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

Annual Report to the Newborn Screening Ontario Advisory Council
Calendar Year 2024

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
www.newbornscreening.on.ca · newbornscreening@cheo.on.ca

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

For the first time in 5 years, the birth rate has increased to projected pre-COVID levels, with a significant ~5% jump to over 146,000 newborns in 2024. This is a consistent sign of post pandemic growth, and we have certainly felt its impacts across the system. For example, there is a comparable increase in the number of screen positives that have been referred this year as well as a corresponding increase in unsatisfactory samples. While some of the increased unsatisfactory rate is due to increasing volume, the NSO team has also monitored this indicator on the submitter report cards, and has reached out to multiple submitter sites with increasing unsat rates to provide guidance and education. The issues experienced in previous years with samples being delayed or lost in the transport system have improved significantly through a strong partnership with our courier vendors.

The first quarterly indicator report went out to regional treatment centres (RTCs) in 2024. This report provides four key quality indicators for each treatment centre as a whole, as well as indicators stratified by medical specialty. The indicators included are as follows: timeliness of retrieval, timeliness of initial diagnosis, timeliness of definitive diagnosis, and the timeliness as well as quality of DERF (Diagnostic Evaluation Report Form) feedback. The feedback and discussions with the RTCs have resulted in modifications to existing workflows and improvements across most indicators. One key improvement that will be noted in this annual report is the DERF submission rate; only ~6% of 2024 DERFs were still outstanding at the time the data was pulled.

NSO continues to build on a public facing brand presence with excellent success in both social media advertising and influencer campaigns. A proposal has been submitted to the MOH for a roll out of the universal hemoglobinopathies carrier disclosure model. As we await its review and funding NSO worked with three influencers who posted content about carrier information being available upon request. This content was posted in late August and we saw a resulting increase in requests in September and October, directly resulting from the content.

This year NSO and the National Centre for Audiology (NCA) at Western University were selected by MCCSS to become the partnered Oversight Agency for the Infant Hearing Program (IHP). The goal of the IHP Oversight Agency is to streamline oversight and support quality improvement towards achievement of international benchmarks necessary for the best possible child developmental outcomes. NSO and the NCA now oversee delivery of the core component areas of the IHP, including hearing screening, and audiology assessment, surveillance, and intervention. This includes the management of contracts/financials with IHP Lead Agencies, provision of operational support for service delivery, protocol development and training of service providers. It was a successful first year, which involved learning and discovery, and relationship-building with program partners.

Project planning and development was ongoing throughout 2024 for the launch of XALD, which involves a redesign of the core mass spectrometry assays to an underivitized multiplexed method. NSO looks forward to the launch in summer of 2025.

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1. SCREENING CHARACTERISTICS

In 2024, NSO estimated the birth rate to be 146,661, based on NBS data and data from BORN.

Table 1. The coverage of screening in Ontario for 2024.

Infants Screened	DBS Panel	CCHD	Hearing Panel
Fully	145,999	140,875	137,494
Partially	111	-	180
No screening	551	5,786	8,987
Total	**146,661**		

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.

The rate of non-screened infants increased for the hearing panel as this screen moved back to a consented model in early March 2024. More details regarding this can be found in Section 1.3.

1.1 DRIED BLOOD SPOT

The overall number of samples received by NSO in 2024 is higher than last year.

Table 2. Screening sample volumes between 2020-24.

Sample Type	2024	2023	2022	2021	2020
Satisfactory	149,013	141,186	139,779	145,785	141,548
Unsatisfactory*	2,475	1,909	1,639	1,560	1,785
Routine Screening – Total	**151,475**	**143,095**	**141,418**	**147,345**	**143,333**

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

1.1.1 INFANTS SCREENED

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

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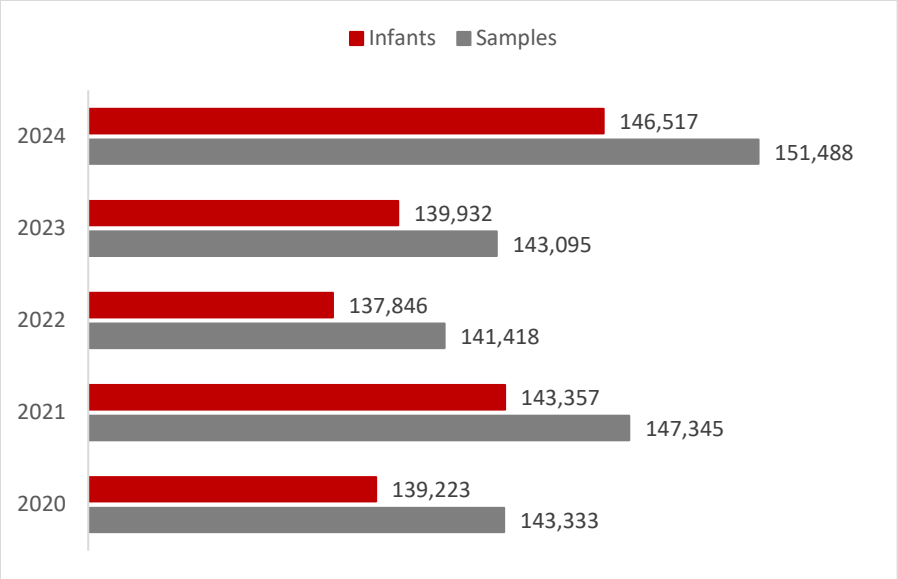

Figure 1: Total number of infants and samples screened between 2020-24.
The number of newborns is estimated by subtracting the number of samples determined to be from the same infant as another sample from the total number of received samples. This estimate be impacted by the efficiency of the linking 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 2024, NSO received 983 completed decline/defer forms. The number of declines documented using this form has increased with 248 declines in 2024 compared with 168 in 2023. The remaining 735 forms received indicated a parent's desire to defer screening, and samples were eventually received for all but 12 of these deferred cases. Seven families declined (but 5 elected to have CCHD screening). No additional information is known about the remaining 5 defer cases.

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Table 3. Declined, deferred samples indicated on card between 2020-24.

Case Type	2024	2023	2022	2021	2020
Declined/deferred form received	983	861	758	819	713
Decline	248	168	151	96	76
Deferral	735	693	607	723	637

An additional 141 declined screens were also identified via missed screen alerts. There were 96 infants for which a decline form and a DBS missed screen decline case were received/created and 11 infants for whom a decline form was completed where a sample was received. In total there were 279 infants where newborn dried blood spot screening was declined, which is a similar total to last year of 264. There were 246 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 (>5% of submitted samples). NSO will be following up with those sites to offer education and resources regarding the importance of NBS.

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1.1.3 MISSED SCREENS

Table 4. Potential missed screen alerts requiring follow-up in 2024, by reason and responsible submitter, and samples received post follow-up.

Category		Total (2024)	Total (2023)	Total (2022)
Other	Deceased/ Palliative	65 (12%)	99 (15%)	101 (15%)
	Declined	141 (26%)	112 (17%)	116 (17%)
	Sample received same day as missed screen alert	25 (5%)	<5 (<1%)	30 (4%)
	Incorrect or incomplete information (sample already received)	35 (6%)	41 (6%)	53 (8%)
	NBS done in other jurisdiction/ family moved out of province	39 (7%)	29 (4%)	24 (4%)
	Parents deferred NBS	10 (2%)	0	<5 (<1%)
	Sample collected prior to missed screen alert and received after alert	152 (28%)	227 (35%)	178 (26%)
Total: Non-Missed Screens		**467 (85%)**	**512 (78%)**	**506 (74%)**
True Missed Screens	Hospital birth midwife care	5 (<1%)	5 (<1%)	9 (1%)
	Interhospital transfer (between hospitals)	<5 (<1%)	11 (2%)	<5 (<1%)
	Intrahospital transfer (between units in same hospital)	<5 (<1%)	0	<5 (<1%)
	Intrahospital/interhospital transfer with midwife involvement	0	0	<5 (<1%)
	Sample collected, package lost	21 (4%)	69 (11%)	101 (15%)
	Not taken in error	37 (7%)	47 (7%)	54 (8%)
	Unknown reason	14 (3%)	12 (2%)	10 (1%)
Total: True Missed Screens		**80 (15%)**	**144 (22%)**	**179 (26%)**
Grand Total		**547**	**656**	**685**

There were 547 potential missed screen alerts that required follow up in 2024. Hospitals were the responsible facility in 76% of the missed screen alerts and midwives were involved in 24% of the cases.

There were 467 potential missed cases logged that were not truly missed (top section of table above). There were 65 deceased/palliative cases logged and 141 declines (fewer deceased/palliative infants but an increase in declined screens). 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 (177), 100 of the samples were delayed

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pickup by the submitter, 41 experienced shipping delays by Purolator, and 31 were both batched and had Purolator shipping delays. Five cases did not have any delays noted.

In 2024, there were 80 true missed newborn screen alerts that required follow up by NSO (bottom section of table above). Action on the part of NSO resulted in 57 of the 80 (71%) truly missed screens being completed.

1.1.4 AGE AT COLLECTION

Table 5. Age at collection for 2022-2024, initial samples only.

Age at Collection	Number of Initial Samples (2024)	% of Initial Samples (2024)	% of Initial Samples (2023)	% of Initial Samples (2022)
Less than 24 hours	830	0.56%	0.56%	0.61%
24-47 hours (1-2 days)	144,943	98.59%	98.45%	98.27%
48-71 hours (2-3 days)	855	0.58%	0.62%	0.72%
72-168 hours (3-7 days)	273	0.19%	0.24%	0.29%
Greater than 168 hours (7 days)	118	0.08%	0.14%	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.

1.1.5 UNSATISFACTORY SAMPLES

The unsatisfactory rate increased in 2024, up to 1.31% compared to 1.01% in 2023. 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 49 samples that were deemed unsatisfactory for both a lab and a data unsat reason. There were 146 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 2,329 unsatisfactory samples that required follow up.

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Table 6. Unsatisfactory samples by reason between 2020-24.

			2024	2023	2022	2021	2020
SAMPLES	Satisfactory Samples		149,013	141,186	145,220	143,333	146,099
	Unsatisfactory Samples		2,475	1,909	2,125	2,332	2,044
	Unsatisfactory Rate		**1.63%**	**1.33%**	**1.44%**	**1.63%**	**1.40%**
	Samples Collected at <24hrs		488*	457	565	547	697
	Unsatisfactory Samples excluding <24hr samples		1,987	1,452	1,560	1,785	1,347
	Unsatisfactory Rate excluding <24hr samples		**1.31%**	**1.01%**	**1.06%**	**1.25%**	**0.90%**
REASONS	Lab Unsat Reasons	Quantity of blood insufficient	905	639	927	1,297	919
		Blood spots appear scratched or abraded	174	68	142	94	118
		Blood spots are supersaturated	47	21	35	42	97
		Blood spots appear clotted or layered	525	178	217	155	202
		Blood spots appear diluted	<5	6	0	<5	<5
		Blood spots exhibits serum rings	199	44	96	70	82
		Blood spots are wet and/or discolored	11	9	9	14	10
		Other	55	25	24	25	50
	Data Unsat Reasons	Blood dot collection paper is expired	11	49	54	38	14
		Insufficient data provided	6	<5	<5	11	9
		Damaged or delayed in transit	15	0	6	5	5
		Delivered to lab > 14 days after collection	22	81	38	33	19
		Sample collected at <24hrs	514	514	565	547	697
		Other/Mislabel	33	22	22	27	6

*Of the 514 samples collected at <24 hours, 26 had additional laboratory unsatisfactory reasons so were excluded from the <24 hours count. There were 45 samples that were unsatisfactory for both data and laboratory reasons.

