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

Annual Report to the Newborn Screening Ontario Advisory Council

Calendar Year 2017

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1. Sample Volumes in 2017

Table 1. Sample volumes between 2015-2017 by sample type.

Indication	Sample Type	2017	2016	2015
Routine screening	Satisfactory	145,405	145,018	144,812
	Unsatisfactory*	2,248	1,755	1,367
Routine Screening – Total		**147,653**	**146,773**	**146,179**
Referred-in screening: full panel	Satisfactory	396	410	400
	Unsatisfactory	11	6	22
Referred-in Screening: – Total		**407**	**416**	**422**
Referred-in screening: AAAC only	Satisfactory	1,371	410	400
	Unsatisfactory	0	6	22
Referred-in Screening: – Total		**1,371**	**416**	**422**
Cord Blood	Cord blood - Hemoglobin Screen	1,023	914	900
Post Mortem	Satisfactory	357	300	295
	Unsatisfactory	8	-	-
Diagnostic/Monitoring Bloodspot	Satisfactory	1,002	669	529
	Unsatisfactory	30	14	11
Research DBS samples	Satisfactory	2,388	1,552	n/a
	Unsatisfactory	108	40	n/a
Non-screening sample – Total		**4,916**	**3,489**	**1,735**
Grand Total		**154,347**	**151,094**	**148,758**

*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 2017 as compared to 2016, due to a slightly higher unsatisfactory rate, and emergency backup coverage for AAAC screening for another province's screening program. There has also been an increase in diagnostic and monitoring samples received with the addition of CF diagnostic samples from out of province. Research samples continue to increase with the 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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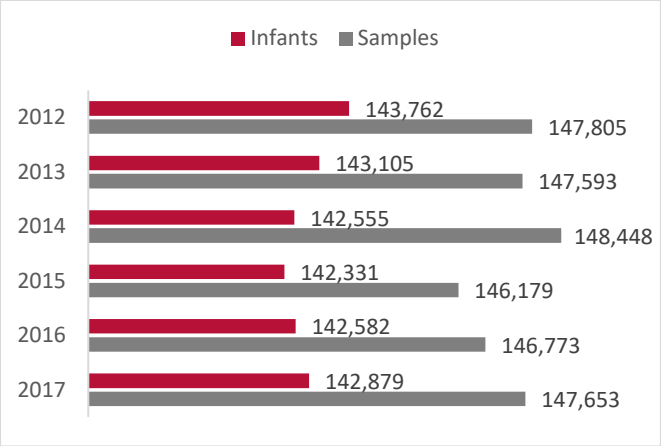

The overall number of infants tested is relatively constant each year with only ~1500 infants difference between the highest and lowest years.

Based on defers/ declines, missed screen alerts from BORN, and newborn screening sample counts, NSO estimates the total number of infants in Ontario as 143, 430 and the rate of screening uptake in 2017 as 99.6% , 0.1% lower than in previous years.

Figure 1: Total number of infants and samples screened between 2013-2017.

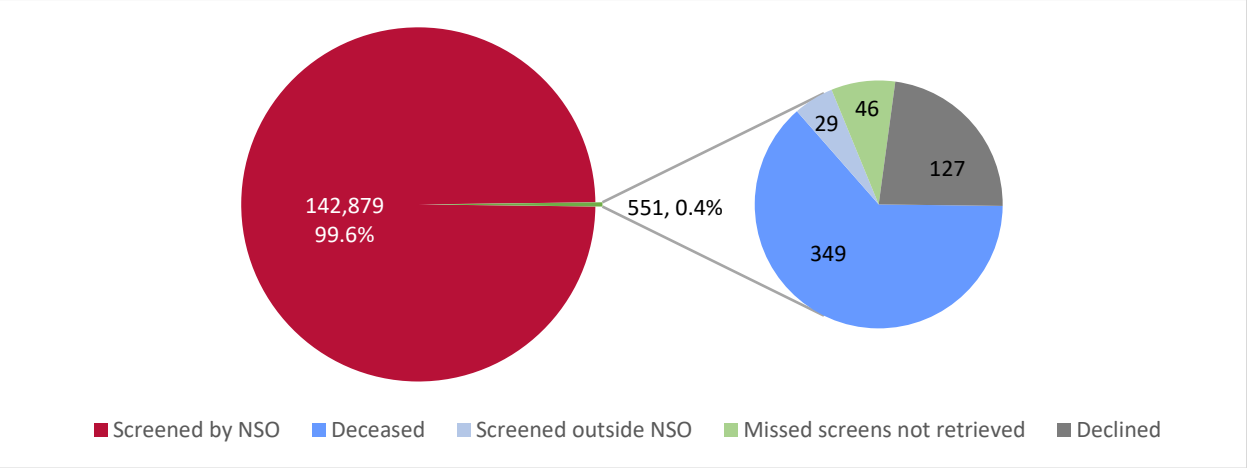

Figure 2. Coverage of screening in Ontario births.

1.1.2 Declined/Deferred Testing

If parents wish 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 2017, NSO received 499 completed decline/defer forms, a substantial increase from previous years. The number of declines documented using this form has increased with 50 declines in 2017 compared with 28 in 2016. In four cases a decline form was completed but a sample was subsequently received so these have been counted as deferrals. The remaining 445 forms received indicated a parent's desire to defer screening, and

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samples were eventually received for all but five of these deferred cases. Defer forms primarily came from four hospitals, but the total number of hospitals and midwifery practice groups using the defer form is up to 24 in 2017 from 9 in 2016. 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 cards between 2017.

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

An additional 77 declined screens were also identified via missed screen alerts (6 missed screens also had a decline form received after the alert was received so the total number in Table 4 is 83). Timely use of the decline form would help reduce the missed screen alert rate and eliminate the follow up required. Additional education may be required for the submitters involved in these cases.

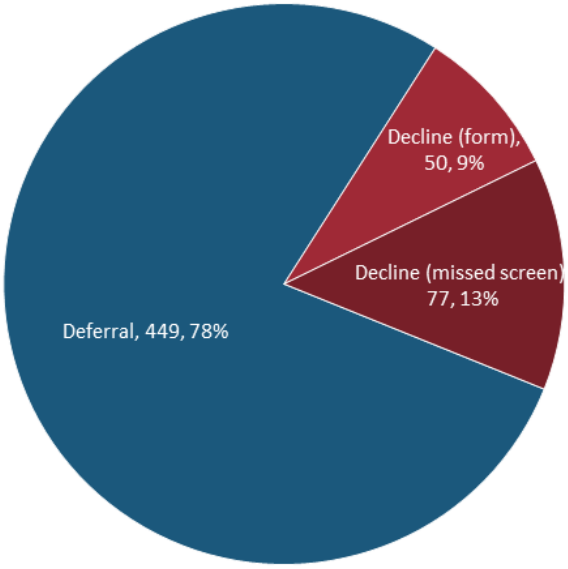

Figure 3. Declines and deferrals in 2017

Table 3. Overall declined screens between 2014-2017.

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

The overall decline rate continues to increase slightly, but remains below 0.1% of the population.

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1.1.3 Missed Screens

Table 4. Potential missed screen alerts requiring follow-up in 2017, by reason and samples received post follow-up.

Category		Total (2017)	Samples received	Percent received	Total (2016)
Other	Deceased/ Palliative	35			42
	Declined	83			88
	Incorrect or incomplete BORN information (ex. infant <8days old, stillborn/TA)	<5			<5
	Incorrect or incomplete information (sample already received)	18			11
	NBS done in other jurisdiction	29			26
	Parents deferred NBS	<5			<5
	Sample received, collected prior to missed screen alert	66			22
Total: Non-Missed Screens		**237**			**194**
True Missed Screens	Home birth/birth centre midwife care	11	7	64%	8
	Hospital birth midwife care	39	37	95%	40
	Interhospital transfer (between hospitals)	16	12	75%	11
	Intrahospital transfer (between units in same hospital)	<5	<5	100%	8
	Intrahospital/interhospital transfer with midwife involvement	<5	<5	100%	5
	Sample collected, package lost	41	38	93%	18
	Not taken in error	62	45	73%	51
	Unknown reason hospital birth	27	11	41%	27
Total: True Missed Screens		**202**	**156**	**79%**	**168**
Grand Total		**439**			**362**

In 2017, there were 439 potential missed newborn screen alerts that required follow up by NSO. This is up by approximately 80 cases from 2016. In February 2017 NSO changed the timing to flag an alert for a possible missed screen from 14 days after birth to 8 days and this has influenced the increased number of cases requiring follow up. Hospitals were the responsible facility in 64% of the missed screen alerts and midwives were involved in roughly 36% of the cases. Action on the part of NSO resulted in 156 of the 202 (77%) 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. In 2017 true missed screen alert ages ranged from 7 to 1054 days at time of alert, 75% of true misses were identified by two weeks of age.

In addition, there were 99 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 35 samples from midwives, 1 from a health

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centre, and 63 from hospitals. Although the number of cases is higher than last year's total of 77, given the change to alerting at 8 days of age from 14, this shows an improvement in timely BORN entry.

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 11 missed screen alerts that were initiated by outstanding report requests as the BORN entry had not yet been completed.

Missed Screens and Declines

In 2017 there were 83 declines identified by the missed screen alert process, compared to the 88 declines identified this way in 2016 (Table 3). Combined with the declines received via the decline form process outlined above, the total number of declines increased by 11 from 2016. Midwives were the health care provider in 76% (n=91) 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 2017. Subsequent to diagnostic testing, all of these infants were found to be unaffected.

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 2017, 10 packages (41 samples) were identified as delayed or lost via missed screen follow up. Due to the earlier missed screen alert at 8 days of age, 16 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 volumes are relatively steady from 2013, with the biggest volume being from PKU home monitoring. Additional diagnostic testing for SCID correlates with the increase in screen positive referrals described in section 4.

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Table 5. Monitoring/Diagnostic Sample volumes between 2013-2017 by sample type.

