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

Newborn Screening Ontario
Annual Report
Calendar Year 2023

415 Smyth Road, Ottawa Ontario K1H 8M8 Phone: 613-738-3222 · 1-877-NBS-8330 · Fax: 613-738-0853
www.newbornscreening.on.ca · newbornscreening@cheo.on.ca

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415 Smyth Road, Ottawa Ontario K1H 8M8 Phone: 613-738-3222 · 1-877-NBS-8330 · Fax: 613-738-0853
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Executive Summary

In 2023 Newborn Screening Ontario "went social" with a new emphasis on parent engagement and awareness via social media and influencer campaigns. With the launch of Biliary Atresia (BA) screening and the Infant Stool Colour Card (ISCC), parents are now directly involved in the performance of the screen. As such, NSO needed a way to engage with expectant and new parents more directly in the venues that are most effective. The initial advertising and influencer campaigns were very successful, with positive engagement and higher than average performance for the target audiences. The impact on the effectiveness of the campaign on BA screening outcomes will be evaluated in the coming year, but the data from the first year shows promising trends in uptake, identification of screen positives, and decreased time to treatment. During implementation the focus has been on dissemination of information about BA and the ISCC to parents and health care providers, as well as establishing standard workflows for referrals to treatment centres. Regular tracking of metrics such as volumes of calls or distribution of cards at submitter sites has allowed for agile quality improvements in the ISCC and educational materials to address confusion. In 2023, NSO referred 41 BA screen positives for further investigation. True positive cases, as well as some secondary targets of idiopathic cholestasis or infection, were detected.

Continuing the social media success, NSO followed the BA focussed campaign with general newborn screening awareness advertising to build brand awareness and trust. In future campaigns we will build on this trusted brand to communicate about other topics such as carrier reporting, secondary use and storage of samples, or research participation. An important metric to watch when communicating NSO messaging more broadly, particularly in the post-pandemic era where there is a higher mistrust of the healthcare system in some demographics, was the impact on decline rates. While decline rates have increased in previous years, there has not been a significant increase in declined screening in 2023, or any notable impact on requests for returned samples.

The rate of unsatisfactory samples has increased slightly this year, due primarily to blood sample collection issues such as quantity of blood or layered samples. This may be a result of turnover in front line staffing which is prevalent across the hospital system, resulting in staff being less educated on the proper techniques. To support our submitters, NSO has released a new e-learning module for blood spot collection, in addition to many other electronic resources on the new Submitter Hub website.

Last year a significant cause of unsatisfactory samples, missed screens, and longer turn around times were linked to issues with transportation of samples, such as delayed or lost packages. NSO has engaged Purolator leadership to identify problem areas, educate courier staff, and implement new strategies to increase on time (overnight) delivery of packages from 79% to over 90%. Work continues to ensure all shipments are received as soon as possible.

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1. SCREENING CHARACTERISTICS

In 2023, NSO estimated the birth rate to be 140,370, based on NBS data and data from BORN. NSO estimates the rate of screening uptake in 2023 as 99.7% (similar to previous years of 99.7% uptake).

Table 1. The coverage of screening in Ontario for 2023.

Infants Screened	DBS Panel	CCHD	Hearing Panel
Fully	139,731	134,514	139,788
Partially	173	-	<5
No screening	466	5,856	581
Total	**140,370**		

Fully screened infants had all aspects of the screen completed. In the case of the DBS and hearing panel this may have been through testing more than one sample or with the CCHD screen, having additional screens completed. Infants who were considered partially screened for a panel did not have all aspects of the screen completed including only partial panels completed in the case of laboratory unsatisfactory samples or test level unsats and transfused infants where a post transfusion sample was never received. Infants who had no screening included infants where an initial sample was received but was unsatisfactory for any testing and a subsequent sample was not received and infants where no sample was received.

For CCHD screening, there are circumstances where infants are not eligible for screening. While they are included in the count of no screening, they are appropriately not screened. There are no partial screens for CCHD as the screen was either completed to satisfaction or it was not.

1.1 DRIED BLOOD SPOT

The overall number of samples received by NSO in 2023 is higher than last year.

Table 2. Screening sample volumes between 2019-2023.

Sample Type	2023	2022	2021	2020	2019
Satisfactory	141,186	139,779	145,785	141,548	146,099
Unsatisfactory*	1,909	1,639	1,560	1,785	1,356
Routine Screening – Total	**143,095**	**141,418**	**147,345**	**143,333**	**147,455**

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

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1.1.1 INFANTS SCREENED

The total number of newborns screened and newborn screening samples received is shown in Figure 1.

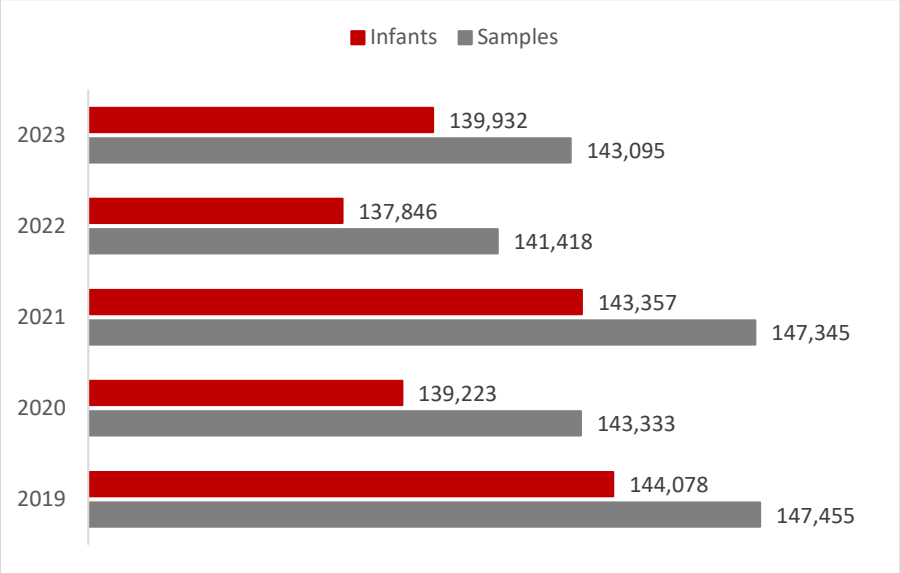

Figure 1: Total number of infants and samples screened between 2019-2023.
The number of newborns is estimated by subtracting the number of samples determined to be from the same infant as another sample from the total number of received samples. This estimate be impacted by the efficiency of the linking 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.

1.1.2 DECLINED/DEFERRED SCREENING

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 2023, NSO received 861 completed decline/defer forms. The number of declines documented using this form has increased slightly with 168 declines in 2023 compared with 151 in 2022. The remaining 693 forms received indicated a parent's desire to defer screening, and samples were eventually received for all but 11 of these deferred cases.

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Table 3. Declined, deferred samples indicated on card between 2019-2023.

Case Type	2023	2022	2021	2020	2019
Declined/deferred form received	861	758	819	713	607
Decline	168	151	96	76	68
Deferral	693	607	723	637	539

An additional 112 declined screens were also identified via missed screen alerts. There were 8 infants for which a decline form and a DBS missed screen decline case were received/created and 8 infants for whom a decline form was completed where a sample was received. In total there were 264 infants where newborn dried blood spot screening was declined, which is a similar total to last year. There were 137 families that declined the DBS screen but had the CCHD screen. NSO reviewed the number of declines received by site and have identified a few sites with a higher than average number of declines. NSO will be following up with those sites to offer education and resources regarding the importance of NBS. In 2023, there were five deferred cases that screened positive once samples were received.

1.1.3 MISSED SCREENS

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Table 4. Potential missed screen alerts requiring follow-up in 2023, by reason and responsible submitter, and samples received post follow-up.

Category		Total (2023)	Samples received	Percent received	Total (2022)	Total (2021)
Other	Deceased/ Palliative	99			101 (15%)	73 (13%)
	Declined	112			116 (17%)	80 (14%)
	Sample received same day as missed screen alert	<5			30 (4%)	44 (8%)
	Incorrect or incomplete information (sample already received)	41			53 (8%)	28 (5%)
	NBS done in other jurisdiction/ family moved out of province	29			24 (4%)	27 (5%)
	Parents deferred NBS	0			<5 (<1%)	<5 (<1%)
	Sample collected prior to missed screen alert and received after alert	227			178 (26%)	162 (29%)
Total: Non-Missed Screens		**512 (78%)**			**506 (74%)**	**415 (74%)**
True Missed Screens	Hospital birth midwife care	5	0	0	9 (1%)	10 (2%)
	Interhospital transfer (between hospitals)	11	8	73%	<5 (<1%)	13 (2%)
	Intrahospital transfer (between units in same hospital)	0			<5 (<1%)	0
	Intrahospital/interhospital transfer with midwife involvement	0			<5 (<1%)	<5 (<1%)
	Sample collected, package lost	69	69	100%	101 (15%)	17 (3%)
	Not taken in error	47	42	89%	54 (8%)	87 (15%)
	Unknown reason hospital birth	12	0	0	10 (1%)	17 (3%)
Total: True Missed Screens		**144 (22%)**	**119**	**83%**	**179 (26%)**	**148 (26%)**
Grand Total		**656**			**685**	**563**

There were 656 potential missed screen alerts that required follow up in 2023. There were 512 potential missed cases logged that were not truly missed (top section of table above). There were 99 deceased/palliative cases logged and 112 declines (very similar to last year). There were many cases where the sample was collected and received either the same day as the missed screen alert or after. Of these cases (227), 95 of the samples were batched by the submitter, 6 were delayed collections, 103 experienced shipping delays by Purolator, and 19 were both batched and had Purolator shipping delays.

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In 2023, there were 144 true missed newborn screen alerts that required follow up by NSO (bottom section of table above). Of the 144 cases counted as true misses, 69 were cases where a package was lost. Action on the part of NSO resulted in 119 of the 144 (83%) truly missed screens being completed.

Missed Screens and Screen Positive Results

There were 11 infants identified in missed screen alerts who ultimately screened positive for a disease in 2023. The majority of infants were found to be not affected but the outcomes are not yet known in all the cases.

1.1.4 AGE AT COLLECTION

Table 5. Age at collection for 2021-2023, initial samples only.

Age at Collection	Number of Initial Samples (2023)	% of Initial Samples (2023)	% of Initial Samples (2022)	% of Initial Samples (2021)
Less than 24 hours	776	0.56%	0.61%	0.59%
24-47 hours (1-2 days)	137,065	98.45%	98.27%	98.09%
48-71 hours (2-3 days)	864	0.62%	0.72%	0.89%
72-168 hours (3-7 days)	330	0.24%	0.29%	0.32%
Greater than 168 hours (7 days)	191	0.14%	0.11%	0.11%

The majority of newborn screening samples are collected between 24-48 hours of age. Greater than 99% 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.

1.1.5 UNSATISFACTORY SAMPLES

The unsatisfactory rate increased in 2023, up to 1.33% compared to 1.16% in 2022. 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.

There were 66 samples that were deemed unsatisfactory for both a lab and a data unsat reason. There were 195 unsatisfactory samples that did not require follow up as a repeat sample had already been received or testing of all analytes was able to be completed through two partially saturated samples. There were 1,714 unsatisfactory samples that required follow up.

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Table 6. Unsatisfactory samples by reason between 2019-2023.

			2023	2022	2021	2020	2019
SAMPLES	Satisfactory Samples		141,186	139,779	145,220	143,333	146,099
	Unsatisfactory Samples		1,909	1,639	2,125	2,332	2,044
	Unsatisfactory Rate		**1.33%**	**1.16%**	**1.44%**	**1.63%**	**1.40%**
	Samples Collected at <24hrs		457*	514	565	547	697
	Unsatisfactory Samples excluding <24hr samples		1,452	1,125	1,560	1,785	1,347
	Unsatisfactory Rate excluding <24hr samples		**1.01%**	**0.80%**	**1.06%**	**1.25%**	**0.90%**
REASONS	Lab Unsat Reasons	Quantity of blood insufficient	775	639	927	1,297	919
		Blood spots appear scratched or abraded	125	68	142	94	118
		Blood spots are supersaturated	17	21	35	42	97
		Blood spots appear clotted or layered	291	178	217	155	202
		Blood spots appear diluted	<5	6	0	<5	<5
		Blood spots exhibits serum rings	69	44	96	70	82
		Blood spots are wet and/or discolored	8	9	9	14	10
		Other	80	25	24	25	50
	Data Unsat Reasons	Blood dot collection paper is expired	36	49	54	38	14
		Insufficient data provided	<5	<5	<5	11	9
		Damaged or delayed in transit	<5	0	6	5	5
		Delivered to lab > 14 days after collection	77	81	38	33	19
		Sample collected at <24hrs	468	514	565	547	697
		Other/Mislabel	23	22	22	27	6

*Of the 468 samples collected at <24 hours, 11 had additional laboratory unsatisfactory reasons so were excluded from the <24 hours count. There were 66 samples that were unsatisfactory for both data and laboratory reasons.

Of the 468 samples collected at <24 hours, the subsequent samples for these infants indicated a transfusion was given for 129 infants. Taking the pre-transfusion sample, even when collected at <24 hours, and a post-transfusion sample collected at ≥24 hours, often means that a subsequent 4-6 month sample is not required to complete screening for the infant as hemoglobin and galactosemia screening are not impacted by age at collection (but are impacted by packed red blood cell transfusions).

1.1.5.1 Repeat Rates for Unsatisfactory Specimens

The majority (~79%) of repeat samples are received within 2 weeks of the initial sample. By 6 weeks, ~92% of unsatisfactory samples have had screening completed via a repeat sample. Of the 102 cases where a repeat sample was not received, partial testing was able to be completed on existing samples for 48 cases and another 22 were data unsats.

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Table 7. Repeats received on unsatisfactory samples from 2021-2023.

Time to receipt of unsatisfactory repeat sample	2023		2022		2021	
Total unsatisfactory samples	**1,714**		**1,440**		**1,951**	
< 1 week	843	49.2%	886	61.5%	1,255	64.3%
1 - <2 weeks	508	29.6%	264	18.3%	310	15.9%
2 - <3 weeks	111	6.5%	86	6.0%	95	4.9%
3 - <6 weeks	119	6.9%	79	5.5%	103	5.3%
≥ 6 weeks	31	1.8%	17	1.2%	31	1.6%
Not received	102	6.0%	108	7.5%	157	8.0%

1.1.5.2 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 on 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 include Metabolic diseases (AAAC platform), Galt deficiency, CH (TSH) and CAH (17OHP).

In 2023, NSO performed 880 priority panels (~64% of laboratory unsatisfactory samples). These samples are still counted as unsatisfactory (Section 1.1.5), and a repeat is requested. The results of the priority diseases are also reported.

Table 8. Repeat samples for priority panel unsats 2021-2023.

