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

Annual Report to the Newborn Screening Ontario Advisory Council

Calendar Year 2016

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1. Sample Volumes in 2016

Table 1. Sample volumes between 2016-2012 by sample type.

Indication	Sample Type	2016	2015	2014	2013	2012
Routine screening	Satisfactory	145,018	144,812	144,864	145,327	144,793
	Unsatisfactory	1,755	1,367	3,584	2,266	3,012
Routine Screening – Total		**146,773**	**146,179**	**148,448**	**147,593**	**147,805**
Referred-in screening: full panel	Satisfactory	410	400	192	8	17
	Unsatisfactory	6	22	5	0	0
Referred-in Screening: Full panel – Total		**416**	**422**	**197**	**8**	**17**
Cord Blood	Cord blood - Hemoglobin Screen	914	900	469	160	0
Post Mortem	Post Mortem – blood	152	150	164	149	106
	Post Mortem – bile	148	145	169	127	89
Diagnostic/Monitoring Bloodspot	Amino acids/Acylcarnitine	2	3	4	3	6
	CAH Monitoring	4	3	0	7	2
	Glutaric Aciduria Type 1	29	45	29	22	25
	Tyrosenimia	23	42	38	51	31
	Phenylalanine monitoring	564	407	368	330	249
	SCID Diagnostic	42	24	32	29	0
	Identity testing (discrepant results, positives)	3	2	5	1	2
	Other	2	3	2	17	4
	Unsatisfactory	14	11	3	11	9
Research DBS samples	Bangladesh Cord Satisfactory	168	n/a	n/a	n/a	n/a
	Bangladesh Heel Satisfactory	115	n/a	n/a	n/a	n/a
	Guyana Satisfactory	1,269	n/a	n/a	n/a	n/a
	Unsatisfactory	40	n/a	n/a	n/a	n/a
Non-screening sample – Total		**3,489**	**1,724**	**1,283**	**907**	**523**
Grand Total		**151,038**	**148,325**	**149,928**	**148,508**	**148,345**

*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

There was a modest increase in the overall number of samples received by NSO in 2016 as compared to 2015, due to the addition of dried bloodspot samples for research purposes, explained further in Section 1.2.

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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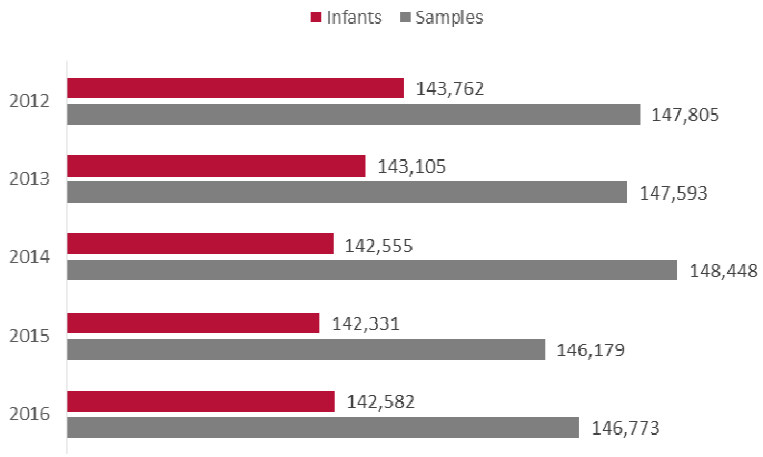

The overall number of infants tested is relatively constant each year with only ~1500 infants difference between the highest and lowest years.

Based on defers/ declines, missed screen alerts from BORN, and newborn screening sample counts, NSO estimates the total number of infants in Ontario as 143,067, and the rate of screening uptake in 2016 as 99.7%, the same rate of uptake as in two previous years.

Figure 1: Total number of infants and samples screened between 2016-2012

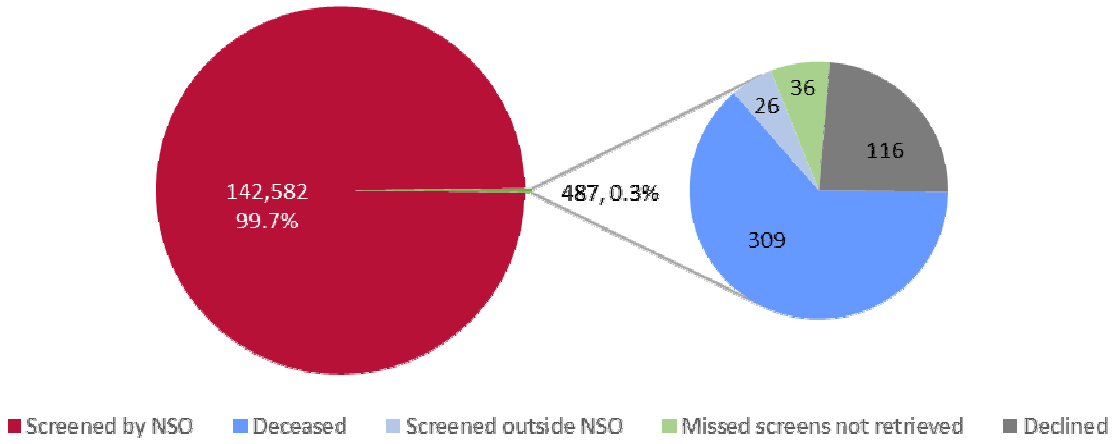

Figure 2. Coverage of screening in Ontario births.

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.

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In 2016, NSO received 396 completed decline/defer forms, a substantial increase from previous years. The number of declines documented using this form has remained steady, with 28 declines in 2016 compared with 29 in 2015. In two cases a decline form was received and a sample was received the following day. The remaining 368 forms received indicated a parent's desire to defer screening, and samples were eventually received for all but one of these deferred cases. The number of deferrals documented using the form has increased by almost 80% over last year's deferrals.

Table 2. Declined, deferred samples and potential missed screen alerts between 2016-2012.

Case Type	2016	2015	2014	2013	2012
Declined/deferred form received	396	234	54	1	N/A
Decline	28	29	23		
Deferral	368	205	32		
Potential missed newborn screen alerts	362	390	454	558	212
Decline	88	75	83		
Deferral	2	3	1		

1.1.3 Missed Screens

Table 3. Potential missed screen alerts requiring follow-up in 2016, by reason and responsible submitter, and samples received post follow-up.

Category		Hospital	Midwife	Total (2016)	Samples received	Percent received	Total (2015)
Other	Deceased/ Palliative	42	0	**42***			63
	Declined	18	70	**88**			75
	Incorrect or incomplete BORN information (ex. infant <14days old, stillborn/TA)	3	0	**3**			17
	Incorrect or incomplete information on req. (sample already received)	8	3	**11**			4
	NBS done in other jurisdiction	15	11	**26**			28
	Parents deferred NBS	1	1	**2**			3
	Sample taken but not yet received (DOC ≤ 14 days)	10	12	**22**			34
Total: Non-Missed Screens		**97**	**97**	**194**			**224**
True Missed Screens	Home birth/birth centre midwife care	0	8	**8**	6	75%	11
	Hospital birth midwife care	0	40	**40**	39	98%	41
	Interhospital transfer (between hospitals)	11	0	**11**	7	64%	11
	Intrahospital transfer (between units in same hospital)	8	0	**8**	8	100%	16
	Intrahospital/interhospital transfer with midwife involvement	2	3	**5**	4	80%	4
	Not taken in error	51	0	**51**	39	76%	71
	Sample collected, package lost	18	0	**18**	14	78%	-
	Unknown reason hospital birth	27	0	**27**	15	56%	12
Total: True Missed Screens		**117**	**51**	**168**	**132**	**79%**	**166**
Grand Total		**214**	**148**	**362**			**390**

*There were an additional 267 neonatal deaths in 2016 that were appropriately cataloged as such in BORN and did not result in a missed screen notification.

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In 2016, there were 362 potential missed newborn screen alerts that required follow up by NSO. This is down by approximately 30 cases from 2015, and almost 100 cases from 2014. Hospitals were the responsible facility in 60% of the missed screen alerts and midwives were involved in roughly 40% of the cases. There were 63 different midwifery practices involved in the alerts and 63 different hospitals. Action on the part of NSO resulted in 132 of the 168 (79%) 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. Of the missed screen alerts, 205 (82 true misses) were received at greater than 14 days of age. The 82 true missed screen alerts received greater than 14 days of age ranged from 15 to 319 days of age. In addition, there were 77 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 29 samples from midwives, 1 from a health centre, and 47 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 is relatively unchanged since 2015.

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 9 missed screen alerts that were initiated by outstanding report requests as the BORN entry had not yet been completed. These babies were true misses.

Missed Screens and Declines
In 2016 there were 88 declines identified by the missed screen alert process, compared to the 75 declines identified this way in 2015 (Table 2). Combined with the 28 declines received via the decline form process outlined above, the total number of declines increased by 16 from 2015. Midwives were the health care provider in 78% (n=91) of declined cases.

Missed Screens and Screen Positive Results
There was 1 infant identified in the missed screen alerts who ultimately screened positive for a disease, this baby was found to be not affected for Galactosemia after diagnostic testing.

Missed Screens and Transportation
As NSO and submitters have implemented much more rigorous package tracking processes (see section 4.1), it has become more evident when packages are lost in the courier system, resulting in missed screens. In 2016, 8 packages were lost in transit, requiring recollection of 18 samples.

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 volumes are relatively steady from 2013, with the biggest volume being from PKU home monitoring.

