 hours	119,140	83.92%	78.50%
48-72 hours	14,063	9.91%	10.71%
3-7 days	6,123	4.31%	5.83%
Greater than 7 days	1,842	1.30%	4.36%
Not specified	21	0.01%	0.05%

The majority of newborn screening samples are collected between 24-48 hours of age. Approximately 94% of samples are collected by 72 hours of age. NSO will be looking into possibly changing the recommended age of collection to 24-48 hours of age from 48-72 hours in the upcoming year.

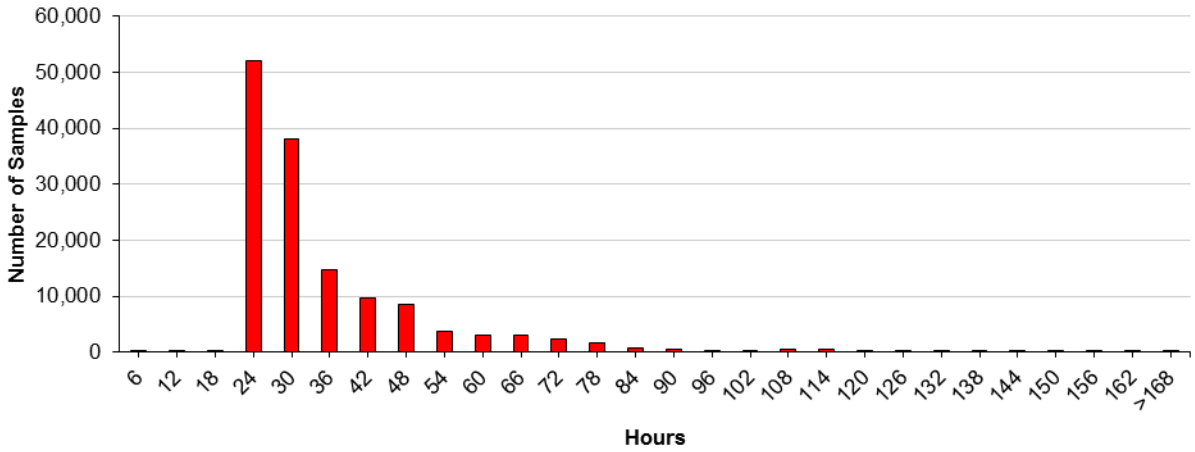


Figure 3. The number of samples collected by the age in hours of the infant.

There were 778 samples that were collected at <24 hours of age, with 603 of these considered unsatisfactory (175 samples were collected in the 10 min grace period). Of the 778 samples, 111 were reported to have had early hospital discharge. A further 57 were collected early due to a pending transfusion. The majority of <24 hour samples that were unsatisfactory were taken early for an unknown reason.

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. Samples received between 4-6 months are sent to NSO without a reminder having been sent to the submitter (i.e. the submitter has their own tracking system in place). At 6 months submitters receive a reminder by fax that a repeat NBS is required. If the submitter responds to the fax that a health care provider (HCP) has been notified, NSO also sends a letter to the HCP. At 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 8. Transfusion cases in 2015

Repeat Requirement	# of cases
Repeat Not Required	213 (53.3%)
Repeat Received	53 (13.2%)
Repeat Not Received (e.g. deceased, family moved, etc.)	134 (33.5%)

Table 9. Age at which transfusion repeats were received in 2015

Age	# of samples
4-6 months	12
6-12 months	39
>12 months	<5

There were 400 transfusion cases created in 2015. For 67% of cases either a repeat was received or a repeat was not required as a satisfactory pre-transfusion sample was already received. There were 17 cases where letters were sent to submitters from NSO advising of the need for a repeat sample. A repeat transfusion sample was received in 13% cases, the majority of which were received between 6-12 months of age. Currently 86 cases for 2015 remain open with no repeat received, 52 of these cases are still within the 4-6 month waiting period.