Time to receipt of priority panel repeat sample	2023		2022		2021	
Total priority panels	**880**		**718**		**1,030**	
< 1 week	327	37.2%	397	55.3%	617	58.3%
1 - <2 weeks	343	39.0%	171	23.8%	209	19.8%
2 - <3 weeks	73	8.3%	50	7.0%	57	5.5%
3 - <6 weeks	74	8.4%	39	5.4%	54	5.1%
≥ 6 weeks	15	1.7%	9	1.3%	20	1.9%
Not received	48	5.5%	52	7.2%	73	7.5%

There were 17 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 balance panel where there was sufficient quantity of blood in the second sample to be able to complete the untested assays.

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1.1.5.3 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. Samples that are unsatisfactory to complete initial testing require a routine repeat sample. These requests follow a similar workflow to regular unsatisfactory samples. Samples that are unsatisfactory to complete confirm testing require an urgent repeat sample. Urgent samples are requested to be sent to NSO within a week. If a repeat has not been received within a week (or a shorter timeframe if requested) the clinical team contacts the submitting hospital to obtain an update. If a family has not been reached or has declined coming back, the clinical team reviews the case with the appropriate Medical Scientist lead at NSO to determine next steps.

Regardless of urgency, results on these samples are reported 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 2023 there were 7 TLU where a repeat was not received. The table below shows the time to receipt of repeat samples after a TLU.

Table 9. Repeat samples for TLU 2021-2023.

Time to receipt of TLU repeat sample	2023		2022		2021	
Total Test Level Unsats – Routine	**64**		**70**		**81**	
< 1 week	16	25.0%	33	47.1%	43	53.1%
1 - <2 weeks	33	51.6%	21	30.0%	20	24.7%
2 - <3 weeks	8	12.5%	7	10.0%	6	7.4%
3 - <6 weeks	<5	<7.8%	7	10.0%	5	6.2%
≥ 6 weeks	0	0	0	0	<5	<6.2%
Not received	<5	<7.8%	<5	<7.1%	6	7.4%
Total Test Level Unsats - Urgent	**94**		**74**		**69**	
< 1 week	25	26.6%	22	29.7%	28	40.6%
1 - <2 weeks	48	51.1%	33	44.6%	23	33.3%
≥2 weeks	17	18.1%	17	23.0%	16	23.2%
Not received	<5	<7.8%	<5	<7.1%	<5	<6.2%

1.1.6 SCREENING TIMELINESS – RECEIPT AND AGE AT RESULTS

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. The goal would be to have 90% of the screened population meet the benchmarks.

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Each cell contains the percentage of infants meeting benchmarks. 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%.

Initial results refers to results from first tier screening. All infants undergo first tier testing. After interpretation the majority of infants will be screen negative and testing is complete. The second columns of numbers under each year are the age of their final results. There were 137,977 initial samples went through first tier screening in 2023. Of these, 128,258 (92.96%) were screen negative on all assays after first tier. Some infants require additional testing to determine if they are negative or positive. Age at final results is the subset of infants who required additional testing (through second and third screening) and the age that their results are final (either positive or negative).

The percentage of infants meeting the benchmarks increased across the board this year. This can be directly tied to improvements in on time shipments by Purolator. NSO met with Purolator managers to strategize ways to improve sample shipments to Ottawa and hope to see improved transit times in early 2023. Data from Purolator shows that from January – June 2023 on time delivery percentage for NSO samples was on average 79.3%. For July – December 2023 that increased to 90.8%.

The SCID and SMA screening assays have a lower percentage reported by day 5 and 7 of life. The samples for these assays are punched a day after the biochemical assays. As well, the SCID and SMA assays include molecular testing as part of the first-tier testing (whereas cystic fibrosis and MPS1 are 2nd and 3rd tier) which takes 2 business days to complete. Unlike the biochemical laboratory, which is screening for the more aggressive disorders, the molecular laboratory does not operate on weekends. All of this leads to longer TAT for results of 3-5 days compared to the biochemical assays.

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Table 10a. The percentage of infants meeting the defined benchmarks for each indicator for age at receipt and availability of initial and final results in 2022 and 2023 (*note that GAMT screening only began in October 2022).

	Screening (Initial Samples) 2023 Only			Screening (Initial Samples) 2022 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, CblA &B, CUD, FAOD, GA1, GAMT*, HCY, IVA, LCHAD/TFP, MCAD, MSUD, PA/MMA, PKU, TYR1, VLCAD	**79%**	**79%**	**97%**	**76%**	**76%**	**96%**
Biotinidase Deficiency	**79%**	**78%**	**97%**	**76%**	**75%**	**96%**
Galactosemia	**79%**	**79%**	**97%**	**76%**	**76%**	**96%**
Mucopolysaccharidosis Type 1	**79%**	**78%**	**97%**	**76%**	**75%**	**96%**
Guanidinoacetate Methyltransferase Deficiency	**79%**	**79%**	**97%**	**77%**	**77%**	**95%**
Congenital Adrenal Hyperplasia	**79%**	**79%**	**97%**	**76%**	**76%**	**96%**
Congenital Hypothyroidism	**79%**	**78%**	**97%**	**76%**	**76%**	**96%**
Cystic Fibrosis	**79%**	**78%**	**94%**	**76%**	**75%**	**93%**
Hemoglobinopathies	**79%**	**65%**	**96%**	**76%**	**64%**	**95%**
Severe Combined Immune Deficiency	**79%**	**11%**	**54%**	**76%**	**12%**	**53%**
Spinal Muscular Atrophy	**79%**	**12%**	**57%**	**76%**	**12%**	**55%**

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Table 10b. Median and 90th centile values for age of receipt of initial samples, and availability of initial and final results, 2022 and 2023.

Category	Screening (Initial Samples) 2023 Only					Screening (Initial Samples) 2022 Only				
	Age at Initial Results		Age at Final Results			Age at Initial Results		Age at Final Results		
	Median	90th Centile	n	Median	90th Centile	Median	90th Centile	n	Median	90th Centile
CIT/ASA	4	6	46	5	8	4	7	43	6	9
CUD			342	5	7			294	5	8
FAOD			<5	7	8			<5	4	4
GA1			35	5	8			44	6	8
HCY			47	6	14			48	6	7
IVA			31	5	7			19	5	6
LCHAD/TFP			40	7	8			23	6	9
MCAD			27	5	7			27	5	8
MSUD			22	6	10			18	7	20
PA/MMA			139	6	8			146	6	9
PKU			127	6	7			138	5	7
TYR1			12	6	8			11	7	8
VLCAD			183	5	7			199	6	8
Biotinidase Deficiency			104	5	8			103	6	9
Galactosemia			125	7	9			99	7	9
GAMT			191	11	16			101	10	14
MPS1H			603	9	22			556	10	20
CAH			671	6	8			605	6	8
CH			756	5	7			770	5	7
Cystic Fibrosis			5,552	9	12			5,648	9	17
Hemoglobinopathies	5	7	121	6	8	5	7	105	6	8
SCID	7	10	800	10	13	7	11	949	10	14
SMA	7	10	21	8	12	7	10	33	12	23

The median age (4 days) at receipt remained unchanged between 2022 and 2023, however the 90th centile decreased for the majority of conditions screened. The median and 90th centile decreased for SMA for the age at final results. While there were more samples that went on to second tier for GAMT in 2023, this is expected 2023 was the first full year of screening for that condition.

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Table 11. Median and 90th centile values for time from receipt to initial results, and time from receipt to final results, 2022 and 2023.

Category	Screening (Initial Samples) 2023 Only					Screening (Initial Samples) 2022 Only				
	Receipt To Initial Results (hours)		Receipt To Final Results (hours)			Receipt To Initial Results (hours)		Receipt To Final Results (hours)		
	Median	90th Centile	n	Median	90th Centile	Median	90th Centile	n	Median	90th Centile
CIT/ASA	24	26	46	50	75	24	26	43	50	89
CUD			342	49	51			294	49	52
FAOD			<5	123	144			<5	49	51
GA1			35	48	50			44	49	73
HCY			47	49	51			48	49	51
IVA			31	50	74			19	49	73
LCHAD/TFP			40	50	74			23	49	75
MCAD			27	48	51			27	49	57
MSUD			22	49	52			18	51	58
PA/MMA/CblA&B			139	50	98			146	50	99
PKU			127	49	51			138	49	58
TYR1			12	72	74			11	50	76
VLCAD			183	49	59			199	49	72
Biotinidase Deficiency			104	50	73			103	50	74
Galactosemia			125	50	73			99	49	51
GAMT			191	147	289			101	170	199
MPS1H	25	27	603	150	435	25	27	556	151	387
CAH	24	25	671	50	98	24	26	605	51	99
CH	24	26	756	50	74	24	26	770	49	73
Cystic Fibrosis	25	26	5,552	129	176	24	26	5,648	129	342
Hemoglobinopathies	26	73	121	73	101	26	73	105	52	121
SCID	100	145	800	148	217	99	149	949	148	218
SMA	99	144	21	123	219	99	148	33	218	485

While the median age of initial results for hemoglobinopathies is reported as 5 days (Table 10b), when looking at the data in terms of hours (Table 11), it is only 1-2 hours from the other conditions reported which means initial results would be reported the same day as the metabolic, endocrine and cystic fibrosis conditions.

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1.2 CRITICAL CONGENITAL HEART DISEASE

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 2023 was 142,466 representing 139,605 infants. The number of infants in Ontario who had a completed CCHD screen was 134,514.

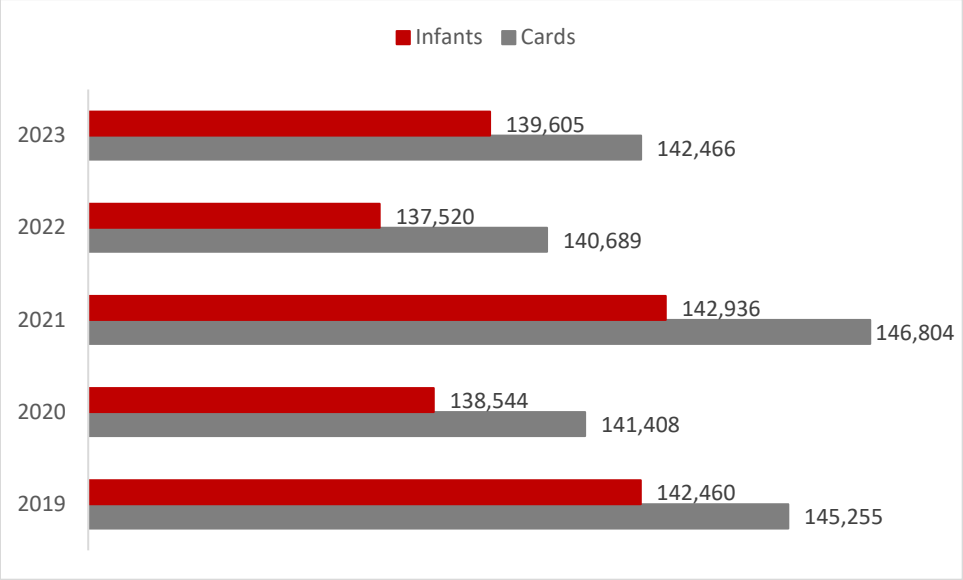

Figure 2. CCHD cards received at NSO and total number of infants between 2019-2023.

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 2023, 7,462 of the requisitions submitted did not include screening information.

Table 12. CCHD cards received from 2019-2023.

CCHD Cards received	2023		2022		2021		2020		2019	
Screen Completed	135,004	94.76%	133,617	94.97%	139,264	94.86%	134,834	95.40%	138,775	95.50%
Screen Not Done	7,462	5.24%	7,072	5.03%	7,540	5.14%	6,574	4.60%	6,480	4.50%
	142,466		140,689		146,804		141,408		145,255	

1.2.1 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, 99.09% 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 0.79% required a second test and 0.12% required three tests to complete the screen.

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Table 13. Tests required to complete screen between 2019-2023.

Tests Done	2023		2022		2021		2020		2019	
1 Test	133,778	99.09%	130,639	99.13%	138,050	99.13%	131,592	98.80%	136,935	98.70%
2 Tests	1,064	0.79%	997	0.76%	1,067	0.77%	1,431	1.10%	1,621	1.20%
3 Tests	162	0.12%	150	0.11%	147	0.11%	222	0.20%	218	0.20%
	135,004		131,786		139,264		133,245		138,775	

1.2.2 Screens Not Done

In 2023, CCHD screens were not done on 5.24% of the cards received. The most common reason for CCHD screen not done is because the infant is expected to be in the NICU for > 7 days.

Table 14. Reasons for CCHD Screen not done between 2019-2023.

	2023		2022		2021		2020		2019	
'Screen Not Done' cards submitted	7,462		7,072		7,540		6,574		6,480	
Declined	149	2.00%	132	1.87%	139	1.84%	66	1.00%	26	0.40%
Infant diagnosed prenatally with heart defect	146	1.96%	170	2.40%	178	2.36%	101	1.50%	74	1.10%
Infant diagnosed with heart defect by physical exam	40	0.54%	50	0.71%	70	0.93%	33	0.50%	47	0.70%
Infant is not appropriate for screening (e.g. NICU > 7 days, on oxygen, IV in right hand, limb anomaly, etc.)	4,413	59.14%	4,336	61.31%	4,745	62.93%	4,725	71.90%	4,732	73.00%
Already done	633	8.48%	503	7.11%	514	6.82%	169	2.60%	17	0.30%
Insufficient information provided/blank card	1,139	15.26%	1,062	15.02%	1,005	13.33%	671	10.20%	704	10.90%
Decline/deferred (back page of form not completed)	83	1.11%	113	1.60%	106	1.41%	95	1.40%	93	1.40%
Deferred	515	6.90%	441	6.24%	541	7.18%	565	8.60%	542	8.40%
Other	344	4.61%	265	3.75%	242	3.21%	149	2.30%	245	3.80%

Of the decline/deferred group (83) where the back of the form was not fully completed to know if the family was declining or deferring – 53 had a CCHD screen completed and 6 had cards received indicating infant is expected to be in the NICU for > 7 days. There were 494 defer cards received. Of these 480 had a

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CCHD screen. Of the decline group (144) – 105 had a CCHD screen completed. In total, 68 families declined/did not complete CCHD screening (from the decline forms, the defer forms, the defer/decline forms, and the missed screen notifications). There were 40 families that declined both the CCHD screen and the DBS screen.

There were 633 cards that were blank. Some of these indicated that a previous screen had already been performed and some were just submitted completely blank. These blank cards often accompanied repeat dried blood spot specimens. The check box where submitters can indicate that a screen has already been completed was added in 2020.

1.2.3 CCHD Missed Screens

In 2023, 560 potential missed screens were identified, which is similar to the previous two years. The majority of the potential missed screen notifications were from hospitals (465). The majority of these alerts were due to improper documentation – either the infant was screened but documentation was not sent to NSO (223) or the infant was not suitable for screening and documentation was not sent to NSO (252). There were 58 CCHD screens that were missed for eligible infants. Infants are only eligible for CCHD screening up to 7 days of age. As these infants were >14 days of age, their health care providers were notified that the infant had not had CCHD screening in the newborn period.

Table 15. Potential CCHD missed screen alerts in 2021-2023.