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1.2.1 Screening Research Projects

Guyana Newborn Screening Feasibility Study
In areas of the world where establishing newborn screening programs can be challenging, working together with well-established programs may help in reducing obstacles in the development of new programs. As part of a service agreement with the Georgetown Public Hospital Cooperation in Guyana, NSO is providing newborn screening results to Guyana for congenital hypothyroidism and sickle cell disease. The purpose of this collaboration is to determine prevalence and feasibility of newborn screening in Guyana and to aid in the development of guidelines for routine newborn screening for these diseases in Guyana.

Predicting Gestational Age from Newborn Screening
Funded by the Bill & Melinda Gates Foundation and in collaboration with the Ottawa Hospital Research Institute, NSO is part of a research project aiming to help identify preemies in third-world countries. Preterm birth is the leading cause of neonatal morbidity and mortality, however, evaluating gestational age in low resource settings can be challenging. An algorithm was developed that can estimate gestational age at birth based on analytes obtained from newborn screening in Ontario. For this research project, NSO is performing newborn screening on umbilical cord and heel prick dried blood spots sent from Bangladesh and Zambia, where gestational age is available. The data generated from these samples will be applied to the developed algorithm to see how well it predicts gestational age for these babies. As a secondary objective, NSO will evaluate the feasibility of conducting remote newborn screening programs in low-resource settings and determine incidence rates of preterm birth, screen positive and carrier status for the current newborn screening panel in these countries.

1.2.2 Cytomegalovirus and Hemoglobin Carrier Requests

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 (CMV).

Table 4. CMV requests between 2016-2012.

	2016	2015	2014	2013	2012
Samples tested	189	129	94	96	29
Samples unable to locate (DOB >2006)	4	5		2	
Infants born before April 2006	0	4		5	1
Total Requests	**193**	**138**	**94**	**103**	**30**
Positive CMV results (% of samples tested)	11 (5.8%)	11 (8.5%)	9 (9.6%)	8 (8.3%)	3 (10.3%)

The number of CMV requests continued to increase in 2016. Although the workload associated with retrospective CMV analysis is significant, NSO currently offers this service at no charge.

NSO was unable to fulfill 4 of the CMV requests received. Two of the children were born outside of Canada, one baby did not have a newborn screening sample collected (captured in missed newborn screen alert prior to CMV request) and one sample could not be located and retrieved from storage. Approximately 8-10% of samples tested in previous years have had a positive CMV result, but in 2016 the percentage of positive samples has dropped slightly to 5.8%. The expected CMV positive rate in the NBS population is ~0.6%,

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indicating a higher index of suspicion in the requests for testing received by NSO. The higher number of requests in 2016, however, did not yield a greater number of positive results.

Table 5. Hemoglobin carrier requests between 2016-2012.

	2016	2015	2014	2013	2012
Requests from high risk population	28	34	34	28	32
Total Requests	**45**	**45**	**53**	**45**	**57**
Number of carriers reported	11	14	13	16	18

In 2016, approximately 0.5% of carriers have requested their results. The number of hemoglobin carrier requests has remained relatively constant over time.

Table 6. Carriers identified in 2016

HGB Pattern	Carriers Identified
FAB	4
FAC	318
FAD	171
FAE	283
FAS	1192
FAX	101
Other	28
Grand Total	**2097**

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2. Demographics of Screening Samples

2.1 Age at Collection

Table 7. Age at collection for 2016, initial samples only.

Age at Collection	Number of Initial Samples	% of Initial Samples (2016)	% of Initial Samples (2015)
Less than 24 hours	818	0.58%	0.62%
24-47 hours (1-2 days)	123,468	86.83%	84.70%
48-72 hours (2-3 days)	12,532	8.81%	10.42%
73-168 hours (3-7 days)	5,074	3.57%	4.02%
Greater than 168 hours (7days)	281	0.20%	0.23%
Not specified	28	0.02%	0.02%

The majority of newborn screening samples are collected between 24-48 hours of age. Approximately 96% of samples are collected by 72 hours of age. There is a positive trend towards samples being collected between 24-48 hours of age, even in advance of any official change to NSO's recommended age of collection.

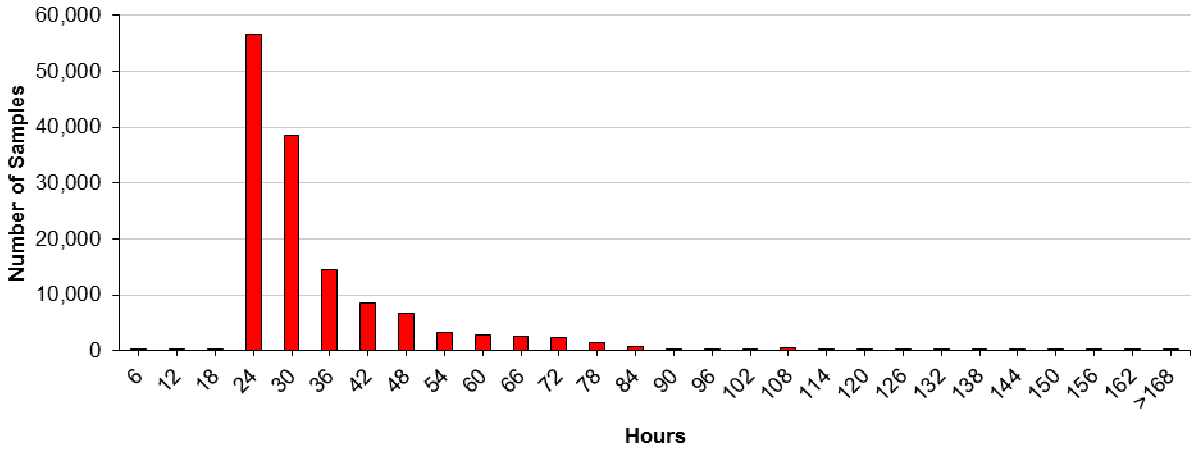

Figure 3. The number of samples collected by the age (in hours) of the infant.

There were 818 samples that were collected at <24 hours of age, with 518 of these considered unsatisfactory (300 samples were collected in the 10 min grace period). Although 50 more samples were collected at <24hrs than in 2015; 100 less were considered unsatisfactory; therefore more early samples are being collected within the 10mins grace period. Of the 818 samples, 71 were collected early due to a pending transfusion. The majority of <24 hour samples that were unsatisfactory were taken early for an unknown reason. A check box has been added to the cards to indicate early discharge for <24 hour samples, to reduce the number of verification calls being made, and to allow for more reportable data in the future.

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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. 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 8. Transfusion cases in 2016

Category		Number of Cases
Repeat Not Required		272 (62.4%)
Repeat Required		146 (33.5%)
Case still open not yet reviewed		18 (4.1%)
Grand Total		**436**
Repeat Required	Repeat Received	38 (26.1%)
	Repeat Not Received	108 (73.9%)
	Case still open	74
	Deceased	16
	Family moved	1
	Parents bringing infant back	6
	Closed case letter sent	11

Table 9. Age at which transfusion repeats were received in 2016

Age	# of samples
4-6 months	5
6-12 months	32
>12 months	1
Grand Total	**38**

There were 436 transfusion cases in 2016. For 272 cases (62%) a repeat was not required as a satisfactory pre-transfusion sample was already received. There are still 18 cases that have not yet been reviewed and categorized as repeat required or repeat not required. For cases requiring a repeat sample, 38 (26.1%) have been received, the majority of which were received between 6-12 months of age. Currently 74 cases for 2016 remain open with no repeat received, 33 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 2016, there were 2114 infants that fit the premature infant policy. Of these, 1651 (78%) had a 3 week (or equivalent) sample obtained.

NSO recommends repeats on premature infants, but does not actively follow up on repeats. In 2016, 49 facilities submitted repeat premature samples of which 48 were hospitals with level II and/or III nurseries. There were only 3 hospitals in the province that have level II and/or III nurseries that did not submit any repeat premature samples. Two of these hospitals have an internal protocol for measuring TSH on premature infants at 3 weeks of age.

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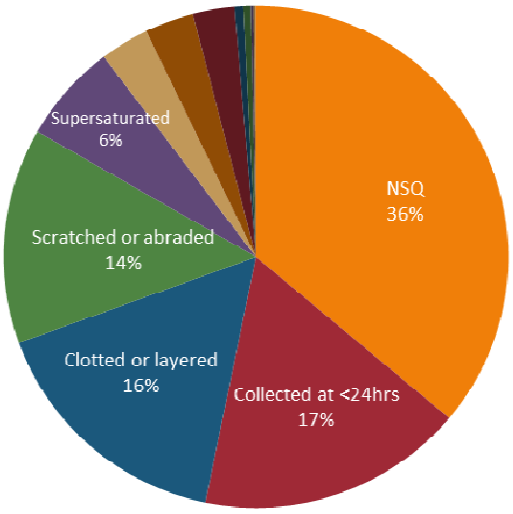
3. Unsatisfactory Samples

Table 10. Unsatisfactory samples by reason between 2016-2012.

