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

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

Calendar Year 2019

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1. Screening Samples in 2019

Table 1. Screening sample volumes from2015-2019.

Sample Type	2019	2018	2017	2016	2015
Satisfactory	146,099	145,724	145,405	145,018	144,812
Unsatisfactory*	1,356	1,365	2,248	1,755	1,367
Routine Screening – Total	**147,455**	**147,089**	**147,653**	**146,773**	**146,179**

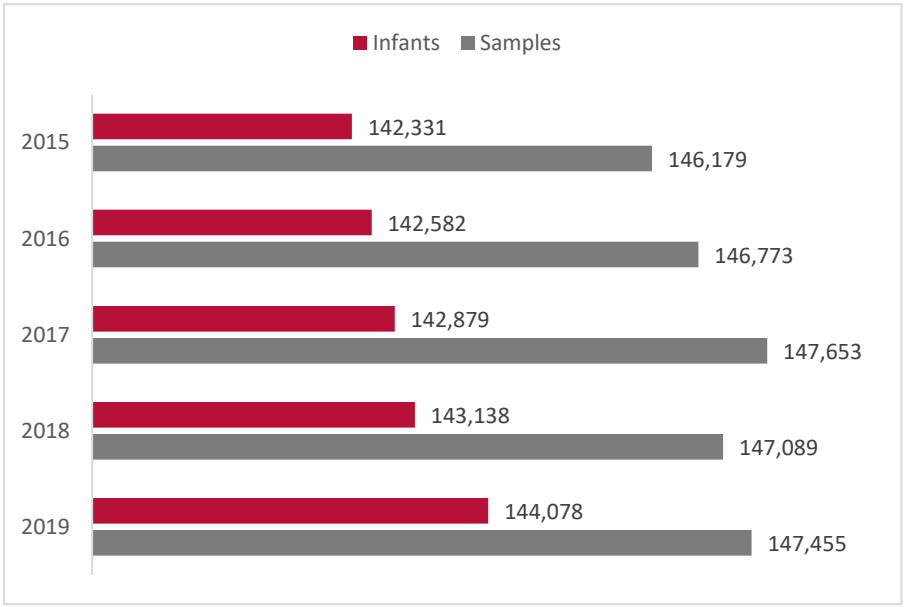
*unsatisfactory in this table is defined as samples unable to be tested fully because of poor sample quality (i.e. laboratory unsats)

1.1 Screening Samples

The overall number of samples received by NSO in 2019 remains relatively consistent with previous years, even though the unsatisfactory rate is slightly lower than last year.

1.1.1 Infants Screened

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



The overall number of infants tested has increased by 940 over last year. Due to a change in NSO information systems mid-year, the number of infants may be an overestimate as infants who may have had multiple samples were counted in both systems.

Based on defers/ declines, missed screen alerts and deceased infants from BORN, and newborn screening sample counts, NSO estimates the total number of infants in Ontario as 144,278 and the rate of screening uptake in 2019 as 99.8% , 0.2% higher than in previous years.

Figure 1: Total number of infants and samples screened from 2015-2019.

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1.1.2 Declined/Deferred Testing

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

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

In 2019, NSO received 607 completed decline/defer forms, a continued increase from previous years. The number of declines documented using this form has increased slightly with 68 declines in 2019 compared with 62 in 2018. The remaining 539 forms received indicated a parent's desire to defer screening, and samples were eventually received for all but one of these deferred cases.

Table 2. Declined, deferred samples indicated on card between 2019.

Case Type	2019	2018	2017	2016	2015
Declined/deferred form received	607	603	499	396	234
Decline	68	62	50	28	29
Deferral	539	541	449	368	205

Table 3. Overall declined screens from 2015-2019.

Infants with declined newborn screening test				
2019	2018	2017	2016	2015
131	120	127	116	104

An additional 63 declined screens were also identified via missed screen alerts. Although the total number of declines has increased, it remains below 0.1% of the population (table 3), the use of the decline form has increased greatly. This is very helpful in reducing the missed screen alert rate and eliminating additional follow up workload.

There were 12 families that declined both the DBS and CCHD screen. There were 75 families that declined the DBS screen but had the CCHD screen. For the remainder of the declined DBS screens no CCHD record was received.

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1.1.3 Missed Screens

Table 4. Potential missed screen alerts requiring follow-up in 2019, by reason and responsible submitter, and samples received post follow-up.

Category		Total (2019)	Samples received	Percent received	Total (2018)
Other	Deceased/ Palliative	26			38
	Declined	63			58
	Incorrect or incomplete BORN information (ex. infant <8days old, stillborn/TA)	<5			<5
	Incorrect or incomplete information (sample already received)	25			5
	NBS done in other jurisdiction	20			36
	Parents deferred NBS	<5			<5
	Sample received, collected prior to missed screen alert	76			117
Total: Non-Missed Screens		**214**			**258**
True Missed Screens	Home birth/birth centre midwife care	6	<5	67%	6
	Hospital birth midwife care	21	19	90%	12
	Interhospital transfer (between hospitals)	7	5	71%	9
	Intrahospital transfer (between units in same hospital)	<5	<5	100%	9
	Intrahospital/interhospital transfer with midwife involvement	<5	<5	100%	<5
	Sample collected, package lost	18	18	100%	64
	Not taken in error	48	37	77%	43
	Unknown reason hospital birth	47	21	44%	25
Total: True Missed Screens		**151**	**108**	**71%**	**169**
Grand Total		**365**			**427**

In 2019, there were 365 potential missed newborn screen alerts that required follow up by NSO. This is down by 62 alerts from 2018, mostly due to a decrease in samples still in transit when the missed screen alert is sent. Hospitals were the responsible facility in 84% of the missed screen alerts and midwives were involved in roughly 16% of the cases. Action on the part of NSO resulted in at least 108 of the 151 (71%) truly missed screens being completed, and this may reflect some cases that were not able to be linked between the two systems.

Missed Screens and Screen Positive Results

There were infants identified in missed screen alerts who ultimately screened positive for a disease in 2019. Subsequently, none of these infants were found to be affected with the disease they screened positive for.

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1.1.4 Hemoglobin Carriers

Table 5. Hemoglobin carrier requests from 2015-2019.

	2019	2018	2017	2016	2015
Requests from high risk population	35	46	61	28	34
Total Requests	**40**	**55**	**69**	**45**	**45**
Number of carriers	16	18	18	11	14

In 2019, approximately 0.5% of carriers requested their results. The number of hemoglobin carrier requests has decreased over the last year.

Table 6. Carriers identified in 2019.

HGB Pattern	Carriers Identified
FAC	355
FAD	216
FAE	430
FAS	1859
FAX	87
Grand Total	**2947**

1.1.5 Age at Collection

Table 7. Age at collection for 2019, initial samples only.

Age at Collection	Number of Initial Samples (2019)	% of Initial Samples (2019)	% of Initial Samples (2018)	% of Initial Samples (2017)
Less than 24 hours	986	0.69%	0.56%	0.60%
24-47 hours (1-2 days)	138654	96.36%	95.20%	90.86%
48-72 hours (2-3 days)	2867	1.99%	2.79%	5.99%
73-168 hours (3-7 days)	720	0.50%	0.81%	2.33%
Greater than 168 hours (7days)	668	0.46%	0.58%	0.18%

The majority of newborn screening samples are collected between 24-48 hours of age. Greater than 97% 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. Unfortunately, the number of samples collected at less than 24 hours has increased, which requires additional follow-up.

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2. Unsatisfactory Samples

Table 8. Unsatisfactory samples by reason from 2015-2019.

			2019	2018	2017	2016	2015
SAMPLES	Satisfactory Samples		146,099	145,045	144,717	144,359	144,074
	Unsatisfactory Samples		2044	2,044	2,936	2,414	2,105
	Unsatisfactory Rate		**1.40%**	**1.41%**	**1.99%**	**1.64%**	**1.44%**
	Samples Collected at <24hrs		697	575	577	518	603
	Unsatisfactory Samples excluding <24hr samples		1347	1,469	2,359	1,896	1,502
	Unsatisfactory Rate excluding <24hr samples		**0.90%**	**1.01%**	**1.60%**	**1.30%**	**1.03%**
REASONS	**Lab Unsat Reasons**	Quantity of blood insufficient	919	710	1471	1094	888
		Blood spots appear scratched or abraded	118	292	531	421	228
		Blood spots are supersaturated	97	176	185	193	222
		Blood spots appear clotted or layered	202	403	639	491	299
		Blood spots appear diluted	<5	<5	5	17	42
		Blood spots exhibits serum rings	82	168	200	95	32
		Blood spots are wet and/or discolored	10	38	<5	5	<5
		Other	50	88	62	35	16
	Data Unsat Reasons	Blood dot collection paper is expired	14	12	77	95	104
		Insufficient data provided	9	11	29	14	22
		Damaged or delayed in transit	5	45	8	<5	-
		Delivered to lab > 14 days after collection	19	8	23	<5	20
		Sample collected at <24hrs	697	575	577	518	603
		Other/Mislabel	6	90	47	46	21

There were 134 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). After July 29, 2019, unsatisfactory samples will only have one lab unsatisfactory reason.

2.1 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.

2.2 Repeat Rates for Unsatisfactory Specimens

The majority (80.9%) of repeat samples are received within 3 weeks of the initial sample. By 6 weeks, 87.9% of unsatisfactory samples have had screening completed via a repeat sample. As NSO switched to a new

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information system on July 29th 2019, repeats for unsatisfactory samples logged in one system may not be recognized as received if in the other system.