Category		Total (2023)	Total (2022)	Total (2021)
Other	Declined	<5 (<0.9%)	<5 (<1.0%)	5 (0.9%)
	Incorrect or incomplete information (requisition already received)	10 (2.0%)	0	<5 (<0.9%)
	Infant not suitable for screening	252 (50.2%)	231 (46.8%)	206 (41.0%)
	Infant born out of province	7 (1.4%)	<5 (<1.0%)	<5 (<0.9%)
	Delayed shipping of card (card received same day as alert)	7 (1.4%)	0	12 (2.4%)
	Infant was screened - documentation not sent/ sent late	223 (44.4%)	196 (39.7%)	274 (54.5%)
Total: Non-Missed Screens		**502 (89.6%)**	**430 (87%)**	**503 (89.5%)**
True Missed Screens	Missed - infant's health care provider notified	**58 (10.4%)**	**64 (13%)**	**59 (10.5%)**
Grand Total		**560**	**494**	**562**

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1.2.4 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 (96.38%) of screening is completed by 48 hours of age which is a continued in improvement from previous years.

Table 16. Age at time of CCHD Screen from 2019-2023.

Age at time of CCHD screen	2023		2022		2021		2020		2019	
	Number of screens	%	Number of screens	%	Number of screens	%	Number of screens	%	Number of screens	%
≤48 hours (1-2 days)	130,118	96.38	128,109	95.88	132,774	95.40	125,382	93.00	128,316	92.40
>48-72 hours (2-3 days)	1,234	0.91	1,377	1.03	1,721	1.20	1,706	1.30	2,571	1.90
>72-168 hours (3-7 days)	822	0.61	846	0.63	940	0.70	928	0.70	1,144	0.80
Greater than 168 hours (> 7 days)	195	0.14	207	0.15	197	0.10	255	0.20	352	0.30
Not specified	2,635	1.95	3,080	2.31	3,632	2.60	6,289	4.70	6,391	4.60

1.2.5 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 in 2023 was 829, which was 0.58% of the cards received. The most frequent error was incomplete documentation – either of a repeat test done after 1 hour or missing screening values. The number of unsatisfactory screens increased in 2019 as NSO started to contact submitters where cards were received with demographic information but no CCHD screening values recorded. With increased submitter education, the unsatisfactory rate decreased in 2020 and has remained below 1%.

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Table 17. Outcomes from unsatisfactory CCHD screen notifications.

		2023	2022	2021	2020	2019
Unsatisfactory Screens		**829**	**1,057**	**1,179**	**1,069**	**1,855**
No screen/ rescreen recommended	Baby >7days	20 (2.4%)	42 (4.0%)	39 (3.3%)	65 (6.1%)	49 (2.6%)
	Baby in hospital	131 (15.8%)	185 (17.5%)	203 (17.2%)	253 (23.7%)	566 (30.5%)
	Documentation inaccurate or incomplete	536 (64.7%)	653 (61.8%)	723 (61.3%)	574 (53.7%)	865 (46.6%)
	Family Declined	0	0	0	0	<5 (<0.3%)
	Missed - baby >7 days	6 (0.7%)	6 (0.6%)	6 (0.5%)	9 (0.8%)	5 (0.3%)
	No action needed	39 (4.7%)	50 (4.7%)	57 (4.8%)	38 (3.6%)	51 (2.7%)
Screen or physical exam recommended	Missed - baby ≤7 days	29 (3.5%)	40 (3.8%)	65 (5.5%)	54 (5.1%)	119 (6.4%)
	Physical exam recommended (screen positive)	<5 (<0.6%)	<5 (<0.5%)	<5 (<0.4%)	0	<5 (<0.3%)
	Rescreen recommended	64 (7.7%)	80 (7.6%)	83 (7.0%)	76 (7.1%)	195 (10.5%)
Total Screening Forms Submitted		**142,466**	**140,689**	**146,804**	**141,408**	**145,255**
Unsatisfactory Rate		**0.58%**	**0.75%**	**0.80%**	**0.76%**	**1.28%**

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

NSO performed follow up on 829 unsatisfactory screens, and in 64.7% of follow up cases the result was amended by the submitter due to incorrect completion of the form. In 7.7% of cases a rescreen was recommended. Through the follow up of unsatisfactory screens NSO was able to follow up with submitters for 93 infants that had not received a proper CCHD screen and needed to be screened (missed) or rescreened.

1.3 HEARING

The Ministry of Children, Community and Social Services' (MCCSS) Infant Hearing Program (IHP) is a well-established program that provides universal newborn hearing screening in hospital or community settings, diagnostic audiology assessments to identify PHL, monitoring of children at risk of developing PHL and language development services. The IHP and NSO began offering dried bloodspot (DBS) risk factor screening for Permanent Hearing Loss (PHL) for babies born on or after July 29, 2019, as a complement to newborn hearing screening. Risk factor screening for PHL uses the newborn DBS to look for Cytomegalovirus (CMV) infection and DFNB1 and DFNB4-associated PHL (variants in the genes GJB2/6 and SLC26A4). These are the most common causes of childhood PHL and children with these risk factors are at risk of congenital or early onset PHL.

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1.3.1 Consent

When risk factor screening for PHL launched, parents/guardians were approached for consent as part of the infant hearing screening process. When the COVID-19 pandemic began in 2020, and all non-essential services were discontinued temporarily, the IHP postponed all audiometric hearing screening and was no longer able to obtain consent for risk factor screening. After careful review and options-analysis with the Ontario Ministry of Health and Ministry of Children Community and Social Services, a decision was made to continue with the risk factor screening without the need for additional consent from the IHP until it became feasible again. This decision was made due to high rate at which approached parents had been consenting and so that babies at high risk for PHL would continue to be identified. All DBS from babies born on or after March 26, 2020, were screened for CMV and genetic risk factors for PHL, and this continued throughout 2023. NSO and the IHP have been working on an improved workflow and electronic system for when consent is reinstated. Risk factor screening for PHL moved back to a consented model in March 2024.

1.3.2 Screens Completed for PHL Risk Factor Screening

The table below shows the number of infants screened for CMV and genetic risk factors for PHL. NSO screened 139,932 infants in 2023. Risk factor screening for PHL (CMV and genetics) was completed for 139, 788 infants in 2023.

Table 18. Number of babies screened for risk factors for PHL

	2023	2022	2021
Infants screened at NSO	139,932	137,842	143,749
IHP Screening Form received	N/A	N/A	N/A
Consent for risk factor screening	N/A	N/A	N/A
Babies screened for CMV and genetic risk factors	139,789	137,737	142,239
Babies screened for CMV	139,789	137,737	143,344
Babies screened for genetic risk factors	139,788	137,737	142, 936

1.4 BILIARY ATRESIA

Biliary atresia (BA) is a rare but serious liver disease that affects newborns in the first month of life. It is the most frequent indication for liver transplant in the pediatric population and is the most common cause of liver related death in children. Abnormally pale stools can be an early sign of BA. Early identification and intervention are key to better outcomes. The incidence in Ontario is reported to be 1 in 16,667 annually (~8-9 cases per year).

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With the help of an infant stool colour card (ISCC) parents can perform screening at home and can identify acholic (pale) stools. Parents are asked to compare their child's stool colour to the numbered images of normal (#7-9) and abnormal (#1-6) stool on the ISCC during regular diaper changes for the first month of life (or for one month past their due date for babies born less than 37 weeks gestation). If parents detect pale stool, the ISCC provides guidance about how to contact the NSO BA clinical team so they can conduct a telephone assessment and facilitate referral to a Pediatric Academic Health Science Centre (PAHSC) hepatologist for measurement and interpretation of a fractionated bilirubin. This is the first parent-led screening program in Ontario, coordinated by NSO.

1.4.1 Implementation

NSO implemented BA screening using the ISCC across the province mid-January 2023. Submitters were sent a launch kit containing ISCC's, educational materials, and caregiver instructions, to implement the parent led screening program. Within eight weeks of the launch, over 75% of submitters confirmed they were distributing the ISCCs, reaching over 10,000 infants. By the middle of June 2023, all delivering hospitals and Midwifery practices confirmed they were handing out the ISCCs to families with newborns born in Ontario.

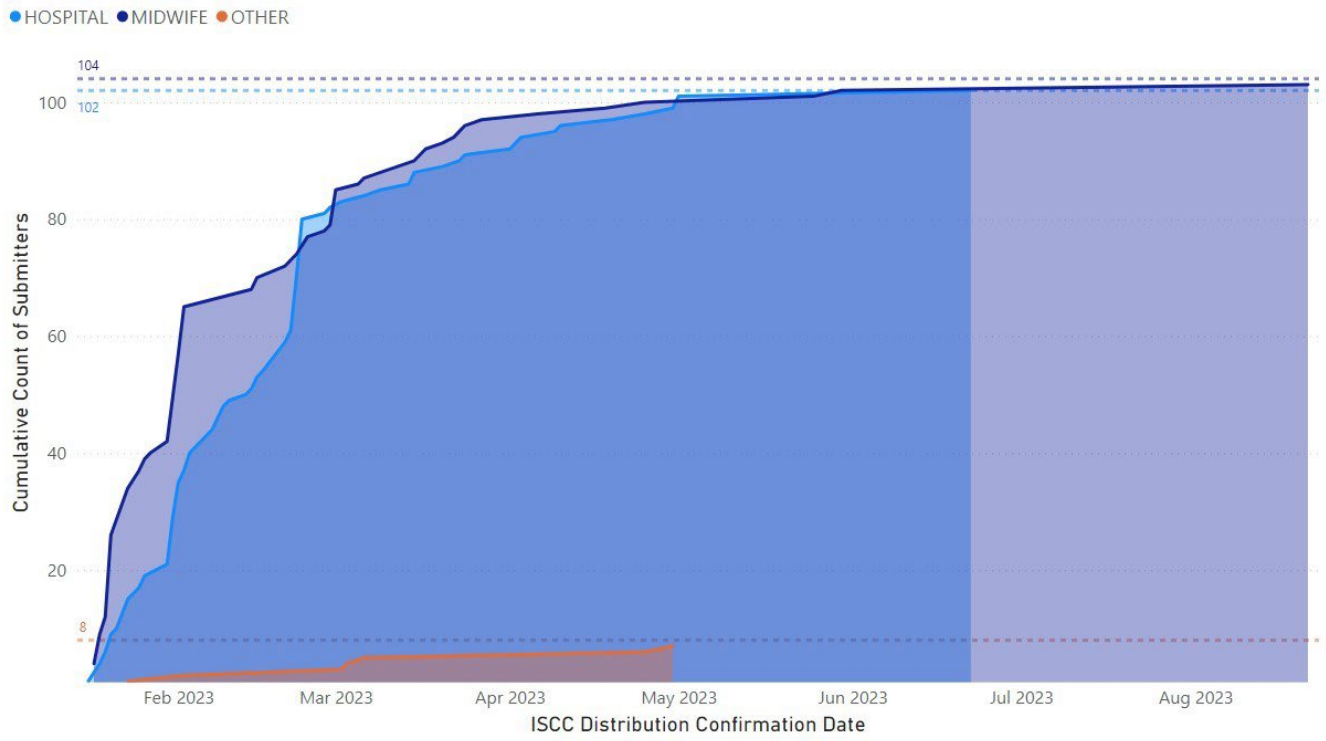

Figure 3. Submitters distributing Infant Stool Colour Cards

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A number of dissemination strategies were used to notify health care providers about this initiative in the fall of 2022 including an article featured in the College of Physicians and Surgeons of Ontario eDialogue, and webinars to NSO Submitters, PAHSC Gastroenterology, and the Association of Ontario Midwives.

Post-launch, NSO has continued with many awareness strategies with efforts primarily directed towards families who are the screeners. This has primarily focused around a social media campaign involving sponsored ads through Meta (Facebook and Instagram) that were run between July 25 – Aug 31, 2023 and paid partnerships with vetted influencers. The ad campaign captured over 4.5 million "impressions" – meaning ads shown to the target audience of men and women, aged 25-45, in Ontario who were selected based on their patterns of baby related search terms. Influencer content was very effective in attracting attention in diverse and multicultural audiences, and with an authentic and personal touch.

Simultaneously, efforts were made to target Ontario Family Doctors, Pediatricians and Public Health units as key care providers to newborns. Dissemination efforts included:

- July 2023 - Collaborated with HSC gastroenterologist (GI) fellows for their grand round presentation on the work-up of neonatal jaundice which included an introduction to the pediatricians attending to NSO BA screening program and the ISCC.
- October 2023 - An article in the Ontario Pediatricians Pearls Update, the monthly newsletter for the Pediatricians Alliance of Ontario, which is distributed to nearly 1,300 Ontario Pediatricians.
- November 2023
  - Collaborated with HSC GI department to assist with preparation for a conference (annual T4) which targets community partners in a session titled: A Light Shade of Pale: Updates on the Management of Biliary Atresia
  - An informative email that was distributed to all Public Health Units across Ontario sent via the Association of Local Public Health agencies.
  - A brief message in the president's message for the College of family physicians, which is shared with over 15,000 members and has an open rate of 70%.
  - External Webinar for Family Physicians, Pediatricians and Public Health Units across Ontario

1.4.2 Infant Stool Colour Card (ISCC) Distribution

For the launch, a 6-month supply of ISCC was sent in a launch kit to all submitters (approx. 77,000 cards). After the first supply shipment, an additional 124,000 ISCCs have been ordered and distributed through VWR in 2023. To track ISCC orders, reports are received from NSO's VWR. These reports allow NSO to calculate an approximation of usage. While it is hard to know how many families are performing screening at home, by tracking orders of ISCC through the ISCC supplier and comparing this to the number of DBS samples received, it is estimated that 121,130 infants have been screened in 2023.

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If a submitter's estimated volume on hand is less than 15%, NSO contacts the organization to ensure prompt re-ordering of ISCCs. Since it is suggested that submitters distribute the ISCC at the time of performing the CCHD screen, a check box will be added to the CCHD screening form in year 2 of the program, which should be completed by the submitter to confirm whether the family has been given an ISCC. This information will be collected, and completion rates will be reported back to the submitters on their report cards.

1.4.3 Biliary Atresia Screening

All parents of infants born in Ontario receive an ISCC shortly after birth and are instructed to screen their infant's stool for the first four weeks of life. If families or healthcare providers observe pale stool, they are instructed to contact NSO either through a phone call, email or webform.