			2016	2015	2014	2013	2012
SAMPLES		Satisfactory Samples	144,359	144,074	144,099	144,402	143,979
		Unsatisfactory Samples	2,414	2,105	4,349	3,191	3,826
		Unsatisfactory Rate	**1.64%**	**1.44%**	**2.93%**	**2.16%**	**2.59%**
		Samples Collected at <24hrs	518	603	628	718	648
		Unsatisfactory Samples excluding <24hr samples	1,896	1,502	3,721	2,473	3,178
		Unsatisfactory Rate excluding <24hr samples	**1.29%**	**1.03%**	**2.51%**	**1.68%**	**2.15%**
REASONS	Lab Unsats	Quantity of blood insufficient (NSQ)	1,094	888	1,707	1,168	1,251
		Blood spots appear scratched or abraded	421	228	1,353	758	1,131
		Blood spots are supersaturated	193	222	1,140	718	1,220
		Blood spots appear clotted or layered	491	299	958	248	154
		Blood spots appear diluted	17	42	65	9	7
		Blood spots exhibits serum rings	95	32	65	28	24
		Blood spots are wet and/or discolored	5	1	16	15	35
		Other	35	16	7	12	10
	Data Unsats	Blood dot collection paper is expired	95	104	120	68	123
		Insufficient data provided	14	22	32	36	43
		Damaged or delayed in transit	1	0	23	1	0
		Delivered to lab > 14 days after collection	4	20	30	120	37
		Sample collected at <24hrs	518	603	628	718	648
		Other	46	21	16	29	22



There were 615 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).

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.

Figure 4. Distribution of unsatisfactory reasons in 2016.

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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 11. Repeat samples for TLU.

Time to receipt of TLU repeat sample	Samples (%)
Total Test Level Unsats	**146**
Repeats Required	**68**
< 3 weeks	56 (82.4%)
≥3 weeks < 6 weeks	4 (5.9%)
≥ 6 weeks	2 (2.9%)
Not received	6 (8.8%)

In 2016 there were 146 TLU, of which 68 required a repeat. Some of the TLUs were also unsatisfactory samples due to collection at <24 hours. Most (82%) repeats were received within 3 weeks. Two infants with TLU were screen positive for other diseases and were referred.

3.3 Data Quality and Process Related Unsats

3.3.1 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.

3.3.2 Expired Cards

Expired cards can fluctuate year to year, depending on when the lots of cards expire. There were three lots of cards that expired in 2016, in January, July and November. Typically, NSO sends out bulletin reminders to submitters when an expiry date is approaching, asking them to check and circulate their stock.

3.3.3 Transportation

Continued efforts to educate submitters on reducing batching practices, and monitoring packages within the courier system have resulted in very low rates of unsats for samples damaged in transit and samples taking >14 days in transit.

3.4 Repeat Rates for Unsatisfactory Specimens

The majority (81.3%) of repeat samples are received within 3 weeks of the initial sample. By 6 weeks, 88.9% of unsatisfactory samples have had screening completed via a repeat sample. A further ~4.3% (total of 93.2%) of

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repeats have been received to date. Repeat samples have not yet been received for 165 (6.8%) of unsatisfactory samples in 2016

Table 12. Repeats received on unsatisfactory samples, 2016 data only.

Time to receipt of repeat sample	Samples (%)
Total Unsats	**2,414**
Up to 3 weeks	1,962 (81.3%)
Greater than 3 weeks up to 6 weeks	183 (7.6%)
Greater than or equal to 6 weeks	104 (4.3%)
Not received	165 (6.8%)

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4. Sample Transportation and Weekend Operations

Delays can occur throughout the screening process (sample handling by submitters, sample transportation, and NSO laboratory operation) and can impact outcomes for newborns, particularly those with aggressive diseases. Through 2015, NSO worked closely with submitters and has seen great improvements in sample transit times using an audit and feedback mechanism ("batchogram" distribution and submitter education campaign). In 2016, significant investments have been made towards optimizing sample transportation, including a pilot of sample tracking software (Track-kit), and the full implementation of weekend operations.

4.1 Sample transportation

Cargo, an internally developed package tracking system implemented in February 2016, supports reduced sample transit times by providing early identification of delayed or lost packages. Cargo reconciles the data from the courier manifest with the packages received daily, and has successfully identified overdue and missing packages triggering earlier follow-up investigation for impacted samples. However, Cargo cannot provide sample level details and depends on documentation provided by submitting hospitals or midwives to obtain this information.

To address the continued challenge of sample level tracking, NSO worked with STACS DNA to develop and pilot Track-Kit™, a web-based software solution that can also integrate with the courier data, to facilitate sample level tracking and provide additional benefits such as collection device expiration warnings, inventory control and the ability to determine accurate transportation metrics.

A pilot test of the Track-Kit system has been underway since October 2016. NSO can track shipped samples to receipt at the laboratory and submitters are notified of sample receipt in the lab. Although additional effort is required for submitters to log individual samples in Track-Kit, courier options are pre-selected, so users see benefit in the ease and speed in preparing the courier shipping request. Forced pre-selection of fields helps to reduce NSO's costs by decreasing shipping errors and misuse of NSO paid courier accounts. While some of the pilot period has been spent troubleshooting, and implementing enhancements, generally the experience to date has been positive. To facilitate broader roll-out, NSO is proposing that STACS DNA add a hybrid capability allowing hospitals to use Track-Kit without the individual sample tracking option as an interim option.

4.2 Weekend operations

In 2015, an internal task force analyzed the benefit, risks, and costs of enhanced weekend sample transportation and laboratory operations. Submitters and treatment centres also provided the feedback that it was important to them that NSO address weekend associated delays. Based on the analysis and business case prepared by a task force, NSO implemented the review and reporting of alert results on Saturdays in October 2015 and a proposal was submitted to the Ministry of Health for additional funding for full weekend operations.

In November 2016 full Saturday laboratory operations were implemented, with alert reporting on Sundays, including shipping of samples from submitters on Saturdays for delivery on Mondays. While integration of the weekend laboratory operations has been successful, continued efforts are required to remind submitters to ship samples on Saturdays. In addition, the ability for the courier system to support the Saturday pickups and

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weekend sorting of packages is less than anticipated. Improvements to the courier system are identified as an area for improvement in 2017.

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5. Screen Positives

In 2016, there were 1598 screen positive referrals. This represents 1.05% of the total number of infants screened by NSO. There were 1694 total screen positives, but 30 had an elevated TSH in samples taken at <24 hours and 67 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. Five SCID prems were referred on repeat samples. Two samples with test level unsats (insufficient quantity to repeat) were referred on initial values only.

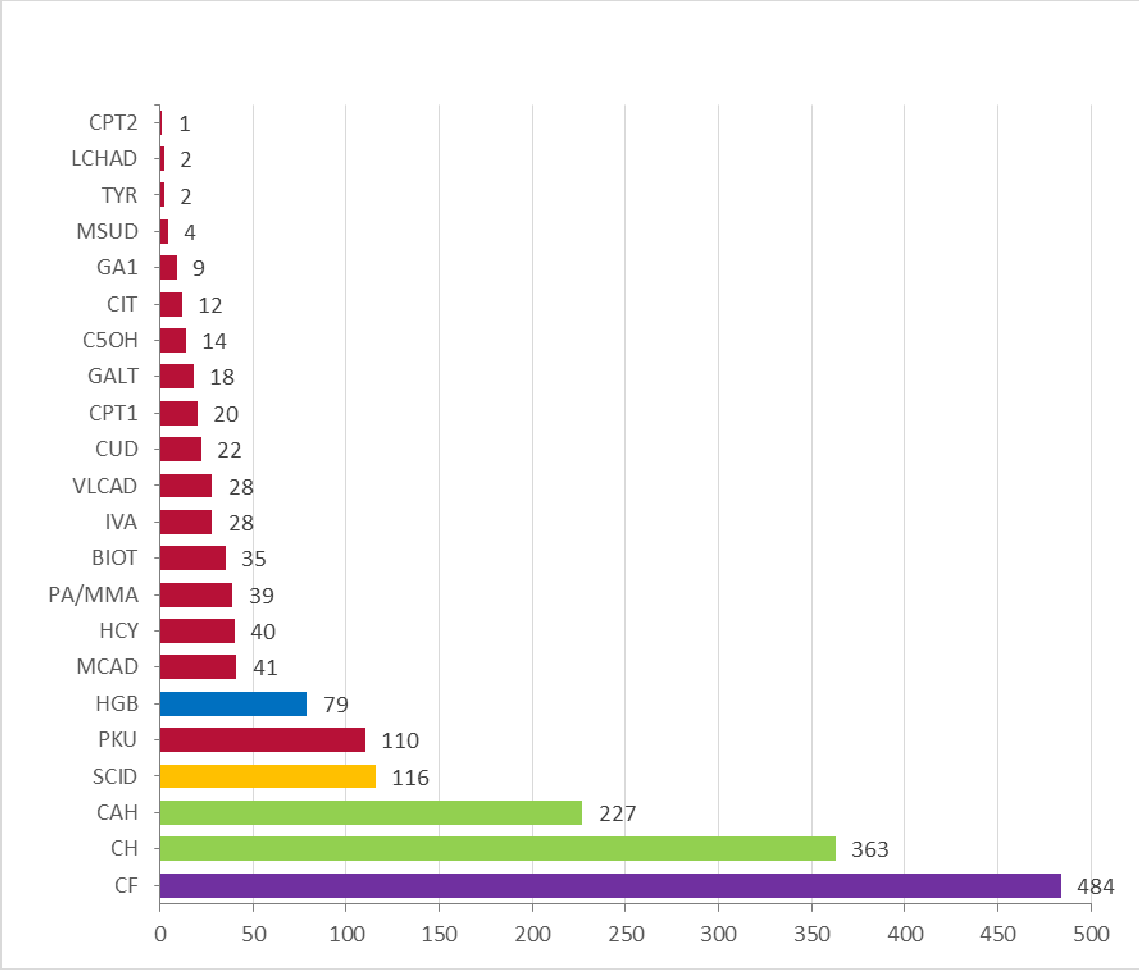

Figure 5. Total number of screen positive cases by disease/analyte in 2016

The number of screen positive infants referred in 2016 decreased from 2015 by just under 80 referrals. This is discussed further in Section 5.2.