Indication	Sample Type	2017	2016	2015	2014	2013
Cord Blood	Cord blood - Hemoglobin Screen	1,023	914	900	469	160
Post Mortem	Post Mortem – blood	183	152	150	164	149
	Post Mortem – bile	174	148	145	169	127
	Unsatisfactory	8	-	-	-	-
Diagnostic/Monitoring Bloodspot	Amino acids/Acylcarnitine	<5	<5	<5	<5	<5
	CAH Monitoring	<5	<5	<5	0	7
	Glutaric Aciduria Type 1	35	29	45	29	22
	Tyrosenimia	40	23	42	38	51
	Phenylalanine monitoring	781	564	407	368	330
	SCID Diagnostic	102	42	24	32	29
	Identity testing (discrepant results, positives)	<5	<5	<5	5	<5
	CF diagnostic & Other	38	<5	<5	<5	17
	Unsatisfactory	30	14	11	<5	11
Research DBS samples	Gates Cord Satisfactory	1,128	168	n/a	n/a	n/a
	Gates Heel Satisfactory	536	115	n/a	n/a	n/a
	Guyana Satisfactory	724	1,269	n/a	n/a	n/a
	Unsatisfactory	108	40	n/a	n/a	n/a
Non-screening sample – Total		**4,916**	**3,489**	**1,735**	**1,283**	**907**

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 between 2013-2017.

	2017	2016	2015	2014	2013
Samples tested	267	189	129	94	96
Positive CMV results (% of samples tested)	20 (7.5)%	11 (5.8)%	11 (8.5)%	9 (9.6)%	8 (8.3)%

The number of CMV requests continued to increase in 2017. Although the workload associated with retrospective CMV analysis is significant, NSO currently offers this service at no charge.

On average for the last 5 years, just under 8% of samples tested have been screen 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.

1.2.1.1 Expanded Hearing Screening

In Spring 2017 funding was announced though the Ministry of Child and Youth Services and the Ministry of Health and Long Term Care to implement expanded hearing screening in Ontario with the introduction of dried blood spot testing for hearing loss risk factors including congenital cytomegalovirus and selected molecular targets. This announcement came as a result of several years of technical and policy work between the Infant

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Hearing Program (IHP) and NSO dating back to 2012. Additional details outlining the history and timeline of this project are described in previous Annual Reports.

In 2017 specifically, project work was focused on implementation readiness with the creation of a Project Structure and the establishment of Project Steering, Clinical, and Joint IHP/NSO Operations Committees to continue to examine key operational issues such as consent, information sharing, the development of referral pathways, and recommendations for follow up of screen positive infants. A Newborn Screening Ontario Advisory Council Working Group was also established to: 1) identify, and advise on mitigating, potential risks and harms associated with CMV testing, and 2) inform and provide advice on the overall evaluation strategy of this initiative.

1.2.3 Hemoglobin Carrier Requests

Table 7. Hemoglobin carrier requests between 2013-2017.

	2017	2016	2015	2014	2013
Requests from high risk population	61	28	34	34	28
Total Requests	**69**	**45**	**45**	**53**	**45**
Number of carriers reported	18	11	14	13	16

In 2017, approximately 0.8% of carriers (2159) requested their results. The number of hemoglobin carrier requests has shown a modest increase over the last year, particularly those from a high risk population. NSO is working with the Institute for Clinical Evaluative Services (ICES) on defining a project to identify physicians in high risk areas to target communications about carrier reporting availability.

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2. Demographics of Screening Samples

2.1 Age at Collection

Table 8. Age at collection for 2017 initial samples only.

Age at Collection	Number of Initial Samples	% of Initial Samples (2017)	% of Initial Samples (2016)
Less than 24 hours	856	0.60%	0.58%
24-47 hours (1-2 days)	129,370	90.82%	86.83%
48-72 hours (2-3 days)	8,814	6.19%	8.81%
73-168 hours (3-7 days)	3,090	2.17%	3.57%
Greater than 168 hours (7days)	255	0.18%	0.20%
Not specified	52	0.04%	0.02%

The majority of newborn screening samples are collected between 24-48 hours of age. Approximately 91% 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.

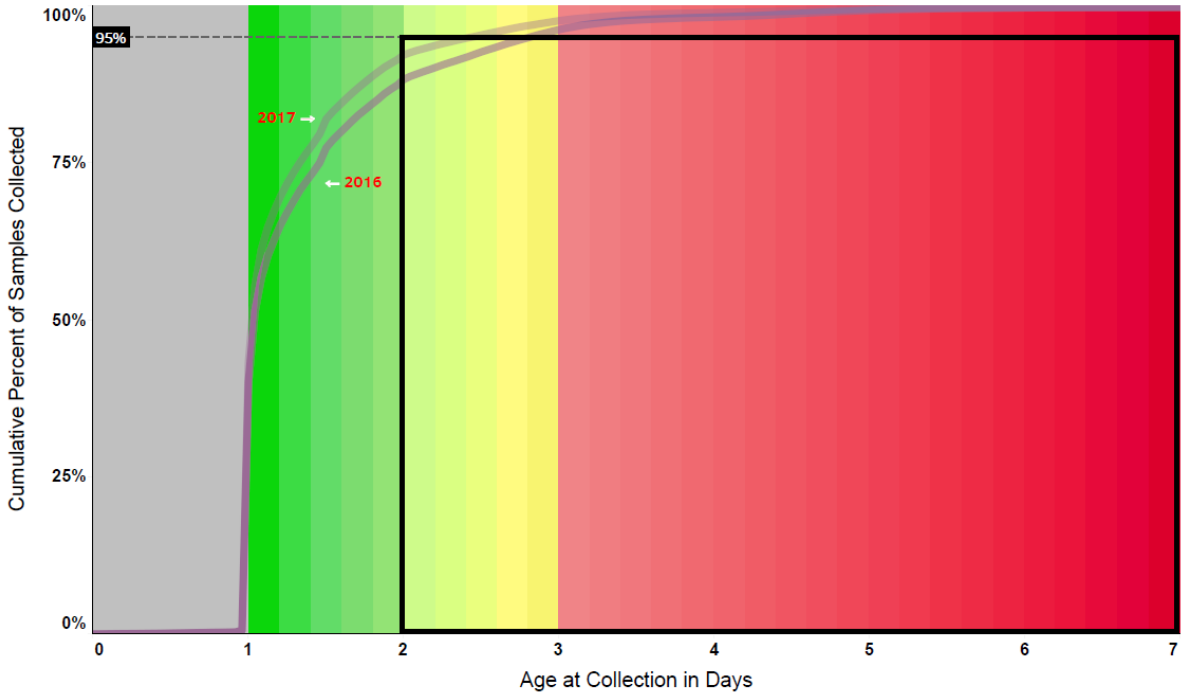

Figure 4. The cumulative percentage of samples collected by the age (in hours) of the infant for 2016 and 2017.

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There were 856 samples that were collected at <24 hours of age, with 577 of these considered unsatisfactory (279 samples were collected in the 10 min grace period). Of the 856 samples, 83 were collected early due to a pending transfusion and notes indicate early discharge on 47 samples. 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, but the use of this checkbox is variable. Additional education could be done to support submitter use of this checkbox.

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 2017

Category		Number of Cases
Repeat Not Required		288
Repeat Required		148
Grand Total		**436**
Repeat Required	Repeat Received	65
	Repeat Not Received	83
	Other	<5
	Deceased	21
	Closed case letter sent	58

Table 10. Age at which transfusion repeats were received in 2017

Age	# of samples
4-6 months	5
6-12 months	54
>12 months	6
Grand Total	**65**

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There were 436 transfusion cases in 2017. For 288 cases (66%) a repeat was not required as a satisfactory pre-transfusion sample was already received. For cases requiring a repeat sample, 65 (44%) 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 is to be discharged to complete screening for congenital hypothyroidism. In 2017, there were 2136 infants that fit the premature infant policy. Of these, 1612 (75%) had a 3 week (or equivalent) sample obtained.

Table 11. Number of premature samples received per year.

Year	Total # patients	Number of repeat samples received between 7-31 days of age	Percentage where prem repeat sample received	Total # of repeat samples received
2013	2162	1117	51.7%	4115
2014	2125	1474	69.4%	4026
2015	2055	1506	73.3%	3754
2016	2178	1653	75.9%	3858
2017	2136	1612	75.5%	3447

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. In 2013 we were receiving repeat samples for only about 50% of cases. In 2017 that number has increased to just over 75%. This suggests improved adherence to the policy.

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 between 2013-2017.

			2017	2016	2015	2014	2013
SAMPLES	Satisfactory Samples		144,717	144,359	144,074	144,099	144,402
	Unsatisfactory Samples		2,936	2,414	2,105	4,349	3,191
	Unsatisfactory Rate		**1.99%**	**1.64%**	**1.44%**	**2.93%**	**2.16%**
	Samples Collected at <24hrs		577	518	603	628	718
	Unsatisfactory Samples excluding <24hr samples		2,359	1,896	1,502	3,721	2,473
	Unsatisfactory Rate excluding <24hr samples		**1.60%**	**1.30%**	**1.03%**	**2.52%**	**1.68%**
REASONS	Lab Unsat Reasons	Quantity of blood insufficient	1,471	1094	888	1,707	1,168
		Blood spots appear scratched or abraded	531	421	228	1353	758
		Blood spots are supersaturated	185	193	222	1140	718
		Blood spots appear clotted or layered	639	491	299	958	248
		Blood spots appear diluted	5	17	42	65	9
		Blood spots exhibits serum rings	200	95	32	65	28
		Blood spots are wet and/or discolored	<5	5	<5	16	15
		EDTA contamination	13	-	-	-	-
		Other	49	35	16	7	12
	Data Unsat Reasons	Blood dot collection paper is expired	77	95	104	120	68
		Insufficient data provided	29	14	22	32	36
		Damaged or delayed in transit	8	<5	0	23	<5
		Delivered to lab > 14 days after collection	23	<5	20	30	120
		Sample collected at <24hrs	577	518	603	628	718
		Other/Mislabel	47	46	21	16	29