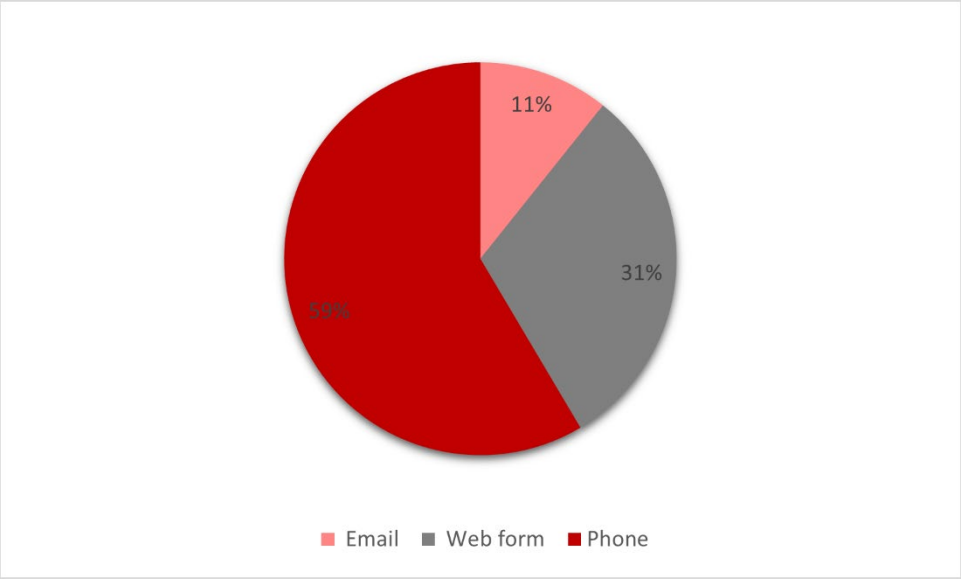

Figure 4. Percentage breakdown of the types of contacts received from families.

The minimum age at first contact in days was 2 days, the maximum age was 229 days, and the mean was 33 days of age. The written instructions on the ISCC and the verbal instructions given with the card at time of distribution recommend that families screen for a total of four weeks post birth for infants born ≥37 weeks gestation and if <37 weeks gestation, four weeks past the baby's due date. Despite this recommendation, families did continue to contact NSO beyond the recommended screening window.

In June 2023, the maximum age to screen was reviewed with the BA Core GI advisory group, which consists of hepatologists from each of the PAHSC, and it was decided to continue to offer the screen to those families who contact NSO with pale stool concerns beyond 100 days of age. In November 2023, the BA Core GI advisory group decided to cap the screening timeframe at 120 days of age given that infants with biliary atresia presenting beyond 120 days are expected to be unwell and would most likely have already required medical assessment and care by a healthcare provider (HCP). When there are contacts to NSO about infants older than 120 days of life, it is recommended that the family present to their healthcare provider and request that a conjugated or direct bilirubin be measured to rule out cholestasis.

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There were 15 cases where caregivers contacted NSO about an infant who was over 100 days of age and 6 of those were greater than 120 days of age.

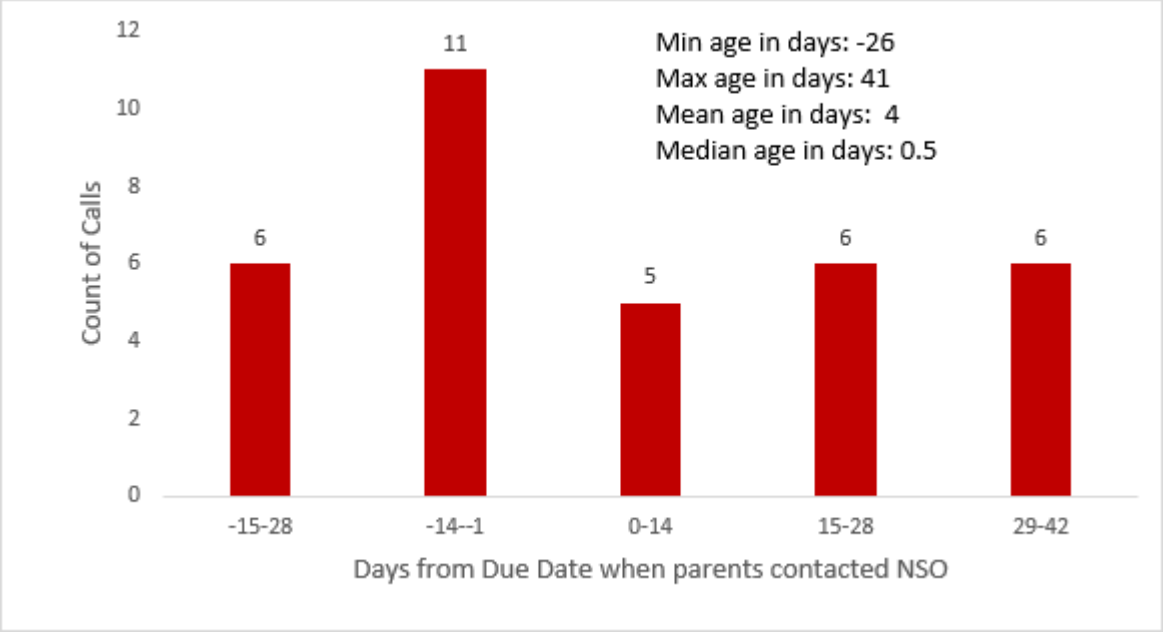

Figure 5a. Age in days (corrected for gestational age at birth) of preterm infants at time of contact with NSO.

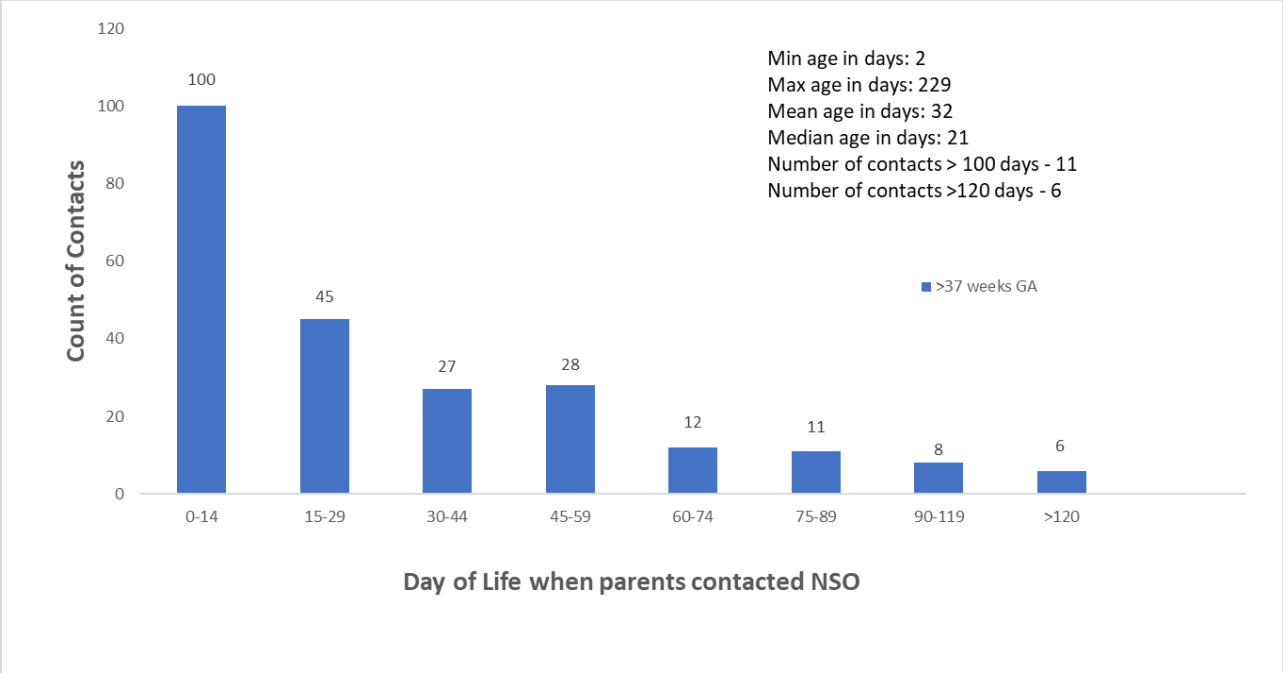

Figure 5b. Age in days of term infants at time of contact with NSO.

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1.4.4 Biliary Atresia Clinical Assessments

In 2023, there were 271 contacts to NSO by families or caregivers regarding infant stool concerns, of which 265 telephone clinical assessments of the cases were conducted (6 families did not return our first telephone call back).

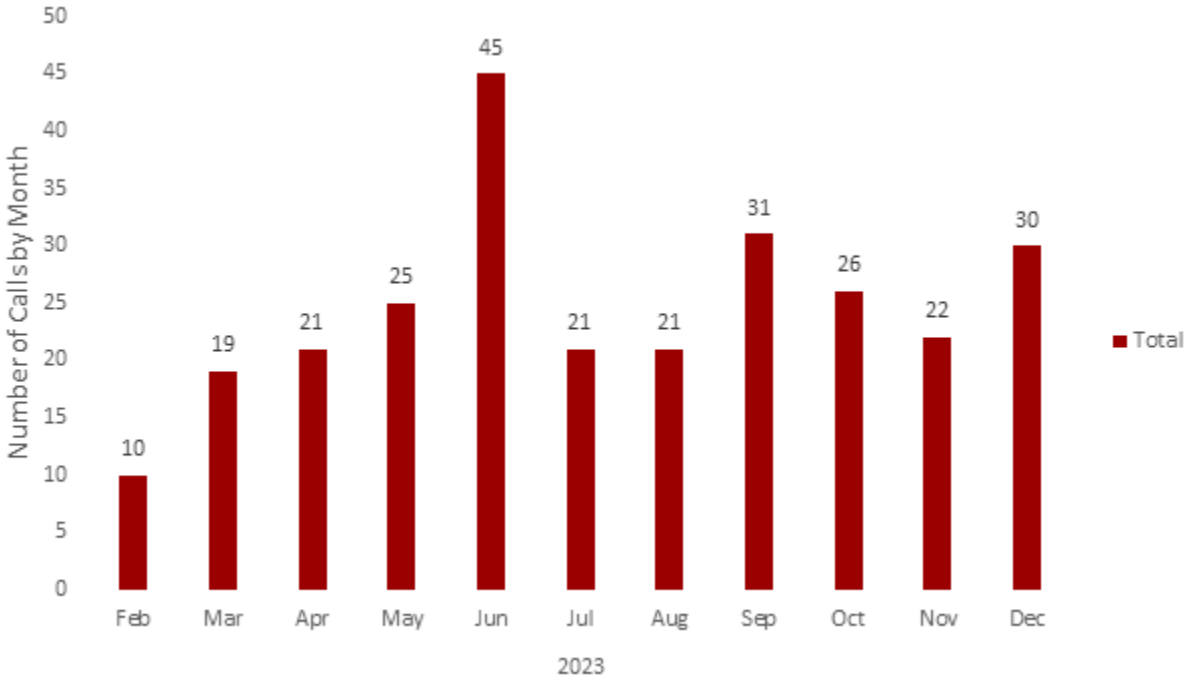

Figure 6. Distribution of call volumes per month

The call volume distribution per month can be seen in the figure above. The spike in contacts in June did not correlate with birth rates in the previous months or the education initiative (which took place in August).

The program's BA clinical team (primarily consisting of RNs), attempts to make contact with the family within one business day to provide a telephone assessment, which includes a stool photo review, to expedite next steps. In 169 telephone assessments, photos were received and a total of 699 photos were submitted, de-identified, renamed, and uploaded to an NSO private drive, which has restricted access.

41% of the time the colour identified by the family on the ISCC aligned with the stool photo colour interpretation by the BA clinical team. #5 was the most frequent parent-identified stool colour and was also the most frequent parent-identified stool colour that was not aligned with the clinical team's impression of the stool colour.

147/271 (54%) of the calls were unrelated to pale stool concerns, as indicated by the caller. Common reasons for these unrelated calls included blood in the stool, other stool colour concerns (a colour not on the card), consistency/texture issues and constipation. In these cases, reassurance was given or the callers were directed to seek out assessment from another HCP for the issue. A year 2 improvement is underway

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to change the wording on the red banner of the ISCC to emphasize that this program is concerned with pale stool. This is planned to happen with the first printing of 2024.

117/271 (43%) contacts were related to pale stool.

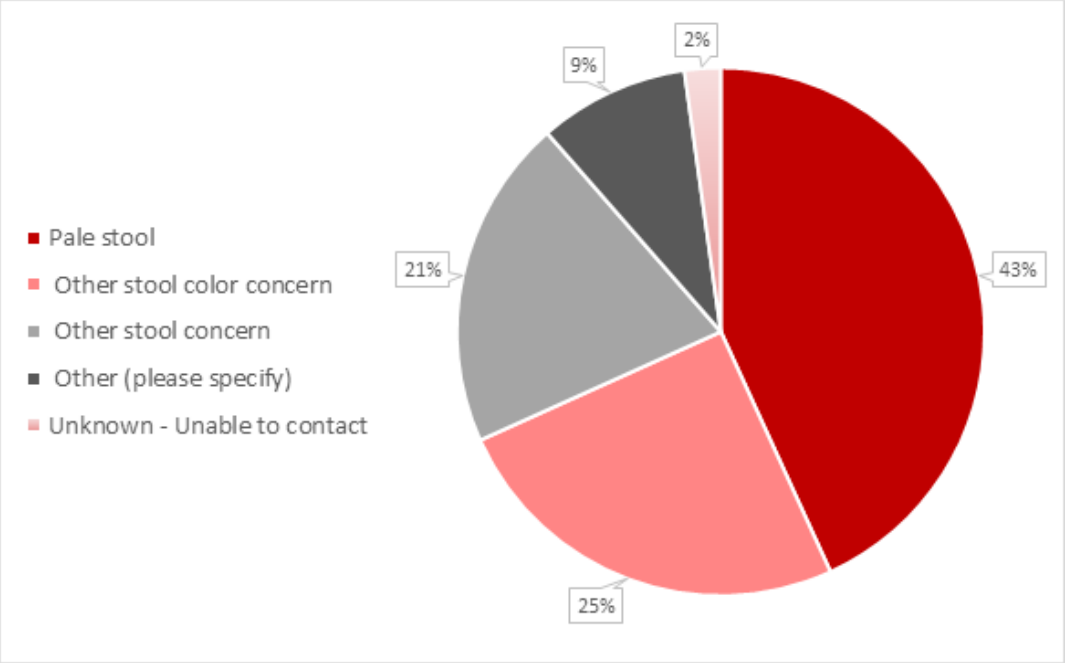

Figure 7. Breakdown for call reason

Some cases required more than one contact by NSO with the family to make a screening determination. 48 pale stool cases required 2 contacts to make a screening determination and 11 cases required 3 contacts to make a screening determination. These subsequent contacts allowed the clinical team to gather more stool photos and information about the infant over time.

In 28/265 (11%) cases the family had already seen another HCP (Family doctor, walk-in clinic, emergency room visit) prior to the NSO telephone clinical assessment. This unsolicited information was shared by families during the NSO telephone assessment and will be formally solicited and recorded in 2024.

After completing a telephone assessment, which includes a targeted history about the infant and photo retrieval and review, a determination of screening status is made. This assessment may also include consultation with the program's Medical Lead. 59% of the contacts by families for pale stool concerns indicated the presence of pale stool for <24 hours, and 41% had pale stool for >24 hours. 75/117 (64%) of calls about pale stool that had a clinical assessment were screen negative and 41/117 (35%) were screen positive. For both screen negative and screen positive determinations a letter is mailed out to families documenting the interaction between the family and BA Clinical team member and a faxed letter is sent to their identified HCP.