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5.1 Referrals by Treatment Centre

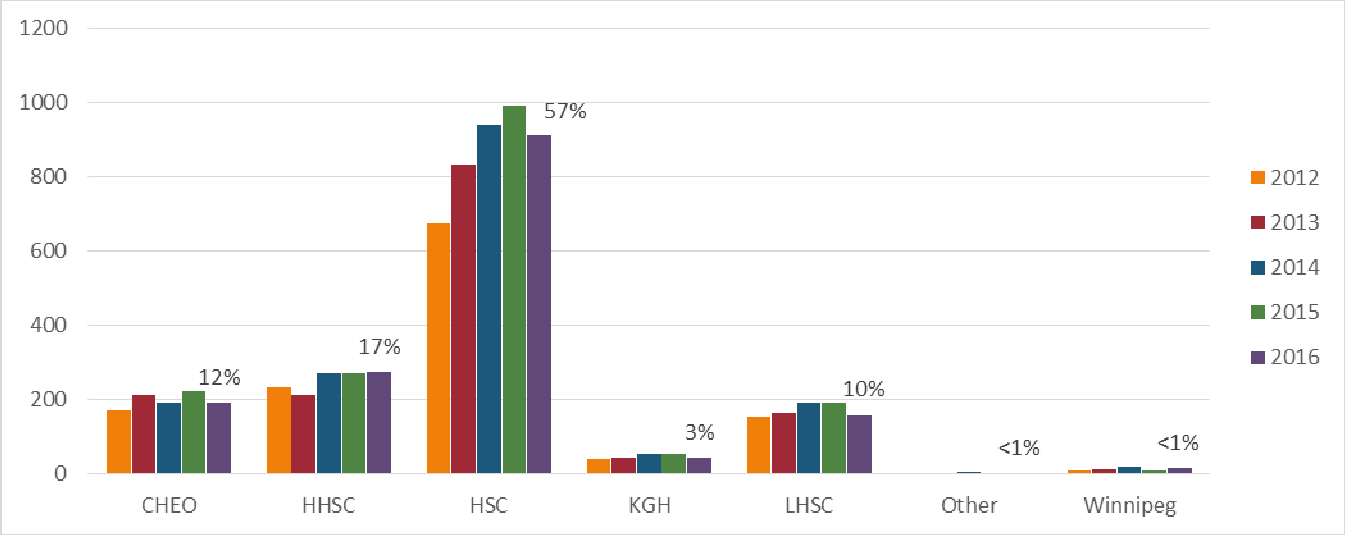

Figure 6. The total number of referrals by treatment centre between 2012-2016

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 decreased in 2016 for CHEO, HSC, KGH and LHSC, but remained constant for HHSC.

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5.2 Screen Positives by Disorder Group

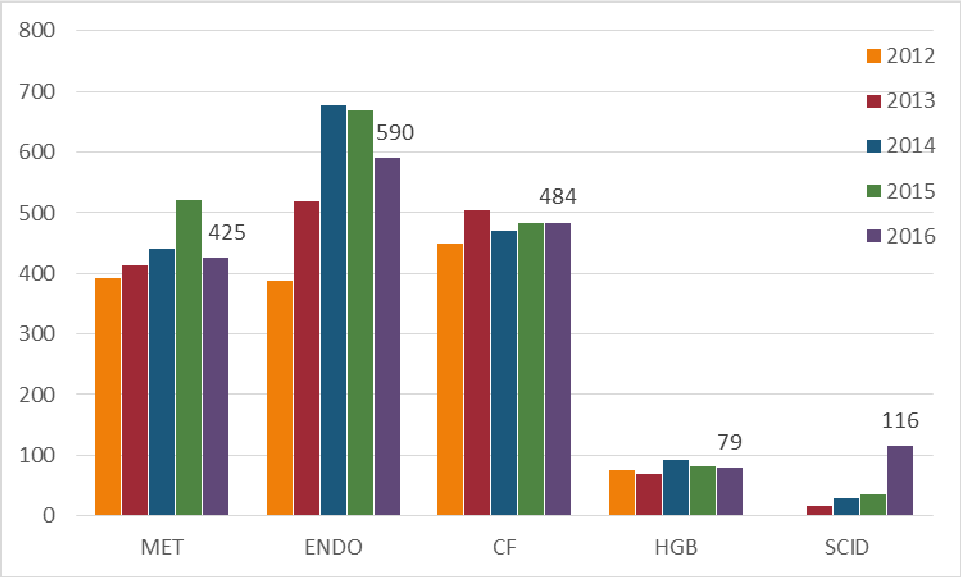

Figure 7. The total number of screen positives by disease grouping between 2012-2016.

The number of screen positives per disease grouping decreased or remained constant in 2016 for all groups except SCID. This is discussed further in section 5.2.6.

5.2.1 Percentage of Screen Positives by Disorder in 2016

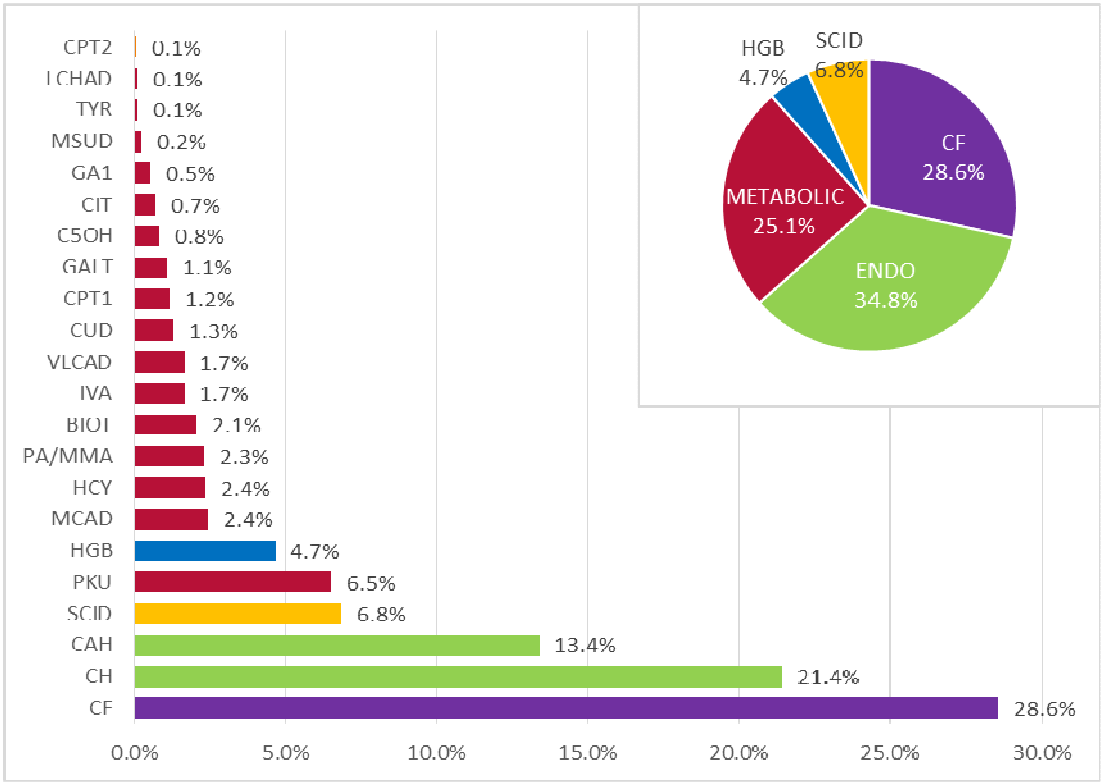

Figure 8. The number and overall percentage of screen positives by disorder in 2016.

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Cystic fibrosis, Endocrinopathies, and Metabolics represent approximately 28%, 35%, and 25% of screen positives respectively. SCID screen positives have rose and now represents 7% of total screen positives. Hemoglobinopathies represent less than 5% of screen positives.

5.2.2 Hemoglobinopathies

The number of screen positives in 2016 remained about the same as 2015, with only a difference of 3 referrals.

5.2.3 Cystic Fibrosis

The number of screen positives in 2016 remained the same as 2015, with only a difference of 2 referrals.

5.2.4 Endocrinopathies

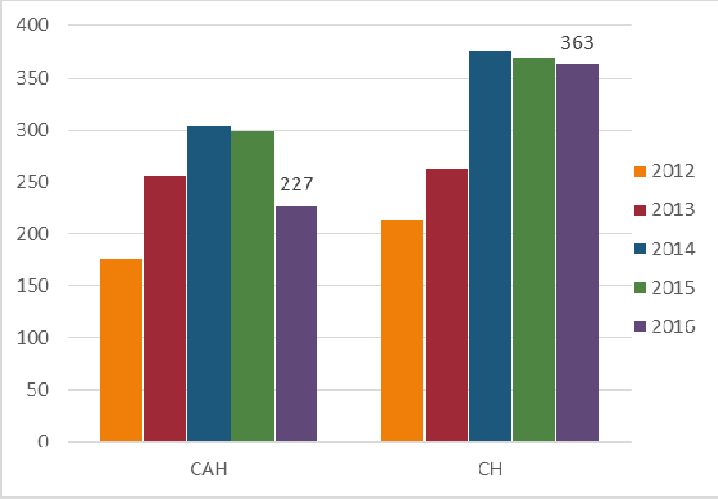

Figure 9. The total number of congenital adrenal hyperplasia and congenital hypothyroidism screen positives between 2012-2016

5.2.4.1 Congenital Adrenal Hyperplasia

The number of screen positives for this condition decreased significantly in 2016. In September 2016, NSO changed the disorder logic to include both birth weight and gestational age. NSO also changed its policy for referring extremely premature infants on their repeat sample if their initial sample was screen negative, 25 samples fell into this category.