There were 811 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 2,875 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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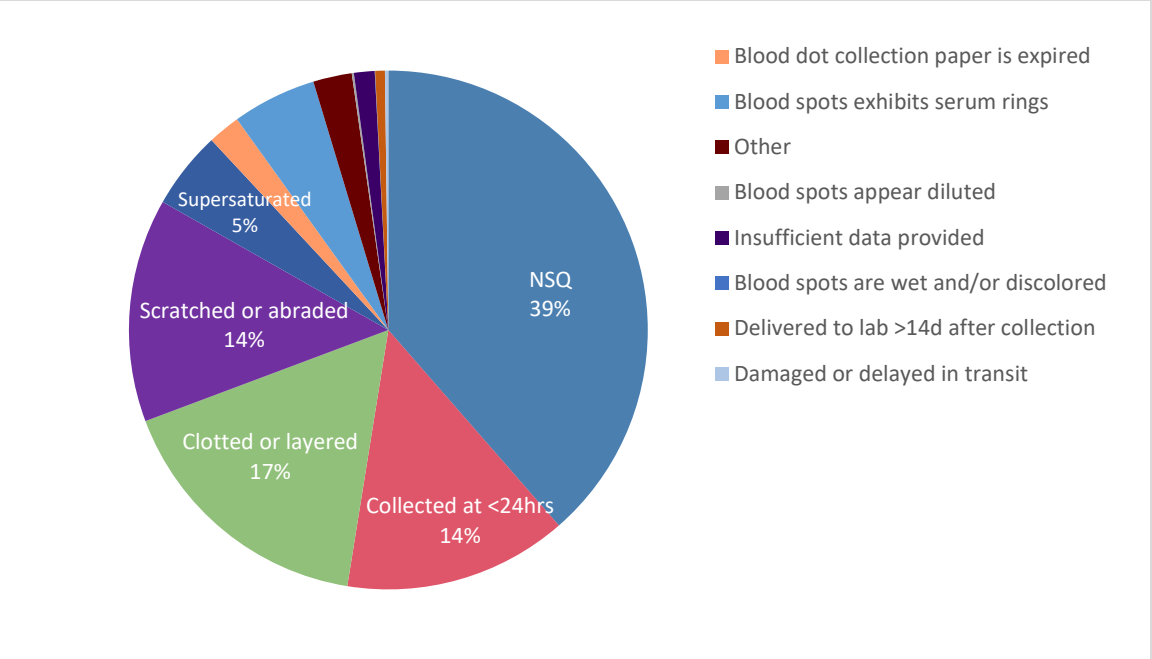

Figure 5. Distribution of unsatisfactory reasons in 2017.

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	**102**
< 3 weeks	(76.5%)
≥3 weeks < 6 weeks	(4.9%)
≥ 6 weeks	(3.9%)
Not received	(14.7%)

In 2017 there were 102 TLU which required a repeat. Some of the TLUs were also unsatisfactory samples due to collection at <24 hours. Most (76.5%) repeats were received within 3 weeks. All of the urgent requests were 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 March and October. NSO sends out bulletin reminders to submitters when an expiry date is approaching, asking them to check and circulate their stock.

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. Although small in numbers, unsats caused by transportation issues are a key area for improvement to be addressed this year.

3.4 Repeat Rates for Unsatisfactory Specimens

The majority (82.6%) of repeat samples are received within 3 weeks of the initial sample. By 6 weeks, 89.7% of unsatisfactory samples have had screening completed via a repeat sample. A further 2.6% (total of 92.4%) of repeats have been received to date. Repeat samples have not yet been received 224 (7.6%) of unsatisfactory samples in 2017.

Table 14. Repeats received on unsatisfactory samples, 2017 data only.

Time to receipt of repeat sample	Samples (%)
Total Unsats 2017	**2,936**
Up to 3 weeks	2425 (82.6%)
Greater than 3 weeks up to 6 weeks	210 (7.2%)
Greater than or equal to 6 weeks	77 (2.6%)
Not received	224 (7.6%)

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4. Screen Positives

In 2017 there were 1464 screen positive referrals. This represents 1.02% of the total number of infants screened by NSO. There were 1592 total screen positives, but 16 had an elevated TSH in samples taken at <24 hours and 113 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, 98 screen negative twin/multiples referrals were made in 2017.

The number of screen positive infants referred in 2017 decreased from 2016 by 134 referrals. This is discussed further in Section 4.2.

4.1 Referrals by Treatment Centre

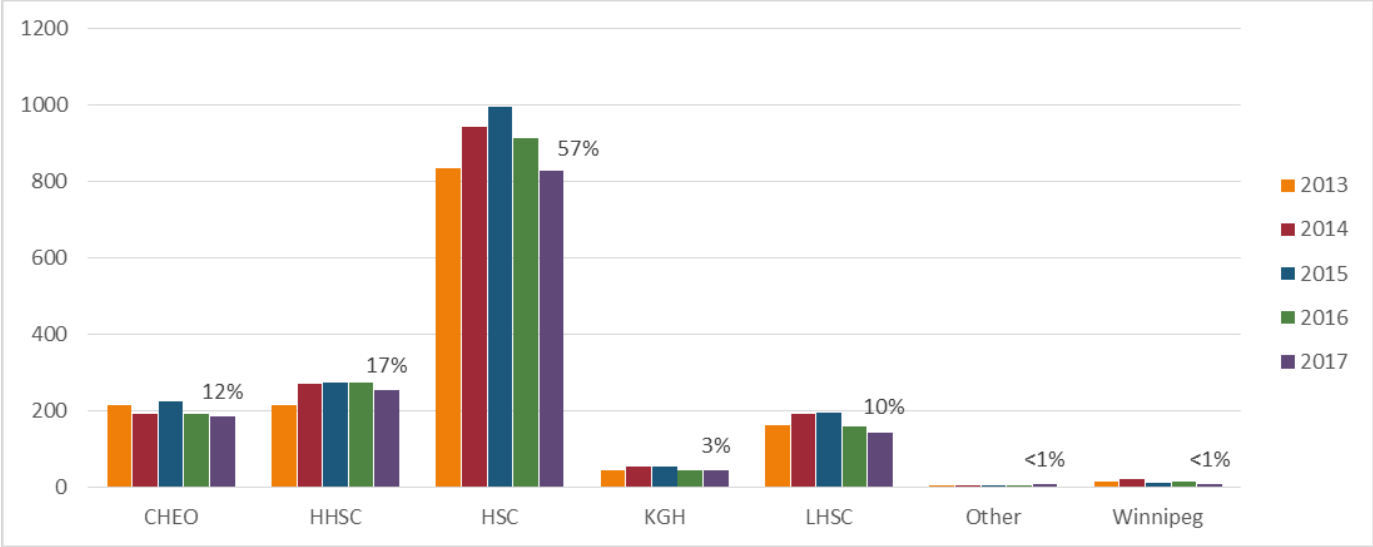

Figure 6. The total number of referrals by treatment centre between 2013-2017

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 2016 and 2017 with The Hospital for Sick Children in Toronto continuing to receive over half of the screen positive referrals. Since there was a reduction in the overall number of screen positive results, referrals decreased in 2017 for CHEO, HHSC, HSC and LHSC, and remained constant for KGH.

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4.2 Screen Positive Referrals by Disorder Group

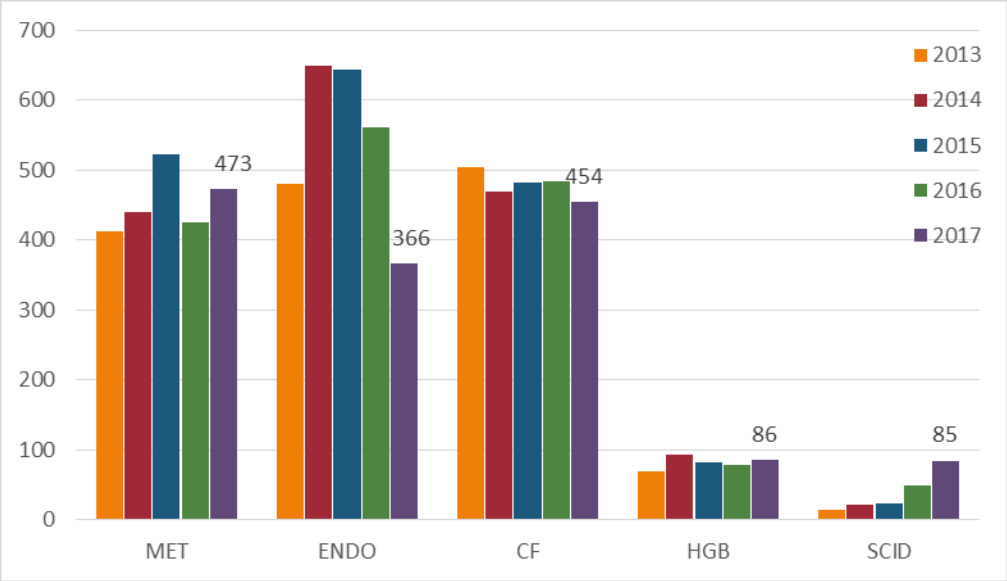

Figure 7. The total number of screen positives by disease grouping between 2013-2017

The number of screen positive referrals per disease grouping increased slightly for metabolic disorders as a whole, and more significantly for SCID in 2017. Numbers remained constant for Hemoglobinopathies, whereas they decreased marginally for Cystic Fibrosis, and decreased significantly for Endocrinopathies. These details are discussed further in sections 4.2.4, 4.2.5, and 4.2.6.