Table 9. Repeats received on unsatisfactory samples, 2019 data only.

Time to receipt of repeat sample	Samples (%)
Total Unsats 2019	**2,044**
Up to 3 weeks	80.9%
Greater than 3 weeks up to 6 weeks	5.3%
Greater than or equal to 6 weeks	1.7%
Not received	12%

2.3 Priority Panels

Priority Panels are a testing panel that became available with the launch of the new laboratory information system (OMNI) in July 2019. Samples that are deemed unsatisfactory for the entire panel of testing are evaluated regarding whether there is sufficient blood for testing a smaller, priority panel of diseases. The priority panel is intended to expedite testing for the most aggressive, early onset diseases and includes Metabolic diseases (AAAC platform), GALT deficiency, CH (TSH) and CAH (17OHP).

Since July 29th, 2019, NSO performed 489 priority panels. These samples are still counted as unsatisfactory (in Table 8), and a repeat is requested. The results of the priority diseases are also reported.

Table 10. Repeat samples for priority panel unsats post OMNI.

Time to receipt of priority panel repeat sample	Samples (%)
Total priority panels 2019	**489**
Up to 3 weeks	82%
Greater than 3 weeks up to 6 weeks	8%
Greater than or equal to 6 weeks	1%
Not received	7%
Repeat not required	2%

There were 11 cases where a 3rd repeat sample was not required as the first sample was an unsat priority panel and the second sample was an unsat priority panel where there was sufficient quantity of blood in the second sample to be able to complete the untested assays.

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2.4 Test Level Unsats

Test Level Unsats (TLU) are samples that are initially satisfactory, but are deemed unsatisfactory for reporting post testing due to poor quality results or insufficient sample to repeat or confirm 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. In 2019 there were 185 TLU, only 85 of which required a repeat.

Table 11. Repeat samples for TLU pre and post OMNI.

Time to receipt of TLU repeat sample	Pre-OMNI	Post-OMNI
Total Test Level Unsats – Routine	**31**	**21**
< 3 weeks	87.1%	66.7%
≥3 weeks < 6 weeks	3.2%	9.5%
≥ 6 weeks	-	4.7%
Not received	6.4%	19.0%
Total Test Level Unsats - Urgent	**11**	**22**
< 3 weeks	81.8%	90.9%
≥3 weeks < 6 weeks	-	4.5%
Not received	18.2%	4.5%

2.5 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.

Expired cards can fluctuate year to year, depending on when the lots of cards expire. There were three lots of cards that expired in 2019, in March, August and November, due to the recall of cards due to Biotinidase issues and redesign to include CCHD in 2016/17. NSO sends out bulletin reminders to submitters when an expiry date is approaching, asking them to check and circulate their stock. In addition, NSO has rolled out the shipment tracking system, Track-Kit, which alerts submitters to expired cards in their inventory. These strategies are having a good impact on reducing the number of expired cards received.

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

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3. Screen Positives

In 2019, there were 1503 screen positive referrals. This represents ~1% of the total number of infants screened by NSO. The number of screen positive infants referred in 2019 increased from 2018 (1453 vs. 1503). This is discussed further in Section 3.2.

3.1 Referrals by Treatment Centre

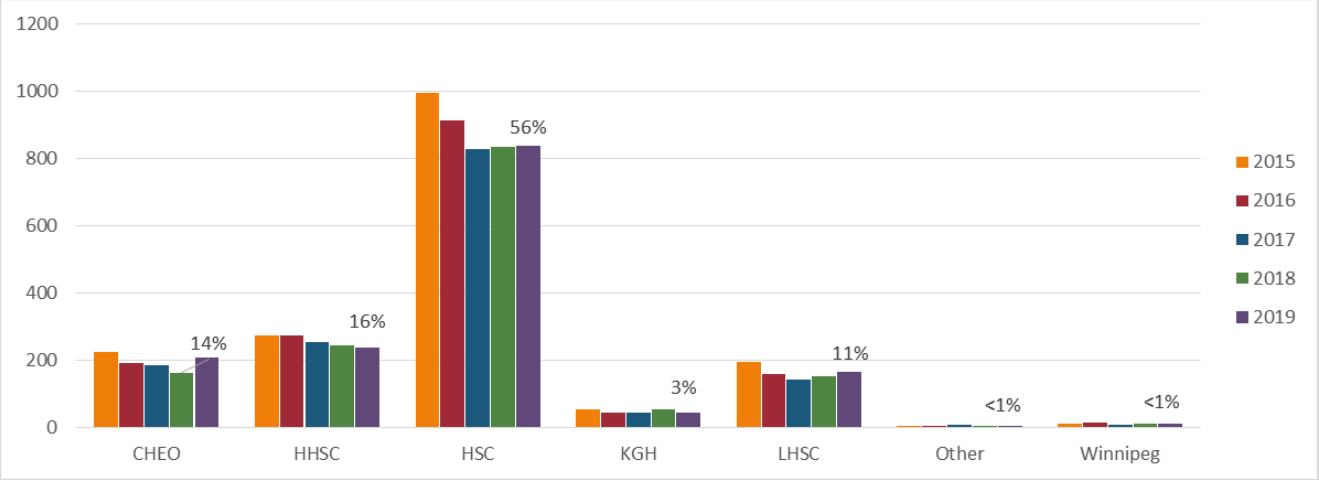

Figure 2. The total number of referrals by treatment centre from 2015-2019.

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 was similar between 2018 and 2019.

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3.2 Screen Positive Referrals by Disorder Group

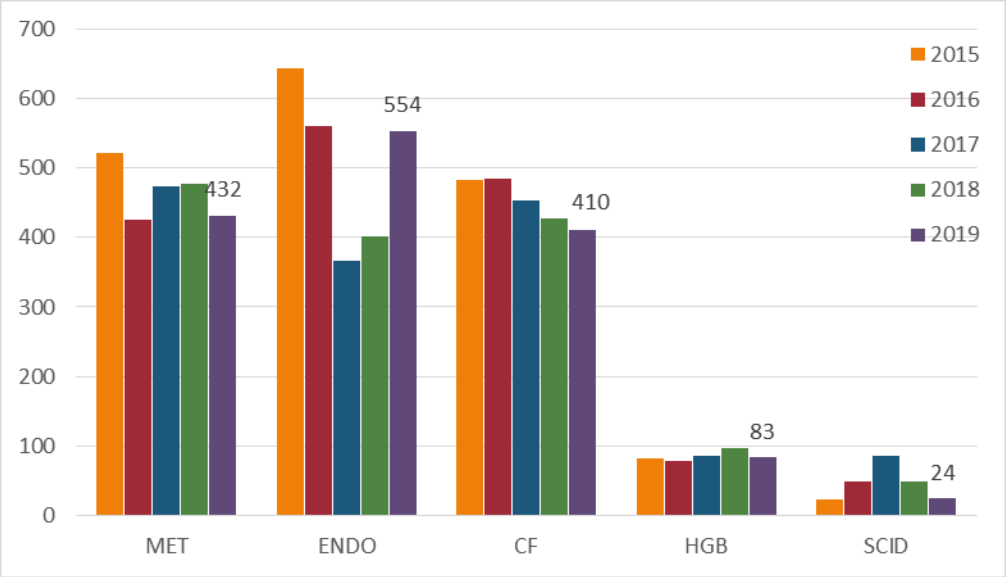

Figure 3. The total number of screen positives by disease grouping from 2015-2019

The number of screen positive referrals per disease grouping increased for endocrine disorders. Numbers remained relatively constant for Hemoglobinopathies, whereas they decreased for Cystic Fibrosis, Metabolic disorders and SCID. These details are discussed further in sections 3.2.2, 3.2.3, 3.2.5 and 3.2.6.

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3.2.1 Percentage of Screen Positive Referrals by Disorder in 2019