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2. SCREEN POSITIVES

2.1 DRIED BLOOD SPOT REFERRALS

2.1.1 Referrals by Treatment Centre

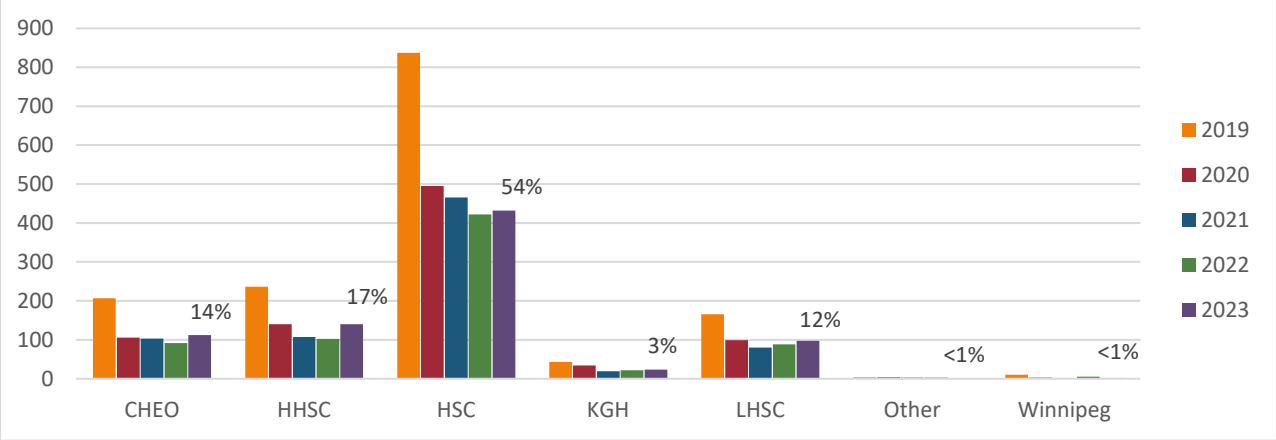

Figure 8a. The total number of referrals by treatment centre between 2019-2023.

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 United States, or a centre in Ontario that is outside of the standard treatment centres. While the number of referrals have decreased since 2020 onward, the proportion of referrals received by each of the five Ontario regional treatment centres has been relatively unchanged with slight increases for CHEO, HHSC and LHSC and a slight decrease for HSC, receiving approximately 54% of referrals.

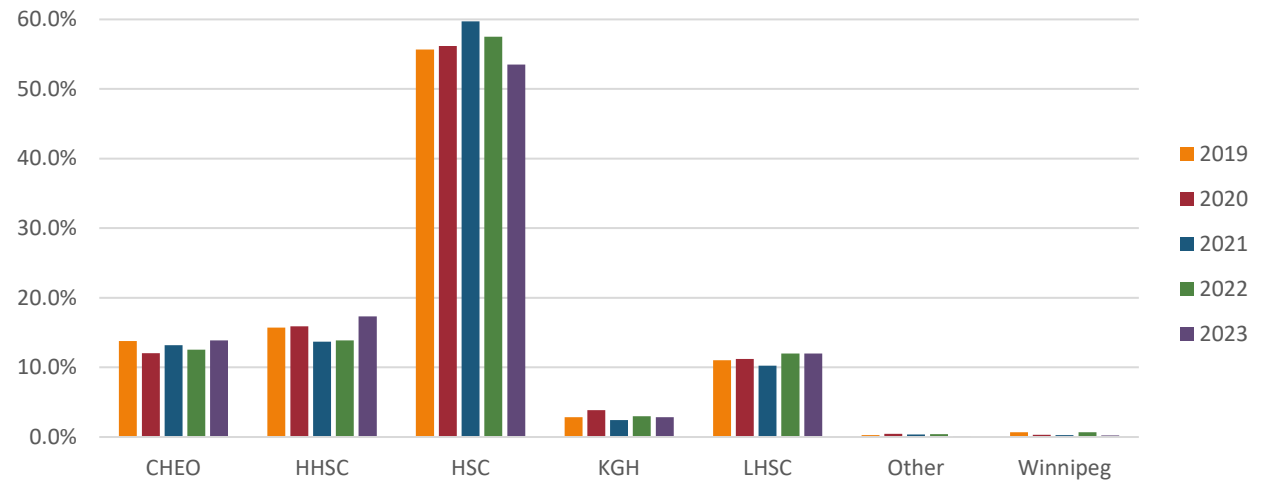

Figure 8b. The percentage of referrals by treatment centre between 2019-2023.

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2.1.2 DBS REFERRALS BY YEAR

In 2023, there were 807 screen positive referrals. This represents ~0.58% of the total number of infants screened by NSO.

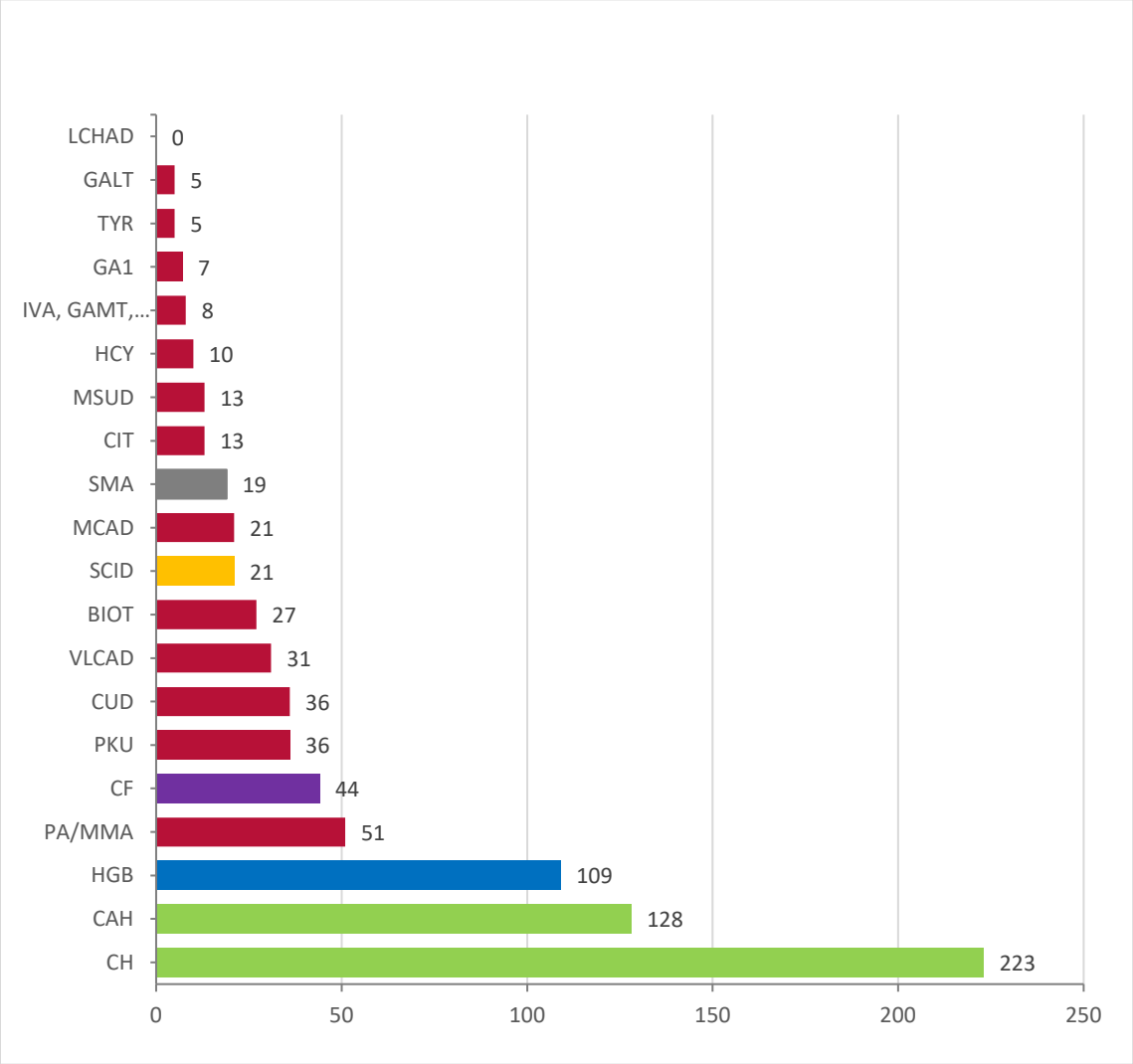

Figure 9. Total number of screen positive referrals by disease in 2023

The number of screen positive infants referred in 2023 increased slightly from 2022 (807 vs. 734).

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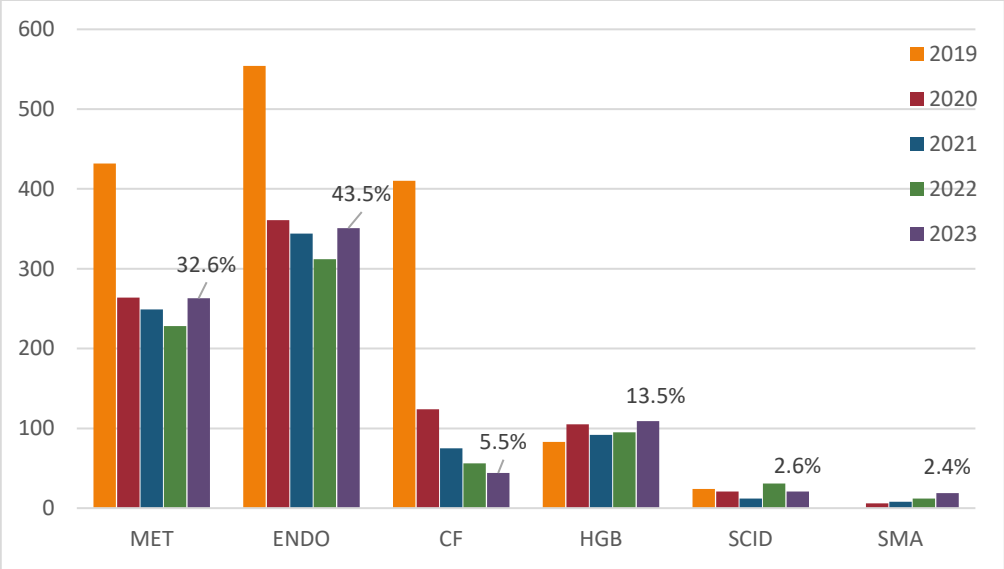

Figure 10. The total number of screen positives by disease grouping between 2019-2023.

The number of screen positive referrals per disease grouping decreased for referral types CF and SCID. The CF algorithm changed in March 2020 with the addition of 3rd tier sequencing of the *CFTR* gene and only infants with 2 or more CFTR variants being referred as positive. This accounts for the decrease in CF referrals (discussed more in section 2.3).

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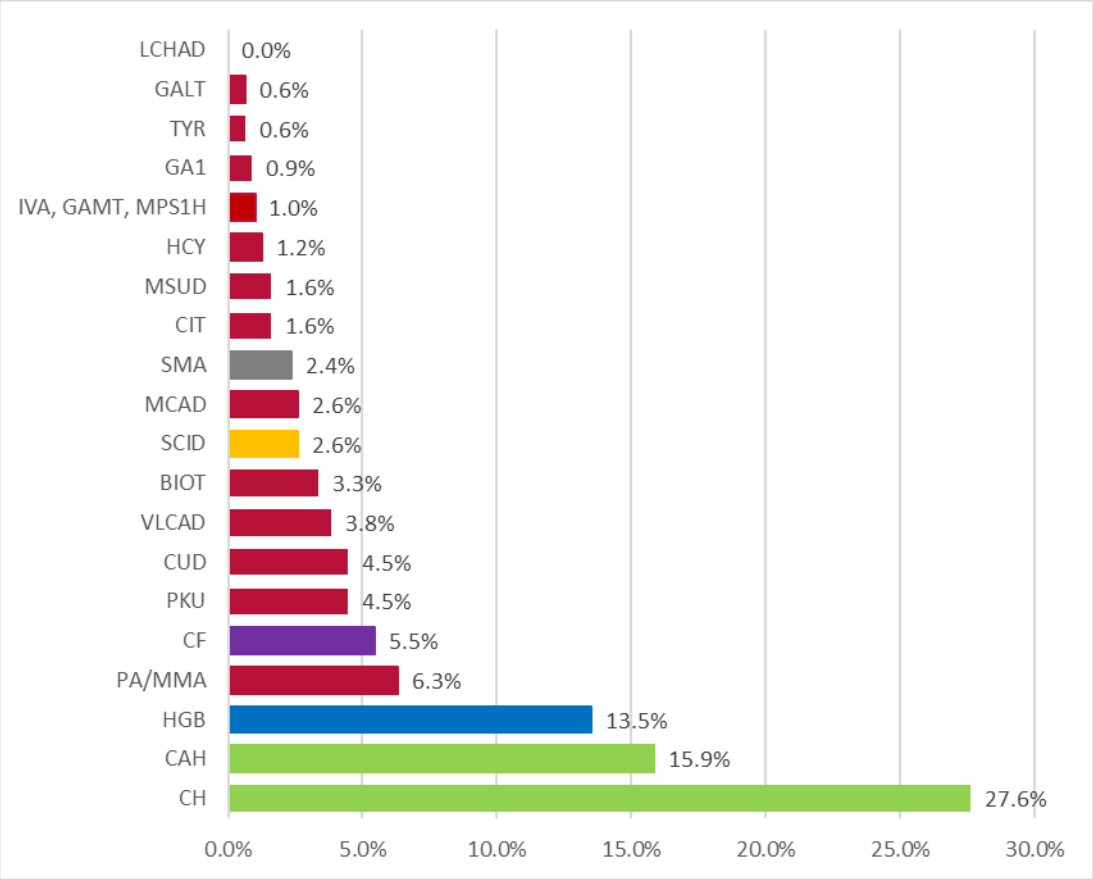

Figure 11. The percentage of screen positive referrals by disorder in 2023.

Endocrinopathies and Metabolics represent ~43.5% and ~32.6% of screen positives respectively. SCID screen positive referrals decreased in 2023 and now represent 2.6% of total screen positive referrals. The number of Cystic Fibrosis referrals continued to decrease in 2023 and now represent 5.5% of total screen positive referrals. Hemoglobinopathies represent approximately 13.5% of screen positive referrals, which is a slight increase from last year. SMA represents 2.4% of referrals. There were no disorder logic changes in 2023.

2.1.3 Diagnostic Feedback

Approximately 9.5% (77 cases) of diagnostic evaluation report forms (DERFs) remain pending for the referrals made in 2023 as of April 1, 2024. The percentage of pending DERFs is the lowest it has been for any annual report. With the use of preliminary data obtained during confirmation of retrieval and initial diagnosis, an outcome was obtained for 28 of these pending DERF cases.