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4.2.1 Percentage of Screen Positive Referrals by Disorder in 2017

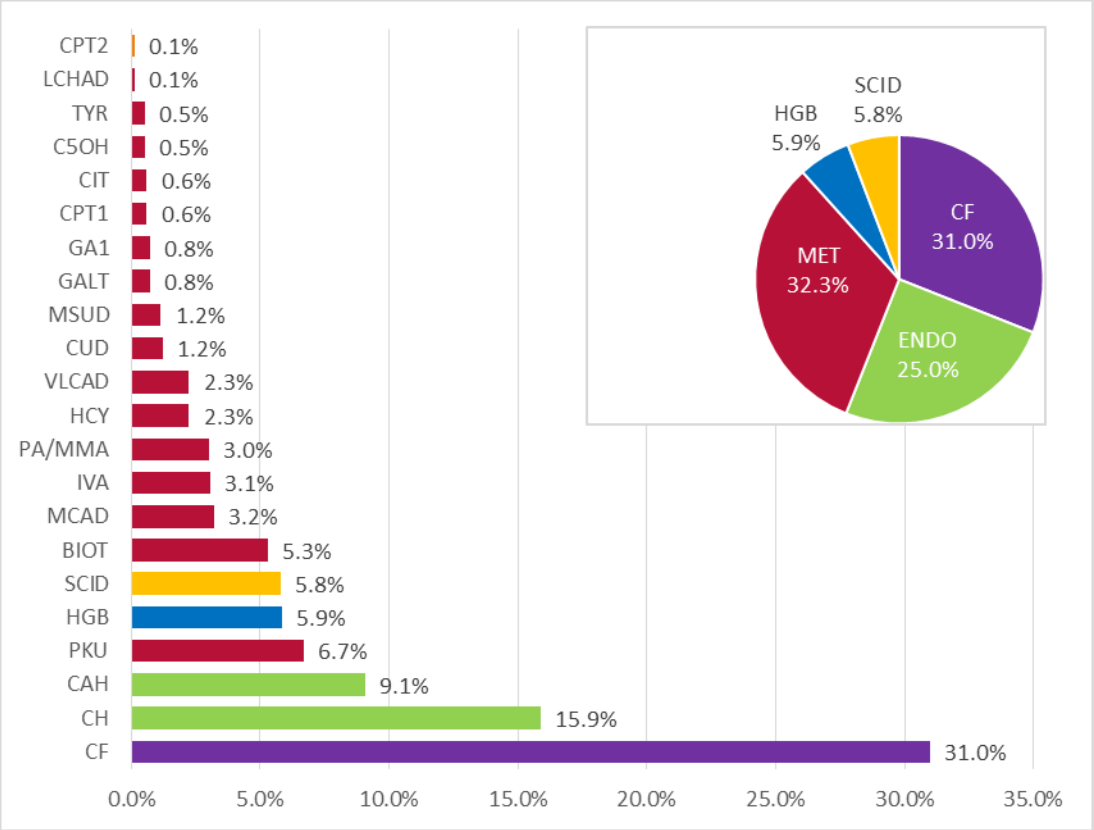

Figure 8. The percentage of screen positive referrals by disorder in 2017.

Cystic fibrosis, Endocrinopathies, and Metabolics represent approximately 31%, 25%, and 31% of screen positives respectively. SCID screen positive referrals increased in 2017 and now represent 5.8% of total screen positive referrals. Hemoglobinopathies represent approximately 5.9% of screen positive referrals.

4.2.2 Hemoglobinopathies

The number of screen positives in 2017 remained about the same as 2016, with only a difference of 7 referrals.

4.2.3 Cystic Fibrosis

The number of screen positives in 2017 decreased slightly as compared to 2016, with a difference of 30 referrals noted.

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4.2.4 Endocrinopathies

4.2.4.1 Congenital Adrenal Hyperplasia

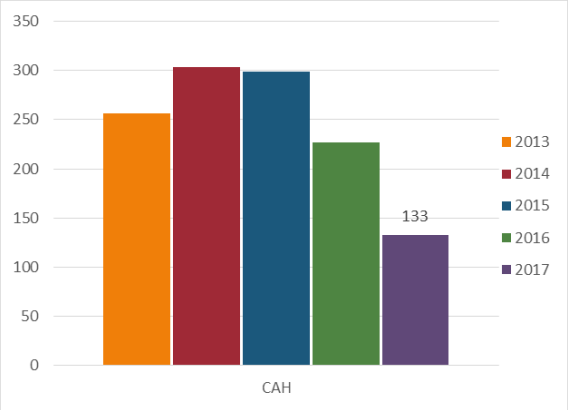

Figure 9. The total number of congenital adrenal hyperplasia screen positives between 2013-2017.

The number of screen positives for this condition decreased significantly in 2017. This decline is likely attributed to 2017 representing a full year of operations with 1) NSO using disorder logic that included both birth weight and gestational age and 2) NSO changing its policy to not refer extremely premature infants on their repeat sample if their initial sample was screen negative; 97 samples fell into this category.

4.2.4.2 Congenital Hypothyroidism

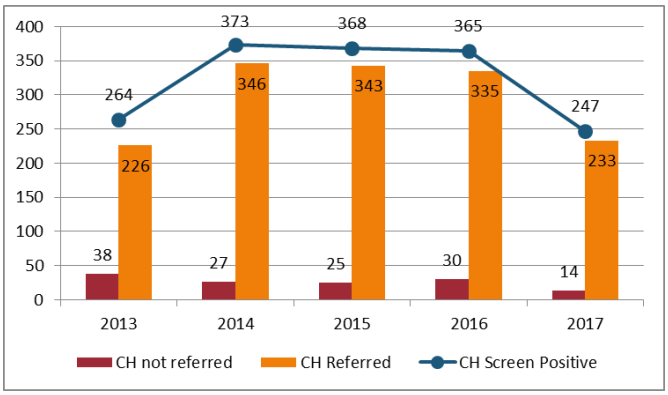

Figure 10. The total number of congenital hypothyroidism screen positives between 2013-2017.

The number of screen positives for this condition decreased significantly in 2017 with approximately a 30% reduction in referrals when compared to 2016. Numbers from 2017 are most comparable to numbers from 2013. Referrals increased and remained constant from 2014 to 2016. There have been no changes to the type of kit used or the cut offs and as discussed in previous reports, 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 between 2014 through 2016. Similarly, the reason for the decline in CH referrals in 2017 is unknown. Work is still ongoing at NSO but no analytical factors have been definitely identified.

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The number of true positive cases has not increased and therefore, this has resulted in a general reduction in the PPV by year since 2013. The PPV for 2017 was similar to values calculated in 2012.

4.2.5 Metabolics

There was an increase in the number of biotinidase deficiency referrals in 2017. The introduction (and ultimate recall) of a new lot of filter paper demonstrated a lower measured biotinidase activity and as a result NSO modified the screen positive cut off for all samples collected on these cards. Of the 78 screen positive cases referred, 23 were cases referred using the modified cut off.

There was an increase in maple syrup urine disease and tyrosinemias referrals in 2017 when compared to 2016, and 2017 numbers for both of these conditions were more comparable to data from 2015. The disorder logic for both of these conditions has not changed and the fluctuation in referral numbers is unknown. Generally, the other amino acidemias (citrullinemia, homocystinuria/hypermethioninemias, and PKU) remained relatively constant, with lower referral numbers noted in all 3 of these disease categories.

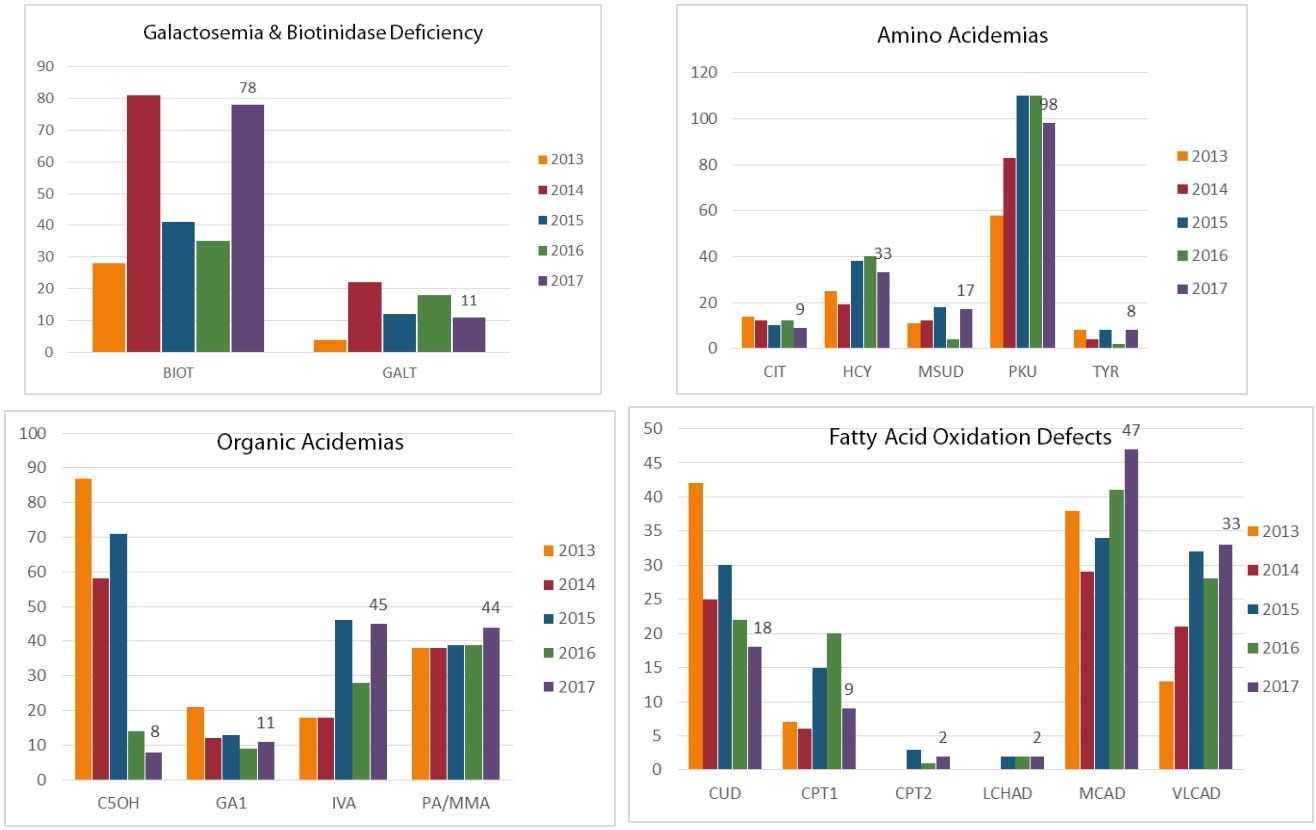

Figure 11. The number of metabolic screen positives between 2013-2017 by disease

The small number of C5OH referrals in 2017 continued to reflect the disorder logic change implemented in December 2015, which significantly reduced referrals with isolated elevations of C5OH. Furthermore, in December 2017 newborn screening for the 4 C5OH-related disorders was discontinued and these targets were removed from the screening panel. This programmatic change was made subsequent to a thorough review of

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Ontario-specific newborn screening data, consultation with metabolic experts, a unanimous vote by the Newborn Screening Ontario Advisory Council and endorsement from the Ministry of Health and Long Term Care.

The number of isovaleric acidemia referrals increased between 2016 and 2017. The majority, two-thirds (67%), of screen positive samples were collected in an NICU setting (5 sites in total). Furthermore, approximately 50% of the NICU collected screen positive samples were from one nursery. Referrals in 2017 were more comparable to 2015 when increased numbers of screen positives from Level III nurseries was also noted, despite these institutions reporting no change to their collection procedures at the time.