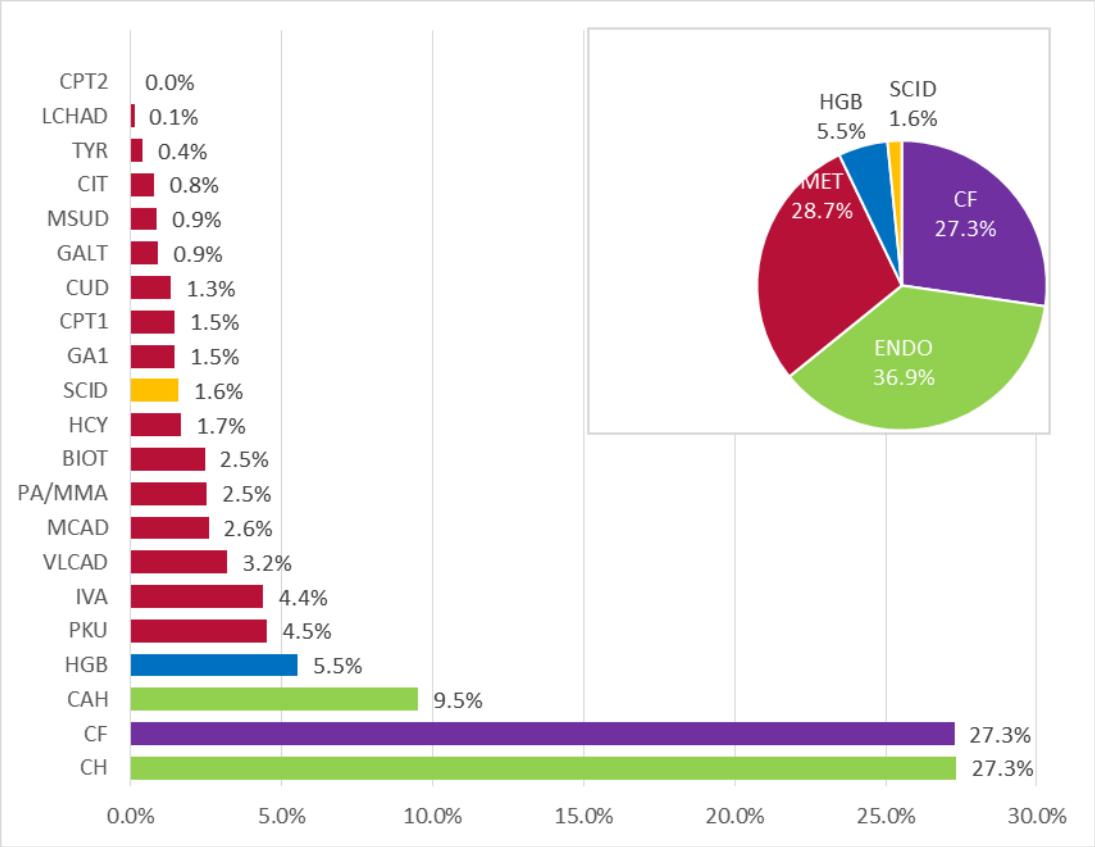

Figure 4. The percentage of screen positive referrals by disorder in 2019.

Endocrinopathies, Metabolics, and Cystic Fibrosis represent 36.9%, 28.7%, and 27.3% of screen positives respectively. SCID screen positive referrals decreased in 2019 and now represent only 1.6% of total screen positive referrals. Hemoglobinopathies represent approximately 5.5% of screen positive referrals.

3.2.2 Hemoglobinopathies

The number of screen positives in 2019 remained about the same as in previous years, with a decrease of 15 referrals from 2018.

3.2.3 Cystic Fibrosis

The number of screen positives in 2019 decreased slightly as compared to 2018, with a difference of 18 referrals noted. Five additional CFTR mutations were added to the existing CFTR panel on July 29, 2019.

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3.2.4 Endocrinopathies

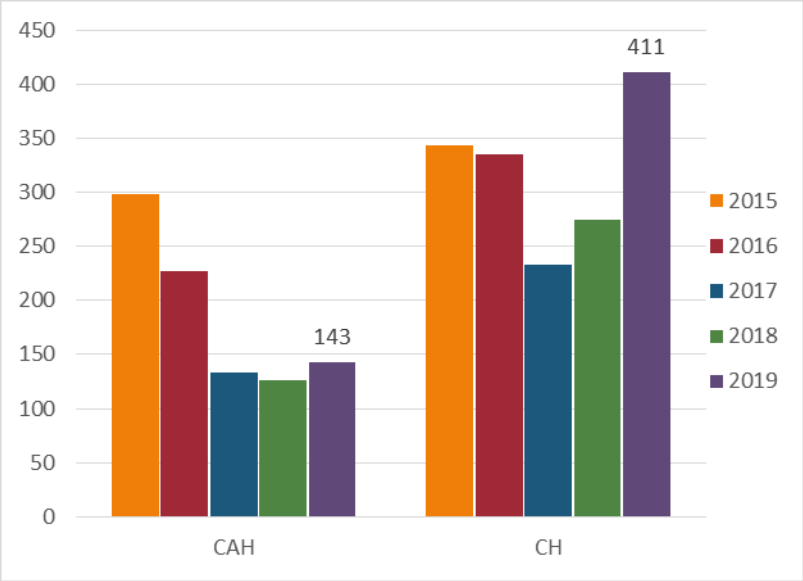

Figure 5. The total number of congenital adrenal hyperplasia and congenital hypothyroidism screen positives from 2015-2019.

The number of screen positives for CAH remained consistent between 2017, 2018 and 2019. NSO has maintained the disorder logic that includes both birth weight and gestational age and does not refer extremely premature infants on their repeat sample if their initial sample was screen negative.

The number of screen positives for CH increased in 2019 for the initial part of the year. In June 2018, NSO began reporting TSH results from Perkin Elmer GSP analyzers. Since the implementation of the GSP screening platform, an increase in the number of CH screen positive cases was observed with a decrease in the positive predictive value. After reviewing the data and following discussion with the Endocrine Disease Specific Working Group, the decision was made to increase the screening threshold from 15 mIU/L to 17 mIU/L. This took effect on July 4, 2019. During the 13 months that the TSH cutoff was 15 mlU/L there were 453 screen positive CH referrals (PPV = 14.3% with 7.5% of DERFs pending). In the last 6 months of 2019 (when the cutoff was 17 mlU/L), there were 123 referrals (PPV = 20.8% with 13% of DERFs pending).

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3.2.5 Metabolic Disorders

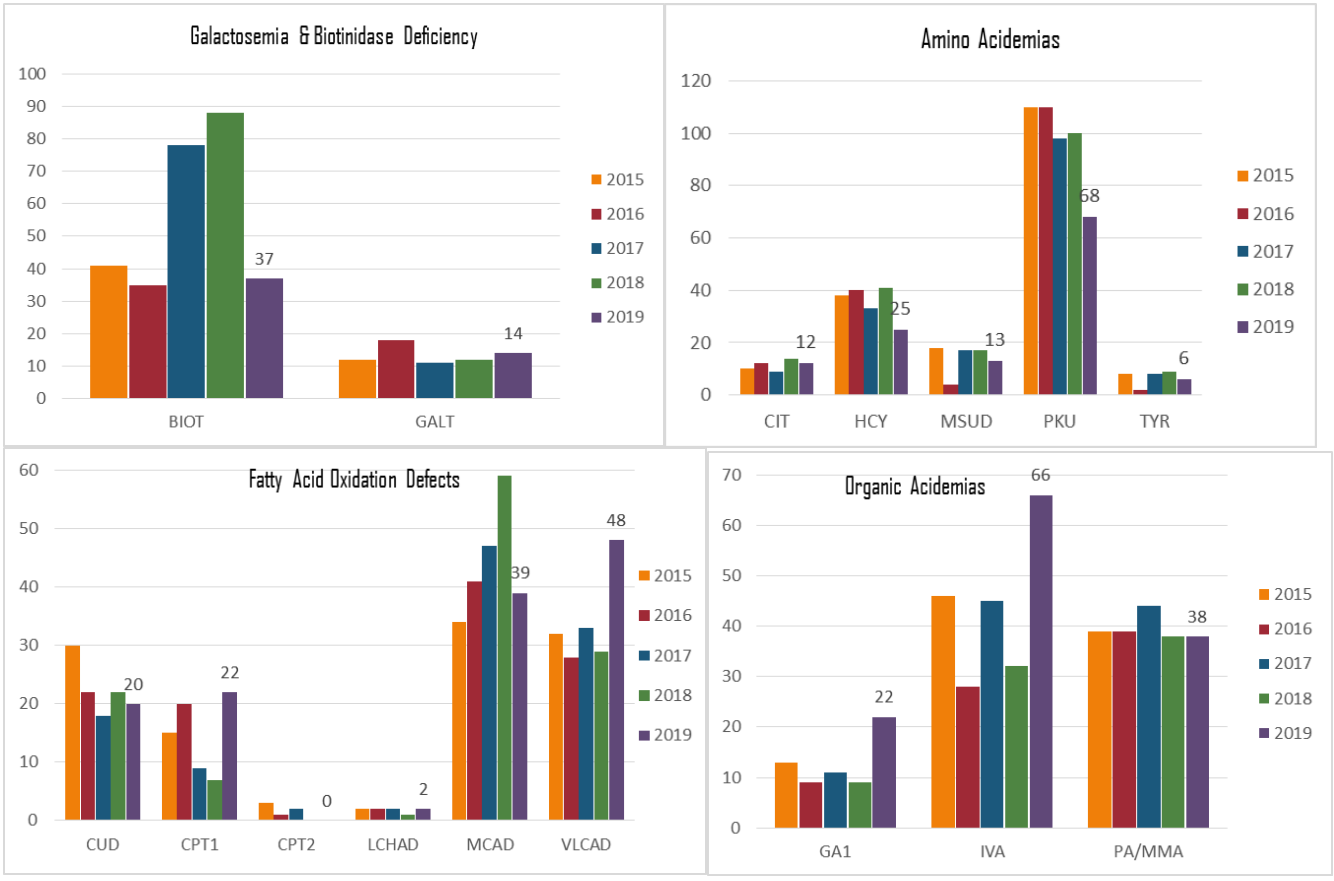

Figure 6. The number of metabolic screen positives from 2015-2019, by disease

Biotinidase deficiency referrals decreased in 2019 due to NSO sequestering cards for acclimatization prior to entering circulation to reduce the interference with newly produced cards with the biotinidase activity.

Disorder logic changes were made for PKU, MCADD and Homocystinuria on July 29, 2019, the date that the new OMNI screening information system went live. In all cases, a decrease in referrals were seen as a result of these mid-year changes.