5.2.4.2 Congenital Hypothyroidism

The screen positive rate for this condition also stabilized in 2015, but is still higher than in previous years with no change to the type of kit used or the cutoffs. As discussed in the 2015 report, internal and external quality control measures are all consistent with NSO values, and discussions with the kit and instrument vendor and other labs have not provided any insight into the shift in measurements in 2014.

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5.2.5 Metabolics

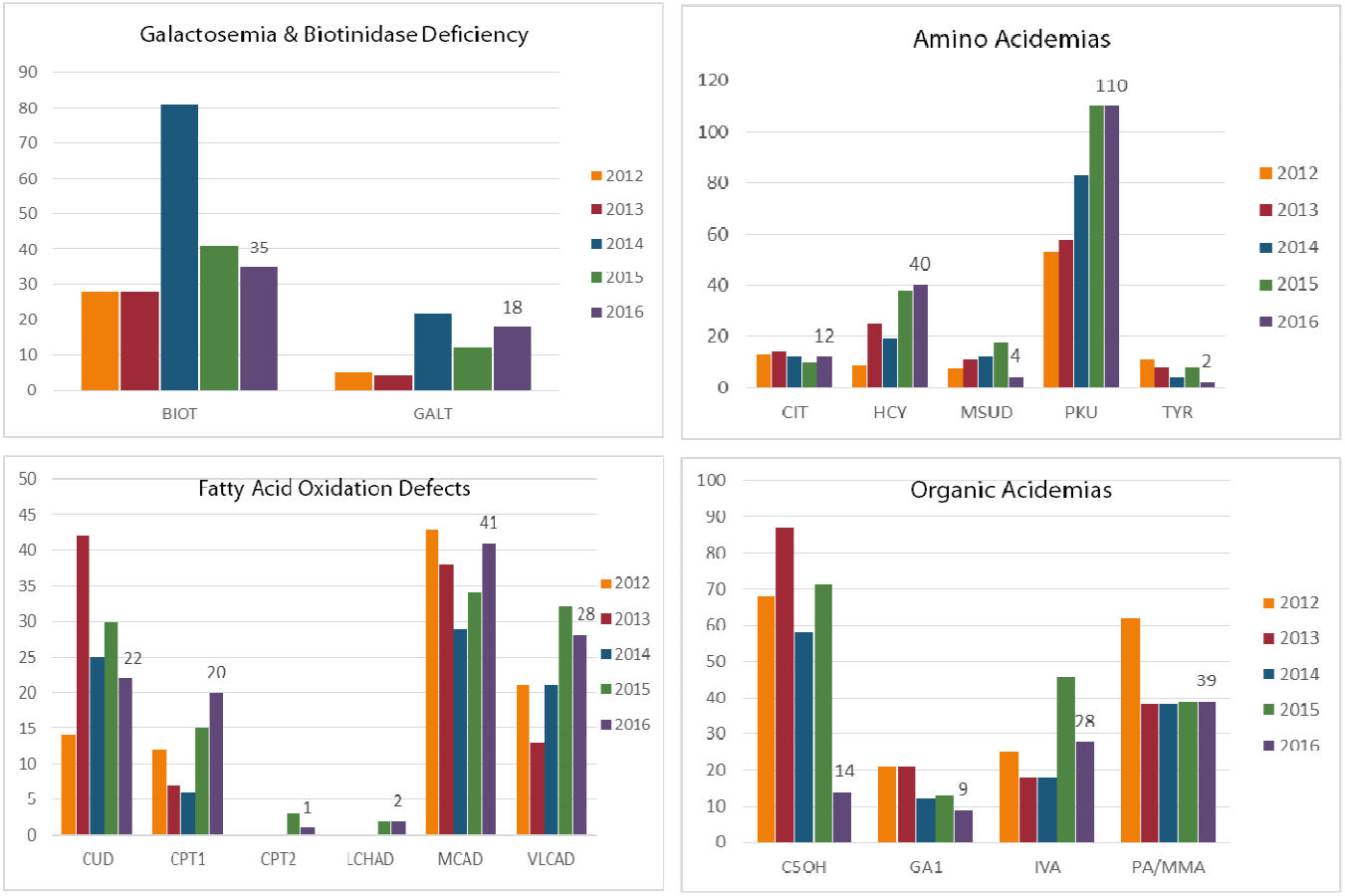

Figure 10. The number of metabolic screen positives between 2012-2016 by disease

There was a disorder logic change for both BIOT and GALT in 2014 with conservative cutoffs selected. The number of referrals for these conditions has stabilized since.

There was a reduction in both the number of maple syrup urine disease referrals in 2016. The cause of this is unknown as the disorder logic has not been modified. The other amino acidemias remained relatively constant from 2015-2016.

There was an increase in the number of carnitine palmitoyltransferase type 1 and medium chain acyl-CoA dehydrogenase deficiency in 2016. Once again the cause is unknown. The number of samples from geographic regions where CPT1 is more prevalent did not increase in 2016.

There was a disorder logic change to the C5OH screening algorithm as recommended by the Newborn Screening Ontario Advisory Council in December 2015. The effects of this change were reflected in the decreased number of referrals in 2016. The change reduced the number of infants referred with

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isolated elevations of C5OH while still maintaining sensitivity to detect β-Ketothioloase Deficiency, HMG CoA Lyase Deficiency and Multiple Carboxylase Deficiency.

The number of isovaleric acidemia referrals decreased in 2016. In 2015 there was a spike in referrals from infants in 3 level III nurseries in the province. The three hospitals reported no change to their procedures which would have accounted for this increase in IVA screen positives and in 2016 these hospitals have not been overrepresented.

5.2.6 Severe Combined Immune Deficiency

The number of screen positives for SCID increased significantly in 2016. In particular the number of premature infants who screened positive for SCID on their initial sample increased without an increase in the number of premature samples received by NSO.

5.2.7 Screen Positive by Sample Type for Premature Infants

In 2016 there were 341 screen positive results that qualified under the preemie policy (255 initial samples and 86 on repeat samples) and 64 of these screen positives were not referred (61 SCID and 3 CH). However, of the 64 not referred, 15 infants were screen positive for a second condition that was referred. The majority of the screen positives in preemies were for SCID, CAH, PKU, HCY, and IVA.

There were 14 infants who screened positive on both their initial and repeat samples, and 53 infants who screened positive on their repeat samples only (44 repeat prem samples, 9 repeat unsat), with the majority of these being screen positive for CAH. Two infants were SCID screen positive on 3 different samples. In September 2016 NSO changed the logic to no longer refer repeat preemie samples.

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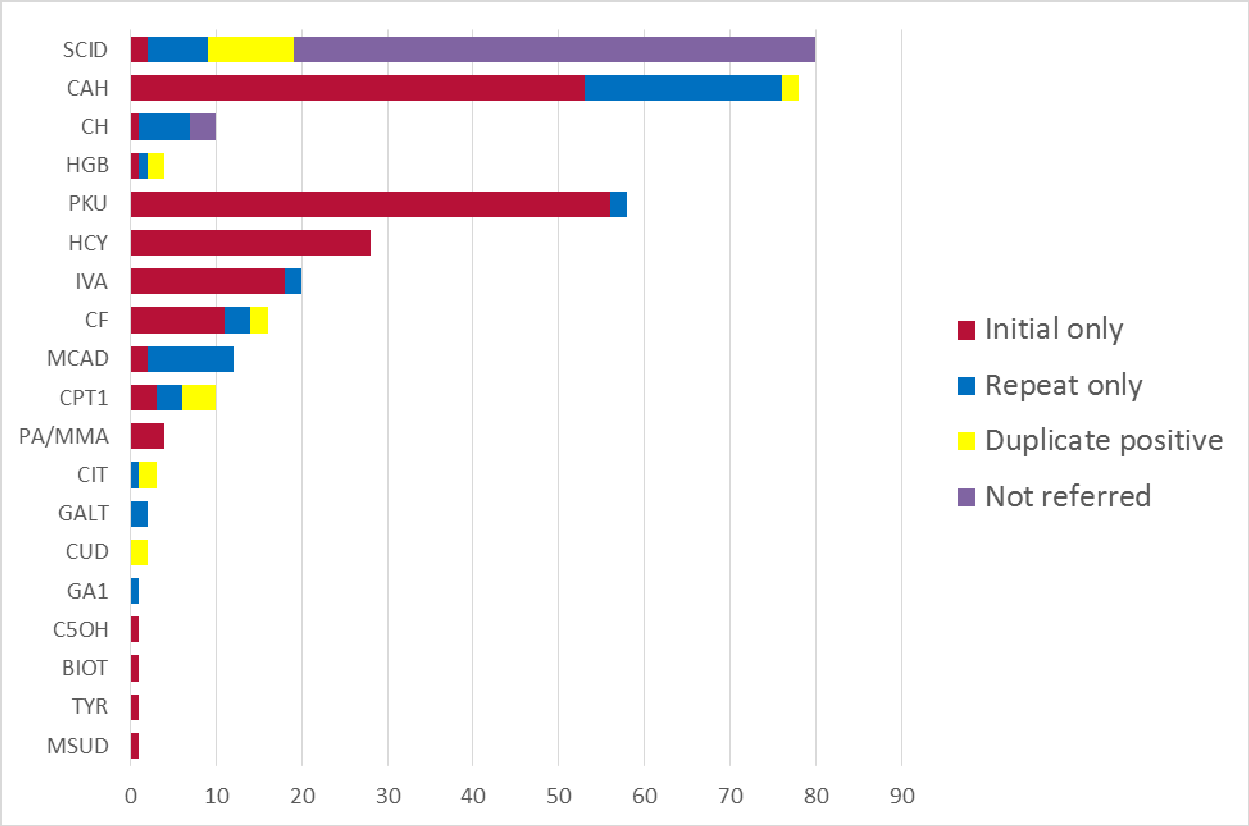

Figure 11. The number of screen positives by disease for extremely premature infants (<33 weeks gestation and/or <1500g); red is initial positive sample only, blue is repeat positive sample only; yellow is two samples for the same infant positive for the same condition; and purple are screen positives that were not referred.