Of the 514 samples collected at <24 hours, the subsequent samples for these infants indicated a transfusion was given for 143 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 (~84%) of repeat samples are received within 2 weeks of the initial sample. By 6 weeks, ~93% of unsatisfactory samples have had screening completed via a repeat sample. Of the 140 cases where a repeat sample was not received, partial testing was able to be completed on existing samples for 60 cases and another 41 were data unsats.

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Table 7. Repeats received on unsatisfactory samples from 2022-24.

Time to receipt of unsatisfactory repeat sample	2024		2023		2022	
Total unsatisfactory samples	**2,329**		**1,714**		**1,440**	
< 1 week	1,439	61.8%	843	49.2%	886	61.5%
1 - <2 weeks	506	21.7%	508	29.6%	264	18.3%
2 - <3 weeks	130	5.6%	111	6.5%	86	6.0%
3 - <6 weeks	89	3.8%	119	6.9%	79	5.5%
≥ 6 weeks	13	0.6%	31	1.8%	17	1.2%
Not received	140	6.0%	102	6.0%	108	7.5%

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). The priority panel also includes hemoglobinopathies to decrease the number of transfusion repeat requests that would be required 4 months post transfusion.

In 2024, NSO performed 1,246 priority panels for unsatisfactory samples that required follow up (~53% 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 2022-24.

Time to receipt of priority panel repeat sample	2024		2023		2022	
Total priority panels	**1,246**		**880**		**718**	
< 1 week	670	53.8%	327	37.2%	397	55.3%
1 - <2 weeks	368	29.5%	343	39.0%	171	23.8%
2 - <3 weeks	84	6.7%	73	8.3%	50	7.0%
3 - <6 weeks	55	4.4%	74	8.4%	39	5.4%
≥ 6 weeks	9	0.7%	15	1.7%	9	1.3%
Not received	60	4.8%	48	5.5%	52	7.2%

There were 35 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. There was 15 cases where a repeat sample was not required.

In 2024 there were 10 TLU cases 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 2022-24.

Time to receipt of TLU repeat sample	2024		2023		2022	
Total Test Level Unsats – Routine	**90**		**64**		**70**	
< 1 week	59	65.6%	16	25.0%	33	47.1%
1 - <2 weeks	21	23.3%	33	51.6%	21	30.0%
2 - <3 weeks	<5	<5.6%	8	12.5%	7	10.0%
3 - <6 weeks	0	0	<5	<7.8%	7	10.0%
≥ 6 weeks	0	0	0	0	0	0
Not received	6	6.7%	<5	<7.8%	<5	<7.1%
Total Test Level Unsats - Urgent	**102**		**94**		**74**	
< 1 week	76	74.5%	25	26.6%	22	29.7%
1 - <2 weeks	19	18.6%	48	51.1%	33	44.6%
≥2 weeks	<5	<4.9%	17	18.1%	17	23.0%
Not received	<5	<4.9%	<5	<5.3%	<5	<6.8%

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,

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have an initial and full diagnosis established. The goal would be to have 90% of the screened population meet the benchmarks.

Each cell contains the percentage of samples 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 samples undergo first tier testing. After interpretation the majority of samples 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 149,504 initial samples went through first tier screening in 2024. Of these, 138,539 (92.7%) were screen negative on all assays after first tier. Some samples require additional testing to determine if they are negative or positive. Age at final results is the subset of samples who required additional testing (through second and third tier 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. Noticeably the age at receipt improved by 5% marks with little change to the age at collection. This can be directly tied to improvements in on time shipments by Purolator following NSO meeting with Purolator managers in 2023, to strategize ways to improve sample shipments to Ottawa.

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 2023 and 2024.

	Screening (Initial Samples) 2024 Only			Screening (Initial Samples) 2023 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	**84%**	**84%**	**98%**	**79%**	**79%**	**97%**
Biotinidase Deficiency	**84%**	**84%**	**98%**	**79%**	**78%**	**97%**
Galactosemia	**84%**	**84%**	**98%**	**79%**	**79%**	**97%**
Mucopolysaccharidosis Type 1	**84%**	**83%**	**98%**	**79%**	**78%**	**97%**
Guanidinoacetate Methyltransferase Deficiency	**84%**	**84%**	**98%**	**79%**	**79%**	**97%**
Congenital Adrenal Hyperplasia	**84%**	**84%**	**98%**	**79%**	**79%**	**97%**
Congenital Hypothyroidism	**84%**	**84%**	**98%**	**79%**	**78%**	**97%**
Cystic Fibrosis	**84%**	**84%**	**96%**	**79%**	**78%**	**94%**
Hemoglobinopathies	**84%**	**69%**	**97%**	**79%**	**65%**	**96%**
Severe Combined Immune Deficiency	**84%**	**13%**	**59%**	**79%**	**11%**	**54%**
Spinal Muscular Atrophy	**84%**	**14%**	**63%**	**79%**	**12%**	**57%**

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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, 2023 and 2024. The 'n' column represents the total number of samples that went on for additional testing.

Category	Screening (Initial Samples) 2024 Only					Screening (Initial Samples) 2023 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	31	6	8	4	6	46	5	8
CUD			239	5	7			342	5	7
FAOD			8	5	6			<5	7	8
GA1			28	5	8			35	5	8
HCY			210	9	13			47	6	14
IVA			27	6	7			31	5	7
LCHAD/TFP			41	5	8			40	7	8
MCAD			14	5	9			27	5	7
MSUD			8	6	9			22	6	10
PA/MMA/CblA&B			145	6	8			139	6	8
PKU			156	5	7			127	6	7
TYR1			17	6	13			12	6	8
VLCAD			199	5	7			183	5	7
Biotinidase Deficiency			88	6	7			104	5	8
Galactosemia			123	6	8			125	7	9
GAMT			174	10	12			191	11	16
MPS1H			841	9	19			603	9	22
CAH			660	6	8			671	6	8
CH			874	5	7			756	5	7
Cystic Fibrosis			5,906	8	13			5,552	9	12
Hemoglobinopathies	5	7	135	6	9	5	7	121	6	8
SCID	7	10	723	11	15	7	10	800	10	13
SMA	7	10	11	9	13	7	10	21	8	12

The median age (4 days) at receipt remained unchanged between 2023 and 2024, however the 90th centile decreased for the majority of conditions screened. With the implementation of changes to the homocystinuria (HCY) screening algorithm to include total homocysteine as a second-tier test, the number of samples that went on to second-tier testing increased. This also resulted in a longer median time to report for HCY.

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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, 2023 and 2024. The 'n' column represents the total number of samples that went on for additional testing.

Category	Screening (Initial Samples) 2024 Only					Screening (Initial Samples) 2023 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	31	73	76	24	26	46	50	75
CUD			239	50	72			342	49	51
FAOD			8	63	82			<5	123	144
GA1			28	49	72			35	48	50
HCY			210	146	196			47	49	51
IVA			27	49	73			31	50	74
LCHAD/TFP			41	50	73			40	50	74
MCAD			14	48	74			27	48	51
MSUD			8	49	50			22	49	52
PA/MMA/CblA&B			145	50	97			139	50	98
PKU			156	50	52			127	49	51
TYR1			17	73	75			12	72	74
VLCAD			199	50	72			183	49	59
Biotinidase Deficiency	25	26	88	50	73			104	50	73
Galactosemia	24	25	123	50	52			125	50	73
GAMT	24	26	174	146	195			191	147	289
MPS1H	25	26	841	148	386	25	27	603	150	435
CAH	24	25	733	51	98	24	25	671	50	98
CH	24	25	874	50	73	24	26	756	50	74
Cystic Fibrosis	24	26	5,906	124	222	25	26	5,552	129	176
Hemoglobinopathies	26	73	135	74	123	26	73	121	73	101
SCID	99	151	723	169	295	100	145	800	148	217
SMA	98	145	11	148	255	99	144	21	123	219

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.

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 2024 was 150,205 representing 146,377 infants. The number of infants in Ontario who had a completed CCHD screen was 140,875.

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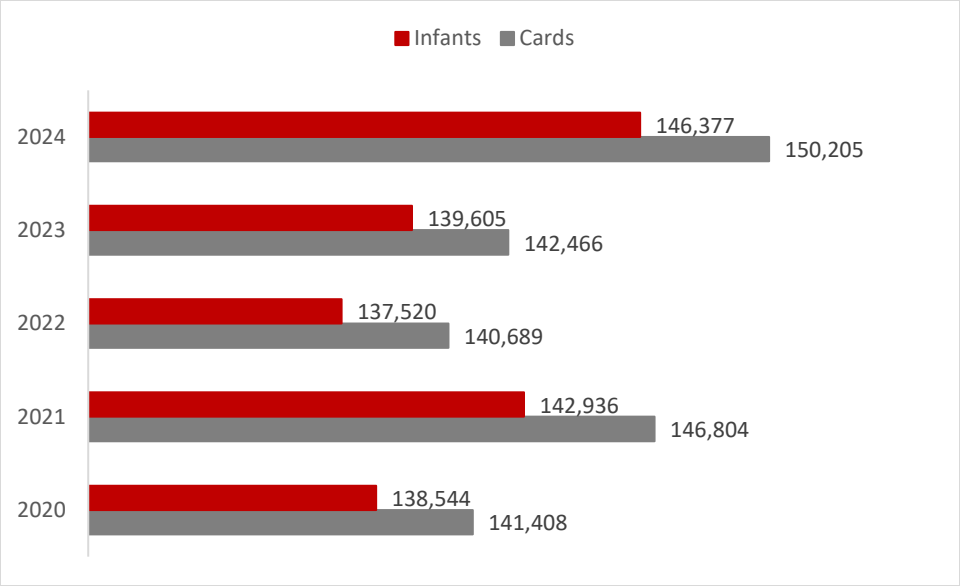

Figure 2. CCHD cards received at NSO and total number of infants between 2020-24.

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 2024, 7,914 of the requisitions submitted did not include screening information.

Table 12. CCHD cards received from 2020-24.

CCHD Cards received	2024		2023		2022		2021		2020	
Screen Completed	142,291	94.73%	135,004	94.76%	133,617	94.97%	139,264	94.86%	134,834	95.40%
Screen Not Done	7,914	5.27%	7,462	5.24%	7,072	5.03%	7,540	5.14%	6,574	4.60%
	150,205		142,466		140,689		146,804		141,408	

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, 99.12% of the screens were resolved after just one test (most often this would be a pass, but this could also be an immediate referral), which is similar to last year. Only 0.78% required a second test and 0.11% required three tests to complete the screen.

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Table 13. Tests required to complete screen between 2020-24.