The number of organic acidemia referrals increased in 2019 for GA1 and IVA. There were 3 NICU submitters in the province that accounted for 64% of the IVA referrals in 2019.

For GA1 there were 15 screen positive referrals made in the first 7 months of 2019 and 7 in the last 5 months. Of the 15 referrals made in the first 7 months, 8 were infants who screened positive for multiple conditions.

The C8 cutoff for MCADD was increased on July 29, 2019 resulting in fewer referrals for the latter half of 2019. Acylglycines began to be reported as a second tier test for all MCADD screen positive infants on a trial basis on November 21, 2018. The data from this pilot was reviewed and it was determined that

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the acylglycines did not provide any additional benefit to differentiate true positives. Acylglycines stopped being reported July 29, 2019.

For VLCAD deficiency, the first C14:1 cutoff was lowered on July 29, 2019. However, the final C14:1 cutoff remained the same. The number of infants referred in the first 7 months of 2019 was 22. The number of infants referred in the last 5 months of 2019 was 26. The mean of initials was reviewed for VCLADD and has not changed. Most of the VLCADD screen positive samples were obtained from term, breast fed infants between 24-48 hours of age.

3.2.6 Severe Combined Immune Deficiency

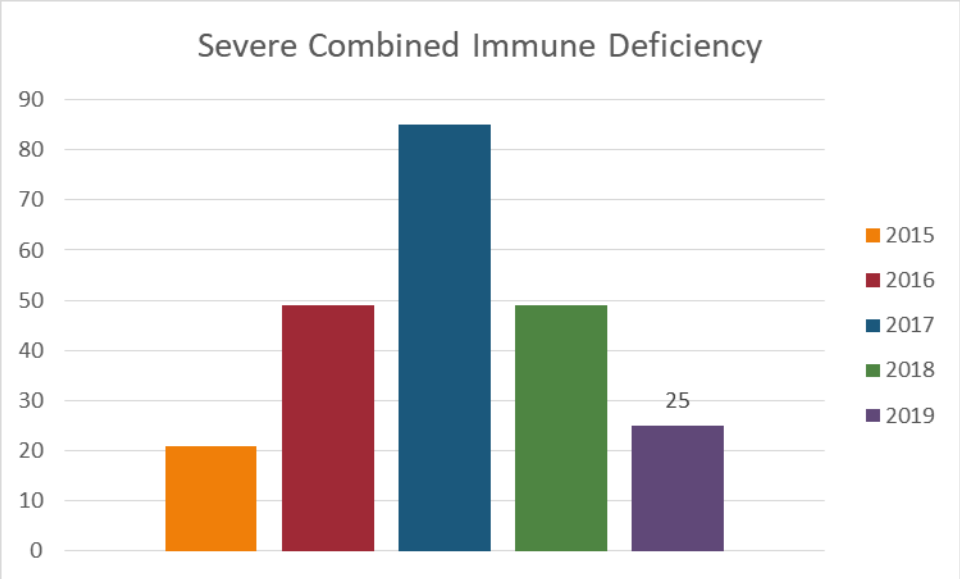

Figure 7. The number of SCID screen positives from 2015-2019.

The overall number of screen positive results for SCID decreased significantly in 2019. TBX1 was no longer tested and reported in 2019 and infants who were screened negative on a previous sample were not referred. At the SCID Disease Specific Working Group meeting held in 2019, it was described how variation in the placement of the standard curve impacts TREC quantification. This variability had been observed and was resulting in a higher number of referrals. NSO proposed "pinning" the calibration curve so this variability was removed. The decision was made to pin the curve with an intercept of 41.5 as an intermediate point to buffer for any imprecision. This was implemented June 1, 2019 by manual adjustment of the calibration curve, and then on September 1, 2019 this was programmed into our new LIS. Targeted mutation screening of the IKBKB and ZAP70 genes was added to the SCID screening algorithm on July 29, 2019.

3.3 Diagnostic Feedback

As of April 1, 2020, approximately 13.5% (203 cases) of diagnostic evaluation report forms (DERFs) remain pending for referrals made in 2019. This is an improvement from 2018 when the percentage of DERFs outstanding was 18%.

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3.4 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 12. 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 13. 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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3.5 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 in the following Table includes all follow up information received prior to April 1, 2020.

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Table 14. The PPV calculations and disease prevalence for diseases screened by NSO.

Disease		Additional information	PPV (Yes)	PPV (Yes + Variant)	PPV (Yes + Variant + Secondary)	% of DERFs Pending	DERFs Pending	Total No. Screen Positive	Disease Prevalence or Primary Targets
Endocrin-opathies	Congenital Hypothyroidism	Past (Jun 12, 2018 - Jul 3, 2019)	14.3%	19.4%	19.4%	7.5%	34	453	1 in 2,062
		Current (Jul 4, 2019 - Dec 31, 2019)	20.8%	29.2%	29.2%	13.0%	16	123	
	Congenital Adrenal Hyperplasia	Past (Sept 2, 2016 - Jun 22, 2018)	5.9%	5.9%	5.9%	5.5%	13	235	1 in 22,612
		Current (Jun 12, 2018 - Dec 31, 2019)	**4.3%**	**4.3%**	**4.9%**	**7.4%**	**15**	**204**	
Hemoglobinopathies		Past (Nov 1, 2010 - July 31, 2015)	64.8%	65.7%	83.7%	1.6%	6	373	1 in 2,952
		Current (Aug 1, 2015 - Dec 31, 2019)	**60.9%**	**61.9%**	**87.8%**	**14.9%**	**57**	**383**	
Cystic Fibrosis		Past (until July 28, 2019) Category A	98.9%	100.0%	100.0%	5.2%	15	289	1 in 4,849
		Past (until July 28, 2019) Category B	2.0%	5.7%	5.7%	1.8%	65	3527	
		Past (until July 28, 2019) Category C	0.4%	0.8%	0.8%	2.8%	31	1124	
		Past (until July 28, 2019) ALL	7.1%	10.0%	10.0%	2.2%	111	5094	
		Current (Jul 29 - Dec 31, 2019) Category A	75.0%	100.0%	100.0%	69.2%	9	13	
		Current (Jul 29 - Dec 31, 2019) Category B	1.1%	2.2%	2.2%	14.5%	16	110	
		Current (Jul 29 - Dec 31, 2019) Category C	0.0%	0.0%	0.0%	9.6%	5	52	
		Current (Jul 29 - Dec 31, 2019) ALL	**2.9%**	**4.3%**	**4.3%**	**17.1%**	**30**	**175**	
Severe Combined Immune Deficiency		Past (Sep 20, 2018 - Jul 28, 2019)	7.1%	7.1%	21.4%	40.7%	11	27	9 in 71,350
		Current (Jul 29, 2019 - Dec 31, 2019)	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0**	**3**	
Organic Acidemia	Glutaric Aciduria type 1		**8.0%**	**8.0%**	**24.1%**	**5.5%**	**10**	**182**	1 in 149,157
	Isovaleric Acidemia		**2.3%**	**3.6%**	**3.6%**	**1.7%**	**7**	**415**	1 in 215,449
	PA/MMA	Past (Feb 16, 2010 - Apr 21, 2013)	3.7%	3.7%	8.3%	0.9%	2	219	1 in 77,562
		Current (Apr 22, 2013 - Dec 31, 2019)	**5.0%**	**5.0%**	**9.5%**	**10.9%**	**28**	**256**	
Fatty Acid Oxidation Defects	CPTI		**4.5%**	**59.1%**	**59.1%**	**3.6%**	**5**	**139**	1 in 323,173
	CPTII		**12.1%**	**12.1%**	**12.1%**	**0.0%**	**0**	**33**	1 in 387,808
	LCHAD		**80.0%**	**80.0%**	**93.3%**	**6.3%**	**1**	**16**	1 in 161,587
	VLCAD		**8.7%**	**13.5%**	**14.8%**	**6.2%**	**21**	**340**	1 in 71,816
	CUD	Past (until Mar 4, 2014)	5.5%	5.5%	5.5%	0.0%	1	300	1 in 96,952
		Current (Mar 5, 2014 - Dec 31, 2019)	**3.6%**	**3.6%**	**3.6%**	**11.5%**	**15**	**130**	
	MCAD	Past (Sep 1, 2016 - Jul 28, 2019))	16.3%	17.1%	17.1%	14.8%	23	155	1 in 16,992
		Current (Jul 29, 2019 - Dec 31, 2019)	**75.0%**	**75.0%**	**75.0%**	**42.9%**	**3**	**7**	
Amino Acidopathies	Citrullinemia		**18.3%**	**20.9%**	**20.9%**	**3.0%**	**5**	**165**	1 in 69,251
	Homocystinuria	Past (until Jul 28, 2019)	**0.5%**	**0.5%**	**3.6%**	**4.2%**	**12**	**287**	1 in 1,939,039
		Current (Jul 29, 2019 - Dec 31, 2019)	**0.0%**	**0.0%**	**0.0%**	**33.3%**	**1**	**3**	
	Phenylketonuria	Past (until Jul 28, 2019)	**14.0%**	**26.6%**	**26.6%**	**3.1%**	**29**	**936**	1 in 16,295
		Current (Jul 29, 2019 - Dec 31, 2019)	**30.8%**	**46.2%**	**46.2%**	**35.0%**	**7**	**20**	
	MSUD	Past (until Nov 14, 2011)	3.8%	3.8%	3.8%	0.0%	0	90	1 in 176,276
		Current (Nov 15, 2011 - Dec 31, 2019)	**9.0%**	**10.1%**	**10.1%**	**7.1%**	**7**	**99**	
	Tyrosinemia	Past (Sep 14, 2009 - Sep 19, 2011)	1.4%	1.4%	1.4%	0.0%	0	70	1 in 215,449
		Current (Sep 20, 2011 - Dec 31, 2019)	**12.5%**	**12.5%**	**16.1%**	**4.8%**	**3**	**62**	
Other Metabolic Diseases	Galactosemia	Past (until Jan 12, 2014)	35.7%	41.4%	41.4%	1.4%	1	72	1 in 50,378
		Current (Jan 13, 2014 - Dec 31, 2019)	**14.5%**	**27.7%**	**27.7%**	**3.4%**	**3**	**89**	
	Biotinidase Deficiency	Past (Jan 13, 2014 - Jul 2, 2014)	2.1%	37.5%	37.5%	0.0%	0	49	1 in 69,036
		Current (Jul 3, 2014 - Dec 31, 2019)	**5.1%**	**35.0%**	**35.0%**	**9.3%**	**29**	**311**	