2.3 Gestational Age and Birth Weight

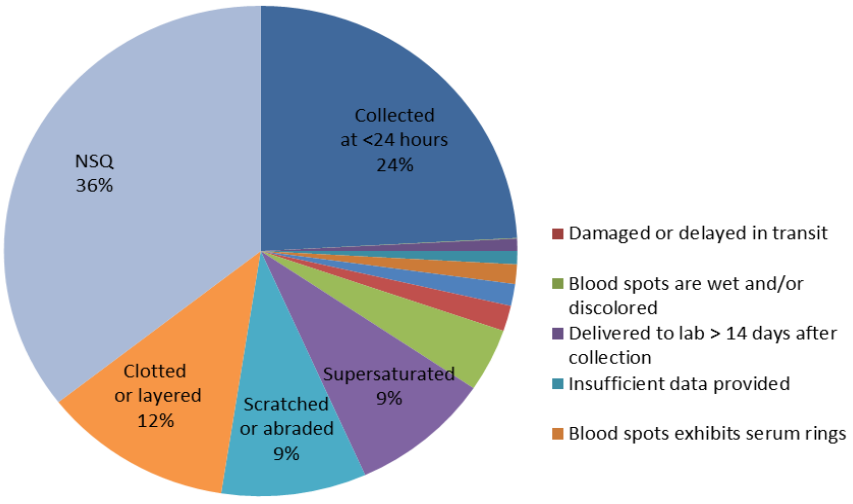
NSO introduced an extreme premature infant policy in January 2013, where any infant <1500 g or <33 weeks gestation would be recommended to have a repeat sample obtained around 21 days of age or sooner if the infant was to be discharged. In 2015, there were 2064 infants that fit the premature infant policy. Of these, 1498 (73%) had a 3 week (or equivalent) sample obtained.

Repeats on premature infants is a recommendation, but NSO does not actively follow up on repeats. In 2015, 49 facilities submitted repeat premature samples of which 46 were hospitals with level II and/or III nurseries. There were 4 hospitals in the province that have level II and/or III nurseries that did not submit any repeat premature samples. One of these hospitals has an internal protocol for measuring TSH on premature infants at 3 weeks of age.

3. Unsatisfactory Samples

Table 10. Unsatisfactory samples by reason between 2015-2011.

		2015	2014	2013	2012	2011
	Satisfactory Samples	144,074	144,099	144,402	143,979	142,993
	Unsatisfactory Samples	2,105	4,349	3,191	3,826	2,912
	Unsatisfactory Rate	1.44%	2.93%	2.16%	2.59%	2.00%
	Samples collected at <24 hours	603	628	718	648	693
	Unsatisfactory Samples excluding <24 h samples	1502	3,721	2,473	3,178	2,219
	Unsatisfactory Rate excluding <24 h samples	**1.03%**	**2.51%**	**1.68%**	**2.15%**	**1.52%**
Lab Unsats	Quantity of blood insufficient	888	1,707	1,168	1,251	863
	Blood spots appear scratched or abraded	228	1,353	758	1,131	595
	Blood spots are supersaturated	222	1,140	718	1,220	810
	Blood spots appear clotted or layered	299	958	248	154	174
	Blood spots appear diluted	42	65	9	7	14
	Blood spots exhibits serum rings	32	65	28	24	23
	Blood spots are wet and/or discolored	<5	16	15	35	41
Data Unsats	Blood dot collection paper is expired	104	120	68	123	62
	Insufficient data provided	22	32	36	43	46
	Damaged or delayed in transit	0	23	<5		
	Delivered to lab > 14 days after collection	20	30	120	37	117
	Other	36	23	41	32	19



The number of unsatisfactory samples decreased dramatically in 2015 due to a revision of the sample review process and requirements. There were 393 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).

Figure 4. Distribution of unsatisfactory reasons in 2015.

3.1 Sample Quality – Laboratory Unsats

The majority of unsatisfactory 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. There has been a significant decrease in these types of unsatisfactory samples in 2015, resulting in an overall unsat rate (excluding <24 h samples) of 1.03%.

Due to the high number of unsats in 2014, resulting from a change to the pre-analytical review process for samples causing a higher number of samples to be rejected, the unsat review procedure and criteria have been modified to reduce the number of rejected samples in 2015. Anecdotally, this change may cause a higher number of test level unsats - samples deemed unsatisfactory for reporting post testing due to poor quality results or insufficient sample to repeat testing. In 2015, there were 103 samples that required a repeat due to test level unsats.