5.3 Diagnostic Feedback

Due to a concerted effort in early 2017 to complete outstanding DERFs (Diagnostic Evaluation Report Forms) approximately 12.7% (204 cases) of feedback information remain pending for the referrals made in 2016 as of April 1, 2017. This is significantly lower than in previous years and will help NSO calculate more relevant PPVs and refine disorder logic.

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Table 13. The number of pending DERFs per year from each Treatment Centre by disease group.

Treatment Centre	Disease Group	2006 - 2010	2011	2012	2013	2014	2015	2016	Total Pending	Total Referrals
CHEO	Metabolic							1	1 (0.2%)	610
	Endocrine								0 (0.0%)	672
	CF							7	7 (1.4%)	508
	Hemoglobinopathy							2	2 (2.1%)	97
	SCID					1		2	3 (18.8%)	16
CHEO Total		0	0	0	0	1	0	12	**13 (0.7%)**	**1903**
HHSC	Metabolic	1	1			6	10	21	39 (5.6%)	696
	Endocrine							5	5 (0.7%)	710
	CF					1	2	6	9 (1.3%)	687
	Hemoglobinopathy								0 (0.0%)	61
	SCID						3	1	4 (21.1%)	19
HHSC Total		1	1	0	0	7	15	33	**57 (2.6%)**	**2173**
HSC	Metabolic	2	4	5	5	2	11	35	64 (2.9%)	2231
	Endocrine	13	3		9	9	18	41	93 (3.3%)	2822
	CF	4	2		1	1	5	10	23 (1.1%)	2006
	Hemoglobinopathy				2	3	13	29	47 (7.1%)	665
	SCID						2	18	20 (35.7%)	56
HSC Total		19	9	5	17	15	49	133	**247 (3.1%)**	**7880**
KGH	Metabolic				2	1		5	8 (5.0%)	161
	Endocrine								0 (0.0%)	96
	CF							1	1 (0.6%)	168
	Hemoglobinopathy					2			2 (50.0%)	4
	SCID								0 (0.0%)	4
KGH Total		0	0	0	2	3	0	6	**11 (2.5%)**	**433**
LHSC	Metabolic	1	1					3	5 (0.9%)	573
	Endocrine			3		4	2	6	15 (2.6%)	585
	CF							4	4 (0.7%)	578
	Hemoglobinopathy	1	2	1		2	4	3	13 (34.2%)	38
	SCID						1	1	2 (16.7%)	12
LHSC Total		2	3	4	0	6	7	17	**39 (2.2%)**	**1786**
Winnipeg	Metabolic					3	3	3	9 (16.4%)	55
	Endocrine			2	1	1	1	1	6 (54.5%)	11
	CF								0 (0.0%)	12
	Hemoglobinopathy								0 (0.0%)	7
Winnipeg Total		0	0	2	1	4	4	4	**15 (19.0%)**	**79**
Grand Total		**22**	**13**	**11**	**20**	**36**	**75**	**205**	**382 (2.7%)**	**14254**

5.4 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:

Table 14. 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	Not Affected

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	related disease	
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 15. 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)

5.5 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 biot def), PKU variant = mild hyperphe (Phe = 120-359), and CPT1 deficiency with the Inuit common mutation (which is questionable as to whether or

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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, 2017.

Table 16. 2016 true positive classification by disease.

Disease	2016						
	Total No. Positive	Total No. DERFs Pending	Yes	Variant	Incidental	Other	No
Congenital Hypothyroidism	363	37	45	16	15	2	248
<24hrs	29	-	-	-	-	-	29
Referred	334	37	45	16	15	2	219
Congenital Adrenal Hyperplasia	227	15	7	0	0	2	203
Hemoglobinopathies	79	34	34	2	9	0	0
Cystic Fibrosis	484	29	26	9	306	16	98
Category A	18	2	16	0	0	0	0
Category B	351	22	10	9	306	4	0
Category C	115	5	0	0	0	12	98
SCID	116	23	0	1	4	5	83
Premature	67	-	-	-	-	-	67
Referred	49	23	0	1	4	5	16
C5OH	14	1	3	0	3	0	7
Glutaric Aciduria Type 1	9	3	1	0	0	0	5
Isovaleric Acidemia	28	4	0	2	1	0	21
PA/MMA	39	5	1	0	13	0	20
CUD	22	4	1	0	4	1	12
FAO (CPT1)	20	3	0	12	0	1	4
FAO (CPT2)	1	1	0	0	0	0	0
LCHAD	2	0	2	0	0	0	0
MCAD	41	7	4	0	2	1	27
VLCAD	28	4	1	0	10	0	13
Citrullinemia	12	1	0	0	0	0	11
Homocystinuria	40	6	0	0	1	4	29
MSUD	4	2	0	0	0	0	2
Phenylketonuria	110	20	6	9	3	5	67
Tyrosinemia	2	0	0	0	0	1	1
Galactosemia	18	1	4	1	5	0	7
Biotinidase Deficiency	35	6	1	6	2	0	20
Total No. Positive	**1694**	**206**	**136**	**58**	**378**	**38**	**878**

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

Disease		Additional information	PPV (Yes)	PPV (Yes + Variant)	% of DERFs Pending	Outcome Classification					DERFs Pending	Total No. Screen Positive
						Yes	Variant	Incidental	No	Other		
Endocrinopathies	Congenital Hypothyroidism	Referred	34.0%	39.3%	3.0%	783	123	115	1285	15	72	2393
	Congenital Adrenal Hyperplasia	Past (Aug 9, 2012 - Sept 1, 2016)	2.8%	2.9%	3.1%	30	1	3	1040	7	35	1116
		Current (Sept 2, 2016 - Dec 31, 2016)	**6.5%**	**6.5%**	**13.5%**	**2**	**0**	**0**	**29**	**1**	**5**	**37**
Hemoglobinopathies		Past (until Oct 31, 2010)	59.5%	60.3%	0.3%	219	3	145	1	8	1	377
		Current (Nov 1, 2010 - Dec 31, 2016)	**66.9%**	**68.1%**	**12.9%**	**281**	**5**	**133**	**1**	**7**	**63**	**490**
Cystic Fibrosis		Category A	99.5%	100.0%	2.8%	208	1	0	0	1	6	216
		Category B	2.1%	5.5%	1.1%	59	98	2696	3	42	32	2930
		Category C	0.4%	0.8%	0.8%	3	3	3	756	59	7	831
		All	**7.0%**	**9.7%**	**1.1%**	**270**	**102**	**2699**	**759**	**102**	**45**	**3977**
Severe Combined Immune Deficiency		Past (Sept 22, 2014 - Dec 20, 2016)	6.7%	13.3%	35.7%	3	3	6	33	9	30	84
		Current (Dec 21, 2016 - Dec 31, 2016)	**0.0%**	**0.0%**	**0.0%**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Organic Acidemia	Glutaric Aciduria type 1		**9.8%**	**9.8%**	**4.3%**	**12**	**0**	**30**	**81**	**12**	**6**	**141**
	Isovaleric Acidemia		**2.0%**	**4.0%**	**3.3%**	**5**	**5**	**2**	**241**	**10**	**9**	**272**
	C5OH	Past (until Dec 7, 2015)	6.2%	6.2%	1.2%	34	0	51	461	17	7	570
		Current (Dec 8 - 31, 2016)	**25.0%**	**25.0%**	**5.9%**	**4**	**0**	**3**	**9**	**0**	**1**	**17**
	PA/MMA	Past (Feb 16, 2010 - Apr 21, 2013)	3.7%	3.7%	0.9%	8	0	57	151	1	2	219
		Current (Apr 22, 2013 - Dec 31, 2016)	**4.9%**	**4.9%**	**7.4%**	**6**	**0**	**38**	**79**	**3**	**10**	**136**
Fatty Acid Oxidation Defects	CUD		**4.8%**	**4.8%**	**2.4%**	**17**	**0**	**61**	**273**	**10**	**9**	**370**
	CPTI		**4.2%**	**56.3%**	**3.0%**	**4**	**50**	**2**	**40**	**2**	**3**	**101**
	CPTII		**9.7%**	**9.7%**	**3.1%**	**3**	**0**	**0**	**28**	**0**	**1**	**32**
	LCHAD		**72.7%**	**72.7%**	**0.0%**	**8**	**0**	**2**	**1**	**0**	**0**	**11**
	VLCAD		**8.9%**	**13.6%**	**3.5%**	**19**	**10**	**83**	**102**	**8**	**8**	**230**
	MCAD	Past (until Aug 30, 2016)	29.9%	36.1%	2.9%	86	18	44	140	14	9	311
		Current (Sept 1, 2016 - Dec 31, 2016)	**16.7%**	**16.7%**	**29.4%**	**2**	**0**	**1**	**9**	**0**	**5**	**17**
Amino Acidopathies	Citrullinemia		**20.3%**	**21.1%**	**0.8%**	**25**	**1**	**8**	**89**	**6**	**1**	**130**
	Homocystinuria		**0.0%**	**0.0%**	**5.2%**	**0**	**0**	**10**	**135**	**36**	**10**	**191**
	Phenylketonuria		**13.8%**	**27.9%**	**3.6%**	**86**	**88**	**13**	**436**	**42**	**25**	**690**
	MSUD	Past (until Nov 14, 2011)	3.8%	3.8%	0.0%	3	0	0	75	12	0	90
		Current (Nov 15, 2011 - Dec 31, 2016)	**10.2%**	**12.2%**	**5.8%**	**5**	**1**	**1**	**42**	**0**	**3**	**52**
	Tyrosinemia	Past (Sep 14, 2009 - Sep 19, 2011)	1.4%	1.4%	0.0%	1	0	6	62	1	0	70
		Current (Sep 20, 2011 - Dec 31, 2016)	**15.6%**	**15.6%**	**5.1%**	**5**	**0**	**8**	**19**	**5**	**2**	**39**
Other Metabolic Diseases	Galactosemia	Past (until Jan 12, 2014)	35.7%	41.4%	1.4%	25	4	0	41	1	1	72
		Current (Jan 13, 2014 - Dec 31, 2016)	**15.7%**	**29.4%**	**1.9%**	**8**	**7**	**8**	**28**	**0**	**1**	**52**
	Biotinidase Deficiency	Past (Jan 13, 2014 - Jul 2, 2014)	2.2%	34.8%	4.1%	1	15	7	23	1	2	49
		Current (Jul 3, 2014 - Dec 31, 2016)	**4.0%**	**41.0%**	**7.4%**	**4**	**37**	**6**	**53**	**0**	**8**	**108**