Tests Done	2024		2023		2022		2021		2020	
1 Test	141,012	99.12%	133,778	99.09%	130,639	99.13%	138,050	99.13%	131,592	98.80%
2 Tests	1,103	0.78%	1,064	0.79%	997	0.76%	1,067	0.77%	1,431	1.10%
3 Tests	153	0.11%	162	0.12%	150	0.11%	147	0.11%	222	0.20%
	142,268		135,004		131,786		139,264		133,245	

1.2.2 Screens Not Done

In 2024, CCHD screens were not done on 5.27% 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 2020-24.

	2024		2023		2022		2021		2020	
'Screen Not Done' cards submitted	7,928		7,462		7,072		7,540		6,574	
Declined	64	0.81%	149	2.00%	132	1.87%	139	1.84%	66	1.00%
Infant diagnosed prenatally with heart defect	175	2.21%	146	1.96%	170	2.40%	178	2.36%	101	1.50%
Infant diagnosed with heart defect by physical exam	51	0.64%	40	0.54%	50	0.71%	70	0.93%	33	0.50%
Infant is not appropriate for screening (e.g. NICU > 7 days, on oxygen, IV in right hand, limb anomaly, etc.)	4,387	55.34%	4,413	59.14%	4,336	61.31%	4,745	62.93%	4,725	71.90%
Already done	893	11.26%	633	8.48%	503	7.11%	514	6.82%	169	2.60%
Insufficient information provided/blank card	1,430	18.04%	1,139	15.26%	1,062	15.02%	1,005	13.33%	671	10.20%
Decline/deferred (back page of form not completed)	143	1.80%	83	1.11%	113	1.60%	106	1.41%	95	1.40%
Deferred	518	6.53%	515	6.90%	441	6.24%	541	7.18%	565	8.60%
Other	267	3.37%	344	4.61%	265	3.75%	242	3.21%	149	2.30%

On September 30, 2024, NSO started to collect multiple reasons why a screen was not performed to try to better ascertain the number of cardiac defects in the province. There were 35 infants who had more than

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one reason why their screen was not performed. These extra 35 reasons are not included in the table above.

Of the decline/deferred group (143) where the back of the form was not fully completed to know if the family was declining or deferring – 118 had a CCHD screen completed and 7 had cards received indicating infant is expected to be in the NICU for > 7 days. There were 518 defer cards received. Of these 506 had a CCHD screen. Of the decline group (64) – 35 had a CCHD screen completed. In total, 63 families declined/did not complete CCHD screening (29 from the decline forms received, 10 from the defer forms, 18 from the defer/decline forms, and 6 from the missed screen notifications). There were 38 families that declined both the CCHD screen and the DBS screen.

There were 893 cards that indicated that a previous screen had already been performed and 1,430 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 2024, 674 potential missed screens were identified. There has been an increase in the number of missed screen notifications over the last few years. The largest increase in numbers last year was in the category of 'infant not suitable for screening'. The majority of the potential missed screen notifications were from hospitals (96.3%). The majority of these alerts were due to improper documentation – either the infant was screened but documentation was not sent to NSO (234) or the infant was not suitable for screening and documentation was not sent to NSO (337). There were 6 families who declined CCHD screening where documentation was not sent prior to the missed screen alert. There were 72 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 2022-24.

Category		Total (2024)	Total (2023)	Total (2022)
Other	Declined	6 (1.0%)	<5 (<1.0%)	<5 (<1.0%)
	Incorrect or incomplete information (requisition already received)	<5 (<1.0%)	10 (2.0%)	0
	Infant not suitable for screening	337 (56.0%)	252 (50.2%)	231 (46.8%)
	Infant born out of province	8 (1.3%)	7 (1.4%)	<5 (<1.0%)
	Delayed shipping of card (card received same day as alert)	16 (2.7%)	7 (1.4%)	0
	Infant was screened - documentation not sent/ sent late	234 (38.9%)	223 (44.4%)	196 (39.7%)
Total: Non-Missed Screens		**602 (89.3%)**	**502 (89.6%)**	**430 (87%)**
True Missed Screens	Missed - infant's health care provider notified	**72 (10.7%)**	**58 (10.4%)**	**64 (13%)**
Grand Total		**674**	**560**	**494**

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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%) of screening is completed by 48 hours of age which is similar to previous years.

Table 16. Age at time of CCHD Screen from 2020-24.

Age at time of CCHD screen	2024		2023		2022		2021		2020	
	Number of screens	%	Number of screens	%	Number of screens	%	Number of screens	%	Number of screens	%
≤48 hours (1-2 days)	136,719	96.09	130,118	96.38	128,109	95.88	132,774	95.40	125,382	93.00
>48-72 hours (2-3 days)	1,556	1.09	1,234	0.91	1,377	1.03	1,721	1.20	1,706	1.30
>72-168 hours (3-7 days)	821	0.58	822	0.61	846	0.63	940	0.70	928	0.70
Greater than 168 hours (> 7 days)	159	0.11	195	0.14	207	0.15	197	0.10	255	0.20
Not specified	3,020	2.12	2,635	1.95	3,080	2.31	3,632	2.60	6,289	4.70

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 2024 was 953, which was 0.63% of the cards received. The most frequent error was incomplete documentation – either of a repeat test done after 1 hour or missing screening values. 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 2020-24.

		2024	2023	2022	2021	2020
Unsatisfactory Screens		**953**	**829**	**1,057**	**1,179**	**1,069**
No screen/ rescreen recommended	Baby >7days	26 (2.7%)	20 (2.4%)	42 (4.0%)	39 (3.3%)	65 (6.1%)
	Baby in hospital	169 (17.7%)	131 (15.8%)	185 (17.5%)	203 (17.2%)	253 (23.7%)
	Documentation inaccurate or incomplete	596 (62.5%)	536 (64.7%)	653 (61.8%)	723 (61.3%)	574 (53.7%)
	Missed - baby >7 days	5 (0.5%)	6 (0.7%)	6 (0.6%)	6 (0.5%)	9 (0.8%)
	No action needed	52 (5.5%)	39 (4.7%)	50 (4.7%)	57 (4.8%)	38 (3.6%)
Screen or physical exam recommended	Missed - baby ≤7 days	31 (3.3%)	29 (3.5%)	40 (3.8%)	65 (5.5%)	54 (5.1%)
	Physical exam recommended (screen positive)	0	<5 (<0.6%)	<5 (<0.47%)	<5 (<0.4%)	0
	Rescreen recommended	74 (7.8%)	64 (7.7%)	80 (7.6%)	83 (7.0%)	76 (7.1%)
Total Screening Forms Submitted		**150,205**	**142,466**	**140,689**	**146,804**	**141,408**
Unsatisfactory Rate		**0.63%**	**0.58%**	**0.75%**	**0.80%**	**0.76%**

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 953 unsatisfactory screens, and in 85.7% of follow up cases the result was amended by the submitter due to incorrect completion of the form. In 7.8% of cases a rescreen was recommended. Through the follow up of unsatisfactory screens NSO was able to follow up with submitters for 105 infants that had not received a proper CCHD screen and needed to be screened (missed) or rescreened.

1.3 HEARING

The Infant Hearing Program (IHP) is Ontario's Early Hearing Detection and Intervention (EHDI) program, which is funded by the Ministry of Children, Community and Social Services (MCCSS). The IHP is a comprehensive program that delivers services including, screening, identification, intervention and family support. Since July 29, 2020, the IHP and NSO have offered screening for some risk factors for PHL using dried bloodspot (DBS) samples. This screening uses the newborn DBS to look for congenital Cytomegalovirus (cCMV) 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.

In 2024, NSO and the National Centre for Audiology (NCA) at Western University were selected by MCCSS to become the partnered IHP Oversight Agency. The goal of the IHP Oversight Agency is to streamline oversight and support quality improvement towards achievement of international benchmarks necessary for the best possible child developmental outcomes. NSO and the NCA now oversee delivery of the core

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component areas of the IHP, including hearing screening, and audiology assessment, surveillance, and intervention. This includes the management of contracts/financials with IHP Lead Agencies, provision of operational support for service delivery, protocol development and training of service providers. It was a successful first year, which involved learning and discovery, and relationship-building with program partners.

1.3.1 Consent

When risk factor screening for PHL launched in 2019, parents/guardians were approached for consent as part of the UNHS process. With the onset of the COVID-19 pandemic in March of 2020, the requirement of additional consent for risk factor screening was waived due to disruptions to UNHS, which impacted the ability to obtain consent in a timely manner. As such, all DBS from babies born between March 26, 2020 and March 3, 2024 were screened for CMV and genetic risk factors for PHL without the requirement of additional consent through the IHP.

Consent for risk factor screening for PHL was re-introduced for babies born on or after March 4, 2024. Consent options were simplified for families (i.e. consent for UNHS includes consent for both the audiometric screening and the DBS risk factor screening), and an electronic interface was established between program information systems to transmit consent.

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 146,517 infants in 2024. Risk factor screening for PHL (CMV and genetics) was completed for 137,494 infants (93.8%) in 2024.

Table 18. Number of babies screened for risk factors for PHL between 2021-24.

	2024		2023	2022	2021
	Jan 1 - Mar 3	Mar 4 - Dec 31			
Infants screened at NSO	24,448	122,069	139,931	137,849	143,364
IHP screening form received	N/A	113,470	N/A	N/A	N/A
Consent for risk factor screening	N/A	113,291	N/A	N/A	N/A
Babies screened for CMV and genetic risk factors	24,402	113,092	139,620	136,724	142,297
Babies screened for CMV	24,403	113,107	139,639	137,619	143,054
Babies screened for genetic risk factors	24,434	113,222	139,837	136,885	142,512

*Note that risk factors for PHL data is pulled by date of birth instead of date of receipt.

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

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intervention are key to better outcomes. The incidence in Ontario is reported to be 1 in 16,667 annually (~8-9 cases per year).

With the help of an infant stool colour card (ISCC) parents can perform screening at home and can identify acholic (pale) stools which are often an early sign of biliary atresia. 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 Continued Dissemination Strategies

As NSO entered year two of the program, communication continued with our valued stakeholders and partners in a variety of manners, such as department rounds, community talks to various HCP groups and a point of care newsletter. Our voice in social media has continued with an "always on" campaign, which ran quarterly BA ads directed at families to remind them to screen for BA with their ISCC.

NSO also developed and distributed a custom ISCC holder for our submitters and other community partners who have a stock of the ISCC available for families. Public health units, Lactation consultant clinics and individual medical practices are some of the community partners who have requested to receive a launch kit along with a stock of ISCC to distribute to their clients if needed.

Survey

In the spring of 2024, NSO started the procurement process to hire a firm to assist with the development and administration of a parent and healthcare provider survey to evaluate and identify areas of improvement for the BA program. Now with our preferred *partner organization* this work has begun, and the survey should be launched by the end of the Spring 2025 with data analysis taking place in the early Fall 2025.

Family Advisors
Another goal of NSO and the BA program is to partner with vetted Family Advisors. Through partnerships with CHEO and The Ottawa Hospital, 2 parent advisors have been identified and have agreed to be available to work with NSO on the BA survey project with plans to expand to other projects at NSO as required.

APP work
As we work towards improving our ability to screen for BA, NSO is investigating the possibility of developing a digital version of the screening tool in the form of a screening application that parents could use on their smartphones alongside the ISCC. This exploratory work was started in 2024 and will continue through 2025.