Regarding the grouping of fatty acid oxidation defects on the newborn screening panel, a greater than 50% reduction in carnitine palmitoyltransferase deficiency, type 1 screen positive referrals was noted from 2016 to 2017. The reason for this decrease is not known. In 2017 the number of medium chain acyl coA dehydrogenase deficiency (MCADD) referrals was the highest recorded within the last 5 years. Of the 47 screen positives for MCADD in 2017 17 cases were premature infants who had an initial screen negative and then a screen positive result on repeat sample collection, and one referral involved an infant who screened positive both on their initial and repeat newborn screens. Due to the increases over the last two years, an analysis was done of all MCADD cases to determine the contributing factors associated with the increase in referrals, and any corrective actions required. This data will be reviewed by the metabolics disease speciality group to determine next steps.

A slight decrease in the overall number of CUD referrals was seen in 2017 and 35 samples from premature infants were not reported out as positives as their initial screens were negative for CUD. Internally, these repeat samples are classified as "test level unsatisfactory". Finally, an increase in VLCADD referrals was noted. The cause of the fluctuations in CUD and VLCADD referrals is unknown.

4.2.6 Severe Combined Immune Deficiency

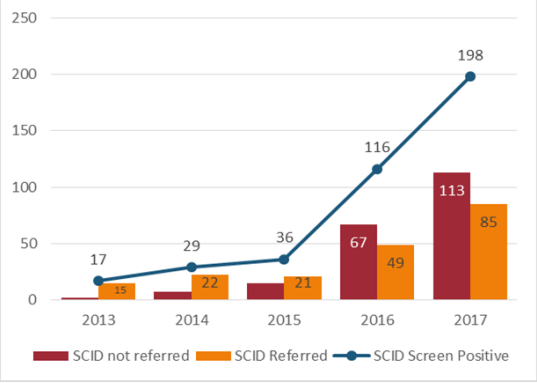

Figure 12. The number of SCID screen positives between 2013-2017.

The overall number of screen positive results for SCID increased significantly in 2017 with increases noted both in referred and not referred (i.e. SCID premature) cases. Although the confirmatory screening assay cut off to screen positive for SCID remained unchanged, the TREC cut off for the initial screening assay was increased from 75 to 100 in December 2016. This change in the cut off for the initial assay could be contributing to the increase in SCID screen positive results.

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4.2.7 Screen Positive by Sample Type for Premature Infants

In 2017 there were 337 laboratory screen positive results that qualified under the prematurity policy. Of these laboratory screen positives 114 were not referred (the majority being SCID cases indicated in green in the figure below). However, of the 114 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, PKU, HCY, and/or IVA on initial samples (indicated in red below). There were 143 infants who were screen positive on their initial sample only, 64 infants who only screened positive on their repeat samples (indicated in blue), and 8 infants who screened positive for the same condition on both their initial and repeat samples (indicated in yellow). Furthermore, an additional 35 CUD and 97 CAH repeat screens (not represented in Figure 13) in premature infants were classified as "unsatisfactory" instead of reported out as screen positives by NSO, as all of these cases had initial negative screening results for either CUD or CAH respectively.

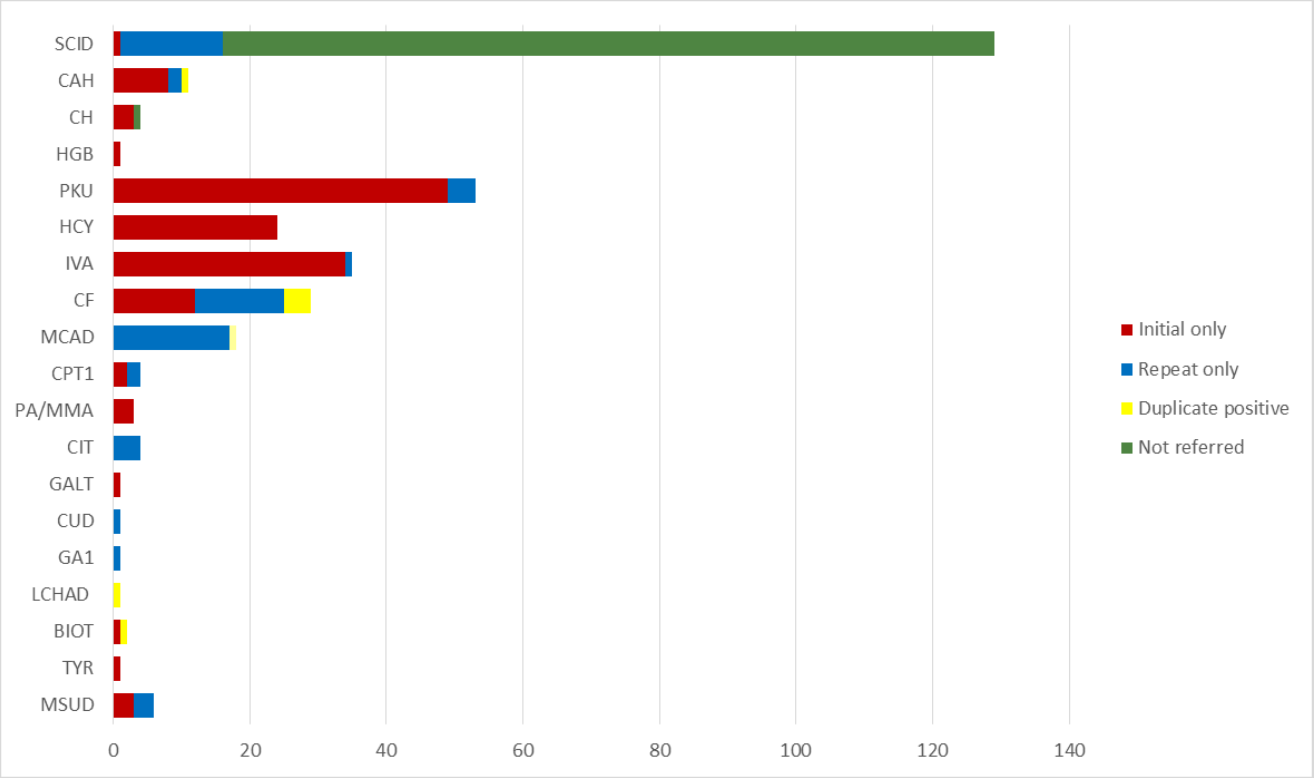

Figure 13. The number of laboratory screen positives (including both those referred and not referred) by disease for extremely premature infants (<33 weeks gestation and/or <1500g); red is initial positive sample only, blue is repeat positive sample only; yellow is two samples for the same infant positive for the same condition; and green are laboratory screen positives that were not referred.

4.3 Diagnostic Feedback

Due to sustained efforts in 2017 to complete outstanding DERFs (Diagnostic Evaluation Report Forms) approximately 15.2% (223 cases) of feedback information remain pending for the referrals made in 2017 as of

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April 1, 2018. This is marginally higher than in 2016 (12.7%) but nonetheless is an improvement from previous years and will help NSO calculate more relevant PPVs and refine disorder logic.

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:

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)

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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, 2018.

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Table 17. The positive predictive values of each disease screened by NSO, including current and previous screening algorithms.

Disease		Additional information	PPV (Yes)	PPV (Yes + Variant)	PPV (Yes + Variant + Secondary)	% of DERFs Pending	Total No. Screen Positive
Endocrinopathies	Congenital Hypothyroidism	Referred	33.2%	38.6%	38.6%	4.2%	2626
	Congenital Adrenal Hyperplasia	Past (Aug 9, 2012 - Sept 1, 2016)	2.2%	2.3%	2.4%	2.8%	1116
		Current (Sept 2, 2016 - Dec 31, 2017)	**4.1%**	**4.1%**	**4.1%**	**14.1%**	**170**
Hemoglobinopathies		Past (Nov 1, 2010 - July 31, 2015)	64.8%	65.7%	83.7%	1.6%	373
		Current (Aug 1, 2015 - Dec 31, 2017)	**65.0%**	**66.4%**	**86.9%**	**29.6%**	**203**
Cystic Fibrosis		Category A	99.1%	99.6%	99.6%	12.2%	255
		Category B	2.0%	5.3%	5.3%	2.1%	3238
		Category C	0.3%	0.7%	0.7%	3.1%	938
		All	**6.7%**	**9.2%**	**9.2%**	**2.9%**	**4431**
Severe Combined Immune Deficiency		Past (Sept 22, 2014 - May 8, 2017)	6.1%	9.2%	15.3%	2.6%	116
		Current (May 9, 2017 - Dec 31, 2017)	**4.3%**	**6.5%**	**8.7%**	**13.2%**	**53**
Organic Acidemia	Glutaric Aciduria type 1		**8.3%**	**8.3%**	**23.6%**	**5.3%**	**152**
	Isovaleric Acidemia		**1.6%**	**3.3%**	**3.3%**	**4.1%**	**317**
	C5OH	Past (until Dec 7, 2015)	6.2%	6.2%	6.2%	0.7%	570
		Current (Dec 8 , 2016 - Dec 1, 2017)	**22.7%**	**22.7%**	**22.7%**	**12.0%**	**25**
	PA/MMA	Past (Feb 16, 2010 - Apr 21, 2013)	3.7%	3.7%	8.3%	0.9%	219
		Current (Apr 22, 2013 - Dec 31, 2017)	**3.8%**	**3.8%**	**6.4%**	**10.0%**	**180**
Fatty Acid Oxidation Defects	CPTI		**3.7%**	**56.9%**	**57.8%**	**0.9%**	**110**
	CPTII		**9.1%**	**9.1%**	**9.1%**	**0.0%**	**33**
	LCHAD		**72.7%**	**72.7%**	**90.9%**	**15.4%**	**13**
	VLCAD		**8.6%**	**12.9%**	**14.5%**	**3.0%**	**263**
	CUD	Past (until Mar 4, 2014)	5.2%	5.2%	5.2%	0.3%	300
		Current (Mar 5, 2014 - Dec 31, 2017)	**2.5%**	**2.5%**	**2.5%**	**6.8%**	**88**
	MCAD	Past (until Aug 30, 2016)	31.3%	37.0%	39.1%	0.0%	311
		Current (Sept 1, 2016 - Dec 31, 2017)	**18.9%**	**18.9%**	**18.9%**	**12.5%**	**64**
Amino Acidopathies	Citrullinemia		**18.4%**	**19.9%**	**20.6%**	**2.2%**	**139**
	Homocystinuria		**0.0%**	**0.0%**	**2.8%**	**4.9%**	**224**
	Phenylketonuria		**12.1%**	**24.2%**	**25.2%**	**3.7%**	**788**
	MSUD	Past (until Nov 14, 2011)	3.8%	3.8%	3.8%	0.0%	90
		Current (Nov 15, 2011 - Dec 31, 2017)	**7.9%**	**9.5%**	**9.5%**	**7.2%**	**69**
	Tyrosinemia	Past (Sep 14, 2009 - Sep 19, 2011)	1.4%	1.4%	1.4%	0.0%	70
		Current (Sep 20, 2011 - Dec 31, 2017)	**11.9%**	**11.9%**	**16.7%**	**4.3%**	**47**
Other Metabolic Diseases	Galactosemia	Past (until Jan 12, 2014)	35.7%	41.4%	41.4%	1.4%	72
		Current (Jan 13, 2014 - Dec 31, 2017)	**13.6%**	**25.4%**	**25.4%**	**6.8%**	**63**
	Biotinidase Deficiency	Past (Jan 13, 2014 - Jul 2, 2014)	2.1%	36.2%	36.2%	2.0%	49
		Current (Jul 3, 2014 - Dec 31, 2017)	**4.0%**	**36.4%**	**36.4%**	**7.0%**	**186**