*Cells in red indicate pending DERF rates >10%

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4. Screening Timeliness

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

4.1 Initial Samples

Table 15: The benchmarks and percentages of initial samples at age of receipt by NSO, and availability of initial and final results, 2018 and 2019

	1. Screening (Initial Samples) 2018 Only			2. Screening (Initial Samples) 2019 ONLY		
Category	Age at Receipt	Age at Initial Results	Age at Final Results	Age at Receipt	Age at Initial Results	Age at Final Results
Benchmark (days)	4	5	7	4	5	7
CIT/ASA, CUD, FAOD, GA1, HCY, IVA, LCHAD/TFP, MCAD, MSUD, PA/MMA, PKU, TYR1, VLCAD	79%	75%	98%	83%	81%	98%
Biotinidase Deficiency	79%	75%	98%	83%	80%	98%
Galactosemia	79%	77%	97%	83%	81%	98%
Congential Adrenal Hyperplasia	79%	77%	98%	83%	81%	98%
Congenital Hypothyroidism	79%	77%	98%	83%	80%	98%
Cystic Fibrosis	78%	75%	93%	83%	78%	93%
Hemoglobinopathies	79%	54%	91%	83%	65%	96%
Severe Combined Immune Deficiency	79%	32%	84%	83%	11%	48%

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 2018 and 2019, the general trend is an overall improvement in age at receipt of samples at NSO, and in turn, improvements regarding age at availability of both initial and final results can be appreciated as well. The majority of newborn screening samples are collected between 24-48 hours of age.

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Table 16: Median and 90th centile values for age of receipt of initial samples, and availability of initial and final results, 2018 and 2019

	2. Screening (Initial Samples) 2018 ONLY								2. Screening (Initial Samples) 2019 ONLY						
Category	Age at Receipt		Age at Initial Results		Age at Final Results			Category	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
CIT/ASA, CUD, FAOD, GA1, HCY, IVA, LCHAD/TFP, MCAD, MSUD, PA/MMA, PKU, TYR1, VLCAD	3	5	4	6	1,086	6	8	CIT/ASA	3	5	4	6	571	6	8
								CUD					664	6	8
								FAOD					568	6	8
								GA1					583	6	8
								HCY					586	6	8
								IVA					680	6	8
								LCHAD/TFP					572	6	8
								MCAD					568	6	8
								MSUD					577	6	8
								PA/MMA					595	6	8
								PKU					624	6	7
								TYR1					581	6	8
								VLCAD					707	6	8
Biotinidase Deficiency					722	6	8	Biotinidase Deficiency					193	6	8
Galactosemia					340	6	9	Galactosemia					221	6	13
Congenital Adrenal Hyperplasia					580	6	8	Congenital Adrenal Hyperplasia					650	6	7
Congenital Hypothyroidism					1,739	6	7	Congenital Hypothyroidism					2,391	5	7
Cystic Fibrosis					6,325	9	12	Cystic Fibrosis					6,199	9	14
Hemoglobinopathies			5	7	102	7	8	Hemoglobinopathies			5	7	180	7	9
Severe Combined Immune Deficiency			6	8	796	9	12	Severe Combined Immune Deficiency			8	12	724	12	19

The median age at receipt did not change between 2018 and 2019. Age at final result refers to any screening sample that requires confirmatory testing prior to being reported as a screen positive or screen negative result. Most times have remained consistent between 2018. The 90th centile for age at final results increased in 2019 for Galactosemia but this is not a result of any reporting change but more to do with the characteristics of a sample that screens positive for the disorder (ie delayed in transit). There has been a decrease in the age at final report for SCID due to a few changes in the laboratory. The part of the NSO laboratory that performs SCID screening moved locations within CHEO. This has resulted in a change in practice where the SCID assay is punched on day 2 and the other NBS targets are punched on day 1. The second change was the addition of the SCID molecular testing. This has added an additional day to all samples that go on to SCID confirmation testing.

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4.2 Screen Positive Infants

Table 17. The benchmarks and percentage of infants achieving benchmarks for all screen positive infants for the 5 year period of 2015-2019.

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	68% 603 / 888	57% 36 / 63	83% 681 / 825	50% 31 / 62	87% 712 / 816	98% 61 / 62	95% 775 / 815
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, CIT, MSUD, TYR1	67% 352 / 523	59% 24 / 41	73% 350 / 482	59% 24 / 41	80% 378 / 474	98% 40 / 41	90% 416 / 462
Galactosemia	GALT	32% 20 / 63	34% 13 / 38	24% 6 / 25	32% 12 / 38	44% 11 / 25	83% 30 / 36	88% 21 / 24
	Benchmark (days)	4	5	7	5	8	90	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	58% 215 / 368	55% 24 / 44	70% 227 / 324	49% 21 / 43	75% 237 / 315	98% 43 / 44	92% 291 / 318
	Benchmark (days)	4	N/A	7	N/A	8	90	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	59% 99 / 168	-	67% 112 / 168	-	71% 116 / 163	-	88% 141 / 161
	Benchmark (days)	4	N/A	10	N/A	12	90	
Organic and Amino Acidemias	GA1, HCY, PKU	72% 489 / 678	-	94% 636 / 678	-	93% 585 / 626	-	96% 593 / 620
Biotinidase Deficiency	BIOT	71% 187 / 265	-	96% 254 / 265	-	95% 249 / 263	-	90% 234 / 259
Congenital Hypothyroidism	CH	80% 1,227 / 1,530	-	98% 1,499 / 1,530	-	98% 1,486 / 1,523	-	97% 1,476 / 1,517
	Benchmark (days)	4	N/A	14	N/A	21	90	
Cystic Fibrosis	CF	74% 1,614 / 2,169	-	93% 2,020 / 2,169	-	65% 1,386 / 2,122	-	92% 1,927 / 2,092
Severe Combined Immune Deficiencies	SCID	69% 116 / 167	-	87% 145 / 167	-	94% 149 / 158	-	74% 108 / 145
	Benchmark (days)	25	N/A	35	N/A	42	111	
	SCID (Prem referrals)	78% 31 / 40	-	93% 37 / 40	-	87% 26 / 30	-	77% 20 / 26
	Benchmark (days)	4	N/A	14	N/A	30	90	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	76% 267 / 353	-	92% 325 / 353	-	56% 193 / 345	-	70% 237 / 338

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 2014-2018, there continue to be improvements in the percentages of infants achieving benchmarks for all screen positive infants throughout the screening experience. Improvements related to Age at Receipt and Age at Screening Results are likely attributed to a combination of factors including earlier age at collection, improved shipping times, and NSO expanding operations to include weekend reporting. However, despite these enhancements, challenges persist regarding the timely receipt of samples at NSO and this in turn ultimately influences the remainder of the screening process and ability to meet downstream benchmarks related to result availability. The percentage of infants meeting the benchmark regarding Age at Retrieval has remained relatively stable with small improvements noted year over year. Regional variation in triage practices and certain clinical criteria/eligibility to pursue diagnostic investigations (e.g. GA and weight requirements for sweat chloride testing) may be influencing the disease categories where a lower % of infants are meeting this benchmark.

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Table 18. The benchmarks and percentage of infants achieving benchmarks for all screen positive infants, 2019 data only (cells with only percentages had numbers <5)

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	76% 102 / 134	86% 6 / 7	87% 110 / 127	86% 6 / 7	94% 118 / 126	100% 7 / 7	98% 120 / 122
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, CIT, MSUD, TYR1	73% 109 / 150	71% 5 / 7	75% 82 / 110	71%	82% 90 / 110	100% 7 / 7	94% 97 / 103
Galactosemia	GALT	31%	57%	0%	43%	17%	80%	83% 5 / 6
	Benchmark (days)	4	5	7	5	8	90	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	75% 51 / 68	45% 5 / 11	91% 52 / 57	55% 6 / 11	95% 54 / 57	100% 11 / 11	98% 55 / 56
	Benchmark (days)	4	N/A	7	N/A	8	90	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	58% 18 / 31	-	71% 22 / 31	-	77% 24 / 31	-	90% 26 / 29
	Benchmark (days)	4	N/A	10	N/A	12	90	
Organic and Amino Acidemias	GA1, HCY, PKU	75% 65 / 87	-	97% 84 / 87	-	98% 85 / 87	-	100% 78 / 78
Biotinidase Deficiency	BIOT	75% 21 / 28	-	89% 25 / 28	-	96% 26 / 27	-	96% 23 / 24
Congenital Hypothyroidism	CH	82% 306 / 375	-	98% 367 / 375	-	98% 367 / 375	-	99% 367 / 372
	Benchmark (days)	4	N/A	14	N/A	21	90	
Cystic Fibrosis	CF	75% 267 / 357	-	94% 336 / 357	-	65% 232 / 357	-	95% 327 / 343
Severe Combined Immune Deficiencies	SCID	82% 9 / 11	-	64% 7 / 11	-	82% 9 / 11	-	78% 7 / 9
	Benchmark (days)	25	N/A	35	N/A	42	111	
	SCID (Prem referrals)	100%	-	100%	-	100%	-	50%
	Benchmark (days)	4	N/A	14	N/A	30	90	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	82% 46 / 56	-	96% 54 / 56	-	69% 37 / 54	-	85% 45 / 53

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4.3 True Positive Infants

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 (Table 19).