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1.4.2 Infant Stool Colour Card (ISCC) Distribution

VWR continues to coordinate orders and supply stock to our submitters for ISCCs through our well-established DBS pathway. To track orders, reports are received from VWR. NSO closely tracked ISCC ordering on a bi-weekly basis until June 2024. By calculating an approximation of usage through the ISCC supplier and comparing this to the number of DBS samples received, we were able to estimate that 134,910 infants likely have been screened in 2024.

If a submitter's estimated volume of ISCCs on hand was less than 15% of their predicted requirement, NSO contacted the organization and inquired about their stock levels and plans for re-ordering. Since June 2024, we are now monitoring the ordering of ISCCs on a broader surveillance, looking at the overall numbers of ISCC ordered every month, versus numbers ordered individual submitters. Along with this broad oversite, we continue to send reminders about the importance of screening for BA and the responsibility of individual organizations to make sure they have a robust supply of the ISCCs on hand along with established workflows to regularly re-order the cards. If needed, we can still receive reports from VWR and we can spot check individual submitter's card ordering practices. Also, towards the end of 2024 and throughout 2025 a rolling audit is ongoing to contact all submitters to confirm that the distribution and ordering process is well established in their organization.

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.

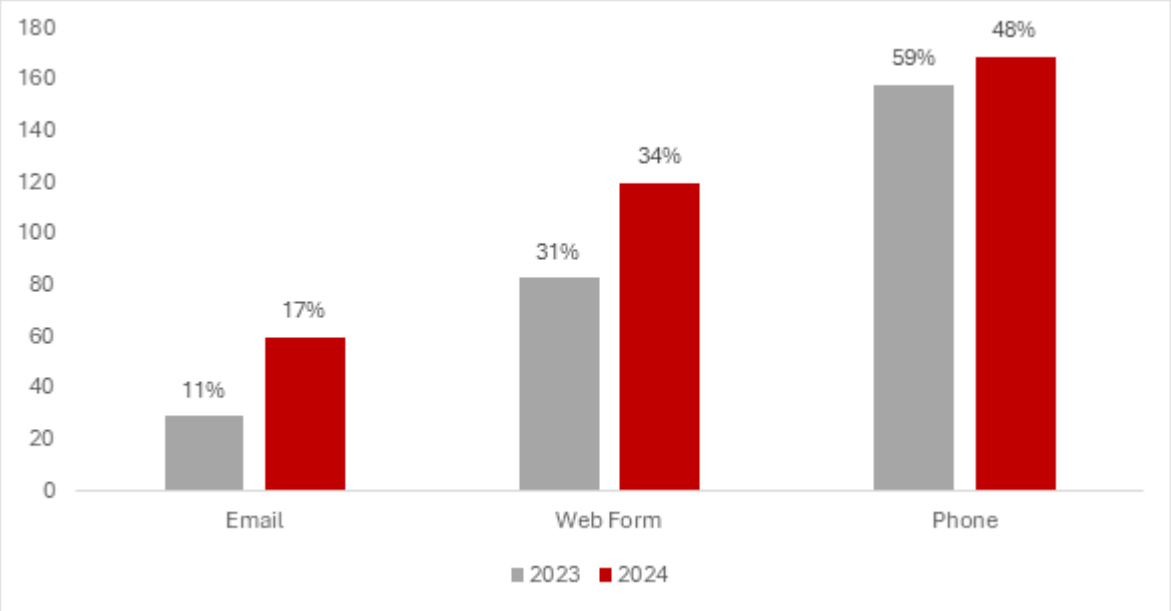

Figure 3. Percentage breakdown of the types of contacts received from families.

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The minimum age at first contact in days was 1 day, the maximum age was 521 days, and the mean was 51 days of age. These late calls occurred despite written instructions on the ISCC, and verbal instructions provided to families at the time of card distribution that recommends families screen for a total of four weeks post birth for infants born ≥37 weeks gestational and if ≤37 weeks gestation, four weeks past the baby's due date. Even with this recommendation, families continued to contact NSO beyond the recommended screening window. There were 7 calls after 1 year of age, and this reflects families that had infants in 2023 and still had the card.

For infants who were older than 120 days of corrected age with a primary concern of pale stool, it was recommended that the family present to their healthcare provider and request that a conjugated or direct bilirubin be measured to rule out cholestasis. For all other concerns, the family was re-directed to the most appropriate healthcare provider.

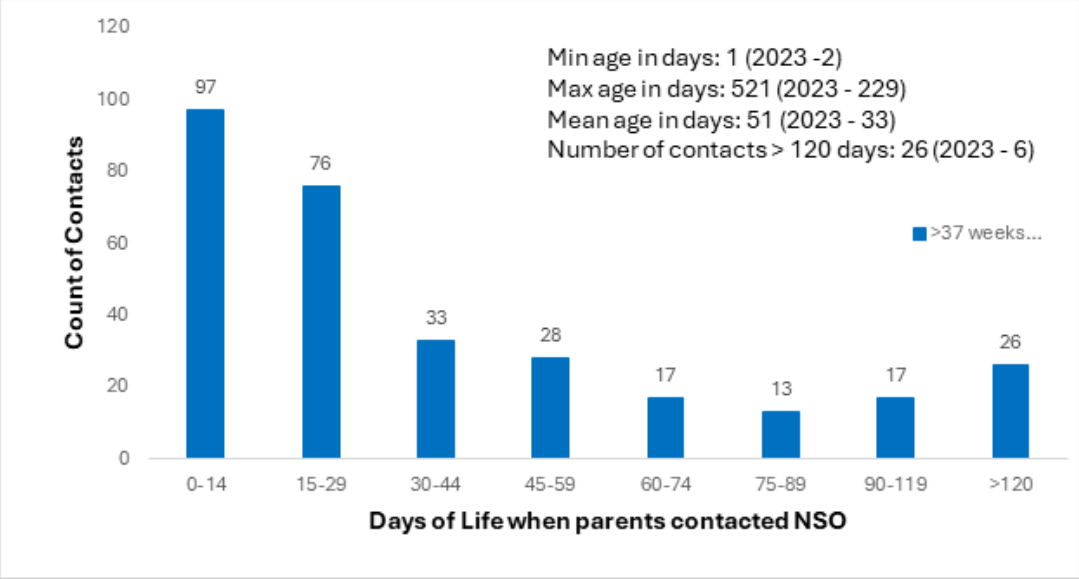

Figure 4. Age in days of term infants at time of contact with NSO.

1.4.4 Biliary Atresia Clinical Assessments

In 2024, there were 349 contacts to NSO by families or caregivers regarding infant stool concerns, of which 339 telephone clinical assessments of the cases were conducted (10 families did not return our first telephone call back). This number of contacts (349) is an 28% increase from 2023.

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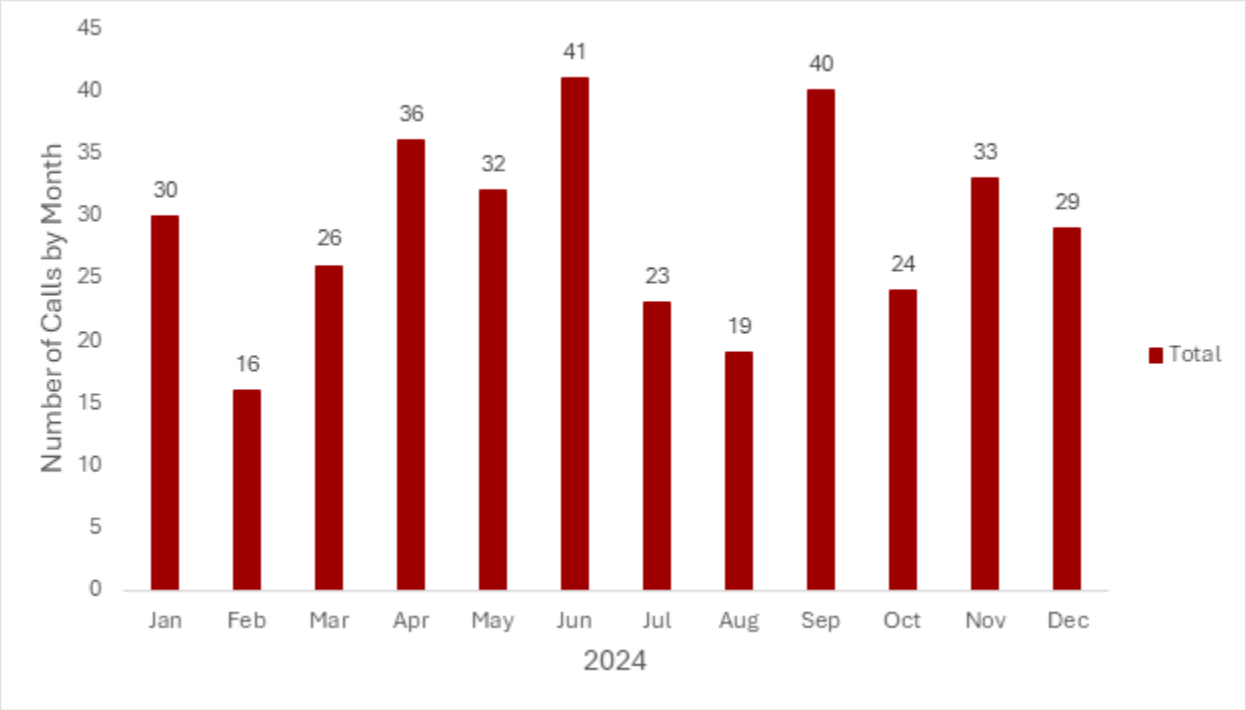

Figure 5. Distribution of call volumes per month

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 228 telephone assessments, photos were received and a total of 1060 photos were submitted, de-identified, renamed and uploaded to a NSO private drive, which has restricted access.

In pale stool clinical assessment cases, 45% 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 again the most frequently parent-identified stool colour and was the most frequent parent-identified stool colour that was not aligned with the clinical team's impression of the stool colour, with #2 closely following behind.

177/349 (51%) of the calls were unrelated to pale stool concerns, as indicated by the caller. Common reasons for these unrelated calls remained similar to year 1; 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 an assessment from another HCP for their concern. 162/349 (46%) of contacts were related to pale stool, which is an increase of 3% from the previous year. 10/349 (3%) of cases resulted in an inability to contact the family, despite our team's best efforts, which included 3 attempts at re-contacting families who had reached out to us.