Based on DERF data returned by the Treatment Centres, outcomes for each referral can be determined. A detailed explanation of the disease classifications can be found in Appendix A. NSO began to track initial diagnosis for all urgent and semi-urgent referrals in mid 2019. This was to ensure with a high PPV referral the correct infant was being referred (ruling out requisition errors) and if the correct infant was referred and found to be not affected, identifying a reason why the screen was positive (maternal factors, infant

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factors, or sample quality). This information is available earlier than DERF completion and is also a way to incorporate information into data analysis.

Table 19. The outcome classifications for all referrals in 2023 (DERF data pulled April 1, 2024). The DERF Pending column is a total of all pending DERFs. The outcomes unknown column reflects cases without an initial or final diagnosis where the DERF is pending. The total number of infants referred is a tally of outcomes unknown, primary, variant, incidental, not affected and other.

Disease	DERFs Pending	Outcomes Unknown	PRIMARY	VARIANT	INCIDENTAL	NOT AFFECTED	OTHER	Total No. Referred
Congenital Hypothyroidism	6	6	50	33	35	95	<5	223
Congenital Adrenal Hyperplasia	8	8	14		9	96	<5	128
Hemoglobinopathies	11	9	61	<5	32	<5	<5	109
Cystic Fibrosis	13	<5	21	13	<5	<5	<5	44
Type 1	6		17	<5			<5	19
Type 2	<5	<5		7				10
Type 3	<5		<5	5	<5	<5	<5	15
SCID	5	<5	<5	<5	<5	9	<5	21
SMA	0		19					19
Biotinidase Deficiency	5	<5	<5	10	<5	10	0	27
Citrullinemia	5	<5				9		13
CUD	<5	<5	<5		10	21		36
FAO (CPT1, CPT2, and GA2)	0							0
Galactosemia	0		<5	<5		<5		5
GAMT	<5					<5		<5
Glutaric Aciduria Type 1	<5		<5		<5	<5	<5	7
Homocystinuria	<5				<5	6		10
Isovaleric Acidemia	0		<5			<5		<5
LCHAD	0							0
MCAD	6	<5	11	<5	<5	5		21
MPS1H	0			<5				<5
MSUD	<5	<5	<5			10		13
PA/MMA	7	6	<5		19	25		51
Phenylketonuria	<5	<5	9	10		14	<5	36
Tyrosinemia	<5	<5			<5	<5		5
VLCAD	0		<5	<5	11	13	<5	31
Total No. Positive	**77**	**50**	**200**	**77**	**132**	**332**	**16**	**807**

2.2 HEMATOLOGY

The number of screen positives (109) in 2023 increased compared to 2021 (92) and 2022 (95).

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Table 20. The PPV calculations for the current and past screening algorithms.

Additional information	PPV (Primary)	PPV (Primary + Variant)	PPV (Primary + Variant + Secondary)	% of Outcomes Unknown
Past (Nov 1, 2010 - July 31, 2015)	64.3%	65.1%	84.3%	0.8%
Current (Aug 1, 2015 - Dec 31, 2023)	**58.2%**	**58.8%**	**90.6%**	**2.9%**

2.2.1 Hemoglobin Carriers

Table 21. Hemoglobin carrier requests between 2019-2023.

	2023	2022	2021	2020	2019
Requests from high-risk population	41	23	unknown	23	35
Total Requests	**51**	**37**	**49**	**32**	**40**
Number of carriers	17	13	17	12	16

NOTE: The way hemoglobin carrier requests are logged was changed in 2021. Therefore, the number of requests from high-risk populations was unknown for that year.

There were 51 hemoglobin carrier requests in 2023. Some of these requests were for individuals with birth dates prior to April 2006 and therefore, were not fulfilled. Of the 17 carriers, they were all from high-risk populations or where risk status was not indicated.

Table 22. Carriers identified in 2023.

HGB Pattern	Carriers Identified
FAC	355
FAD	249
FAE	267
FAS	1,569
FAX	76
Grand Total	**2,516**

Fewer than 1% of carriers request their results with the number of hemoglobin carrier requests remaining low compared to the number of carriers. The NSO-AC struck a task force in 2020 to examine different carrier disclosure models that could be considered in Ontario due to the low uptake in carrier requests. While the task force is looking at Sickle Cell Disease in particular, the modeling could be applied to other conditions screened by NSO, such as Cystic Fibrosis and MPS1H. The task force work wrapped up in 2023.

2.3 Cystic Fibrosis

The number of screen positives in 2023 continued to decrease from previous years. There were 44 referrals this year compared to 56 in 2022. There were 19 Type 1 referrals (genotypes consistent with a high risk of a diagnosis of CF), 10 Type 2 referrals (genotypes consistent with a high risk for a *CFTR* -related disorder NOT meeting CF diagnostic criteria) and 15 Type 3 referrals (genotypes of uncertain clinical significance).

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Table 23. The PPV calculations for the current and past screening algorithms.

Additional information	PPV (Primary)	PPV (Primary + Variant)	PPV (Primary + Variant + Secondary)	% of Outcomes Unknown
Past (Jul 28, 2019 - Mar 18, 2020) Cat A	82.4%	100.0%	100.0%	5.6%
Past (Jul 28, 2019 - Mar 18, 2020) Cat B	2.1%	9.9%	9.9%	3.9%
Past (Jul 28, 2019 - Mar 18, 2020) Cat C	0.0%	1.7%	1.7%	2.8%
Past (until Mar 18, 2020) ALL	7.8%	14.7%	14.7%	3.7%
Current (Mar 19, 2020 - Dec 31, 2023) Type 1	96.7%	100.0%	100.0%	0.0%
Current (Mar 19, 2020 - Dec 31, 2023) Type 2	1.7%	100.0%	100.0%	9.1%
Current (Mar 19, 2020 - Dec 31, 2023) Type 3	10.8%	75.7%	75.7%	1.3%
Current (Mar 19, 2020 - Dec 31, 2023) ALL	**43.4%**	**92.0%**	**92.0%**	**3.0%**

2.4 ENDOCRINOLOGY

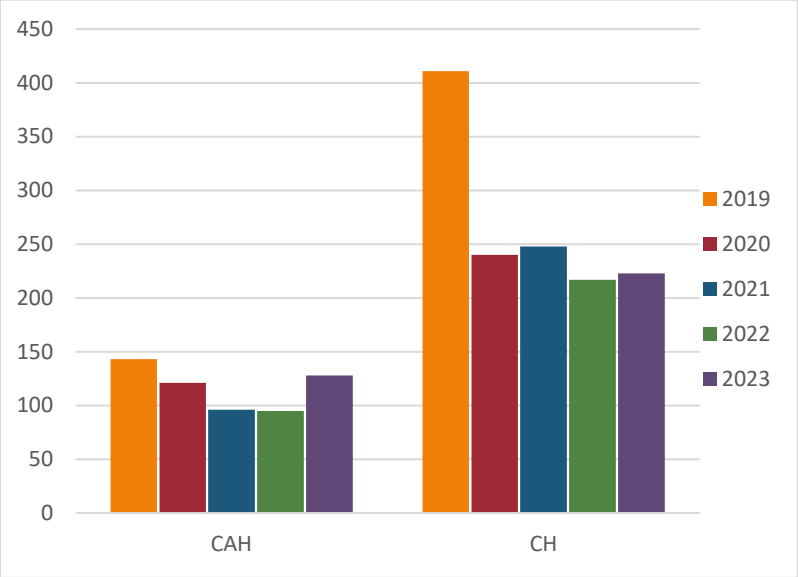

Figure 12. The total number of congenital adrenal hyperplasia and congenital hypothyroidism screen positives between 2019-2023.

The number of screen positives for CAH increased compared to last year. The number of screen positives for CH increased compared to 2022 but is still below referral levels for 2019-2021.

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Table 24. The PPV calculations for the current and past screening algorithms.

Disease	Additional information	PPV (Primary)	PPV (Primary + Variant)	PPV (Primary + Variant + Secondary)	% of Outcomes Unknown
Congenital Hypothyroidism	Past (Jun 12, 2018 - Jul 3, 2019)	16.0%	23.8%	23.8%	0.2%
	Current (Jul 4, 2019 - Dec 31, 2023)	**22.0%**	**38.5%**	**38.5%**	**0.9%**
Congenital Adrenal Hyperplasia	Past (Sept 2, 2016 - Jun 11, 2018)	5.7%	7.0%	7.4%	2.1%
	Current (Jun 12, 2018 - Dec 31, 2023)	**5.5%**	**6.5%**	**6.5%**	**2.2%**

2.5 METABOLIC

NSO began screening for guanidinoacetate methyltransferase (GAMT) deficiency in October 2022. GAMT screening involves a two-tier screening approach. First tier screening measures guanidinoacetate (GUAC) using a derivatized method. Second tier measures GUAC using LC-MS/MS. Approximately 3 infants are expected to be referred annually in Ontario. No infants were reported as screen positive in the first three months of screening in 2022. There were screen positive referrals in 2023.

There was a slight increase in the number of referrals for MSUD and HCY in 2023. However, in general there has been a reduction in the number of referrals for amino acidopathies over time. This is likely in part due to the disorder logic changes implemented mid 2019 but could also be due to the TPN hold initiative underway across some of the NICUs in the province. By holding TPN for 3 hours prior to obtaining the newborn screening sample it is predicted that this would lead to a reduction in the amino acidopathies false positive referrals. In 2020, 6 hospitals were participating and in 2021, 20 hospitals were participating. In 2022 and 2023, 1,172 and 1,010 requisitions respectively were received indicating TPN had been held. Internal reviews are still ongoing to determine if holding TPN prior to NBS collection has had an impact. There is also a research study underway comparing a TPN hold of 1 vs. 3 hours.

CPT1, CPT2, and GA2 referrals are all categorized as FAOD other in the table below. None of these are primary targets of screening but can be identified through the screening process. A task force has been formed to formally review CPT1 to decide if it should officially be added as a primary target of screening. Work is expected to be complete by 2024.

The C5 cutoff for IVA was changed from 0.67 to 1.00 on Feb 18, 2020. This resulted in a significant decrease in the number of IVA referrals in 2020 which continued in the subsequent years.

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Table 25. The PPV calculations for the current and past (where applicable) screening algorithms.

Disease	Additional information	PPV (Primary)	PPV (Primary + Variant)	PPV (Primary + Variant + Secondary)	% of Outcomes Unknown
GAMT Deficiency		**0.0%**	**0.0%**	**0.0%**	**0.0%**
Glutaric Aciduria type 1		**9.6%**	**9.6%**	**23.9%**	**0.5%**
Isovaleric Acidemia	Past (until Feb 17, 2020)	3.0%	4.2%	4.2%	0.0%
	Current (Feb 18, 2020 - Dec 31, 2023)	**17.0%**	**17.0%**	**17.0%**	**4.0%**
PA/MMA/CblA/CblB	Past (Feb 16, 2010 - Apr 21, 2013)	3.7%	3.7%	8.3%	0.5%
	Current (Apr 22, 2013 - Dec 31, 2023)	**3.9%**	**4.2%**	**9.5%**	**5.5%**
FAOD - Other		**8.2%**	**52.3%**	**52.8%**	**1.0%**
LCHAD/TFP		**81.3%**	**81.3%**	**93.8%**	**0.0%**
VLCAD	Past (until Dec 14, 2021)	7.1%	12.2%	14.0%	1.2%
	Current (Dec 15, 2021 - Dec 31, 2023)	**8.2%**	**19.7%**	**19.7%**	**0.0%**
CUD	Past (until Mar 4, 2014)	5.5%	5.5%	5.5%	0.0%
	Current (Mar 5, 2014 - Dec 31, 2023)	**7.9%**	**8.4%**	**8.4%**	**1.8%**
MCAD	Past (Sep 1, 2016 - Jul 28, 2019))	18.8%	20.1%	21.5%	0.6%
	Current (Jul 29, 2019 - Dec 31, 2023)	**52.9%**	**65.9%**	**65.9%**	**1.2%**
Citrullinemia/ASA		**16.7%**	**21.5%**	**21.5%**	**2.3%**
Homocystinuria	Past (until Jul 28, 2019)	**0.4%**	**0.4%**	**4.3%**	**1.0%**
	Current (Jul 29, 2019 - Dec 31, 2023)	**3.7%**	**3.7%**	**25.9%**	**0.0%**
Phenylketonuria	Past (until Jul 28, 2019)	**14.3%**	**27.5%**	**27.5%**	**0.0%**
	Current (Jul 29, 2019 - Dec 31, 2023)	**21.2%**	**44.9%**	**44.9%**	**1.2%**
MSUD	Past (until Nov 14, 2011)	3.8%	3.8%	3.8%	0.0%
	Current (Nov 15, 2011 - Dec 31, 2023)	**7.9%**	**9.5%**	**9.5%**	**2.3%**
Tyrosinemia	Past (Sep 14, 2009 - Sep 19, 2011)	1.4%	1.4%	1.4%	0.0%
	Current (Sep 20, 2011 - Dec 31, 2023)	**8.9%**	**8.9%**	**11.4%**	**3.5%**
Galactosemia	Past (until Jan 12, 2014)	35.7%	41.4%	41.4%	1.4%
	Current (Jan 13, 2014 - Dec 31, 2023)	**17.4%**	**36.5%**	**36.5%**	**0.0%**
Biotinidase Deficiency	Past (Jan 13, 2014 - Jul 2, 2014)	2.1%	37.5%	37.5%	0.0%
	Current (Jul 3, 2014 - Dec 31, 2023)	**7.4%**	**42.1%**	**42.1%**	**0.9%**
MPS1H		26.7%	60.0%	60.0%	0.0%

2.6 IMMUNOLOGY

The number of screen positive referrals for SCID decreased from 31 in 2022 to 21 in 2023.

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Table 26. The PPV calculations for the current and past screening algorithms.

Additional information	PPV (Primary)	PPV (Primary + Variant)	PPV (Primary + Variant + Secondary)	% of Outcomes Unknown
Past (Jan 6, 2020 - Feb 28, 2021)	30.8%	30.8%	30.8%	30.4%
Current (Mar 1, 2021 - Dec 31, 2023)	**15.6%**	**17.8%**	**17.8%**	**14.5%**

*Cells are highlighted in red when >10% of outcomes are unknown for a particular disorder or group of disorders.

2.7 NEUROLOGY

Spinal Muscular Atrophy (SMA) was added as a pilot to the newborn screening panel on January 13, 2020 and officially to the panel on July 27, 2020. SMA screening is performed by screening for homozygous deletions or conversions of the *SMN1* gene and copy number identified of 4 or less of the *SMN2* gene (*SMN2* copy number >4 are screen negative). Carriers are not identified through this screening methodology. Since screening began 6 infants were screen positive for SMA in 2020, 8 in 2021, 12 in 2022, and 19 in 2023.

Table 27. The PPV calculations for the current screening algorithm.