4.4 Treatment Centre Deltas

To review the days from referral to different time points (which eliminates the downstream effects of age at collection, receipt and referral) screening timeliness data was reviewed looking at Treatment Centre metrics (Table 20). As in other analyses, DERFs that were pending and infants diagnosed prior to retrieval were excluded from the analysis. This Table also includes columns for primary and variant targets to have initial diagnoses. In these columns places were N/A is included means that the variant targets included diseases that were not typically treated (ie. CPT1 Inuit Variant, CF indeterminate, etc). The time from referral to retrieval was green or yellow in the majority of disease groups indicating quick action on the part of the treatment centres. The majority of disease groups were meeting benchmarks for age at definitive diagnosis. However, time to initial diagnosis did not improve with this analysis with only alert Galactosemia infants being diagnosed by 1 day after referral.

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Table 19. The benchmarks and percentage of infants achieving benchmarks for all true positive infants with classic disease for 2015 – 2019 (cells with only percentages had numbers <5).

Category	ACMG Code	Age at receipt	Age at Sreening Results		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)	4	5	7	5	8	6	10	90	
Congenital Adrenal Hyperplasia	CAH	75% 15 / 20	89% 8 / 9	100% 11 / 11	89% 8 / 9	100% 11 / 11	78% 7 / 9	73% 8 / 11	100% 9 / 9	91% 10 / 11
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, CIT, MSUD, TYR1	65% 13 / 20	69% 11 / 16	75%	75% 12 / 16	100%	69% 11 / 16	25%	94% 15 / 16	100%
Galactosemia	GALT	89% 8 / 9	75% 6 / 8	100%	75% 6 / 8	100%	88% 7 / 8	100%	88% 7 / 8	100%
	Benchmark (days)	4	5	7	5	8	8	10	90	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	73% 46 / 63	59% 23 / 39	83% 20 / 24	53% 20 / 38	91% 21 / 23	54% 21 / 39	58% 14 / 24	97% 38 / 39	96% 23 / 24
	Benchmark (days)	4	N/A	7	N/A	8	N/A	14	90	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	67%	-	100% 6 / 6	-	100% 6 / 6	-	67%	-	83% 5 / 6
	Benchmark (days)	4	N/A	10	N/A	12	N/A	14	90	
Organic and Amino Acidemias	GA1, HCY, PKU	79% 38 / 48	-	96% 46 / 48	-	100% 48 / 48	-	79% 38 / 48	-	92% 44 / 48
Biotinidase Deficiency	BIOT	85% 11 / 13	-	92% 12 / 13	-	100% 13 / 13	-	62% 8 / 13	-	100% 13 / 13
Congenital Hypothyroidism	CH	70% 215 / 305	-	95% 289 / 305	-	95% 289 / 303	-	82% 248 / 304	-	97% 295 / 304
	Benchmark (days)	4	N/A	14	N/A	21	N/A	30	90	
Cystic Fibrosis	CF	69% 95 / 137	-	96% 131 / 137	-	94% 129 / 137	-	81% 111 / 137	-	87% 119 / 137
Severe Combined Immune Deficiencies	SCID	63% 5 / 8	-	88% 7 / 8	-	100% 8 / 8	-	88% 7 / 8	-	100% 8 / 8
	Benchmark (days)	4	N/A	14	N/A	30	N/A	60	90	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	74% 147 / 198	-	96% 190 / 198	-	63% 125 / 197	-	44% 88 / 198	-	80% 159 / 198

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Table 20. Screening timeliness data for all treatment centres from time of referral to various endpoints for 2015-2019 (cells with only percentages had numbers <5).

Category	ACMG Code	Time from referral to retrieval (% meeting benchmark)		Time from referral to Diagnostic Investigations (% meeting benchmark)		Time from referral to Initial Diagnosis Classical Disease [1] (% meeting benchmark)		Time from referral to Initial Diagnosis Primary, Variant & Secondary Targets (% meeting benchmark)		Time from referral to Definitive Diagnosis and Disposition [2] (% meeting benchmark)		Time from Definitive Diagnosis and DERF submission (% meeting benchmark)	
		ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert	ALERT	Non-Alert
	Benchmark (days)	1	3	1	3	1	4	1	4	85		30	
Congenital Adrenal Hyperplasia	CAH	95% 59 / 62	99% 806 / 816	47% 29 / 62	71% 578 / 815	78% 7 / 9	64% 7 / 11	78% 7 / 9	64% 9 / 14	98% 61 / 62	97% 792 / 815	34% 21 / 62	52% 422 / 814
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, CIT, MSUD, TYR1	100% 41 / 41	97% 463 / 475	90% 37 / 41	85% 391 / 460	75% 12 / 16	50%	79% 15 / 19	50% 7 / 14	98% 40 / 41	92% 424 / 463	27% 11 / 41	54% 248 / 463
Galactosemia	GALT	97% 37 / 38	96% 24 / 25	89% 33 / 37	67% 16 / 24	100% 7 / 7	0%	N/A	N/A	83% 30 / 36	96% 23 / 24	28% 10 / 36	58% 14 / 24
	Benchmark (days)	1	3	1	3	1	4	1	4	85		30	
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	95% 41 / 43	99% 313 / 315	81% 35 / 43	86% 267 / 312	47% 18 / 38	57% 13 / 23	49% 19 / 39	50% 14 / 28	95% 42 / 44	93% 295 / 318	18% 8 / 44	48% 153 / 318
	Benchmark (days)	N/A	3	N/A	3	N/A	4	N/A	4	85		30	
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	-	97% 158 / 163	-	82% 115 / 140	-	50%	-	N/A	-	93% 150 / 161	-	83% 73 / 88
	Benchmark (days)	N/A	3	N/A	3	N/A	4	N/A	4	85		30	
Organic and Amino Acidemias	GA1, HCY, PKU	-	97% 609 / 628	-	86% 506 / 591	-	77% 36 / 47	-	56% 54 / 96	-	96% 594 / 621	-	42% 263 / 621
Biotinidase Deficiency	BIOT	-	90% 238 / 263	-	68% 178 / 260	-	58% 7 / 12	-	N/A	-	91% 236 / 259	-	53% 137 / 259
Congenital Hypothyroidism	CH	-	93% 1,411 / 1,524	-	81% 1,241 / 1,524	-	80% 243 / 304	-	66% 279 / 422	-	97% 1,477 / 1,518	-	51% 776 / 1,518
	Benchmark (days)	N/A	7	N/A	14	N/A	16	N/A	16	85		30	
Cystic Fibrosis	CF	-	54% 1,150 / 2,122	-	54% 1,132 / 2,091	-	77% 106 / 137	-	N/A	-	93% 1,944 / 2,092	-	51% 1,073 / 2,091
Severe Combined Immune Deficiencies	SCID	-	90% 172 / 191	-	85% 161 / 190	-	88% 7 / 8	-	78% 14 / 18	-	78% 136 / 174	-	37% 64 / 174
	Benchmark (days)	N/A	16	N/A	35	N/A	55	N/A	55	85		30	
Sickle Cell Disease	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	-	46% 159 / 345	-	66% 224 / 341	-	44% 81 / 184	-	40% 108 / 271	-	74% 249 / 338	-	14% 46 / 338

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5. CCHD Screening

5.1 CCHD cards received

Submitters submit their Critical Congenital Heart Disease (CCHD) screen results to NSO via a tear off sheet on the standard NSO dried blood spot card. These may come with the dried blood spot, or separately, depending on hospital process. The total number of CCHD cards registered at NSO in 2019 is 145,255 representing 142,460 infants. This is lower than the estimated number of infants in Ontario that was derived from the blood spot samples, of 144,078 (Figure 1). However, CCHD data was not affected by the launch of the new NSO information system, and therefore does not have the same uncertainty in matching of multiple requisitions to the same patient.