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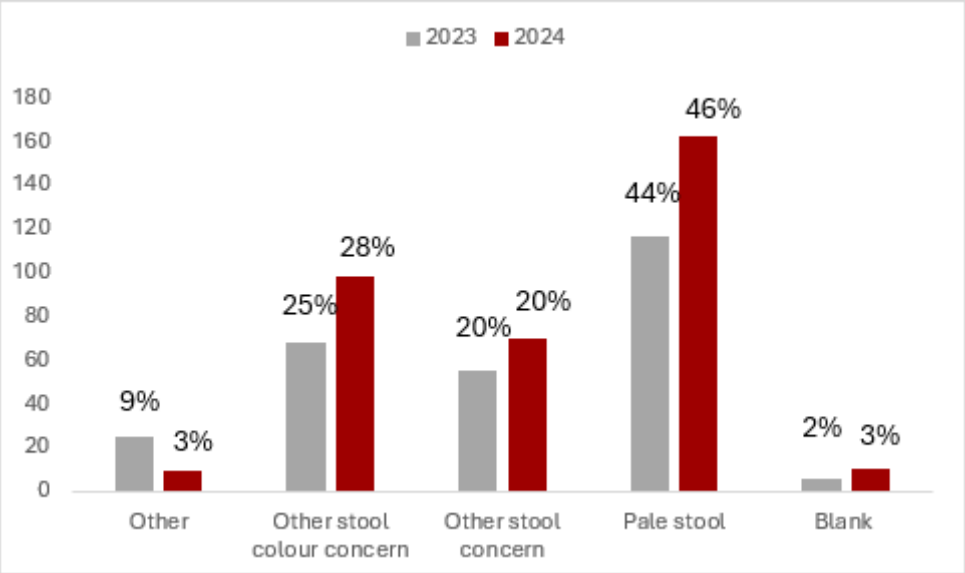

Figure 6. Breakdown for call reason for 2024

Some cases required more than one contact by NSO with the family to make a screening determination. 87 calls required 2 contacts to make a screening determination and 31 required >2 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. 31% of our contacts for term infants happen within the first 2 weeks of life.

In 50/339 (15%) cases the family had already reached out to another HCP (Family doctor, walk-in clinic, emergency room visit) prior to the NSO telephone clinical assessment. Frequently this was due to a weekend or after hours contact to our program.

After completing a telephone assessment, which includes a targeted medical 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. 62% of the contacts from families for pale stool concerns indicated the presence of pale stool for <24 hours, and 38% had pale stool for >24 hours. 119/162 (73%) of calls about pale stool that had a clinical assessment were screen negative and 43/162 (27%) were screen positive. For both screen negative and screen positive determinations a letter was mailed out to families documenting the interaction between the family and BA Clinical team and a faxed letter was 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

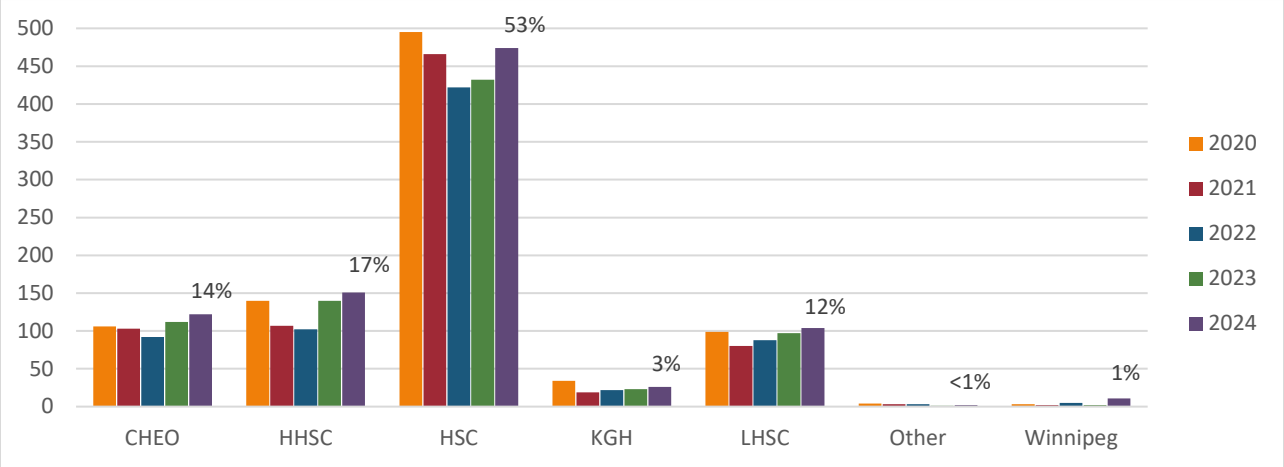

Figure 7. The total number of referrals by treatment centre between 2020-2024.

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. The proportion of referrals received by each of the five Ontario regional treatment centres has been relatively unchanged with a slight decrease for HSC, now receiving ~53% of referrals annually.

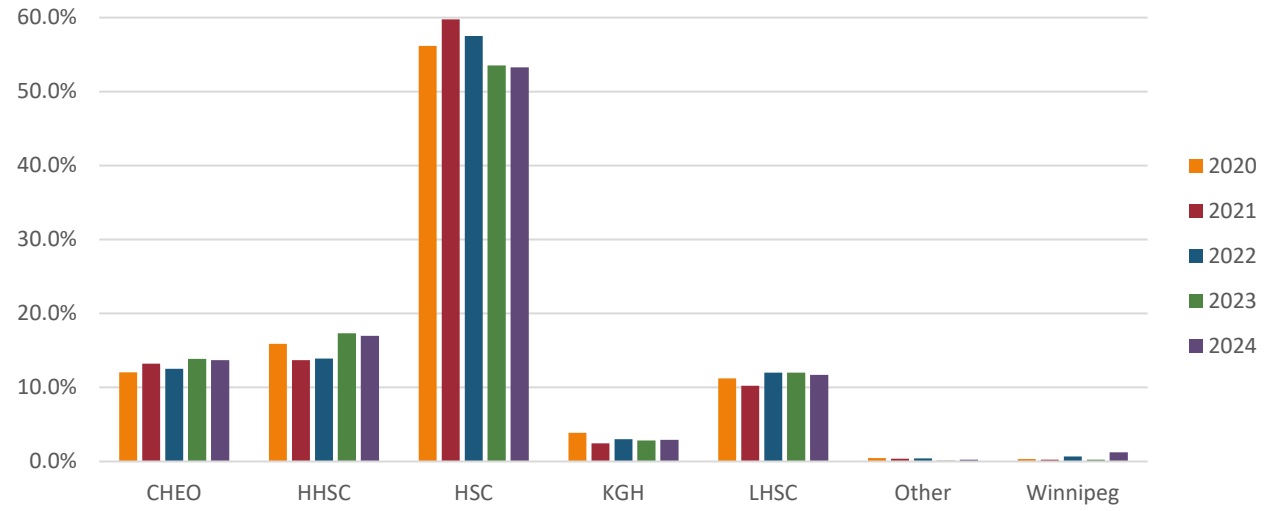

Figure 8. The percentage of referrals by treatment centre between 2020-24.

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2.1.2 DBS REFERRALS BY YEAR

In 2024, there were 890 screen positive referrals. This represents ~0.61% of the total number of infants screened by NSO. The number of screen positive infants referred in 2024 increased slightly from 2023 (890 vs. 807).

Endocrinopathies and Metabolics represent ~47.3% and ~27.8% of screen positives respectively. SCID screen positive referrals increased in 2024 and now represent 3.7% of total screen positive referrals. The number of Cystic Fibrosis referrals increased in 2024 and now represent 6.1% of total screen positive referrals. Hemoglobinopathies represent approximately 14.5% of screen positive referrals, which is a slight increase from last year. SMA represents 0.7% of referrals. There was a disorder logic change for homocystinuria in 2024 (more details to follow below).

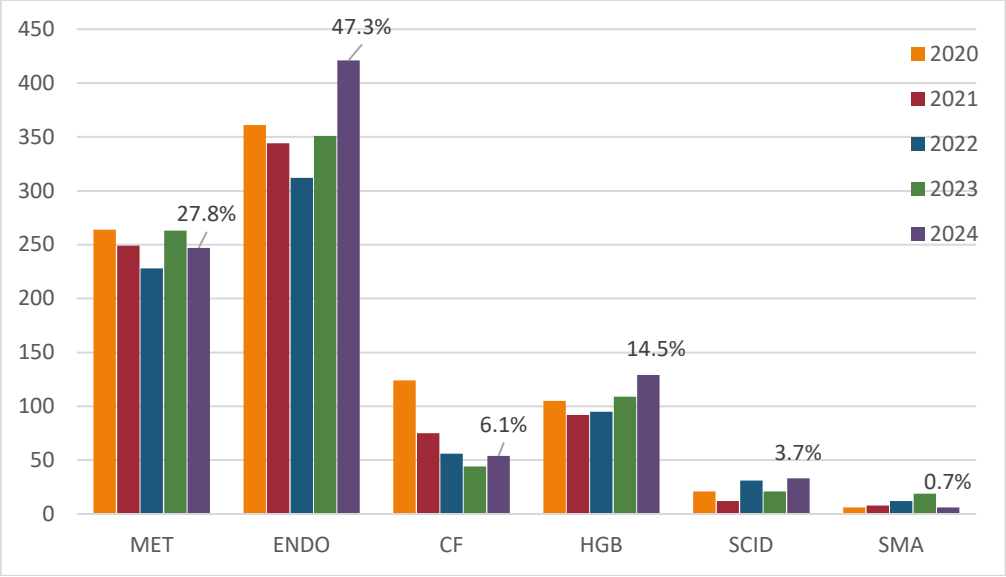

Figure 9. The total number of screen positives by disease grouping between 2020-24.

The number of screen positive referrals per disease grouping decreased for referral types metabolic and spinal muscular atrophy (SMA).

2.1.3 Diagnostic Feedback

Approximately 6.1% (54 cases) of diagnostic evaluation report forms (DERFs) remain pending for the referrals made in 2024 as of April 1, 2025. 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 19 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 2024 (DERF data pulled April 1, 2025). 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	<5	0	40	45	52	129	<5	267
Congenital Adrenal Hyperplasia	<5	<5	5	<5	14	128	<5	154
Hemoglobinopathies	7	7	63	0	48	6	5	129
Cystic Fibrosis	<5	<5	25	24	<5	0	0	54
Type 1	<5	<5	23	<5	0	0	0	26
Type 2	0	0	0	9	0	0	0	9
Type 3	0	0	<5	13	<5	0	0	19
SCID	12	8	<5	0	5	13	<5	33
SMA	0	0	6	0	0	0	0	6
Biotinidase Deficiency	<5	<5	<5	17	0	<5	0	26
Citrullinemia	<5	<5	<5	0	<5	5	0	9
CUD	0	0	<5	0	14	9	0	27
FAO (CPT1, CPT2, and GA2)	0	0	<5	0	0	<5	0	<5
Galactosemia	0	0	<5	<5	<5	<5	0	6
GAMT	0	0	<5	0	<5	<5	0	<5
Glutaric Aciduria Type 1	0	0	0	0	0	5	0	5
Homocystinuria	<5	0	<5	0	<5	7	0	9
Isovaleric Acidemia	<5	<5	<5	0	<5	<5	0	7
LCHAD	0	0	<5	0	0	0	0	<5
MCAD	<5	0	7	0	<5	<5	0	12
MPS1H	0	0	<5	<5	<5	0	0	6
MSUD	0	0	<5	0	<5	8	0	10
PA/MMA	21	12	<5	0	25	14	<5	57
Phenylketonuria	<5	0	5	10	0	12	0	27
Tyrosinemia	0	0	0	0	<5	<5	0	<5
VLCAD	0	0	<5	<5	17	11	<5	35
Total No. Positive	**54**	**35**	**180**	**106**	**191**	**362**	**16**	**890**

2.2 HEMATOLOGY

The number of screen positives (129) in 2024 increased compared to 2023 (109) 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, 2024)	**56.7%**	**57.3%**	**90.3%**	**1.8%**

2.2.1 Hemoglobin Carriers

Table 21. Hemoglobin carrier requests between 2020-24.