PPV(Primary)	PPV (Primary + Variant)	PPV (Primary + Variant + Secondary)	% of Outcomes Unknown
100.0%	**100.0%**	**100.0%**	**0.0%**

2.8 CARDIOLOGY

Table 28. Age at time of screen positive

Age at Screen Positive	Total No.
< 24 hours	<5
24-48 hours	162
> 48 hours	<5
Not available	<5
Grand Total	168

There were 168 CCHD screen positives in 2023, most of which were screened within 24-48 hours of life.

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Table 29. Definitive diagnosis for CCHD Screen Positives (individual years and cumulative)

Definitive Diagnosis Categorization	2023	2022	2021	2020	2019
Primary target	**<5**	**6**	**9**	**11**	**15**
Secondary target	**89**	**61**	**69**	**48**	**36**
Coarctation of the aorta	<5	<5	<5	<5	<5
Ebstein anomaly	<5	0	0	<5	<5
Interrupted aortic arch		0	<5	0	0
Infection	5	6	9	8	7
Persistent fetal circulation *(including pulmonary hypertension and delayed transition)*	19	11	13	6	5
PPHN**	15	9	18	8	-
Pulmonary disease *(non-infectious)*	48	34	25	24	20
Double outlet right ventricle	0	0	0	0	<5
Incidental Finding	**27**	**31**	**38**	**47**	**44**
CHD *arrhythmia*	0	<5	<5	0	0
CHD *structural*	<5	10	15	7	10
CHD *Other*	11	10	5	13	<5
Other	<5	<5	6	11	12
No disease, no definitive diagnosis	8	6	11	16	18
Not affected	**48**	**49**	**51**	**90**	**72**
Lost to follow up	**0**	**<5**	**0**	**<5**	**0**
Grand Total	**168**	**148**	**167**	**197**	**167**

**Please note PPHN was previously included in persistent fetal circulation but has since been separated out.

Of the 168 screen positives received in 2023, 120 were diagnosed with a critical congenital heart defect, a secondary CHD target or were diagnosed with an incidental finding such as pulmonary disease or infection, and 48 were found to be not affected.

2.8.1 CCHD Definitive Diagnosis Data and Positive Predictive Values

In 2023, the Positive Predictive Value (PPV) for CCHD screening was 2.38% for primary targets and 55.36% for primary and classical secondary target diseases. Cumulatively since the beginning of the program, the PPV is 5.10% for primary targets, and 37.87% for primary and classical secondary target diseases. Of the 1,117 screen positives since the initiation of CCHD screening (the lost to follow up DERFs have been excluded from analysis), 452 (40.47%) have been determined to be not affected after diagnostic follow up.

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Table 30. PPV calculations for CCHD Screen Positives 2019-2023 and cumulative.

Data set	PPV (Primary)	PPV (Primary + Secondary)	Total No. Screen Positive	Outcome Classification				
				Primary Targets	Secondary Targets	Incidental Findings	Not Affected	Lost to follow up
2019	9.00%	30.50%	167	15	36	44	72	0
2020	5.60%	30.10%	197	11	48	47	90	<5
2021	5.40%	46.70%	167	9	69	38	51	0
2022	4.08%	45.58%	148	6	61	31	49	<5
2023	2.38%	55.36%	168	<5	89	27	48	0
Cumulative	5.10%	37.87%	1,119	57	366	242	452	<5

2.9 HEARING

Table 31. Number of risk factor screen positive babies in 2023

Risk Factor	2023 # screen positives (% rate)	2022 # screen positives (% rate)	2021 # screen positives (% rate)	2020 # screen positives (% rate)
CMV	184 (0.13%)	190 (0.13%)	140 (0.097%)	159 (0.12%)
Genetics	43 (0.031%)	37 (0.027%)	32 (0.022%)	22(0.016%)

The table above shows the number of risk factor screen positive infants for the last three years. In 2023, there were 184 CMV screen positive infants. The CMV screen positive rate was 0.13%. This was a decrease in 6 cases from the year previously. We are aware of some cases of cCMV that were ascertained clinically but missed through screening (i.e. false negatives) in 2023.

There were 43 infants with genetic screen positive results in 2023. Since October 19, 2020, reflexive screening for the GJB2 p.(V37I) variant has been performed for infants who have a single GJB2 variant identified on the common variant panel use for genetic risk factor screening. The GJB2 p.(V37I) variant is therefore only reported in compound heterozygous state with another variant on the panel. That is, homozygosity for this variant is not assessed. The referral rate has since remained consistent. There were not any SLC26A4 screen positives in 2023. This is not unexpected; it is well known that SLC26A4-related PHL is less common than GJB2/6-related PHL. We are not aware of any missed cases of PHL involving the variants included on the screening panel. We continue to evaluate the frequency of variants screened in our population and they are as expected.

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2.9.1 CMV screen positive referrals and outcomes

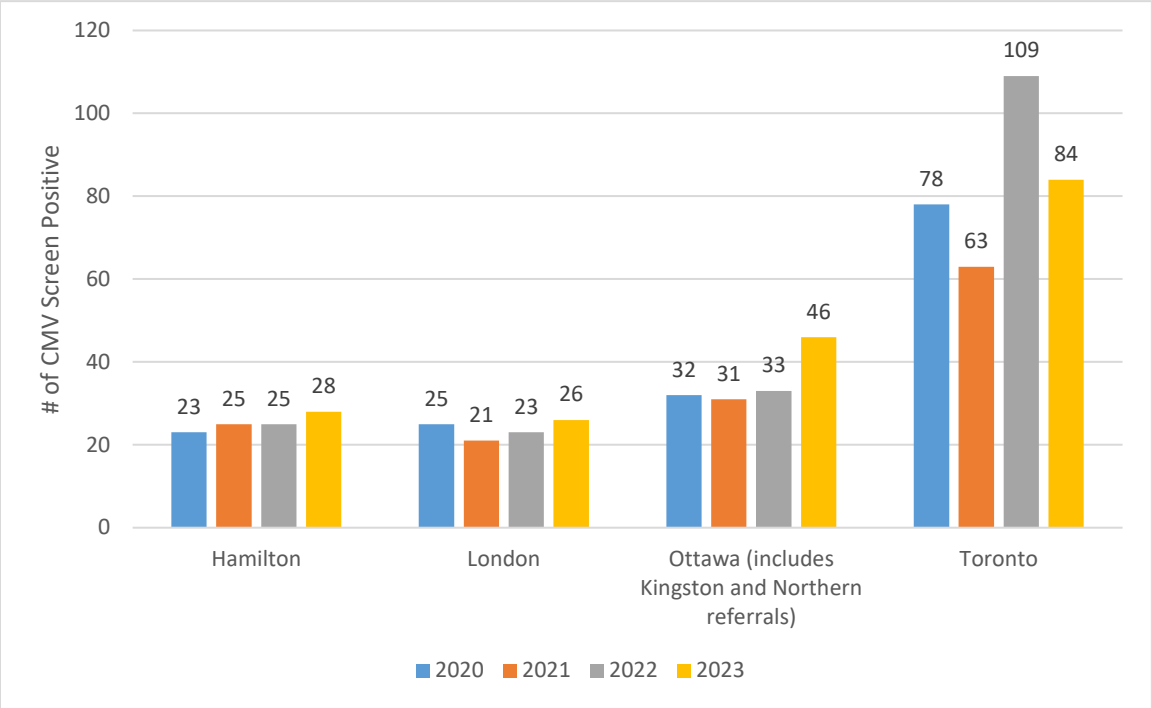

Figure 13. CMV screen positives by referral region

The figure above shows the breakdown of CMV screen positive referrals by region. Similarly to the previous year, Toronto received the largest number of CMV referrals (84/184, 46%), followed by Ottawa (46/184, 25%) Hamilton (28/184, 15%) and London (26/184, 14%). The Ottawa referral region includes the following areas; Ottawa which had 24 cases, Kingston which had 8 and Northern Ontario which had 14. This distribution is similar to that observed in 2022; however, Ottawa had an increase in referrals (13 more than the previous year) and Toronto had decrease (25 fewer than the previous year). There were no changes in the referral regions, therefore it is difficult to ascertain what contributed to these changes.

The majority of CMV screen positive infants were referred to a community pediatrician for their initial assessment (164/184, 89%). The remaining infants were referred directly to Infectious Disease (ID) for their initial assessment (20/184, 11%). This proportion is the same that was observed in 2022, where 89% were seen for their initial assessment by community pediatricians and 11% by ID. Reasons for a direct referral to ID were geographical/travel related, coverage for pediatricians, the infant was hospitalized at time of referral, or the infant had symptoms of cCMV at the time of retrieval.

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Table 32. Confirmatory urine CMV PCR results for CMV screen positive infants

	Confirmatory Urine CMV PCR Results								
	Results available			Results not available					
DBS Screening Result	Detected	Not Detected	TOTAL available	Not Done	Pending	Total not available	**GRAND TOTAL 2023**	**GRAND TOTAL 2022**	**GRAND TOTAL 2021**
Robust	155	11	166	6	<5	7	173	170	120
Borderline	6	<5	10	<5	0	<5	11	20	20
TOTAL	161	15	176	7	<5	8	184	190	140

The table above summarizes the urine CMV PCR results in 2023. Urine CMV PCR results are available for 176 (96%) of the screen positive infants. Of these, 160 (91%) had positive/detected results. There were 16 cases (9%) where the DBS was positive, but the confirmatory urine CMV PCR results were negative/not detected. These infants were referred to ID for further testing and interpretation of results. On June 26th, 2023, NSO started a new initiative with Public Health Ontario (PHO) where all urine samples are sent to the PHO lab for initial testing and if the result is negative further testing is completed. This involves a viral culture at the PHO lab and the urine sample is also sent to NSO for CMV PCR testing. If the follow-up testing is negative (culture at PHO lab and NSO urine CMV PCR result) then the patient is discharged from the program as a false positive screening result.

NSO introduced a result category of "borderline positive" in 2021 to help parse out the screen positives with weaker viral amplification that may be more likely to have negative urine CMV PCR results. Data from 2023 showed that a larger proportion of borderline screen positives had negative urine CMV PCR results as compared to robust screen positives. This is similar to 2022 data that showed 7/20 of borderline screen positives cases had negative urine CMV PCR results as compared to 8/164 of robust screen positives. This suggests that a borderline result at NSO is more likely to result in a negative urine CMV PCR result but is not entirely predictive on its own.

Table 33. Definitive diagnoses for CMV screen positive infants

Definitive Diagnosis	Positive Urine CMV Results	Negative Urine CMV PCR Results	Urine CMV PCR not done	Urine CMV PCR Pending	2023 Total	2022 Total	2021 Total
Asymptomatic cCMV	120	0	<5	<5	**123**	**145**	**97**
Symptomatic cCMV	36	0	0	0	**36**	**22**	**18**
Indeterminate/ Inconclusive	0	7	0	0	**7**	**6**	**<5**
cCMV excluded (false positive)	0	8	0	0	**8**	**6**	**7**
Non-congenital CMV	<5	0	0	0	**<5**	**-**	**-**
LTFU	<5	0	5	0	**7**	**<5**	**5**
Pending	<5	0	0	0	**<5**	**8**	**11**
TOTAL	**161**	**15**	**7**	<5	**184**	**190**	**140**

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Of the CMV screen positive infants with positive confirmatory urine CMV PCR results, 75% (120/161) were deemed to have asymptomatic cCMV infection and 22% (36/161) were classified as symptomatic, with the remainder being lost to follow-up or pending. Based on the literature, we would expect that approximately 10-15% of babies with cCMV would be symptomatic. Our data this year demonstrates an increase in symptomatic patients from the year previous, with no changes to follow up assessment and treatment procedures.

Five (14%) infants with symptomatic cCMV infection were ascertained clinically prior to newborn screening results being available. This underscores the importance of screening, as symptoms of cCMV infection can be subtle and non-specific, making clinical diagnosis a challenge. In the symptomatic group, 9 (25%) infants had PHL identified at the initial diagnostic audiology assessment. There were no infants with isolated PHL. The importance of ongoing hearing surveillance must be underscored for all CMV screen positive infants as there is there is risk of developing PHL for both asymptomatic (~10%) and symptomatic (~30%) cases. It will be important to review IHP outcome information from audiologic surveillance to learn what proportion of infants develop non-congenital PHL and at what age to better understand any predictors.

The table above shows that definitive diagnoses of "indeterminate/inconclusive" and "cCMV excluded (false positive)" were primarily given to infants with negative urine CMV PCR results. We had one infant with a positive urine result with a confirmed CMV diagnosis but after assessment by an ID specialist the exposure was determined to be postnatal. Currently outcome classifications are at the discretion of the ID specialist however this topic will be brought to our DSWG for further discussion. Between January 1, 2023 and June 25th, 2023 there were 7 infants that screened positive, had negative urine result, and they all had an indeterminate/inconclusive diagnosis. After the new process that started on June 26th, 2023 there were 8 infants that had a negative urine result, and all were discharged from the program as false positive results based on follow-up testing. This demonstrates the benefit of additional testing for infants that screen positive but have a negative urine PCR result.

2.9.2 Genetic screen positive outcomes

In 2023, there were no genetic screen positive infants from the following IHP regions: Southeast, Thunder Bay, or Kenora Rainy River, and Simcoe Muskoka-Parry Sound received their first genetic screen positive referrals. Referral numbers remained relatively consistent across IHP regions, except for Central West and Tri-Region, which saw an increase in referral numbers.

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Table 34. Genetic screen positive results and PHL interventions

	Genotype Class				
Intervention	Panel/Panel Genotype	Panel/V37I genotype	TOTAL 2023	TOTAL 2022	TOTAL 2021
Cochlear implant candidate	11	0	11	11	8
Amplification	9	<5	11	9	9
Monitoring+	<5	<5	5	6	9
Surveillance**	0	13	13	11	6
Pending	0	<5	<5	0	0
LTFU	0	<5	<5		
TOTAL	22	21	43	37	32

+ Infants with minimal hearing loss are offered close audiologic monitoring
** Infants with normal hearing were offered audiologic surveillance in accordance with IHP protocols

Overall, there were 43 genetic risk factor screen positive infants in 2023, which is consistent with observations from 2022. All screen positives were due to variants identified in the gene *GJB2*. Interestingly, 12 of these infants had a family history of a first degree relative with PHL, some who were identified through genetic risk factor screening.

There were 22 infants with panel/panel genotypes, and as expected, the majority of these were confirmed to have permanent hearing loss.

There were 19 infants with panel/V37I genotypes. The majority (13/18, 72%) had normal hearing at their initial diagnostic audiology assessment and were enrolled in audiologic surveillance. The proportion of infants with normal hearing at their initial assessment was greater this year compared to 2022, where about half were identified with some degree of PHL. As more infants are screened, we will learn more about the true risks associated with the V37I variant and will continue to monitor this to ensure we are providing accurate risk estimations to families.