3.2 Data Quality and Process Related Unsats

3.2.1 Insufficient Information

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.

3.2.2 Expired Cards

Expired cards can fluctuate year to year, depending on when the lots of cards expire. There were two lots of cards that expired in 2015, in March and August. Typically, NSO sends out bulletin reminders to submitters when an expiry date is approaching, asking them to check their stock and to circulate it.

3.2.3 Transportation

In 2015, NSO introduced batchograms (described in section 4.1.1 below) which has had a positive impact on the number of samples received later than 14 days after collection. In addition, following the change to Purolator in 2014 there have been no samples deemed unsat due to damage or delay in transit.

3.3 Repeat Rates for Unsatisfactory Specimens

The majority (82.1%) of repeat samples required due to unsatisfactory initial samples are received within 3 weeks of the initial sample. By 6 weeks, 89.2% of unsatisfactory samples have had screening completed via a repeat sample. A further ~5.1% (total of 94.3%) of repeats have been received to date. Repeat samples have not yet been received for 118 (5.7%) of unsatisfactory samples in 2015.

Table 11. Repeats received on unsatisfactory samples, 2015 data only.

Time to receipt of repeat sample	Samples (%)
Total Unsats	2105
Up to 3 weeks	1729 (82.1%)
Greater than 3 weeks up to 6 weeks	150 (7.1%)
Greater than or equal to 6 weeks	108 (5.1%)
Not received	118 (5.7%)

4. Turn Around Times

A number of turnaround times and other quality indicators are monitored to ensure timely and good quality service.

The reasons for using mode, 85th centile, and 94th centile are outlined below:

1) The **mode** will primarily reflect samples where at most one weekend interrupts transportation or analysis, and the time at which all tests are completed such that an initial screening determination can be made. For example, a sample which has a screen positive result will have initial results available one working day before the report due to the practice of reanalyzing for confirmation. The mode will reflect better the time at which that initial result is examined for an alert result.

2) The **85th centile** will reflect primarily the turnaround times for samples where at least one weekend interrupts either transportation or analysis, an initial screening result is positive and where analytical QC issues cause a delay in reporting.

3) the **94th centile** will primarily reflect the turnaround times for samples where transportation or analysis is interrupted by a long weekend or by two weekends, while still excluding those initially positive for Cystic Fibrosis where NSO is aiming to introduce a delay in reporting.

Both centiles and the mode will be sensitive to issues such as reporting or data entry delays.

4.1 Transportation Time

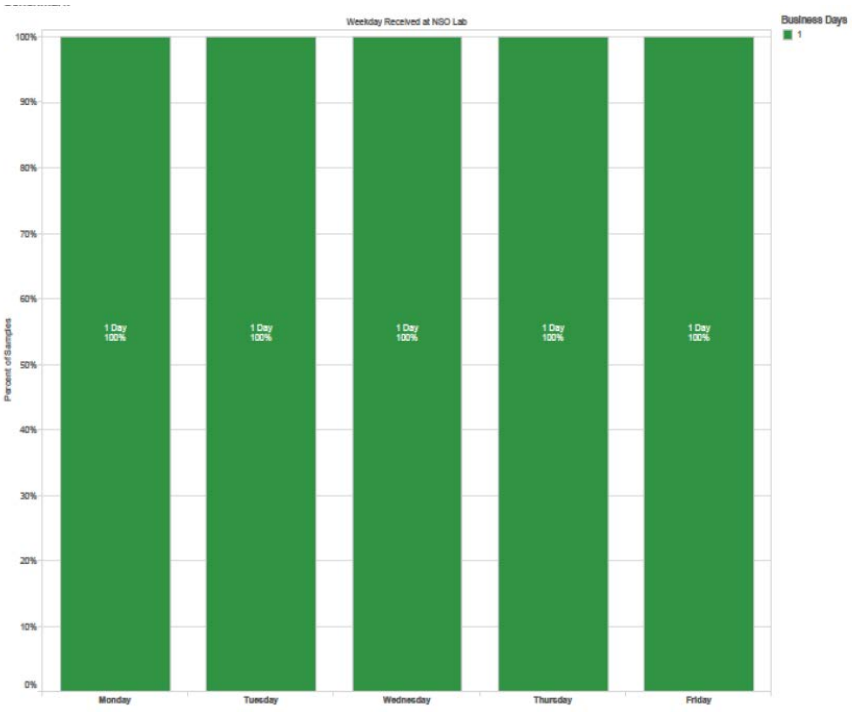
Currently the best measurement of transportation time at the sample level is the difference between the date of collection (DOC) and the date the sample is received in the laboratory. Submitting institutions are asked to dry samples for three hours prior to sending via courier to NSO. Most submitters have a scheduled pick up once daily; therefore, any samples that are not yet dry and/or packaged for shipment will be delayed by at least 24 hours.