	2024	2023	2022	2021	2020
Requests from high-risk population	54	41	23	unknown	23
Total Requests	**80**	**51**	**37**	**49**	**32**
Number of carriers	13	17	13	17	12

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.

Table 22. Carriers identified in 2024.

HGB Pattern	Carriers Identified
FAC	404
FAD	340
FAE	277
FAS	1,796
FAX	89
Grand Total	**2,906**

There were 80 hemoglobin carrier requests in 2024. Some of these requests were for individuals with a birth date prior to the start of screening for hemoglobinopathies and therefore, were not fulfilled. Of the 13 carriers, 12 were from high-risk populations or where risk status was not indicated.

Fewer than 1% of carriers request their results with the number of hemoglobin carrier requests remaining low compared to the number of carriers. There was a task force of the NSO-AC that examined different carrier disclosure models that could be considered in Ontario due to the low uptake in carrier requests. NSO has responded to the report from that task force by submitting a proposal to the Ontario Ministry of Health with a plan to implement the recommended changes. In the interim, NSO worked with three influencers who posted content about Hgb carrier information being available upon request. This content was posted in late August and we saw an increase in requests in September (n=14) and October (n=16). November and December saw a return to historical request volumes.

2.3 Cystic Fibrosis

There were 54 referrals this year compared to 44 in 2023. There were 26 Type 1 referrals (genotypes consistent with a high risk of a diagnosis of CF), 9 Type 2 referrals (genotypes consistent with a high risk for a *CFTR* -related disorder NOT meeting CF diagnostic criteria) and 19 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, 2024) Type 1	95.7%	100.0%	100.0%	0.8%
Current (Mar 19, 2020 - Dec 31, 2024) Type 2	1.4%	100.0%	100.0%	5.3%
Current (Mar 19, 2020 - Dec 31, 2024) Type 3	10.6%	75.5%	75.5%	1.0%
Current (Mar 19, 2020 - Dec 31, 2024) ALL	**43.6%**	**91.8%**	**91.8%**	**2.1%**

2.4 ENDOCRINOLOGY

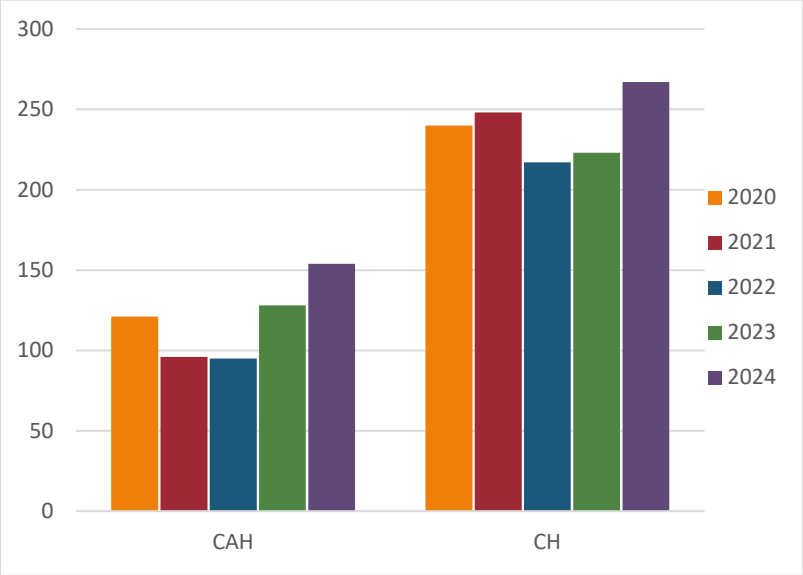

Figure 10. The total number of congenital adrenal hyperplasia and congenital hypothyroidism screen positives between 2020-24.

The number of screen positives for CAH increased compared to last year. However, this number is expected to be significantly decreased in 2025 following the addition of 21-deoxycortisol to the screening algorithm in January 2025. The number of screen positives for CH increased compared to 2023. There were no trends that might explain this increase when the data was reviewed for the year.

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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, 2024)	**20.4%**	**37.4%**	**37.4%**	**0.4%**
Congenital Adrenal Hyperplasia	Past (Sept 2, 2016 - Jun 11, 2018)	5.6%	6.9%	7.8%	1.3%
	Current (Jun 12, 2018 - Dec 31, 2024)	**3.9%**	**6.1%**	**6.5%**	**1.3%**

2.5 METABOLIC

NSO began screening for guanidinoacetate methyltransferase (GAMT) deficiency in October 2022. GAMT screening involves a two-tier screening approach. The number of referrals are in keeping with the expected annual referral rate

All of the amino acidemias had a reduction in the number of referrals in 2024. There was a disorder logic change for HCY in July 2024. Total homocysteine (tHcy) was added as a second-tier test in an effort to decrease the false positive rate. There was a slight decrease in the number of HCY referrals in 2024.

CPTIA, CPTII, and GA2 referrals are all categorized as FAOD other in the table below. Currently, these are not primary targets of screening but can be identified through the screening process. CPTIA and CPTII were recently reviewed by the NSO-AC and were recommended to become primary targets of screening on the NSO panel. A date for this to occur has not yet been decided.

There has been a gradual increase in the number of PA/MMA screen positive referrals over time. A review of the screening algorithm has not determined a cause for this increase. The other organic acidemias and most of the fatty acid oxidation defects saw a decrease in the number of screen positive referrals in 2024.

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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		**14.3%**	**14.3%**	**14.3%**	**0.0%**
Glutaric Aciduria type 1		**9.5%**	**9.5%**	**22.7%**	**0.0%**
Isovaleric Acidemia	Past (until Feb 17, 2020)	3.0%	4.2%	4.2%	0.0%
	Current (Feb 18, 2020 - Dec 31, 2024)	**17.0%**	**17.0%**	**17.0%**	**6.0%**
PA/MMA/CblA/CblB	Past (Feb 16, 2010 - Apr 21, 2013)	3.7%	3.7%	8.3%	0.0%
	Current (Apr 22, 2013 - Dec 31, 2024)	**4.2%**	**4.4%**	**9.3%**	**5.3%**
FAOD - Other		**9.5%**	**52.8%**	**53.3%**	**1.0%**
LCHAD/TFP		**82.4%**	**82.4%**	**94.1%**	**0.0%**
VLCAD	Past (until Dec 14, 2021)	7.1%	12.1%	13.9%	0.7%
	Current (Dec 15, 2021 - Dec 31, 2024)	**8.4%**	**18.9%**	**20.0%**	**0.0%**
CUD	Past (until Mar 4, 2014)	5.5%	5.5%	5.5%	0.0%
	Current (Mar 5, 2014 - Dec 31, 2024)	**9.0%**	**9.4%**	**9.4%**	**0.8%**
MCAD	Past (Sep 1, 2016 - Jul 28, 2019)	18.8%	20.1%	21.5%	0.6%
	Current (Jul 29, 2019 - Dec 31, 2024)	**52.0%**	**65.3%**	**65.3%**	**0.0%**
Citrullinemia/ASA		**16.4%**	**20.9%**	**20.9%**	**1.3%**
Homocystinuria	Past (until Jul 29, 2019 - July 21, 2024)	**3.0%**	**3.0%**	**27.0%**	**0.0%**
	Current (Jul 22 - Dec 31, 2024)	**17.0%**	**17.0%**	**17.0%**	**0.0%**
Phenylketonuria	Past (until Jul 28, 2019)	**14.3%**	**27.5%**	**27.5%**	**0.0%**
	Current (Jul 29, 2019 - Dec 31, 2024)	**20.5%**	**47.0%**	**47.0%**	**0.0%**
MSUD	Past (until Nov 14, 2011)	3.8%	3.8%	3.8%	0.0%
	Current (Nov 15, 2011 - Dec 31, 2024)	**8.0%**	**9.5%**	**9.5%**	**1.4%**
Tyrosinemia	Past (Sep 14, 2009 - Sep 19, 2011)	1.4%	1.4%	1.4%	0.0%
	Current (Sep 20, 2011 - Dec 31, 2024)	**9.5%**	**9.5%**	**11.9%**	**1.1%**
Galactosemia	Past (until Jan 12, 2014)	35.7%	41.4%	41.4%	1.4%
	Current (Jan 13, 2014 - Dec 31, 2024)	**18.2%**	**37.2%**	**37.2%**	**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, 2024)	**7.6%**	**44.7%**	**44.7%**	**1.1%**
MPS1H		28.6%	66.7%	66.7%	0.0%

2.6 IMMUNOLOGY

The number of screen positive referrals for SCID increased from 22 in 2023 to 33 in 2024. While there are still a large number of DERFs pending, the immunology group is working hard to get caught up on their DERF submission.

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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)	33.3%	33.3%	33.3%	30.4%
Current (Mar 1, 2021 - Dec 31, 2024)	**15.9%**	**17.4%**	**17.4%**	**17.0%**

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

2.7 NEUROLOGY

Since screening began in 2020, the number of screen positive referrals has fluctuated by year, ranging from 6 referrals in 2024 and 2020, to 19 referrals 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	0
24-48 hours	152
> 48 hours	5
Not available	0
Grand Total	**157**

There were 157 CCHD screen positives in 2024, most of which were screened within 24-48 hours of life. The true positives were screened between 24-26 hours of age.

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

Definitive Diagnosis Categorization	2024	2023	2022	2021	2020
Primary target	**<5**	**<5**	**6**	**9**	**11**
Tetralogy of Fallot	<5	<5	<5	<5	<5
Total anomalous pulmonary venous return	<5	<5	<5	6	5
Transposition of the great arteries	<5	0	<5	<5	<5
Tricuspid atresia	0	0	0	0	0
Truncus arteriosus	0	0	0	0	<5
Hypoplastic left heart syndrome	0	0	0	0	0
Pulmonary atresia w/ intact septum	0	<5	0	<5	<5
Secondary target	**85**	**89**	**61**	**69**	**48**
Coarctation of the aorta	<5	<5	<5	<5	<5
Ebstein anomaly	<5	<5	0	0	<5
Interrupted aortic arch	<5	0	0	<5	0
Infection	<5	5	6	9	8
Persistent fetal circulation *(including pulmonary hypertension and delayed transition)*	16	19	11	13	6
PPHN	13	15	9	18	8
Pulmonary disease *(non-infectious)*	46	48	34	25	24
Double outlet right ventricle	0	0	0	0	0
Incidental Finding	**30**	**27**	**31**	**38**	**47**
CHD *arrhythmia*	<5	0	<5	<5	0
CHD *structural*	9	<5	10	15	7
CHD *Other*	11	11	10	5	13
Other	<5	<5	<5	6	11
No disease, no definitive diagnosis	5	8	6	11	16
Not affected	**38**	**48**	**49**	**51**	**90**
Lost to follow up	**0**	**0**	**<5**	**0**	**<5**
Grand Total	**157**	**168**	**148**	**167**	**197**

When CCHD was first implemented in Ontario it was believed the prenatal ultrasound detection rate for CCHD was ~50%. Since CCHD has been implemented it is believed that this rate is actually closer to 65% (personal communication from pediatric cardiology).