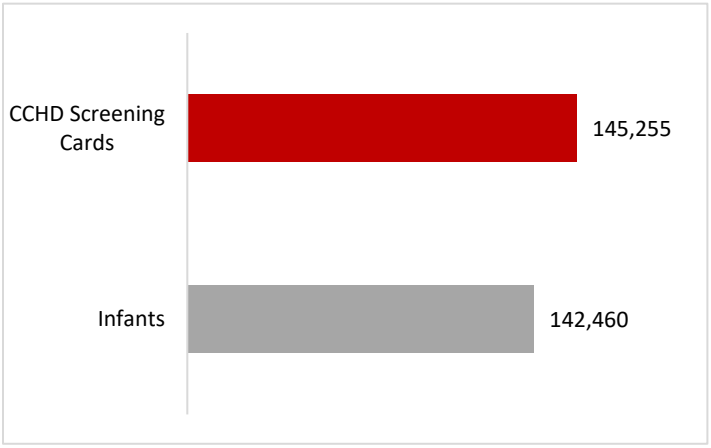

Figure 8. CCHD Cards and Infants, 2019

There are also expected reasons why the CCHD screen would not be done, such as a long NICU stay or a prenatal diagnosis. These would also contribute to the lower estimate of infants screened, but efforts have been made to encourage submission of the form in these circumstances to document that the screen was not done. In 2019, 6480 of the requisitions submitted were for screens not done.

Table 21. CCHD cards received.

CCHD Cards received	2019	2018
Screen Completed	138,775	132,134
Screen Not Done	6,480	4,462
	145,255	136,596

5.2 Screens Completed

The NSO CCHD algorithm allows for up to 3 repeat tests done one hour apart prior to making a referral. In the cards where screening was done, 98.7% 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 1.2% required a second test and 0.1% required three tests to complete the screen. The need for 2nd or 3rd tests has decreased over time, which may indicate increased skill in performing the test and applying the probes.

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Table 22. Tests required to complete screen

Tests Done	2019	2018
1 Test	98.7%	98.3%
2 Tests	1.2%	1.5%
3 Tests	0.1%	0.2%
	138,775	132,134

5.3 Screens Not Done

In 2019, CCHD screens were not done on 4.5% of the cards received. The most common reason for CCHD screen not done is because the infant is expected to be in the NICU for > 7 days. In 2019, NSO also began tracking blank cards submitted in preparation for launching missed screen reporting in 2020. This was accompanied by education of submitters on the completion of the card even when the screen was not being completed.

Table 23. Reasons for CCHD Screen not done, 2018 and 2019.

	2019	2018
'Screen Not Done' cards submitted	6480	4,462
Decline/deferred (back page of form not completed)	1.4%	1.7%
Declined	0.4%	0.6%
Deferred	8.4%	10.4%
Infant diagnosed prenatally with heart defect	1.2%	1.3%
Infant diagnosed with heart defect by physical exam	0.7%	1.3%
Infant is not appropriate for screening (e.g. NICU > 7 days, on oxygen, IV in right hand, limb anomaly, etc.)	73.0%	83.7%
Already done	0.2%	0.2%
Insufficient information provided/blank card	10.7%	0.4%
Other	3.8%	0.4%

Of the 26 declines, 46% of these families also declined dried blood spot screening, 50% had the DBS screen performed, and 4% had no DBS record in the system.

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5.4 Age at time of CCHD Screen

The recommended age for CCHD screening is 24-48 hours of age, with an optimal window between 24 and 36 hours. The majority (87.9%) of screening has been done in the recommended range.

Table 24. Age at time of CCHD Screen, 2017 to 2019

Age at time of CCHD screen	2019	2018	2017
	%	%	%
Less than 24 hours	4.5	4.5	1.7
24-48 hours (1-2 days)	87.9	87.8	76.8
>48-72 hours (2-3 days)	1.9	2.4	14.2
>72-168 hours (3-7 days)	0.8	0.9	1.8
Greater than 168 hours (> 7 days)	0.3	0.2	0.4
Not specified	4.6	4.2	5.2

The percentage of screens done at less than 24 hours is 4.5% overall and 4.6% for midwives. However, midwives are testing later than hospitals, with 4.9% of their testing being done after 48 hours, compared to 3.0% overall.

5.5 Unsatisfactory CCHD Screens

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

The number of unsatisfactory screens done in 2019 was 1,855, which is 1.28% of the total screens done. The most frequent error is incomplete documentation – either of a repeat test done after 1 hour or missing screening values (Table 28). The number of unsatisfactory screens has increased as NSO started to contact submitters where cards were received with demographic information but no CCHD screening values recorded. Many of these infants (30.5%) were NICU infants who were not suitable for screening (566 compared to 33 in 2018).

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Table 25. Outcomes from unsatisfactory CCHD screen notifications.

	2019	2018
Satisfactory Screens	**143,400**	**135,980**
Unsatisfactory Screens	**1,855**	**615**
Baby >7days, no rescreen recommended	2.6%	5.0%
Baby in hospital, no screen recommended	30.5%	5.4%
Documentation inaccurate or incomplete	46.6%	48.3%
Family Declined	0.16%	-
Missed - baby >7 days, no screening recommended	0.27%	(included under rescreen recommended)
Missed - screening recommended	6.4%	
No action needed	2.7%	-
Physical exam recommended (screen positive)	0.11%	0.49%
Rescreen recommended	10.5%	40.8%
Total Screening Forms Submitted	**145,255**	**136,596**
Unsatisfactory Rate	**1.28%**	**0.45%**

Note: No action needed includes infants that were later identified as a premature with no response from the submitter (information obtained by the dried blood spot card) or a satisfactory CCHD screen located that was previously unlinked to infant.

NSO performed follow up on the 1,855 unsatisfactory screens, and in 46.6% of follow up cases the result was amended by the submitter due to incorrect completion of the form. In 10.5% of cases a rescreen was recommended. Through the follow up of unsatisfactory screens NSO was able to over 300 infants that had not received a proper CCHD screen and needed to be rescreened. An instance of incomplete documentation in an infant with a refer result who was identified to have a congenital cardiac defect was also noted in follow-up.

Missed screens specifically were not captured prior to 2019 but if an infant was identified as missed at <8 days of age the recommendation was to screen the infant and if identified >7 days the recommendation was made to contact the infant's primary care provider. Potential missed CCHD screen notifications to submitters started in January 2020 and will be reported in next year's annual report.

5.6 CCHD Screen Positives – 2019 data

There were 167 CCHD screen positives in 2019, most of which were screened within 24-48 hours. A screen positive identified after an early screen at less than 24 hours, which was determined to be a false positive after follow up. 83% of infants referred in 2018 had diagnosis within 24 hours of the screen, and a further 4% before 72 hours.

Table 26. Age at time of screen positive

Age at Screen Positive	Total No.
< 24 hours	<5
24-48 hours	151
> 48 hours	7
N/A	7
Grand Total	**167**

Of the 167 screen positives received in 2019, 11 were diagnosed with a critical congenital heart defect, 79 had a secondary CHD target or were diagnosed with an incidental finding such as pulmonary disease or infection, and 72 were found to be not affected.

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Of note, 38 screen positives (23%) were from a single institution, which continues to use the Eve software for the full screening algorithm. Of these screen positives, 5 were diagnosed with secondary targets of pulmonary disease or infection, and all others were false positive.

5.7 CCHD Definitive Diagnosis Data and Positive Predictive Values

In 2019, the Positive Predictive Value (PPV) for CCHD screening is 9% for primary targets only, and 30.5% for primary and classical secondary target diseases (Table 30). Cumulatively since the beginning of the program, the PPV is 6.1% for primary targets, and 28.6% for primary and classical secondary target diseases. Of the 440 screen positives since the initiation of CCHD screening, 214 (48.6%) have been determined to be not affected after diagnostic follow up.

Table 27. PPV calculations for CCHD Screen Positives (2019 and cumulative)

Data set	PPV		Total No. Screen Positive	Outcome Classification			
				Yes	Incidental		No
	PPV (Yes)	PPV (Yes + Classic Secondary)			Classic Secondary Targets	All Other Incidentals	
2019 only	9.0%	30.5%	167	15	36	44	72
Cumulative	6.1%	28.6%	440	27	99	99	214

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Table 28. Definitive diagnosis for CCHD Screen Positives (cumulative)

Definitive Diagnosis Categorization	Cumulative
Primary target	**27**
Tetralogy of Fallot	6
Total anomalous pulmonary venous return	5
Transposition of the great arteries	8
Tricuspid atresia	<5
Truncus arteriosus	<5
Hypoplastic left heart syndrome	<5
Pulmonary atresia w/ intact septum	<5
Secondary target- Classic	**99**
Coarctation of the aorta	<5
Ebstein anomaly	<5
Infection	19
Persistent fetal circulation *(including pulmonary hypertension an delayed transition)*	24
Pulmonary disease *(non-infectious)*	50
Double outlet right ventricle	<5
Secondary target- Untargeted disease	**99**
CHD *arrhythmia*	5
CHD *structural*	24
CHD *Other*	7
Other	33
No disease, no definitive diagnosis	40
Not affected	**214**
Grand Total	**440**

5.8 CCHD detection rates

Prior to implementation of the screening program, expected rates of CCHD in Ontario were identified. Based on rates of CCHD found in current literature, there is expected to be 1 - 2 infants born with CCHD per 1000 births. Considering that there are approximately 145,000 infants born in Ontario per year, the expected rates of CCHD are approximately 145 - 290 annually. Of these, CCHD screening is expected to identify 10 - 30% of these cases, assuming the majority will be identified prenatally or by physical examination at birth.