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6. Turn Around Times and Benchmarks

The purpose of the benchmarks was to establish goals in days of age at which infants should be referred, retrieved, have an initial and full diagnosis established. Keeping in mind that the model of newborn screening in Ontario is a centralized screening system, each disease group developed clinically meaningful benchmarks where the goal would be to have 90% of the screened population meet the benchmarks. Aggressive diseases were assigned alert and non-alert benchmarks. The data below is for the 5 year period of 2012-2016.

Table 18. The benchmarks and percentage of infants achieving benchmarks for all screen positive infants.

		All screen positive (January 1 2012 to December 31 2016) - Proportions meeting benchmark							
Category	ACMG Code	Age (days) at referral (% meeting benchmark)		Age (days) at retrieval (contact with family) (% meeting benchmark)		Age (days) at Initial Diagnosis Classical Disease [1] (% meeting benchmark)		Age (days) at Definitive Diagnosis and Disposition [2] (% meeting benchmark)	
		ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert
	Benchmark (days)	5	7	5	8	6	10	90	
Congenital Adrenal Hyperplasia	CAH	45% 118 / 265	74% 739 / 997	37% 93 / 250	77% 743 / 971	70% 14 / 20	83% 10 / 12	94% 231 / 246	95% 842 / 889
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, HMG, βKT, ASA, CIT, MSUD, TYR1	24% 16 / 67	50% 215 / 431	25% 16 / 63	61% 250 / 407	53% 10 / 19	63% 5 / 8	80% 49 / 61	80% 276 / 343
Galactosemia	GALT	14% 6 / 42	47% 9 / 19	17% 7 / 41	56% 10 / 18	90% 9 / 10	100% 2 / 2	93% 39 / 42	73% 8 / 11
	Benchmark (days)	5	7	5	8	8	10	90	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	40% 19 / 48	59% 152 / 256	31% 13 / 42	64% 156 / 242	44% 14 / 32	19% 4 / 21	88% 30 / 34	79% 168 / 214
	Benchmark (days)	N/A	7	N/A	8	N/A	14	90	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	-	46% 91 / 197	-	49% 89 / 183	-	33% 2 / 6	-	78% 119 / 152
	Benchmark (days)	N/A	10	N/A	12	N/A	14	90	
Organic and Amino Acidemias	MCD, 3-MCC, GA1, HCY, PKU	-	89% 821 / 918	-	92% 796 / 864	-	70% 38 / 54	-	86% 634 / 733
Biotinidase Deficiency	BIOT	-	92% 196 / 213	-	93% 189 / 203	-	75% 3 / 4	-	77% 140 / 181
Congenital Hypothyroidism	CH	-	95% 1,482 / 1,553	-	94% 1,306 / 1,386	-	77% 233 / 302	-	95% 1,214 / 1,274
	Benchmark (days)	N/A	14	N/A	21	N/A	30	90	
Cystic Fibrosis	CF	-	79% 1,880 / 2,389	-	58% 1,346 / 2,334	-	75% 114 / 153	-	93% 2,079 / 2,241
Severe Combined Immune Deficiencies	SCID	-	67% 87 / 130	-	62% 47 / 76	-	100% 4 / 4	-	90% 60 / 67
	Benchmark (days)	N/A	14	N/A	30	N/A	60	60	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	-	77% 305 / 398	-	48% 165 / 347	-	44% 90 / 205	-	27% 84 / 311

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%. A higher number of cells are highlighted in green in the true positive benchmarks.

Compared to last year, which was based on data from 2011-2015, there has been an overall improvement in the percentage of infants achieving benchmarks. In particular, there was a decrease in the age at referral and therefore age at retrieval resulting in a higher percentage of benchmarks achieved. The improvements are likely a reflection of both improved shipping times of NBS samples as well as earlier ages at collection. The percentage achieving benchmarks for age at initial diagnosis remained largely unchanged but there was a marked improvement in the age at definitive diagnosis with all disease groups being yellow or green with the exception of Hemoglobinopathies.

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Table 19. The benchmarks and percentage of infants achieving benchmarks for all true positive infants with classic disease.

		True positive w classic disease (January 1 2012 to December 31 2016) - Proportions meeting benchmark							
Category	ACMG Code	Age (days) at referral (% meeting benchmark)		Age (days) at retrieval (contact with family) (% meeting benchmark)		Age (days) at Initial Diagnosis Classical Disease [1] (% meeting benchmark)		Age (days) at Definitive Diagnosis and Disposition [2] (% meeting benchmark)	
		ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert
	Benchmark (days)	5	7	5	8	6	10	90	
Congenital Adrenal Hyperplasia	CAH	40% 8 / 20	67% 8 / 12	45% 9 / 20	83% 10 / 12	70% 14 / 20	83% 10 / 12	100% 20 / 20	92% 11 / 12
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, HMG, βKT, ASA, CIT, MSUD, TYR1	42% 8 / 19	63% 5 / 8	47% 9 / 19	88% 7 / 8	53% 10 / 19	63% 5 / 8	84% 16 / 19	75% 6 / 8
Galactosemia	GALT	70% 7 / 10	50% 1 / 2	80% 8 / 10	100% 2 / 2	90% 9 / 10	100% 2 / 2	100% 10 / 10	100% 2 / 2
	Benchmark (days)	5	7	5	8	8	10	90	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	31% 10 / 32	67% 14 / 21	31% 10 / 32	67% 14 / 21	44% 14 / 32	19% 4 / 21	88% 28 / 32	81% 17 / 21
	Benchmark (days)	N/A	7	N/A	8	N/A	14	90	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	-	67% 4 / 6	-	67% 4 / 6	-	33% 2 / 6	-	83% 5 / 6
	Benchmark (days)	N/A	10	N/A	12	N/A	14	90	
Organic and Amino Acidemias	MCD, 3-MCC, GA1, HCY, PKU	-	94% 51 / 54	-	94% 51 / 54	-	70% 38 / 54	-	91% 49 / 54
Biotinidase Deficiency	BIOT	-	75% 3 / 4	-	100% 4 / 4	-	75% 3 / 4	-	100% 4 / 4
Congenital Hypothyroidism	CH	-	91% 275 / 303	-	91% 275 / 302	-	77% 233 / 302	-	99% 298 / 302
	Benchmark (days)	N/A	14	N/A	21	N/A	30	90	
Cystic Fibrosis	CF	-	75% 115 / 153	-	84% 128 / 153	-	75% 114 / 153	-	88% 135 / 153
Severe Combined Immune Deficiencies	SCID	-	100% 4 / 4	-	100% 4 / 4	-	100% 4 / 4	-	100% 4 / 4
	Benchmark (days)	N/A	14	N/A	30	N/A	60	60	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	-	73% 149 / 205	-	47% 97 / 205	-	44% 90 / 205	-	32% 65 / 205

Table 20. The benchmarks and percentage of infants achieving benchmarks for all positive infants (2016 data only).