2.8.1 CCHD Definitive Diagnosis Data and Positive Predictive Values

In 2024, the Positive Predictive Value (PPV) for CCHD screening was 2.55% for primary targets and 56.69% for primary and classical secondary target diseases. Cumulatively since the beginning of the program, the PPV is 4.79% for primary targets, and 40.19% for primary and classical secondary target diseases. Of the

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1,274 screen positives since the initiation of CCHD screening (the lost to follow up DERFs have been excluded from analysis), 490 (38.46%) have been determined to be not affected after diagnostic follow up.

Table 30. PPV calculations for CCHD Screen Positives 2019-24 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
2024	2.55%	56.69%	157	<5	85	30	38	0
Cumulative	4.79%	40.19%	1,276	61	451	272	490	<5

2.9 HEARING

Table 31. Number of risk factor screen positive babies between 2020-24.

Risk Factor	2024 # screen positives (% rate)	2023 # screen positives (% rate)	2022 # screen positives (% rate)	2021 # screen positives (% rate)	2020 # screen positives (% rate)
CMV	172 (0.13%)	184 (0.13%)	190 (0.13%)	140 (0.10%)	159 (0.12%)
Genetics	31 (0.023%)	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 five years. In 2024, there were 172 CMV screen positive infants. The CMV screen positive rate was 0.13%. There was a decrease in 12 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 2024. The number in 2024 (<5) is the same as the previous year. In 2024, NSO introduced a pilot project to screen dried saliva samples (DSS) for CMV. More information about the pilot can be found below.

There were 31 infants with genetic screen positive results in 2024. 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 increased after this was implemented. 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 DBS screen positive referrals and outcomes

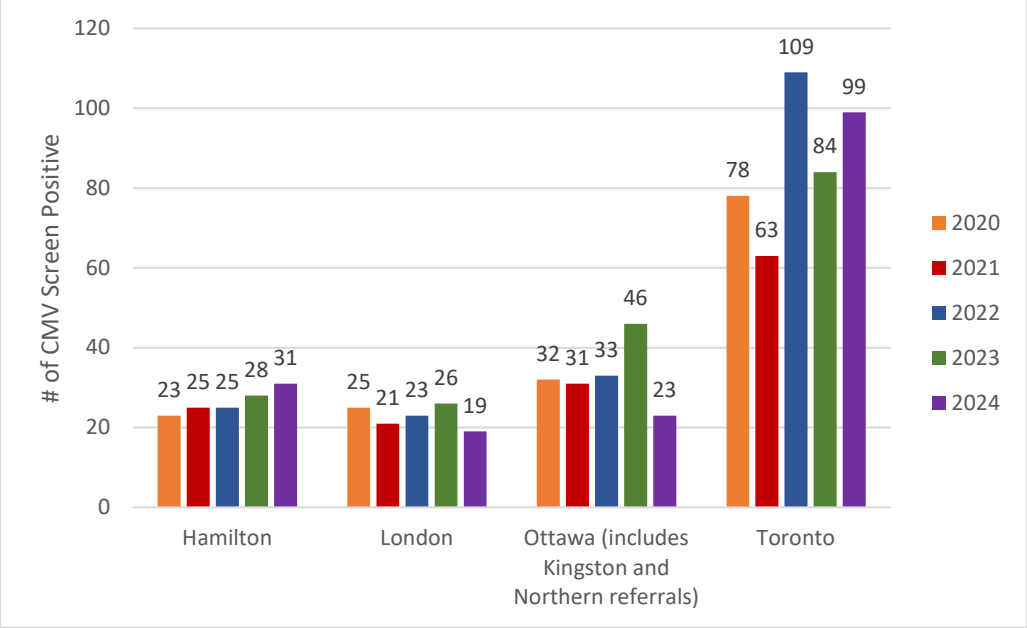

Figure 11. CMV screen positives by referral region

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 (99/172, 58%), followed by Hamilton (31/172, 18%), Ottawa (23/172, 13%) and London (19/172, 11%). The Ottawa referral region includes the following areas; Ottawa which had 13 cases, Kingston which had 5 and Northern Ontario which had 5. This distribution is similar to that observed in 2023; however, Ottawa had a decrease in referrals (23 less than the previous year) and Toronto had an increase (15 more than the previous year).

The majority of CMV screen positive infants were referred to a community pediatrician for their initial assessment (158/172, 92%). This proportion is like what was observed in 2023, 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.

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 2024**	**GRAND TOTAL 2023**	**GRAND TOTAL 2022**
Robust	146	14	160	<5	<5	6	166	173	170
Borderline	<5	<5	6	0	0	0	6	11	20
TOTAL	148	18	166	<5	<5	6	172	184	190

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The table above summarizes the urine CMV PCR results in 2024. Urine CMV PCR results are available for 166 (97%) of the screen positive infants. Of these, 146 (88%) had positive/detected results. There were 18 cases (10%) 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 were sent to the PHO lab for initial testing and if the result is negative further testing is completed (viral culture and CMV PCR at NSO). The majority of patients with a negative urine result had reflexive testing done (unless the initial sample was not sent to PHO lab for testing) and all reflexive testing was concordant.

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 2024 showed that the proportion of borderline screen positives that had negative urine CMV PCR results compared to the robust screen positives was similar to 2023 data.

Table 33. Definitive diagnoses for CMV screen positive infants between 2021-24.

Definitive Diagnosis	Positive Urine CMV Results	Negative Urine CMV PCR Results	Urine CMV PCR not done	Urine CMV PCR Pending	2024 Total	2023 Total	2022 Total	2021 Total
Asymptomatic cCMV	92	0	0	0	**92**	**123**	**145**	**97**
Symptomatic cCMV	53	0	0	0	**53**	**36**	**22**	**18**
Indeterminate/ Inconclusive	0	0	<5	0	**<5**	**7**	**6**	**<5**
cCMV excluded (false positive)	0	18	0	0	**18**	**8**	**6**	**7**
Non-congenital CMV	<5	0	0	0	**<5**	**<5**	**-**	**-**
LTFU	<5	0	<5	0	**<5**	**7**	**<5**	**5**
Pending	<5	0	0	<5	**<5**	**<5**	**8**	**11**
TOTAL	**148**	**18**	**<5**	**<5**	**172**	**184**	**190**	**140**

Of the CMV screen positive infants with positive confirmatory urine CMV PCR results, 62% (92/148) were deemed to have asymptomatic cCMV infection and 36% (53/148) 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 a significant increase in symptomatic patients from the year previous. This is likely due to a change in the NSO CMV Assessment and Treatment Guidelines which recommend an MRI for all infants with any findings on their head ultrasound. This practice recommendation resulted in an increase in MRIs for infants with no other findings on their diagnostic work-up which could have led to additional symptomatic cases being identified.

A small percentage of 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, 12 (23%) infants had PHL identified at the initial diagnostic audiology assessment. The importance

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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.

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. All 18 infants that had a negative urine PCR result were deemed to be false positive due to reflexive testing at PHO lab and NSO. This demonstrated the benefit of additional testing for infants that screen positive but have a negative urine PCR result.

2.9.1.1 CMV DSS screen positive referrals and outcomes

On February 11, 2024, NSO started a pilot to receive dried saliva samples for CMV testing from the following ten birth hospitals; Mount Sinai, St. Michael's, Sunnybrook Health Sciences, Ottawa General Hospital, Ottawa Civic Hospital, Hopital Montfort, Kingston Health Science Centre, Hamilton Health Sciences Centre, St. Joseph's Healthcare, and London Health Sciences Center. Once consent was obtained from the family both the DBS and DSS were screened for CMV. The following were possible results; positive/borderline DBS and positive/borderline DSS, positive/borderline DBS and negative DSS, and negative DBS and positive/borderline DSS. The goals of this project are to: define the birth prevalence of cCMV in Ontario using DSS, determine the clinical sensitivity of CMV PCR testing of DBS versus DSS, and examine cost effectiveness. This project will continue until over 50,000 samples are tested.

Overall, in 2024 there were 29,416 DSS samples received and 93 referrals with screen positive results noted in the table below. A large proportion of infants (91% (29/32)) that screened positive on both the DBS ad DSS had confirmed cCMV, however a much smaller proportion (20% (12/61)) of infants that had a positive or borderline DSS had confirmed cCMV.

Table 34. DSS referral outcomes.

CMV Screening Result	2024 Screen Positive (#)	Positive Urine Results
DBS Positive/DSS Positive	32	91%
DBS Borderline/DSS Positive	0	-
DBS Positive/DSS Borderline	0	-
DBS Negative/DSS Positive	46	22%
DBS Negative/DSS Borderline	15	20%
Total referrals	93	

2.9.2 Genetic screen positive outcomes

Overall, there were 31 genetic risk factor screen positive infants in 2024, which was a decrease form 2023. Interestingly, 8 of these infants had a family history of a first degree relative with PHL, some who were identified through genetic risk factor screening.

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Table 35. Genetic screen positive results and PHL interventions

	Genotype Class					
Intervention	Panel/Panel Genotype	Panel/V37I Genotype	TOTAL 2024	TOTAL 2023	TOTAL 2022	TOTAL 2021
Cochlear implant candidate	9	0	9	11	11	8
Amplification	11	<5	15	11	9	9
Monitoring+	0	0	0	5	6	9
Surveillance**	<5	6	7	13	11	6
Pending	0	0	0	0	0	0
LTFU	0	0	0	<5	0	0
TOTAL	21	10	31	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

There were 21 infants with panel/panel genotypes, and as expected, the majority of these were confirmed to have permanent hearing loss. There were 10 infants with panel/V37I genotypes. The majority (6/10, 60%) 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 closer to the 2022 data (in 2023 72% had normal hearing at their first assessment), 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 and was successful in establishing an electronic transfer of consent. Areas of improvement have been identified and NSO will continue to work with the IHP in the coming year to monitor the timeliness and completeness of consent to identify areas for potential quality improvement.
- Clinical guidelines and algorithms continue to be updated to assist with establishing a definitive diagnosis in CMV screen positive infants with negative CMV PCR results, as well as providing a clinical pathway for patients screening positive only on a dried saliva sample.
- We continue to improve the genetic risk factor screening positive care pathway in preparation to begin reporting infants who are homozygous for the *GJB2* p.(V37I) variants screen positive.
- We will continue to collect dried saliva samples in 2025 to reach our goal of 50,000 samples. Once this collection is complete, we will begin to analyze data to determine the sensitivity, specificity as well as feasibility of CMV detection through dried saliva samples.

2.10 BILIARY ATRESIA

In 2024, NSO made the determination that 43/162 pale stool calls (27%) 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

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one of the 5 PAHSC hepatologists for measurement and interpretation of a fractionated bilirubin level. Toronto received the largest percentage of referrals.

Some of the screen positive families were lost to follow up as the family declined to have fractionated bilirubin measurement performed. Reasons given for refusal of follow up included that the infant's stool returned to a normal colour, and the family elected to follow up with their own HCP who provided reassurance. A year 2 improvement was the development of a standard procedure for documentation of these instances, including standardized letters that are faxed to the HCP and mailed via registered mail to the family.