Table 11. Days in transit (date of collection to receipt of sample in laboratory).

Statistic	2015	2014	2013	2012	2011	2010
Average	2.6	3.0	3.2	3.2	3.3	3.4
Median	2	3	3	3	3	3
Mode	2	2	2	2	2	2
85th Percentile	3.5	4	5	5	5	5
94th Percentile	4	5	6	6	6	6

4.1.1 Submitter Report Cards

In January 2015, NSO launched a monthly, individualized report for submitters called the "Batchogram". This easily-legible visualization uses stoplight-coloring to illustrate submitter-specific sample transit times.



The tool reliably indicated suboptimal transportation practices (i.e. batching) while providing a clear goal to be achieved: a green graph indicating all samples being received one business day after collection. The "Batchogram" became the first indicator on the NSO Submitter Report Card. Alongside this information tool, guidance, support, and quality improvement resources were made available to sample submitters by a quality coordinator who also assisted with implementing optimized processes at submitting sites.

Figure 5. Example Benchmark Batchogram

4.2 Reporting Times

Table 12. Time from receipt of sample to report by date of collection and date of birth, 2015 data only.

Statistic	DOC to received	Received to report	DOB to report	DOC to report
Average	2.6	3.5	7.5	6
Median	2	3	7	6
Mode	2	2	7	6
85th Percentile	3.5	5	9	7
94th Percentile	4	6	10	9

The turnaround times from various points to the printing of a full report are described in the tables below. Screen positive infants may be referred prior to the full report being available, due to ongoing testing or review.

Table 13. Date of sample collection to report

Statistic	2015	2014	2013	2012	2011	2010
Average	6.1	6.6	7.2	6.8	6.5	6.3
Median	6	6	7	6	6	6
Mode	6	6	6	6	6	6
85th Percentile	7	9	10	9	9	8
94th Percentile	9	10	12	11	11	11

For most infants, results are available by the time they are a week old. Logically, the time from collection to report is 1-2 days less than the time from birth to report, since most infants are sampled at 24-48 hours of age. These periods include the time for sampling, transportation, and analysis of the sample, and may be impacted by later sampling, batching of samples at the hospital/midwifery practice, delays in transport, or delays in reporting due to further testing or quality issues.

Table 14. Date of sample receipt to report.

Statistic	2015	2014	2013	2012	2011	2010
Average	3.5	3.6	4.1	3.3	3.3	2.9
Median	3	3	3	3	2	2
Mode	2	2	2	3	2	2
85th Percentile	5	6	6	5	5	5
94th Percentile	6	7	8	5	7	6

Once a sample is received in the laboratory, the demographic entry must be completed and all test results accepted before a report is available for printing. Reports are generated once daily in time for the mail run. Due to the batching of reporting for hemoglobinopathies, cystic fibrosis, and SCID (these test results are not accepted on a daily basis) there are some delays in printing the reports. The turnaround times for reporting have remained constant over the last four years, with the majority of reports being available within 2 days of receipt. Some outliers in turn-around-time reports are due to older children being screened.

5. Screen Positives

In 2015, there were 1751 screen positive referrals. This represents 1.2% of the total number of infants screened by NSO. There were 1789 total screen positives, but 24 had an elevated TSH in samples taken at <24 hours and 14 were premature infants who screened positive for SCID. These 38 infants were all screen negative on repeat sample testing and were not referred.