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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, 2016 and 2017.

	1. Screening (Initial Samples) **2016 ONLY**			2. Screening (Initial Samples) 2017 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**
C5OH-Related Disorders, Cit, FAOD, GA1, HCY, PKU, IVA, LCHAD, MCAD, MSUD, PA/MMA, PKU, Tyr, VLCAD	**65%**	**55%**	**93%**	**72%**	**70%**	**96%**
Biotinidase Deficiency	**65%**	**55%**	**94%**	**72%**	**70%**	**96%**
Galactosemia	**65%**	**55%**	**94%**	**72%**	**71%**	**97%**
Congenital Adrenal Hyperplasia	**65%**	**55%**	**94%**	**72%**	**70%**	**97%**
Congenital Hypothyroidism	**65%**	**54%**	**93%**	**72%**	**70%**	**97%**
Cystic Fibrosis	**65%**	**51%**	**100%**	**72%**	**67%**	**92%**
Hemoglobinopathies	**65%**	**40%**	**81%**	**72%**	**51%**	**91%**
Severe Combined Immune Deficiency	**65%**	**36%**	**83%**	**72%**	**40%**	**86%**

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 2016 and 2017 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. Recall that in January 2017 NSO officially changed their recommendation of age at sample collection to 24-48 hours (from 24-72 hours) and a continued positive shift toward samples being collected within the 24-48 hour window has been noted with approximately 91% of samples being collected by 48 hours of age.

Table 19: Median and 90th centile values for age of receipt of initial samples, and availability of initial and final results, 2016 and 2017.

	1. Screening (Initial Samples) **2016 ONLY**							2. Screening (Initial Samples) 2017 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	1,053	7	9	4	6	5	7	1,078	6	8
Biotinidase Deficiency					273	7	9					1,457	6	8
Galactosemia					108	7	11					333	7	11
Congenital Adrenal Hyperplasia					879	5	7					628	6	8
Congenital Hypothyroidism					1,733	7	8					1,097	6	7
Cystic Fibrosis					6,264	10	13					6,281	9	12
Hemoglobinopathies			6	8	119	8	12					104	8	10
Severe Combined Immune Deficiency			6	8	314	9	12			6	8	1,099	9	12

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Age at final result refers to any screening sample requiring confirmatory testing prior to being reported as a screen positive or screen negative result. Samples requiring screening confirmation for biotinidase deficiency and Severe Combined Immune Deficiency were notably increased between 2016 and 2017. For biotinidase deficiency, this was likely attributed the introduction (and eventual recall) of a lot of filter paper which demonstrated a lower measured biotinidase activity. As a result, NSO modified the screen positive cut off for all samples collected on these cards. For SCID, increased sample volumes requiring screening confirmation can be attributed to a change made in December 2016 to increase the initial TREC screening assay cut off.

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 2013-2017.

Category	ACMG Code	Age at receipt	Age at Sreening Results		Age (days) at retrieval (contact with family) (% meeting benchmark)		Age (days) at Definitive Diagnosis and Disposition [2] (% meeting benchmark)	
			ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert
Benchmark (days)		4	5	7	5	8	90	
Congenital Adrenal Hyperplasia	CAH	54% 657 / 1218	47% 37 / 78	76% 871 / 1,140	41% 29 / 70	80% 864 / 1,085	99% 69 / 70	95% 1,020 / 1,078
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, HMG, βKT, ASA, CIT, MSUD, TYR1	57% 286 / 503	40% 16 / 40	64% 296 / 463	44% 14 / 32	75% 316 / 420	84% 27 / 32	86% 359 / 416
Galactosemia	GALT	25% 17 / 67	19% 8 / 42	28% 7 / 25	18% 7 / 39	50% 12 / 24	92% 36 / 39	83% 20 / 24
Benchmark (days)		4	5	7	5	8	90	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	52% 169 / 322	58% 21 / 36	59% 169 / 286	38% 11 / 29	68% 177 / 260	93% 27 / 29	86% 223 / 260
Benchmark (days)		4	N/A	7	N/A	8	90	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	44% 87 / 200	-	50% 100 / 200	-	56% 101 / 181	-	81% 145 / 180
Benchmark (days)		4	N/A	10	N/A	12	90	
Organic and Amino Acidemias	MCD, 3-MCC, GA1, HCY, PKU	61% 557 / 918	-	92% 845 / 917	-	93% 733 / 784	-	91% 711 / 781
Biotinidase Deficiency	BIOT	64% 168 / 263	-	92% 243 / 263	-	92% 227 / 247	-	83% 204 / 247
Congenital Hypothyroidism	CH	71% 1,051 / 1,483	-	96% 1,431 / 1,483	-	96% 1,357 / 1,413	-	96% 1,359 / 1,413
Benchmark (days)		4	N/A	14	N/A	21	90	
Cystic Fibrosis	CF	65% 1,565 / 2,394	-	84% 2,001 / 2,394	-	62% 1,386 / 2,251	-	93% 2,083 / 2,251
Severe Combined Immune Deficiencies	SCID	52% 99 / 192	-	69% 133 / 192	-	81% 129 / 160	-	80% 117 / 147
Benchmark (days)		4	N/A	14	N/A	30	60	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	64% 262 / 410	-	82% 337 / 410	-	51% 172 / 334	-	28% 93 / 334

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%.

Compared to data from 2012-2016, 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

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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.

Finally, infants who screened positive for Hemoglobinopathies have the lowest percentage meeting the benchmark regarding Age at Definitive Diagnosis/Disposition of all disease categories. This is thought to be attributed to the dates that Regional Treatment Centres have chosen to enter into the DERF. NSO is working with the Regional Treatment Centres to ensure consistent interpretation of data/date fields in these DERFs, which is anticipated to help improve this benchmark in future.

Table 21. The benchmarks and percentage of infants achieving benchmarks for all positive infants, 2017 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	75% 100 / 133	100%	86% 112 / 130	100%	90% 103 / 115	100%	98% 106 / 108
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, HMG, βKT, ASA, CIT, MSUD, TYR1	67% 82 / 123	63% 5 / 8	72% 83 / 115	75%	78% 76 / 97	100%	94% 91 / 97
Galactosemia	GALT	9%	17%	0%	0%	50%	100%	75%
	Benchmark (days)	4	5	7	5	8	90	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	57% 47 / 82	55% 6 / 11	63% 45 / 71	29%	73% 40 / 55	100% 7 / 7	98% 54 / 55
	Benchmark (days)	4	N/A	7	N/A	8	90	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	76% 22 / 29	-	72% 21 / 29	-	84% 21 / 25	-	92% 23 / 25
	Benchmark (days)	4	N/A	10	N/A	12	90	
Organic and Amino Acidemias	MCD, 3-MCC, GA1, HCY, PKU	76% 115 / 151	-	93% 140 / 151	-	93% 99 / 107	-	99% 106 / 107
Biotinidase Deficiency	BIOT	79% 62 / 78	-	95% 74 / 78	-	94% 64 / 68	-	99% 67 / 68
Congenital Hypothyroidism	CH	83% 194 / 233	-	99% 231 / 233	-	98% 199 / 203	-	99% 200 / 203
	Benchmark (days)	4	N/A	14	N/A	21	90	
Cystic Fibrosis	CF	79% 359 / 454	-	94% 425 / 454	-	65% 251 / 386	-	95% 367 / 386
Severe Combined Immune Deficiencies	SCID	61% 52 / 85	-	74% 63 / 85	-	85% 60 / 71	-	75% 48 / 64
	Benchmark (days)	4	N/A	14	N/A	30	60	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	79% 68 / 86	-	94% 81 / 86	-	54% 15 / 28	-	46% 13 / 28

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5.3 True Positive Infants

Table 22. The benchmarks and percentage of infants achieving benchmarks for all true positive infants with classic disease for 2013 – 2017 (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	46% 13 / 28	44% 7 / 16	92% 11 / 12	50% 8 / 16	92% 11 / 12	75% 12 / 16	92% 11 / 12	100% 16 / 16	100% 12 / 12
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, HMG, βKT, ASA, CIT, MSUD, TYR1	50% 13 / 26	40%	75% 12 / 16	50% 5 / 10	81% 13 / 16	60% 6 / 10	75% 12 / 16	80% 8 / 10	94% 15 / 16
Galactosemia	GALT	73% 8 / 11	71% 5 / 7	50%	71% 5 / 7	75%	86% 6 / 7	75%	86% 6 / 7	100%
	Benchmark (days)	4	5	7	5	8	8	10	90	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	69% 41 / 59	67% 18 / 27	72% 23 / 32	46% 11 / 24	84% 26 / 31	67% 16 / 24	58% 18 / 31	92% 22 / 24	87% 27 / 31
	Benchmark (days)	4	N/A	7	N/A	8	N/A	14	90	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	57%	-	71% 5 / 7	-	71% 5 / 7	-	57%	-	71% 5 / 7
	Benchmark (days)	4	N/A	10	N/A	12	N/A	14	90	
Organic and Amino Acidemias	MCD, 3-MCC, GA1, HCY, PKU	60% 33 / 55	-	95% 52 / 55	-	95% 52 / 55	-	73% 40 / 55	-	89% 49 / 55
Biotinidase Deficiency	BIOT	56% 5 / 9	-	89% 8 / 9	-	100% 9 / 9	-	89% 8 / 9	-	89% 8 / 9
Congenital Hypothyroidism	CH	60% 195 / 327	-	92% 300 / 327	-	93% 302 / 325	-	78% 255 / 325	-	99% 321 / 325
	Benchmark (days)	4	N/A	14	N/A	21	N/A	30	90	
Cystic Fibrosis	CF	59% 97 / 165	-	84% 138 / 165	-	87% 143 / 164	-	78% 128 / 164	-	90% 147 / 164
Severe Combined Immune Deficiencies	SCID	44%	-	89% 8 / 9	-	100% 9 / 9	-	89% 8 / 9	-	100% 9 / 9
	Benchmark (days)	4	N/A	14	N/A	30	N/A	60	60	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	57% 119 / 210	-	81% 170 / 210	-	52% 109 / 209	-	38% 79 / 209	-	32% 66 / 209

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.