The average age in days at referral was 43 and 83% of referrals happened with 1 day (range 0-4 days) of the family's initial contact with the NSO BA clinical team. Once screen positive cases were referred to a PAHSC it took an average of 1.3 days (range of 0-4 days) to complete the initial bloodwork.

Of the 40 referred cases that underwent diagnostic testing, 34 (85%) were discharged from the PAHSC due to fractionated bilirubin measurements below the threshold for cholestasis. 6 (15%) showed evidence of cholestasis, defined as a conjugated bilirubin >17 umol/L.

Table 36. The definitive diagnosis classification of the screen positive BA referral cases in 2023-24.

Definitive Diagnosis Categorization	2023	2024
Primary Target – Biliary Atresia	<5	<5
Secondary Target- Classic (A1AT, gallstones, biliary sludge)		<5
Infection-Other (UTI, Viral Gastroenteritis)	<5	
Incidental – Idiopathic Cholestasis	6	<5
Not Affected	28	34
Lost to Follow up	<5	<5
DERF Pending *		
Grand Total	41	43

Table 37. 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)
					Classic Secondary Targets	All Other Incidental		
2023*	7.6%	12.8%	41	<5	<5	6	28	<5
2024	2.5%	12.5%	43	<5	<5	<5	34	<5

*Data updated from 2023 annual report as pending DERF has been submitted.

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2.10.1 Future Directions

We are now sending DBS samples from all BA screen positive babies who had cholestasis (conjugated or direct bilirubin > 17umol/L) and all SDRF cases to be stored at -80 C to facilitate any possible future development of a DBS-based BA assay.

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3. SCREENING SYSTEM SUPPORT

3.1 BIOCHEMICAL

NSO receives samples for biochemical testing – both for diagnostic testing and monitoring of affected patients. In 2024, NSO received 7,778 samples from 3,189 patients. This was an increase of over 2,000 samples compared to last year (5,728). Monitoring samples accounted for 1,882 of the samples received. Screen positive follow up accounted for 905 of the 7,778 samples received.

3.2 MOLECULAR

NSO performs molecular diagnostic testing for targets of newborn screening, nuclear mitochondrial conditions, and primary immune deficiencies. The number of requests has increased annually, with 484 samples received in 2020, 532 in 2021, 795 in 2022, and 1,058 in 2023. In 2024, 1,269 samples were received of which 181 were requests for targets of screening following a positive NBS referral to one of the regional treatment centres.

3.3 SURVEILLANCE FOR FALSE NEGATIVES

3.3.1 POST MORTEM

For 15 years NSO received post mortem samples at the request of the coroner's office. The samples were typically run for inborn errors of metabolism. Following a review of the data from these cases, it was determined that 1) NSO never missed a target of screening leading to death and 2) the process was not typically helpful to the pathologists/coroners and was labour intensive for NSO. In October 2024, NSO and the provincial coroner's office decided to stop this routine practice, but continue to accept samples for testing on special request.

3.3.2DISCREPANT 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 NBS 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 screen program – dried blood spot, CCHD and BA.

3.4 RESEARCH

NSO's research program focuses on program development and evaluation, 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 15 research projects, 9 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, and pilot newborn screening studies. NSO research studies are reviewed and approved by

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the CHEO Research Ethics Board, and studies using residual newborn screening samples are performed in accordance with NSO's policy on Storage and Secondary Use of Newborn Screening Samples.
Below is a summary of study activities and publications from 2024 and upcoming activities:

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. Data analysis is in progress.

SMA Economic Evaluation and Pan-Canadian Collaboration
A systematic literature review on health economic evaluations of newborn screening (NBS) for spinal muscular atrophy (SMA) was accepted for publication in the Journal of Neuromuscular Diseases. Another manuscript is under review with the details of a health economic model for NBS and treatment for SMA patients in Canada. The study showed 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. The Pan-Canadian collaboration group, the NBS Working Group, which includes leaders from all Canadian provinces and territories worked 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 published in 2024 and early 2025.

Machine learning at NSO
Graduate students Alexander De Furia and Nicole Sabarin working with Paula Branco in the School of Electrical Engineering and Computer Science and Matthew Henderson at NSO been working on novel hierarchical filter-based learning algorithms to improve screening for congenital hypothyroidism, congenital adrenal hyperplasia, and fatty acid oxidation defects. 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 newborn screening while maintaining high sensitivity. With promising results to date, the research team are continuing to refine their approach for machine learning based newborn screening in 2025.

Congenital CMV ANd HEARing in Ontario: Optimizing Screening to Improve Child Health Outcomes (CAN HEAR Ontario)
Beginning in February 2024, dried saliva specimens (DSS) have been collected alongside the standard of care dried blood specimen (DBS) from babies born in selected hospitals in Ontario to help determine the best newborn screening method for CMV in hopes of improving outcomes for babies at risk for hearing loss. Babies who had a DSS sample and DBS sample collected and screened positive on either sample type have the opportunity to participate in a long-term follow-up research study where clinical information is collected about the infants over time. Recruitment for the study began in 2024 and will continue into 2025.

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Study activities which include data collection through study visits, surveys and review of investigation results that are stored at NSO are currently underway. Dried saliva specimen collection will conclude in summer 2025.

Canadian Population Screening for Risk of Type 1 Diabetes Research Consortium (CanScreenT1D)
CanScreenT1D is a research consortium led by SickKids Hospital focused on studying how to create Canada's first trial screening program for Type 1 Diabetes (T1D). NSO is co-leading the pilot of the T1D screening system, which is based upon either genetic risk score or autoantibody testing and surveillance. This pilot study is being done to understand the acceptability and feasibility of the piloted screening system and to generate evidence to support policy decisions around population implementation of T1D screening. It also seeks to identify additional questions and evidence gaps to enable pan-Canadian implementation. Other CanScreenT1D projects that will inform the development of the pilot study got underway in 2024. The pilot is expected to launch end of 2025/early 2026.

NBS Target Chart Review/MPS I Case Series
Research Ethics Board (REB) approval has been obtained to conduct retrospective chart reviews of patients who screened positive for and/or were diagnosed with a newborn screening (NBS) targeted condition. This protocol aims to characterize the overall health status and clinical features of these individuals, comparing those who experienced morbidity and/or mortality with those who did not. The protocol can be leveraged for program evaluations and publications, with the correct permissions.
A retrospective chart review is currently underway, focusing on the first five years of MPS I screening in Ontario. This analysis will help evaluate how effectively NBS meets its long-term objectives in this population—specifically, improvements in health, growth, development, and functional outcomes.

Untargeted Metabolomics for Glutaric Aciduria Type 1
A research study is underway to further understand the metabolic perturbations in glutaric aciduria type 1. While screening and presymptomatic treatment is highly effective at reducing the negative health outcomes associated with GA1, the risk of acute encephalopathic crisis remains high in individuals homozygous for the GCDH variant IVS-1 +5gàt. An untargeted metabolomics approach using liquid chromatography coupled to high resolution mass spectrometry was employed to derive metabolite signatures of control DBS relative to GA1 DBS, including a small subset of DBS with the IVS-1+5gàt variant. DBS from individuals with GA1 cluster distinctly away from control, screen-negative DBS based on the abundance of multiple metabolites, including those analytes measured in screening and diagnosis. Furthermore, distinct clustering based on genotype was also seen. Analysis of a 600-compound standard library is underway to facilitate identification of the significant metabolites to better understand the biochemical perturbations that may contribute to differences in disease outcomes.

Identifying at risk Newborns From the Analysis of NGS Testing (INFANT)
Kristin Kernohan is leading a Genome Canada Canadian Precision Health Initiative (CPHI)-funded project: Identifying at risk Newborns From the Analysis of NGS Testing (INFANT) that will look at the use of next generation sequencing in newborn screening (also called genetic Newborn Screening or gNBS). INFANT has four study activities: 1. develop a gNBS panel of diseases and variants to be used for targeted genome sequencing analysis; 2. genome sequencing of 9,000 infants and associated data collection (standard of care newborn screening results, health records, metabolomics); 3. genome sequencing of 1,000 infants who have screened positive on standard of care newborn screening, to assess sensitivity of gNBS for those

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conditions; and 4. contribute data to the Pan Canadian Genome Library (PCGL). Study activities will begin in 2025 and conclude in 2029 and will provide valuable information to NSO on introduction of gNBS. Once recruitment is open, parents who have had babies in the past 6 months and have completed newborn screening in Ontario can consent to gNBS for their babies.

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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)	04-Apr-06	0.5%	1 in 2,215	84%
Congenital Adrenal Hyperplasia (CAH)	14-May-07	0.8%	1 in 23,290	33%
Sickle Cell Disease	24-Nov-06	1.2%	1 in 2,736	95%
Cystic Fibrosis (CF)	09-Apr-08	0.8%	1 in 4,705	80%
Severe Combined Immune Deficiency (SCID)	12-Aug-13	3.8%	1 in 52,729	45%
Glutaric Aciduria type 1 (GA1)	09-Aug-06	0.0%	1 in 132,304	100%
Guanidinoacetate Methyltransferase Deficiency (GAMT)	17-Oct-22	0.0%	1 in 314,651	14%
Isovaleric Acidemia (IVA)	09-Aug-06	0.4%	1 in 155,652	60%
Propionic Acidemia (PA)	09-Aug-06	2.7%	1 in 240,553	37%
Methylmalonic Acidemia (MMA)			1 in 155,652	
Cobalamin A Deficiency			1 in 882,028	
Cobalamin B Deficiency			1 in 1,323,042	
Long-chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHAD)	09-Aug-06	0.0%	1 in 203,545	89%
Trifunctional Protein Deficiency (TFP)			1 in 2,646,084	
Very-long-chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)	09-Aug-06	0.6%	1 in 73,502	60%
Carnitine Uptake Defect (CUD)	09-Aug-06	0.4%	1 in 67,848	21%
Medium-chain Acyl-CoA Dehydrogenase Deficiency (MCADD)	04-Apr-06	0.2%	1 in 15,3669	88%
Citrullinemia (CIT)	09-Aug-06	1.3%	1 in 120,277	40%
Argininosuccinic Acid Lyase Deficiency (ASA)			1 in 189,006	
Cystathionine beta-synthase (CBS) deficiency	09-Aug-06	0.6%	1 in 661,521	3%
Phenylketonuria (PKU)	04-Apr-06	0.0%	1 in 16,636	67%
Maple Syrup Urine Disease (MSUD)	09-Aug-06	0.9%	1 in 132,304	22%
Tyrosinemia type 1	09-Aug-06	0.5%	1 in 264,608	71%
Galactosemia (GALT)	19-Feb-07	0.5%	1 in 52,470	21%
Biotinidase Deficiency (BIOT)	19-Feb-07	0.7%	1 in 54,703	20%
Mucopolysaccharidosis type 1 Hurler (MPS1H)	27-Jul-20	0.0%	1 in 104,699	27%
Spinal Muscular Atrophy (SMA)	13-Jan-20	0.0%	1 in 13,577	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
RTCs = Regional Treatment Centres
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

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