The number of screen positive infants referred in 2015 rose from 2014 by just under 80 referrals. This is discussed further in Section 5.2

5.1 Referrals by Treatment Centre

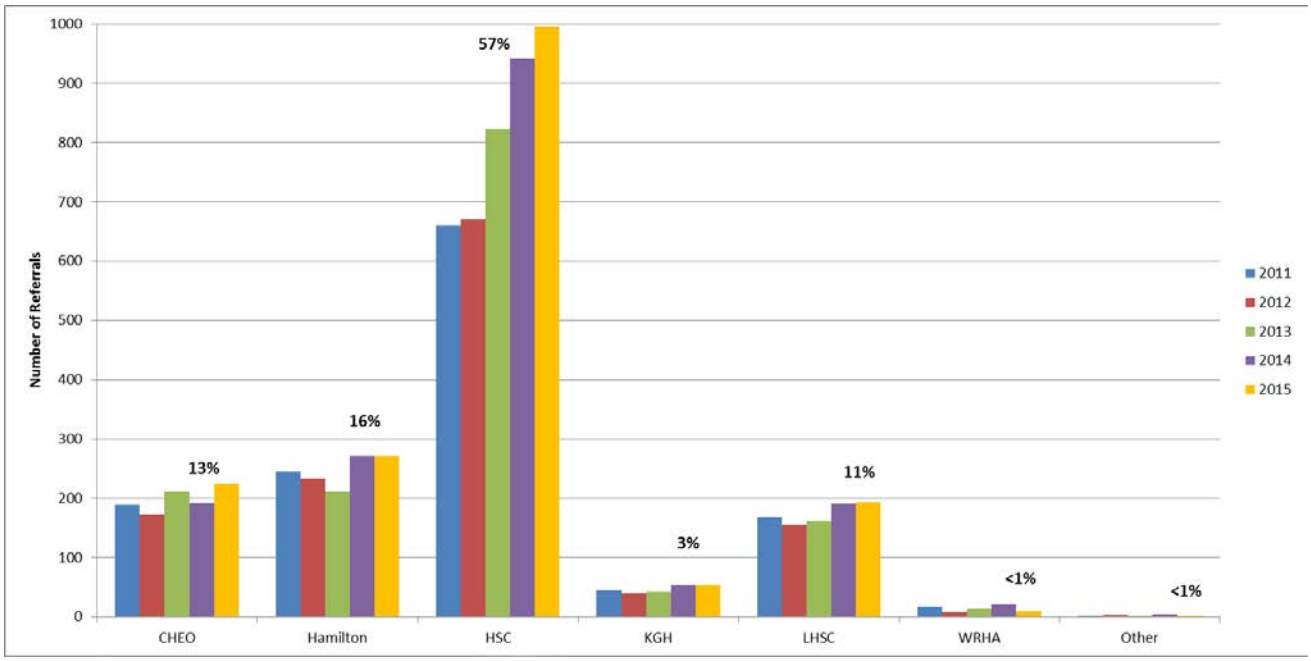


Figure 7. The total number of referrals by treatment centre between 2011-2015.

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 Hospital for Sick Children in Toronto receives over half of the screen positive referrals. The total number of referrals for CHEO and HSC increased in 2015, but decreased or remained constant for the other centres.