In 2017 at the request of the Newborn Screening Ontario Advisory Council, NSO performed additional data analyses on the screening timeliness dataset from 2012-2016. Screen positive data was stratified by distance to a Regional Treatment Centre (>/< 200km) and by health status of the infant (well/unwell; hospitalized/not hospitalized; symptomatic/asymptomatic) at the time of retrieval. No trends were noted when these analyses were completed. NSO also examined the data by age at sample collection and by initial samples only. As would be expected, when the data was reviewed in this fashion, benchmarks improved. Finally, data was also examined by Regional Treatment Centre, and for CF, by screening positive categorization (A/B/C). Regional Treatment Centre and CF categorization data will also be examined using data from 2013-2017 and this will be presented at the disease specific working group meetings and provided to the treatment centres, upon request.

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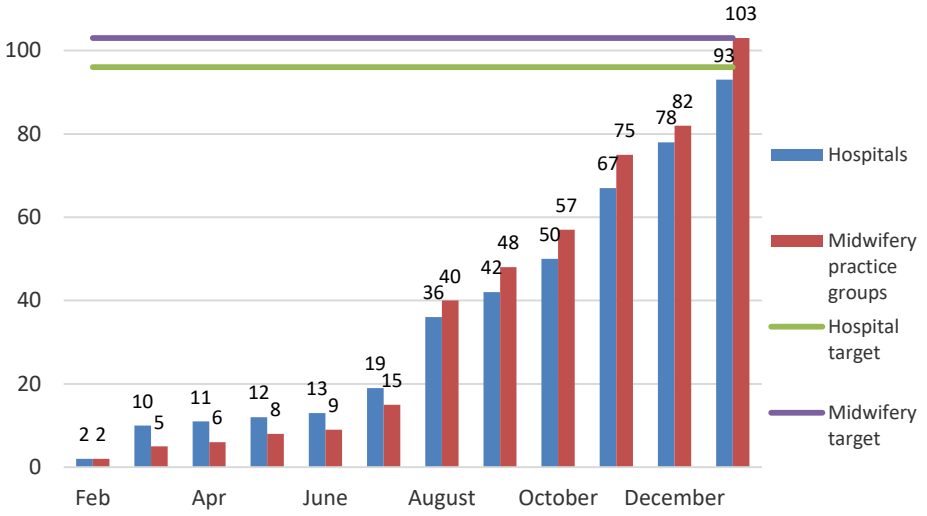
6. CCHD Implementation

7.1 Phased roll-out

NSO implemented a phased roll-out approach to Critical Congenital Heart Disease (CCHD) screening. Beginning in February 2017 select submitters began sending CCHD pulse oximetry screening data to NSO. These phase 1 sites provided feedback and input on the data collection card, recommended protocols, education materials, pulse oximeters, and all other CCHD screening material and tools.



All other organizations began their NSO CCHD screening during phase 2 (starting in June 2017), with the goal of having all organizations screening by December 2017. Figure 12 shows the progress towards the goal of 103 midwifery practices and 96 hospitals implementing CCHD screening throughout 2017.

Figure 14. Submitters Implementation of CCHD Screening

Submitters submit their 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 2017 is 42,921, representing 42,600 infants.

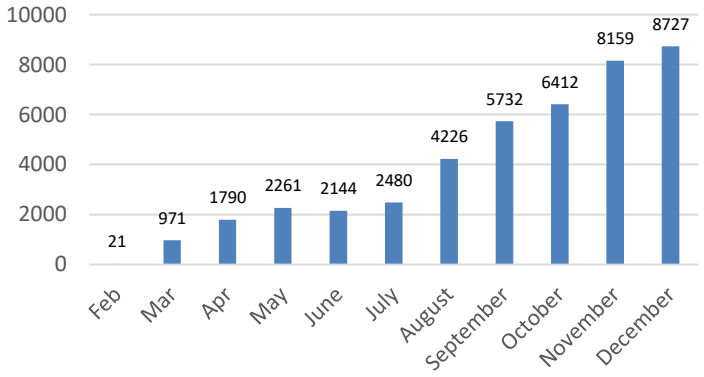


Figure 15. CCHD Cards Registered Feb-Dec 2017

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7.2 Screens Completed

In 2017 CCHD screens were not done on 2% of the infants for which NSO received cards. The most common reason for CCHD screen not done is because the infant is expected to be in the NICU for > 7 days.

Table 23. CCHD cards received and infants screened.

	Cards	Infants
CCHD Screen Done	41,847	41,677
CCHD Screen Not Done	1,074	923
Total	**42,921**	**42,600**

Table 24. Reasons for CCHD Screen not done.

Case Type	Cards Submitted	Infants
'Screen Not Done' card submitted	**1074**	**923**
Decline/deferred (back page of form not completed)	17	14
Declined	5	<5
Deferred	56	26
Infant diagnosed prenatally with heart defect	20	19
Infant diagnosed with heart defect by physical exam	12	10
Infant in or is expected to be in NICU/SCN/PICU over 7 days	876	792
Already done	24	7
Echocardiogram or cardiology investigations already done	9	9
Insufficient information provided	30	26
Early discharge	10	6
Hospital transfer	10	6
Other	5	5

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, 97.9% 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 1.8% required a second test and 0.2% required three tests to complete the screen.

Table 25. Tests required to complete screen

Tests Done	Count	(%)
1 Test	40,984	97.9
2 Tests	766	1.8
3 Tests	97	0.2
	41,847	**100.0**

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7.3 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 (86.2%) of screening has been done in the recommended range.

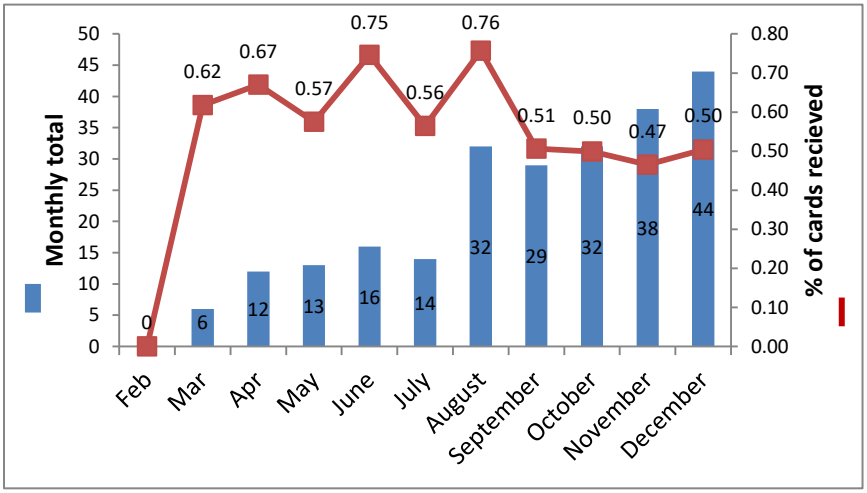
Table 26. Age at time of CCHD Screen, 2017

Age at time of screen	Number of initial CCHD screens done	% of initial CCHD screens done
Less than 24 hours	1627	3.90%
24-48 hours (1-2 days)	35,930	86.21%
> 48-72 hours (2-3 days)	1,428	3.43%
>72-168 hours (3-7 days)	369	0.89%
Greater than 168 hours (> 7 days)	106	0.25%
Not specified	2217	5.32%

Of the 1627 infants with screens done at earlier than 24 hours, 23 had repeat screens submitted and 13of the 23 were done in the recommended timeframe. 3.8 % of screens submitted by hospitals were done at less than 24 hours, compared to 4.9 % of screens submitted by midwifery practices. Similarly, 4.3 % of screens submitted by hospitals were done at over 48 hours, compared to 8.8 % of screens submitted by midwifery practices.

7.4 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.



As CCHD screening rolled out across the province, the % of cards received that required follow up has dropped as submitters became more familiar with the algorithm and process. The number of unsatisfactory screens done in 2017 was 232, which is 0.56% of the total screens done.

The most frequent error is incomplete documentation of a repeat test done after 1 hour.

Figure 16. Total number and percentage of unsatisfactory CCHD Screens received

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Table 27. Reasons for Unsatisfactory CCHD Screen

Satisfactory Screens Done	41,615
Unsatisfactory Screens Done	232
Referral not documented	46
Repeat not documented	148
Incomplete	33
Other	5
Total Screens Done	41,847
Unsatisfactory Rate	0.56%

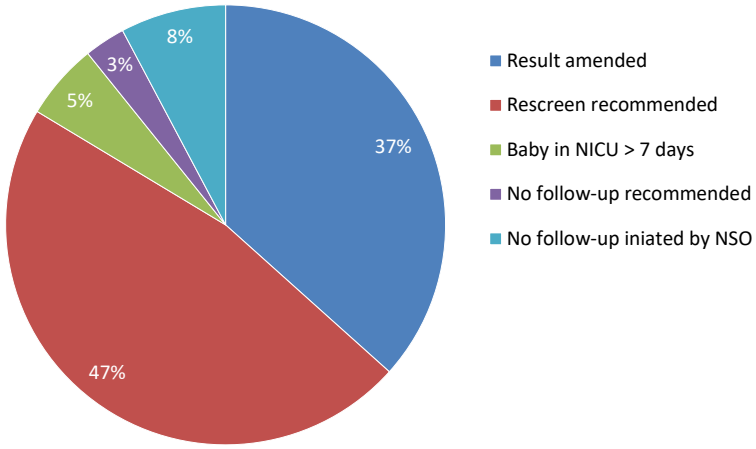

Figure 17. Actions taken on Unsatisfactory CCHD Screens

NSO performed follow up on the 232 unsatisfactory screens, most often resulting in a recommendation to rescreen the infant (47%). In 37% of follow up cases the result was amended by the submitter due to incorrect completion of the form. The remaining cases required no follow up.