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Table 29. Expected and observed rates of CCHD in 2019 and cumulative

	Expected			Observed	
	CCHD cases	**Percentage identified by PO screening**	**True positive cases**	**Primary targets**	**Primary and secondary targets**
2019	**145 - 290**	10-30%	15-87	15	51
Total (2.5 years)	**362-725**	10-30%	36-217	27	126

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6. Appendix A: Detailed Screening Timeliness Data

Table 1A: Median, 70th and 90th Centile for All Screen Positive Samples by Disease Category, 2015-2019

					Alert Confirmation				Routine Confirmation				ALERT				Non-Alert				ALERT				Non-Alert			
Category	ACMG Code	Age at Receipt			Age at Referral				Age At Referral				Age at retrieval (contact with family)								Age at Definitive Diagnosis and Disposition [2]							
		Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile
Benchmark (days of age)		4			5				7				5				8				90							
Congenital Adrenal Hyperplasia	CAH	4	5	7	63	5	6	10	825	6	7	9	62	5	6	11	816	6	7	10	62	16	28	55	815	17	27	65
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, CIT, MSUD, TYR1	4	5	9	41	5	7	9	482	6	7	11	41	5	7	8	474	7	8	12	41	10	19	44	462	27	35	89
Galactosemia	GALT	6	13	26	38	7	9	24	25	15	27	32	38	7	10	24	25	15	28	34	36	40	54	100	24	50	61	91
Benchmark (days of age)		4			5				7				5				8				90							
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	4	5	21	44	5	6	7	324	7	7	24	43	6	7	7	315	7	8	24	44	21	35	78	318	34	49	86
Benchmark (days of age)		4							7								8				90							
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	4	5	25	No Type 1				168	7	8	28	No Type 1				163	7	8	28	No Type 1				161	23	31	108
Benchmark (days of age)		4							10								12				90							
Organic and Amino Acidemias	GA1, HCY, PKU	4	4	6	No Type 1				678	6	7	9	No Type 1				626	6	7	9	No Type 1				620	26	30	60
Biotinidase Deficiency	BIOT	4	4	6	No Type 1				265	6	7	8	No Type 1				263	7	8	11	No Type 1				259	27	42	86
Congenital Hypothyroidism	CH	3	4	5	No Type 1				1530	6	7	8	No Type 1				1523	7	7	9	No Type 1				1517	12	19	47
Benchmark (days of age)		4							14								21				90							
Cystic Fibrosis	CF	3	4	6	No Type 1				2169	10	11	14	No Type 1				2122	18	23	32	No Type 1				2092	31	41	77
Severe Combined Immune Deficiencies	SCID	4	5	7	No Type 1				167	10	11	15	No Type 1				158	11	14	19	No Type 1				145	40	79	161
	Benchmark (days of age)	25							35								42				111							
	SCID (prem referrals)	24	25	30	No Type 1				40	29	30	33	No Type 1				30	31	35	52	No Type 1				26	86	103	152
Benchmark (days of age)		4							14								30				90							
Hemoglobinopathies	Hb SS, Hb S/ßTh, Hb SC, Hb S/HPFH	3	4	6	No Type 1				353	9	10	14	No Type 1				345	27	38	51	No Type 1				338	68	90	149

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Table 2A: Median, 70th, 90th Centile for All screen Positive samples by Disease Category, 2019 only

Category	ACMG Code	Age at Receipt			Alert Confirmation				Routine Confirmation				ALERT				Non-Alert				ALERT				Non-Alert			
		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	5	7	4	N/A	N/A	127	6	7	8	7	5	N/A	N/A	126	6	7	8	7	10	N/A	N/A	122	13	17	37
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, CIT, MSUD, TYR1	3	4	7	7	4	N/A	N/A	110	6	7	9	7	4	N/A	N/A	110	6	7	9	7	6	N/A	N/A	103	25	31	55
Galactosemia	GALT	7	23	26	7	5	N/A	N/A	6	27	N/A	N/A	7	6	N/A	N/A	6	28	N/A	N/A	5	15	N/A	N/A	6	48	N/A	N/A
Benchmark (days of age)		4			5				7				5				8				90							
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	3	4	5	11	6	6	6	57	6	7	7	11	5	6	7	57	6	7	8	11	13	15	46	56	23	42	64
Benchmark (days of age)		4							7								8				90							
Fatty Acid Oxidation Diseases	CUD, CPT1, CPT2	4	5	23	No Type 1				31	6	7	26	No Type 1				31	7	8	29	No Type 1				29	15	26	87
Benchmark (days of age)		4							10								12				90							
Organic and Amino Acidemias	GA1, HCY, PKU	4	4	6	No Type 1				87	6	7	8	No Type 1				87	6	7	8	No Type 1				78	17	26	45
Biotinidase Deficiency	BIOT	3	4	7	No Type 1				28	6	7	10	No Type 1				27	6	7	10	No Type 1				24	18	21	41
Congenital Hypothyroidism	CH	3	4	5	No Type 1				375	6	7	8	No Type 1				375	6	7	9	No Type 1				372	11	15	29
Benchmark (days of age)		4							14								21				90							
Cystic Fibrosis	CF	3	4	8	No Type 1				357	10	11	13	No Type 1				357	18	24	33	No Type 1				343	30	39	65
Severe Combined Immune Deficiencies	SCID	4	4	5					11	11	15	26					11	12	15	26					9	40	N/A	N/A
	Benchmark (days of age)	25							35								42				111							
	SCID (prem referrals)	25	N/A	N/A	No Type 1				2	32	N/A	N/A	No Type 1				2	33	N/A	N/A	No Type 1				2	125	N/A	N/A
Benchmark (days of age)		4							14								30				90							
Hemoglobinopathies	Hb SS, Hb S/β Th, Hb SC, Hb S/HPFH	3	4	5	No Type 1				56	8	9	11	No Type 1				54	22	32	46	No Type 1				53	60	71	98

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Table 3A: Median, 70th and 90th Centile for all True Positive Samples by Disease Category, 2015-2019

Category	ACMG Code	Age at Receipt			Alert Confirmation	Age at Alert Screening Result			Routine Confirmation	Age At Screening Result			ALERT	Age at retrieval (contact with family)			Non-Alert				ALERT	Age at Initial Diagnosis Classical Disease [1]			Non-Alert				ALERT				Non-Alert	Age at Definitive Diagnosis and Disposition [2]			
		Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile	# of Samples Prioritized	Median	70th Centile	90th Centile	# of Samples Confirmed	Median	70th Centile	90th Centile
Benchmark (days of age)		4			5				7				5				8				6				10				90							
Congenital Adrenal Hyperplasia	CAH	3	4	5	9	4	N/A	N/A	11	6	6	7	9	4	N/A	N/A	11	6	6	7	9	5	N/A	N/A	11	9	10	14	9	5	N/A	N/A	11	10	13	38
Aggressive Organic and Amino Acidemias	PROP, MUT, Cbl A,B, IVA, ASA, CIT, MSUD, TYR1	4	5	6	16	4	5	7	4	7	N/A	N/A	16	4	5	7	4	6	N/A	N/A	16	5	7	36	4	15	N/A	N/A	16	6	9	36	4	36	N/A	N/A
Galactosemia	GALT	4	N/A	N/A	8	5	N/A	N/A	1	4	N/A	N/A	8	5	N/A	N/A	1	4	N/A	N/A	8	5	N/A	N/A	1	9	N/A	N/A	8	19	N/A	N/A	1	22	N/A	N/A
Benchmark (days of age)		4			5				7				5				8				8				10				90							
Aggressive Fatty Acidopathies	MCAD, VLCAD, LCHAD, TFP	4	4	6	39	5	6	7	24	6	6	9	38	5	7	8	23	6	6	8	39	8	12	22	24	9	15	52	39	20	33	81	24	28	41	84
Benchmark (days of age)		4							7								8								14				90							
Fatty Acid Oxidation Diseases	CUD, CPT1,CPT2	4	N/A	N/A	No Type 1				6	6	N/A	N/A	No Type 1				6	6	N/A	N/A	No Type 1				6	11	N/A	N/A	No Type 1				6	49	N/A	N/A
Benchmark (days of age)		4							10								12								14				90							
Organic and Amino Acidemias	GAL HCY, PKU	3	4	5	No Type 1				48	6	6	8	No Type 1				48	6	6	8	No Type 1				48	8	9	26	No Type 1				48	9	14	60
Biotinidase Deficiency	BIOT	3	3	5	No Type 1				13	6	8	9	No Type 1				13	6	8	9	No Type 1				13	13	19	30	No Type 1				13	18	33	56
Congenital Hypothyroidism	CH	4	4	6	No Type 1				305	6	7	8	No Type 1				303	6	7	9	No Type 1				304	8	9	28	No Type 1				304	8	11	35
Benchmark (days of age)		4							14								21								30				90							
Cystic Fibrosis	CF	3	5	6	No Type 1				137	9	11	13	No Type 1				137	11	13	18	No Type 1				137	15	22	47	No Type 1				137	31	44	128
Severe Combined Immune Deficiencies	SCID	4	N/A	N/A	No Type 1				8	10	N/A	N/A	No Type 1				8	10	N/A	N/A	No Type 1				8	16	N/A	N/A	No Type 1				8	28	N/A	N/A
Benchmark (days of age)		4							14								30								60				90							
Hemoglobinopathies	Hb SS, Hb S&Th, Hb SC, Hb S/HPFH	4	4	6	No Type 1				198	8	9	13	No Type 1				197	23	35	43	No Type 1				198	71	91	128	No Type 1				198	60	79	105

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