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		All screen positive (January 1 2016 to December 31 2016) - Proportions meeting benchmark							
Category	ACMG Code	Age (days) at referral (% meeting benchmark)		Age (days) at retrieval (contact with family) (% meeting benchmark)		Age (days) at Initial Diagnosis Classical Disease [1] (% meeting benchmark)		Age (days) at Definitive Diagnosis and Disposition [2] (% meeting benchmark)	
		ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert
	Benchmark (days)	5	7	5	8	6	10	90	
Congenital Adrenal Hyperplasia	CAH	63% 143 / 227	N/A	50% 106 / 213	N/A	60% 3 / 5	N/A	95% 199 / 210	N/A
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, HMG, βKT, ASA, CIT, MSUD, TYR1	40% 4 / 10	76% 57 / 75	50% 3 / 6	88% 60 / 68	100% 1 / 1	N/A	83% 5 / 6	92% 61 / 66
Galactosemia	GALT	46% 6 / 13	60% 3 / 5	46% 6 / 13	50% 2 / 4	100% 4 / 4	N/A	92% 12 / 13	75% 3 / 4
	Benchmark (days)	5	7	5	8	8	10	90	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	60% 6 / 10	61% 37 / 61	43% 3 / 7	60% 32 / 53	71% 5 / 7	N/A	100% 7 / 7	85% 44 / 52
	Benchmark (days)	N/A	7	N/A	8	N/A	14	90	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	-	59% 24 / 41	-	57% 20 / 35	-	0% 0 / 1	-	88% 29 / 33
	Benchmark (days)	N/A	10	N/A	12	N/A	14	90	
Organic and Amino Acidemias	MCD, 3-MCC, GA1, HCY, PKU	-	94% 163 / 173	-	95% 140 / 147	-	80% 8 / 10	-	94% 126 / 134
Biotinidase Deficiency	BIOT	-	97% 34 / 35	-	100% 29 / 29	-	0% 0 / 1	-	89% 25 / 28
Congenital Hypothyroidism	CH	-	96% 322 / 334	-	97% 290 / 300	-	77% 34 / 44	-	96% 283 / 294
	Benchmark (days)	N/A	14	N/A	21	N/A	30	90	
Cystic Fibrosis	CF	-	92% 443 / 484	-	56% 257 / 455	-	65% 17 / 26	-	93% 407 / 439
Severe Combined Immune Deficiencies	SCID	-	61% 30 / 49	-	54% 14 / 26	-	N/A	-	89% 17 / 19
	Benchmark (days)	N/A	14	N/A	30	N/A	60	60	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	-	87% 68 / 78	-	52% 24 / 46	-	39% 13 / 33	-	30% 13 / 44

When comparing the percentage of benchmarks achieved for all positive infants from 2012-2016 with 2016 alone, the percentages are higher overall, particularly for the aggressive diseases. This likely reflects an earlier age at collection and shipping to NSO.

Table 21. The benchmarks and percentage of infants achieving benchmarks for all true positive infants with classic disease (2016 data only).

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		True positive w classic disease (January 1 2016 to December 31 2016) - Proportions meeting benchmark							
Category	ACMG Code	Age (days) at referral (% meeting benchmark)		Age (days) at retrieval (contact with family) (% meeting benchmark)		Age (days) at Initial Diagnosis Classical Disease [1] (% meeting benchmark)		Age (days) at Definitive Diagnosis and Disposition [2] (% meeting benchmark)	
		ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert
	Benchmark (days)	5	7	5	8	6	10	90	
Congenital Adrenal Hyperplasia	CAH	40% 2 / 5	N/A	40% 2 / 5	N/A	60% 3 / 5	N/A	100% 5 / 5	N/A
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, HMG, βKT, ASA, CIT, MSUD, TYR1	100% 1 / 1	N/A	100% 1 / 1	N/A	100% 1 / 1	N/A	0% 0 / 1	N/A
Galactosemia	GALT	100% 4 / 4	N/A	100% 4 / 4	N/A	100% 4 / 4	N/A	100% 4 / 4	N/A
	Benchmark (days)	5	7	5	8	8	10	90	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	43% 3 / 7	N/A	43% 3 / 7	N/A	71% 5 / 7	N/A	100% 7 / 7	N/A
	Benchmark (days)	N/A	7	N/A	8	N/A	14	90	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	-	100% 1 / 1	-	100% 1 / 1	-	0% 0 / 1	-	100% 1 / 1
	Benchmark (days)	N/A	10	N/A	12	N/A	14	90	
Organic and Amino Acidemias	MCD, 3-MCC, GA1, HCY, PKU	-	90% 9 / 10	-	90% 9 / 10	-	80% 8 / 10	-	90% 9 / 10
Biotinidase Deficiency	BIOT	-	100% 1 / 1	-	100% 1 / 1	-	0% 0 / 1	-	100% 1 / 1
Congenital Hypothyroidism	CH	-	89% 40 / 45	-	91% 40 / 44	-	77% 34 / 44	-	100% 44 / 44
	Benchmark (days)	N/A	14	N/A	21	N/A	30	90	
Cystic Fibrosis	CF	-	85% 22 / 26	-	81% 21 / 26	-	65% 17 / 26	-	85% 22 / 26
Severe Combined Immune Deficiencies	SCID	-	N/A	-	N/A	-	N/A	-	N/A
	Benchmark (days)	N/A	14	N/A	30	N/A	60	60	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	-	88% 29 / 33	-	58% 19 / 33	-	39% 13 / 33	-	30% 10 / 33

When looking at the 2016 data alone for infants with classic disease, there are a greater number of green cells. However, the total number of infants per cell is quite small for most disease groups.

NSO will need to review the data for infants not meeting benchmarks to determine why benchmarks are not being met and try to determine where improvements can be made.

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7. Appendix: Updated data from the 2015 Annual Report

Table 1A. Transfusion cases in 2015.

Repeat Requirement	# of cases	
	Current	2015 Annual Report
Repeat Not Required	234 (58.9%)	213 (53.3%)
Repeat Received	77 (19.4%)	53 (13.2%)
Repeat Not Received	86 (21.7%)	134 (33.5%)
Case still open	0	86
Deceased	25	19
Family moved	2	2
Parents bringing infant back	0	3
Closed case letter sent	59	24
Total	**397**	**400**

Since the 2015 Annual Report data was pulled, there have been 24 additional repeat transfusion samples received and all of the cases from 2015 have been closed. Three cases were removed as the reminder letter to submitter indicated that they did not receive PBRCs. Of the 3 parents who indicated they would bring their children back for testing from the last report, 2 samples were received. The other status was changed to repeat not received.

Table 2A. Age at which transfusion repeats were received in 2015.

Age	# of samples	
	Current	2015 Report
4-6 months	15	12
6-12 months	58	39
>12 months	4	2
Grand Total	**77**	**53**

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Table 3A. Screen positives from 2015 by true positive classification from the 2015 Annual report and the current status of DERFs.

Disease	2015 Current							2015 (as reported in 2015 Annual Report)						
	Total No. Positive	Total. No DERFs Pending	Yes	Variant	Incidental	Other	No	Total No. Positive	Total. No DERFs Pending	Yes	Variant	Incidental	Other	No
Congenital Hypothyroidism														
Referred	345	11	67	38	12	1	216	345	132	40	20	1	2	150
< 24 hrs	24	0	0	0	0	0	24	24	0	0	0	0	0	24
Total	369	11	67	38	12	1	240	369	132	40	20	1	2	174
Congenital Adrenal Hyperplasia	299	10	3	0	0	2	284	299	83	2	0	0	2	212
Hemoglobinopathies	82	17	37	0	27	1	0	82	53	15	0	14	0	0
Cystic Fibrosis														
Category A	33	0	33	0	0	0	0	32	10	22	0	0	0	0
Category B	327	5	6	7	303	5	1	327	76	4	4	239	3	1
Category C	122	2	0	0	0	6	114	123	50	0	0	0	4	69
Total	482	7	39	7	303	11	115	482	136	26	4	239	7	70
SCID														
Referred	22	6	1	1	1	3	10	22	7	1	1	1	3	9
Premature	14	0	0	0	0	0	14	14	0	0	0	0	0	14
Total	36	6	1	1	1	3	24	36	7	1	1	1	3	23
Citrullinemia	10	0	3	0	1	0	6	10	5	1	0	0	0	4
PA/MMA	39	3	3	0	10	2	21	39	22	2	0	4	0	11
Isovaleric Acidemia	46	2	1	0	1	0	42	46	27	0	0	0	0	19
Glutaric Aciduria type 1	13	0	2	0	0	2	9	13	7	2	0	0	1	3
C5OH	71	1	6	0	5	1	58	71	34	4	0	3	1	29
CUD	30	2	0	0	8	0	20	30	19	0	0	3	0	8
CPTI	15	0	0	9	0	0	6	15	4	0	9	0	0	2
CPTII	3	0	2	0	0	0	1	3	1	1	0	0	0	1
Homocystinuria	38	4	0	0	0	3	31	38	24	0	0	0	1	13
LCHAD	2	0	1	0	1	0	0	2	1	0	0	1	0	0
MCAD	34	1	13	1	4	0	15	34	14	7	0	2	0	11
Phenylketonuria	110	5	3	10	1	3	88	110	55	3	6	1	3	42
Tyrosinemia	8	2	0	0	1	2	3	8	4	0	0	1	1	2
MSUD	18	1	3	0	0	0	14	18	6	1	0	0	0	11
Galactosemia	12	0	2	2	1	0	7	12	8	1	0	0	0	3
Biotinidase Deficiency	41	2	3	22	2	0	12	41	19	2	11	1	0	8
VLCAD	32	1	3	0	7	1	20	32	15	1	0	3	0	13
Total	**1790**	**75**	**192**	**90**	**385**	**32**	**1016**	**1790**	**676**	**109**	**51**	**274**	**21**	**659**

Differences between the 2015 Annual Report and now are highlighted in grey. The number of outstanding DERFs was 676 at the time of the 2015 Annual Report and has now decreased to 75.

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