In 199 (86%) cases NSO performed a same-day telephone call and follow-up. A further 12 cases had follow up in 1-2 days and 3 cases within 4-7 days. No follow up was done for 18 cases as the infant was greater than 7 days when entered into the system or a repeat screen was identified as a pass.

7.5 CCHD Screen Positives

Table 28. PPV calculations for CCHD Screen Positives

Disease	PPV		Total No. Screen Positive	Outcome Classification				
					Incidental			
	PPV (Yes)	PPV (Yes + Secondary)		Yes	Secondary Targets	All Other Incidentals	No	Other
Critical Congenital Heart Disease (CCHD)	4.6 %	14.9 %	87	<5	9	16	58	<5

Of the 87 screen positives received in 2017 <5 were diagnosed with a critical congenital heart defect, 25 had a secondary CHD target or were diagnosed with an incidental finding such as pulmonary disease or infection, and 58 were found to be not affected. All primary targets were referred after a saturation of <90% during the screen.

Referrals to a physician were all made on the day of the screen, although paediatric cardiology appointments were not always the same day. The date of diagnosis was only captured in 45 cases, but of those, diagnosis was made within 24 hours of the screen for 34 (76%) of cases and within 48 hours for a further 8 (18%) cases.

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Of the interventions done on screen positive, oxygen was noted on 8 cases, non-invasive positive pressure was noted on <5 cases, and 27 echocardiograms were done. Eight infants required transfer from hospital to another using either ambulance, transport teams, or parent/guardian. There were 8 screen positives done at home by midwives of which 6 were transferred to hospital.

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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, 2013-2017.

		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	# Prioritized	Median	70th Centile	90th Centile	# Confirmed	Median	70th Centile	90th Centile	# Prioritized	Median	70th Centile	90th Centile	# Confirmed	Median	70th Centile	90th Centile	# Prioritized	Median	70th Centile	90th Centile	# Confirmed	Median	70th Centile	90th Centile
Benchmark (days of age)		4			5				7				5				8				90							
Congenital Adrenal Hyperplasia	CAH	4	5	23	78	6	7	10	1,140	6	7	24	70	6	7	15	1085	6	7	24	70	15	27	56	1,085	21	33	70
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, HMG, βKT, ASA, CIT, MSUD, TYR1	4	5	10	40	6	7	13	463	7	8	12	32	6	7	22	420	7	8	13	32	17	28	140	416	27	41	110
Galactosemia	GALT	7	14	34	42	9	14	28	25	8	25	56	39	8	14	27	24	9	26	56	39	34	47	81	24	59	74	108
Benchmark (days of age)		4			5				7				5				8				90							
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	4	6	22	36	5	6	8	286	7	9	24	29	6	7	9	260	7	9	24	29	26	35	74	260	39	57	105
Benchmark (days of age)		4							7								8				90							
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	5	17	30	No Type 1				200	8	17	33	No Type 1				181	8	16	34	No Type 1				180	30	70	119
Benchmark (days of age)		4							10								12				90							
Organic and Amino Acidemias	MCD, 3-MCC, GA1, HCY, PKU	4	5	7	No Type 1				917	7	7	10	No Type 1				784	7	8	10	No Type 1				781	26	33	84
Biotinidase Deficiency	BIOT	4	5	7	No Type 1				263	7	8	10	No Type 1				247	7	9	12	No Type 1				247	30	53	117
Congenital Hypothyroidism	CH	3	4	6	No Type 1				1617	6	7	8	No Type 1				1413	7	8	10	No Type 1				1410	13	20	50
Benchmark (days of age)		4							14								21				90							
Cystic Fibrosis	CF	4	5	6	No Type 1				2394	11	13	16	No Type 1				2251	19	24	32	No Type 1				2250	32	42	76
Severe Combined Immune Deficiencies	SCID	4	5	14	No Type 1				192	11	15	29	No Type 1				160	12	16	30	No Type 1				147	40	58	160
Benchmark (days of age)		4							14								30				60							
Hemoglobinopathies	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	4	5	6	No Type 1				410	10	12	16	No Type 1				334	30	38	50	No Type 1				334	78	98	158

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Table 2A: Median, 70th, 90th Centile for All screen Positive samples by Disease Category, 2017 only.

					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	3	4	6	<5	4	N/A	N/A	130	6	6	8	<5	5	N/A	N/A	115	6	7	8	<5	0	N/A	N/A	115	14	20	47
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, HMG, βKT, ASA, CIT, MSUD, TYR1	4	5	16	8	5	N/A	N/A	115	6	7	18	<5	5	N/A	N/A	97	6	8	19	<5	10	N/A	N/A	96	25	32	50
Galactosemia	GALT	6	7	39	6	8	N/A	N/A	5	8	N/A	N/A	<5	8	N/A	N/A	<5	9	N/A	N/A	<5	22	N/A	N/A	<5	28	N/A	N/A
Benchmark (days of age)		4			5				7				5				8				90							
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	4	6	22	11	5	6	7	71	7	10	25	7	6	N/A	N/A	55	7	8	25	7	20	N/A	N/A	55	34	44	72
Benchmark (days of age)		4							7								8				90							
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	3	4	7	No Type 1				29	6	7	9	No Type 1				25	7	8	11	No Type 1				25	15	23	81
Benchmark (days of age)		4							10								12				90							
Organic and Amino Acidemias	MCD, 3-MCC, GA1, HCY, PKU	3	4	6	No Type 1				151	6	7	9	No Type 1				107	6	7	10	No Type 1				107	23	26	39
Biotinidase Deficiency	BIOT	3	4	5	No Type 1				78	6	7	8	No Type 1				68	6	8	11	No Type 1				68	25	31	48
Congenital Hypothyroidism	CH	3	4	5	No Type 1				247	6	6	7	No Type 1				203	6	7	9	No Type 1				203	11	19	52
Benchmark (days of age)		4							14								21				90							
Cystic Fibrosis	CF	3	4	5	No Type 1				454	9	11	13	No Type 1				386	17	23	29	No Type 1				386	30	40	69
Severe Combined Immune Deficiencies	SCID	3	4	13	No Type 1				85	10	12	28	No Type 1				71	12	15	29	No Type 1				64	40	79	152
Benchmark (days of age)		4							14								30				60							
Hemoglobinopathies	Hb SS, Hb S/βTh, Hb SC, Hb S/HPFH	4	5	22	No Type 1				86	9	10	13	No Type 1				28	26	36	44	No Type 1				28	65	74	109

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Table 3A: Median, 70th and 90th Centile for all True Positive Samples by Disease Category, 2013-2017

Category	ACMG Code	Age at Receipt			Alert Confirmation				Routine Confirmation				ALERT				Non-Alert				ALERT				Non-Alert				ALERT				Non-Alert			
					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	5	6	7	16	6	7	8	12	6	7	7	16	6	7	9	12	6	7	8	16	5	6	8	12	6	7	9	16	6	7	8	12	8	9	11
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, HMG, βKT, ASA, CIT, MSUD, TYR1	5	5	6	10	6	7	8	16	7	7	9	10	6	7	8	16	6	8	9	10	6	7	31	16	5	8	17	10	8	26	152	16	12	50	67
Galactosemia	GALT	4	4	5	7	5	N/A	N/A	<5	7	N/A	N/A	7	5	N/A	N/A	<5	7	N/A	N/A	7	5	N/A	N/A	<5	7	N/A	N/A	7	19	N/A	N/A	<5	10	N/A	N/A
Benchmark (days of age)		4			5				7				5				8				8				10				90							
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	4	5	7	27	5	6	8	32	6	7	11	24	6	8	11	31	6	7	9	24	6	9	25	31	9	14	52	24	29	35	83	31	33	52	102
Benchmark (days of age)		4							7								8								14				90							
Fatty Acid Oxidation Diseases	CUD, CPT1 CPT2	3	N/A	N/A	No Type 1				7	5	N/A	N/A	No Type 1				7	5	N/A	N/A	No Type 1				7	11	N/A	N/A	No Type 1				7	64	N/A	N/A
Benchmark (days of age)		4							10								12								14				90							
Organic and Amino Acidemias	MCD, 3-MCC, GA1 HCY, PKU	4	5	6	No Type 1				55	7	7	8	No Type 1				55	7	7	10	No Type 1				55	8	13	35	No Type 1				55	9	15	89
Biotinidase Deficiency	BIOT	4	N/A	N/A	No Type 1				9	9	N/A	N/A	No Type 1				9	9	N/A	N/A	No Type 1				9	10	N/A	N/A	No Type 1				9	17	N/A	N/A
Congenital Hypothyroidism	CH	4	5	7	No Type 1				327	7	8	10	No Type 1				325	7	8	11	No Type 1				325	8	11	27	No Type 1				325	9	13	31
Benchmark (days of age)		4							14								21								30				90							
Cystic Fibrosis	CF	4	5	7	No Type 1				165	11	12	16	No Type 1				164	12	16	24	No Type 1				164	18	24	53	No Type 1				164	30	44	91
Severe Combined Immune Deficiencies	SCID	5	N/A	N/A	No Type 1				9	9	N/A	N/A	No Type 1				9	10	N/A	N/A	No Type 1				9	13	N/A	N/A	No Type 1				9	16	N/A	N/A
Benchmark (days of age)		4							14								30								60				60							
Hemoglobinopathies	Hb SS, Hb S/βTh, Hb SC, Hb S/HPFH	4	5	7	No Type 1				210	10	12	16	No Type 1				209	30	36	45	No Type 1				209	74	89	130	No Type 1				209	74	91	126

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