2.9.3 Conclusions and Future Directions

- Many efforts were put into the development of an improved workflow for consent for risk factor screening for PHL, which launched in March 2024.
- Clinical guidelines and algorithms were updated to assist with establishing a definitive diagnosis in CMV screen positive infants with negative CMV PCR results.
- We continue to improve the genetic risk factor screening positive care pathway in preparation for the inclusion of the GJB2 p.(V37I) variant on the first-tier screening panel. This would mean the reporting of homozygous p.(V37I) results as screen positive.
- There an NSO improvement pilot that launched in February 2024 to look at the feasibility, utility and accuracy of dried saliva spot screening for CMV. Infants who screen positive for CMV on the dried saliva sample and are confirmed to have cCMV will be offered to participate in the CAN HEAR study, a CIHR-funded project evaluating the best newborn screening test to detect clinically actionable congenital CMV.

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2.10 BILIARY ATRESIA

In 2023, NSO made the determination that 41/116 pale stool calls (35%) were screen positive for BA, which is defined as a stool colour assessed to be between #1-6 on the ISCC. These cases were then referred to one of the 5 PAHSC hepatologists for measurement and interpretation of a fractionated bilirubin level. Similarly to the DBS screen positive referrals, Toronto received the largest percentage of referrals.

The average age in days at referral was 49 and 80%of referrals happened within 1 day (range 0-3 days) of the initial contact with the NSO BA clinical team. Once the case was referred it took an average of 1.5 days (range 0-7 days) to complete the initial bloodwork.

39 cases had diagnostic testing. 28 (72%) were discharged from the PAHSC due to fractionated bilirubin measurements below the threshold for cholestasis. 11 (28%) showed evidence of cholestasis, defined as a conjugated bilirubin >17 umol/L.

Table 35. The definitive diagnosis classification of the screen positive BA referral cases in 2023.

Definitive Diagnosis Categorization	2023
Primary Target – Biliary Atresia	<5
Secondary Target- Classic	
Infection - Other (Urinary tract infection, Viral Gastroenteritis)	<5
Incidental – Idiopathic Cholestasis (*1 Immune Hemolytic Disease, 1 Dehydration*)	5
Not Affected	28
Lost to Follow up	<5
DERF Pending	<5
Grand Total	41

Table 36. The positive predictive value of BA screening (the cases where outcomes were unknown were excluded from the calculation).

Year	Positive Predictive Value		Total No. of Screen Positives	Outcome Classification					
	PPV (Primary Target)	PPV (Primary Target + Classic Secondary)		Primary Target	Incidental		No	Other (lost to follow up)	DERF pending
					Classic Secondary Targets	All Other Incidental			
2023	7.9%	13.2%	41	<5	<5	5	28	<5	<5

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One of the main reasons to screen for BA is to identify cases of earlier. NBS for BA has resulted in an earlier median age at diagnosis and surgical intervention for infants born in ON.

Table 37. Median age at diagnosis and Kasai procedure for cases of biliary atresia.

Prior to screening For Biliary Atresia		**Cases Identified through the Biliary Atresia Screening Program**	
Median age at Diagnosis	Median age of Kasai procedure	Median age at Diagnosis	Median age of Kasai procedure
62 days	66 days	46 days	50 days

2.10.1 Future Directions

- A simplified BA missed case reporting web portal was developed to decrease the information the GI specialists need to input to notify NSO of a discrepant case. This was launched February 2024.
- Since it is suggested that submitters distribute the ISCC at the time of performing the CCHD screen, a check box will be added to the CCHD screening form in year 2 of the program, which should be completed by the submitter to confirm whether the family has been given an ISCC. This information will be collected, and completion rates will be reported back to the submitters on their report cards.
- A year 2 improvement is underway to change the wording on the red banner of the ISCC to emphasize that this program is concerned with pale stool. This is planned to happen with the first printing of 2024. See image below for proposed change.
- In year two there is a survey planned to solicit feedback from parents and healthcare providers about the program and the ISCC, to help inform program improvements such as BA messaging, education, and the ISCC.
- Efforts will begin to re-evaluate the possibility of adapting an existing BA screening app for use in Ontario, and piloting this alongside our existing ISCC.

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3. SCREENING SYSTEM SUPPORT

2.1 BIOCHEMICAL

NSO receives samples for biochemical testing – both for diagnostic testing and monitoring of affected patients. In 2023, NSO received 5,728 samples from 3,090 patients. Monitoring samples accounted for 1,666 of the samples received. VLCAD enzymology requests accounted for 49 samples and were received from Ontario as well as nationally. Screen positive follow up accounted for 639 of the 5,728 samples received.

2.2 MOLECULAR

NSO performs molecular diagnostic testing for targets of newborn screening, nuclear mitochondrial conditions, and primary immune deficiencies. The number of requests have increased annually, with 484 samples received in 2020, 532 in 2021 and 795 in 2022. In 2023, 1,058 samples were received of which 118 were requests for targets of screening following a positive NBS referral to one of the regional treatment centres.

2.3 SURVEILLANCE FOR FALSE NEGATIVES

2.3.1 POST MORTEM

NSO receives post mortem samples at the request of the coroner's office. The sample types collected and sent can include blood, bile and whole blood/DNA. The samples are typically run for inborn errors of metabolism. It is a service for the coroner's office in their review of what caused the infant/child's death but also serves as a quality review for NSO to ensure that no cases were missed. In 2023, NSO received 226 post mortem case requests.

2.3.2 DISCREPANT RESULTS

Discrepant result cases are situations in which an infant either screen positives for a condition with a high PPV and diagnostic investigations are normal without a clinical explanation for the screening results or an infant has a negative newborn screen but is picked up clinically (either symptomatic or through familial cascade testing) to have a condition for which NSO screens. NSO tracks discrepant results for all the screening programs – dried blood spot, CCHD, and BA.

2.4 RESEARCH

NSO's research program focuses on developing novel laboratory methods and clinical biomarkers, most recently using metabolomics and genomics, studying policy, and clinical research in newborn screening. NSO is involved in approximately 30 research projects, 13 of which are led by NSO. NSO's involvement varies depending on the project, such as secondary use of NSO data and data analysis, secondary use of NSO samples, testing of external samples, review and analysis of screening data, interviews and surveys of collaborators. NSO research studies are reviewed and approved by the CHEO Research Ethics Board, and

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studies using residual newborn screening samples are performed in accordance with NSO's policy on Storage and Secondary Use of Newborn Screening Samples.

TPN hold
A research study is currently underway examining the effect of differential holding of parenteral nutrition on levels of amino acids used as biomarkers for newborn screening. The study is investigating whether there is a difference between target amino acid levels after holding TPN administration for 1 hour (modified screening protocol) and 3 hours (current screening protocol) within individual participants. In 2023, recruitment for the study and sample testing were completed. Data analysis is pending.

SMA economic evaluation
This project includes three streams of work. Part one is a systematic literature review on health economic evaluations of newborn screening (NBS) for spinal muscular atrophy (SMA); the manuscript was written in 2023 with publication anticipated in 2024. Part two, currently underway, involves developing a health economic model for NBS and treatment for SMA patients in Canada. Using Canadian costing parameters and Newborn Screening Ontario statistics, preliminary results indicate that screening and early treatment of SMA in Canada is cost-saving compared to not screening. This provides critical Canadian data on the cost-effectiveness of SMA screening and treatment, aiding policy and decision-makers. Part 2 is set to be completed in 2024, with a manuscript in preparation. Part three is a Pan-Canadian collaboration group for screening programs, the NBS Working Group, which includes leaders from all Canadian provinces and territories. The group has been established and has held multiple meetings to discuss topics such as knowledge sharing and NBS metrics. The group is working with Canada's Drug Agency (CDA) to prepare a report for the federal government on the need for a national newborn screening committee.

CMV and hearing loss genetics screening - manuscripts on NSO experience
Two manuscripts summarizing implementation and first years' experience with CMV and genetic screening for permanent hearing loss were prepared in 2023, with publication anticipated in 2024.

CH machine learning
In Ontario elevated thyroid stimulating hormone (TSH) is used to screen for congenital hypothyroidism (CH), unfortunately this single analyte screening approach results in a large number of false positive screening results. Typical artificial intelligence approaches fail rapidly when exposed to the problem of rare disease screening. However, by integrating specific machine learning techniques for rare event detection and developing new approaches this research aims to improve the specificity of CH screening while maintaining high sensitivity. Undergraduate student Alexander De Furia working with Paula Branco in the School of Electrical Engineering and Computer Science and Matthew Henderson at NSO have been awarded the 2024 Cognos Prize for Innovation, Collaboration, and Ingenuity in Computer Science by the Faculty of Engineering at the University of Ottawa for the novel hierarchical filter-based learning algorithm. With promising results to date, the research team are continuing to refine their approach for machine learning based CH screening in 2024.

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Appendix A: Classifications 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 1A. The definitions of the classification of true positive.

True Positive?	Definition	Example
Primary	confirmed diagnosis of a targeted condition	Classical PKU
Not Affected	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 2A. The true positive categories.

True Positive Categories	
Generic	Detailed
Not Affected	Not Affected
Primary	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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Appendix B: Disease Prevalence and PPV for High PPV Referrals

High PPV referrals are referrals where the screening values are suggestive of disease. These referrals are classified as semi-urgent or urgent and are sometimes also alert referrals with same day confirmation testing.

Table 1B. The disease prevalence rates (including both screen positive and missed cases) for each primary target screened by NSO via dried blood spot screening and positive predictive value calculations for high PPV referrals.

Diseases	Date Screening Initiated	% of Outcomes Unknown	Disease Prevalence of Primary Targets	Positive Predictive Value (PPV) for High PPV Referrals
Congenital Hypothyroidism (CH)	4-Apr-06	0.8%	1 in 2,163	85%
Congenital Adrenal Hyperplasia (CAH)	14-May-07	1.0%	1 in 21,169	32%
Sickle Cell Disease	24-Nov-06	1.8%	1 in 2,772	95%
Cystic Fibrosis (CF)	9-Apr-08	0.9%	1 in 4,674	81%
Severe Combined Immune Deficiency (SCID)	12-Aug-13	5.7%	1 in 57,234	41%
Glutaric Aciduria type 1 (GA1)	9-Aug-06	0.5%	1 in 131,556	100%
Guanidinoacetate Methyltransferase Deficiency (GAMT)	17-Oct-22	0.0%	Unknown	Unknown
Isovaleric Acidemia (IVA)	9-Aug-06	0.2%	1 in 156,223	57%
Propionic Acidemia (PA)	9-Aug-06	2.8%	1 in 227,333	34%
Methylmalonic Acidemia (MMA)			1 in 166,638	
Cobalamin A Deficiency			1 in 1,249,784	
Cobalamin B Deficiency			1 in 1,249,784	
Long-chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHAD)	9-Aug-06	0.0%	1 in 208,297	88%
Trifunctional Protein Deficiency (TFP)			1 in 2,499,567	
Very-long-chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)	9-Aug-06	1.1%	1 in 75,744	60%
Carnitine Uptake Defect (CUD)	9-Aug-06	0.8%	1 in 75,744	21%
Medium-chain Acyl-CoA Dehydrogenase Deficiency (MCADD)	4-Apr-06	0.4%	1 in 15,353	87%
Citrullinemia (CIT)	9-Aug-06	2.8%	1 in 124,978	39%
Argininosuccinic Acid Lyase Deficiency (ASA)			1 in 178,541	
Cystathionine beta-synthase (CBS) deficiency	9-Aug-06	0.9%	1 in 833,189	Unknown
Phenylketonuria (PKU)	4-Apr-06	0.2%	1 in 16,233	67%
Maple Syrup Urine Disease (MSUD)	9-Aug-06	1.3%	1 in 131,556	21%
Tyrosinemia type 1	9-Aug-06	1.6%	1 in 277,730	71%
Galactosemia (GALT)	19-Feb-07	0.5%	1 in 51,585	20%
Biotinidase Deficiency (BIOT)	19-Feb-07	0.6%	1 in 55,103	19%
Mucopolysaccharidosis type 1 Hurler (MPS1H)	27-Jul-20	0.0%	1 in 120,419	27%
Spinal Muscular Atrophy (SMA)	13-Jan-20	0.0%	1 in 12,433	100%

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Appendix C: Glossary

17OHP = 17-hydroxyprogesterone
AAAC = amino acid and acylcarnitine
ASA = argininosuccinic acid lyase deficiency
BA = biliary atresia
BIOT = biotinidase deficiency
CAH = congenital adrenal hyperplasia
CblA = cobalamin A defects
CblB = cobalamin B defects
CCHD = critical congenital heart disease
cCMV = congenital cytomegalovirus
CF = cystic fibrosis
CH = congenital hypothyroidism
CHD = congenital heart defect
CHEO = Children's Hospital of Eastern Ontario
Cit = citrullinemia
CMV = cytomegalovirus
CPT1 = carnitine palmitoyltransferase type 1
CPT2 = carnitine palmitoyltransferase type 2
CUD = carnitine uptake disorder
DBS = dried blood spot
DERF = diagnostic evaluation report form
ENDO = endocrinology
FAOD = fatty acid oxidation defects/disorders
GA1 = glutaric acidemia type 1
GA2 = glutaric acidemia type 2
GALT = galactosemia
GAMT = guanidinoacetate methyltransferase
GI = gastroenterologist
GUAC = guanidinoacetate
HbS/β Th = sickle cell beta-thalassemia
HbSC = hemoglobin sickle C Disease
HbS/HPFH = sickle hemoglobin and hereditary persistence of fetal hemoglobin
HbSS = Sickle Cell Disease
HCP = health care provider
HCY - homocystinuria
HGB = hemoglobinopathy
HHSC = Hamilton Health Sciences Centre
HSC = The Hospital for Sick Children
ID = infectious disease
IHP = Infant Hearing Program
ISCC = infant stool colour card
IV = intravenous
IVA = isovaleric acidemia
KGH = Kingston General Hospital
KP = Kasai procedure
LCHAD = long chain 3-hydroxyacyl-CoA dehydrogenase deficiency
LC-MS/MS = liquid chromatography with tandem mass spectrometry
LHSC = London Health Sciences Centre
LTFU = lost to follow up
MCAD = medium chain acyl-CoA dehydrogenase deficiency
MCCSS = The Ministry of Children, Community and Social Services
MET = metabolic
MMA = methylmalonic acidemia
MPS1 = mucopolysaccharidosis type 1
MPS1H = mucopolysaccharidosis type 1 Hurler
MSUD = maple syrup urine disease
NBS = newborn screen
NICU = neonatal intensive care unit
NSO = Newborn Screening Ontario
NSO-AC = Newborn Screening Ontario Advisory Council
PA = propionic acidemia
PAHSC = Pediatric Academic Health Science Centre
PCR = polymerase chain reaction
PHL = permanent hearing loss
PHO = Public Health Ontario
PKU = phenylketonuria
PPHN = persistent pulmonary hypertension
PPV = positive predictive value
RN = registered nurse
SCID = severe combined immune deficiency
SMA = spina muscular atrophy
TAT = turn around time
TFP = trifunctional protein deficiency
TLU = test level unsatisfactory
TPN = total parenteral nutrition
TSH = thyroid stimulating hormone
TYR = tyrosinemia
TYR1 = tyrosinemia type 1
Unsat = unsatisfactory
VLCAD = very long chain acyl-CoA dehydrogenase deficiency

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