5.2 Screen Positives by Disorder

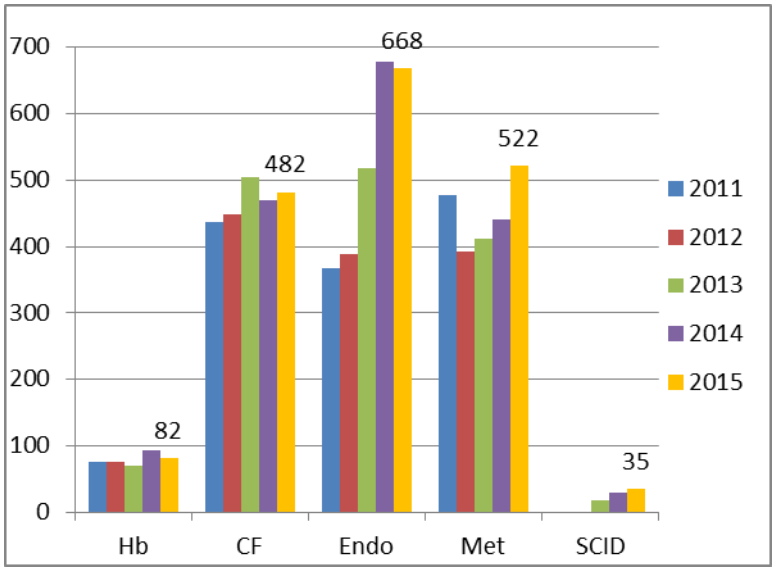


Figure 8. The total number of screen positives by disease grouping between 2011-2015.

5.2.1 Percentage of Screen Positives by Disorder in 2015

Cystic fibrosis, endocrinopathies, and metabolics represent approximately 27%, 37%, and 29% of screen positives respectively. Hemoglobinopathies represent less than 5% of screen positives and SCID 2% of screen positives.

5.3 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:

Table 15. The 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. The 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)

5.4 Definitive Diagnosis Data and Positive Predictive Values

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 biot def), 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, 2016. NSO calculated PPVs initially based on percentage of DERFs completed. Unfortunately, none of the disorders had 98% of DERFs completed by the end of December 2015. However, comparing PPVs between a 90-98% completion rate showed relative consistency, indicating that a particular outcome (ie true positive = yes) was not more likely to be outstanding. Therefore, what is reported below is the PPV for each disease as well as the percentage of DERFs that are outstanding for each calculation.

Table 17. PPVs for each disease

	2015			Current*	
Disease	% DERFs pending	PPV (Yes) %	PPV (Yes + Variant) %	PPV (Yes) %	PPV (Yes + Variant) %
Congenital Hypothyroidism					
Referred	38.3	18.8	28.2	38.5	43.6
< 24 hrs	0.0	0.0	0.0	0.0	0.0
Congenital Adrenal Hyperplasia	27.8	0.9	0.9	2.2	2.2
Hemoglobinopathies	64.6	51.7	51.7	66.8	67.7
Cystic Fibrosis					
Category A	31.3	100.0	100.0	99.4	100.0
Category B	23.2	1.6	3.2	1.8	5.2
Category C	40.7	0.0	0.0	0.5	1.0
Total	28.2	7.5	8.7	6.8	9.4
SCID					
Referred	33.3	7.1	14.3	4.9	8.2
Premature	0.0	0.0	0.0		
Citrullinemia	50.0	20.0	20.0	16.5	17.5
PA/MMA	56.4	11.8	11.8	6.9	6.9
Isovaleric Acidemia	58.7	0.0	0.0	2.0	3.0
Glutaric Aciduria type 1	53.8	33.3	33.3	8.5	8.5
C5OH	47.9	10.8	10.8	0.0	0.0
CUD	63.3	0.0	0.0	5.2	5.2
CPTI	26.7	0.0	81.8		
CPTII	33.3	50.0	50.0		
Homocystinuria	63.2	0.0	0.0	0.0	0.0
LCHAD	50.0	0.0	0.0	62.5	62.5
MCAD	41.2	35.0	35.0	30.1	36.0
Phenylketonuria	50.0	5.5	16.4	16.6	38.1
Tyrosinemia	50.0	0.0	0.0	17.9	17.9
MSUD	33.3	8.3	8.3	5.1	5.1

Galactosemia	66.7	25.0	25.0	8.3	20.8
Biotinidase Deficiency	46.3	9.1	59.1	4.4	42.2
VLCAD	46.9	5.9	5.9	7.8	13.9

*The current PPVs are for current disorder logics. There are 9 conditions in which there have been disorder logic updates since NSO began operations in 2006: CAH, Hemoglobinopathies, SCID, PA/MMA, C5OH relelated disorders, Tyrosinemias, MSUD, Biotinidase Deficiency and Galactosemia. Disorder logics that were updated in 2015 include C5OH related disorders.