NEWBORN SCREENING ONTARIO
DÉPISTAGE NÉONATAL ONTARIO

Newborn Screening Ontario
Annual Report
Calendar Year 2022

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Executive Summary

There is a new format to the 2022 annual report. The first section is geared toward the screening system overall, including sample volumes, demographics and quality indicators for blood spot, CCHD, and hearing screens. This section will be relevant to the practice of hospitals and midwives who are submitting samples, as well as those most interested in the inputs to the system. In the second section the screen positive data is broken down by disease speciality for ease of review when focusing on specific disease targets. Lastly, the third section describes activities that NSO supports to enhance the screening system, such as diagnostic testing, missed case surveillance, and research initiatives. We feel that this new format will make it easier for people when they read the report to find the information relevant to their practice.

The COVID-19 pandemic has changed the landscape of health care in many ways, and one worrisome trend is an increased mistrust in public health and the health care system. In 2022 NSO has seen unprecedented levels of declined screens. This is a trend that will be closely watched as NSO launches broader marketing and social media campaigns in 2023.

The viral flu season and pediatric surge also introduced many challenges to the health care system. Due to the stress on the system, NSO made the decision to delay the launch of biliary atresia screening until 2023. Biliary atresia screening has launched and will be presented in the 2023 annual report.

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

Sample transportation delays continued to be a significant issue in 2022, which are having an impact on the timeliness indicators. Part of this was due to Purolator switching to a centralized hub in May 2022. However, since the switch NSO has continued to experience delays in sample pick up to receipt. This data is presented in section 1.1.6. NSO has met with Purolator managers to strategize ways to improve sample shipments to Ottawa and hope to see improved transit times in 2023.

NSO and the Ontario Ministry of Health and Ministry of Children Community and Social Services, have continued with the waiver of consent for IHP risk factor screening through 2022. NSO and the IHP are currently working on an improved workflow and electronic system for when consent is reinstated. It is expected that risk factor screening for PHL will move back to a consented model in late 2023.

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1. SCREENING CHARACTERISTICS

1.1 DRIED BLOOD SPOT

The overall number of samples received by NSO in 2022 is lower than in previous years.

Table 1. Screening sample volumes between 2018-2022.

Sample Type	2022	2021	2020	2019	2018
Satisfactory	139,779	145,785	141,548	146,099	145,724
Unsatisfactory*	1,639	1,560	1,785	1,356	1,365
Routine Screening – Total	**141,418**	**147,345**	**143,333**	**147,455**	**147,089**

*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.

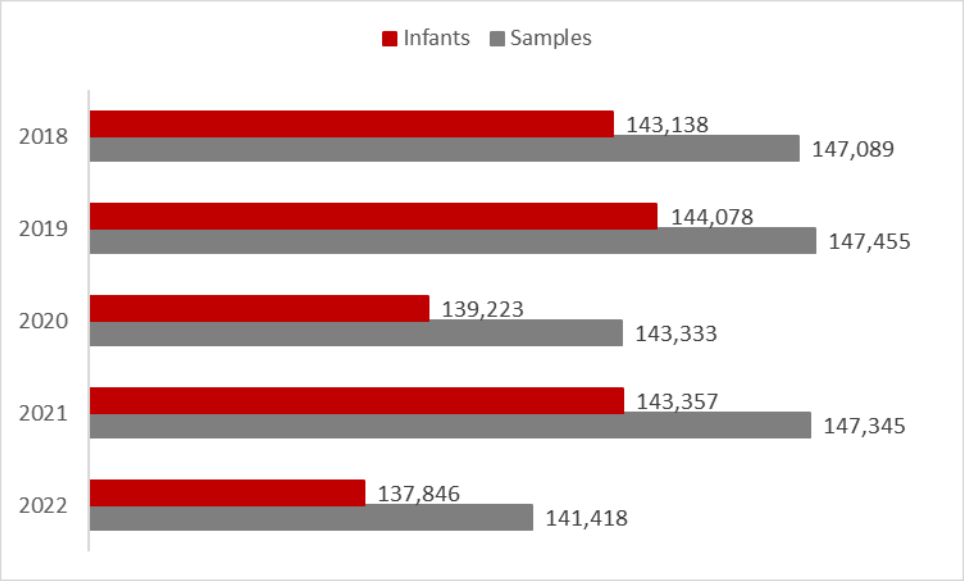

Figure 1: Total number of infants and samples screened between 2018-2022.
The number of newborns is estimated by subtracting the number of samples determined to be from the same infant as another sample from the total number of received samples. This estimate be impacted by the efficiency of the linking 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.

The overall number of infants tested is the lowest number observed over the last 10 years. Based on defers/ declines (Section 1.1.2), missed screen alerts and deceased infants from BORN (Section 1.1.3), and newborn screening sample counts (Table 1), NSO estimates the total number of infants in Ontario as 138,318 and the rate of screening uptake in 2022 as 99.7% (similar to previous years of 99.6% uptake).

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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 2022, NSO received 758 completed decline/defer forms (Table 2). The number of declines documented using this form has increased with 151 declines in 2022 compared with 96 in 2021. The remaining 607 forms received indicated a parent's desire to defer screening, and samples were eventually received for the majority of these deferred cases.

Table 2. Declined, deferred samples indicated on card between 2018-2022.

Case Type	2022	2021	2020	2019	2018
Declined/deferred form received	758	819	713	607	603
Decline	151	96	76	68	62
Deferral	607	723	637	539	541

Table 3. Overall declined screens between 2018-2022.

Declined newborn screens				
2022	2021	2020	2019	2018
257	137	136	131	120

An additional 116 declined screens were also identified via missed screen alerts. There were 7 infants for whom a decline form was completed where a sample was received. In total there were 257 infants where newborn dried blood spot screening was declined (Table 3). There were 151 families that declined the DBS screen but had the CCHD screen. NSO reviewed the number of declines received by site and have identified a few sites with a higher than average number of declines. NSO will be following up with those sites to offer education and resources regarding the importance of NBS.

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1.1.3 MISSED SCREENS

Table 4. Potential missed screen alerts requiring follow-up in 2022.

Category	Total (2022)	Samples received	Percent received	Total (2021)	Total (2020)
Non-Missed Screens	506 (74%)			415 (74%)	323 (69%)
True Missed Screens	179 (26%)	151	84%	148 (26%)	144 (31%)
Grand Total	685			563	467

There was an increase in the number of potential missed screen alerts that required follow up in 2022 with a total of 685 cases logged. Hospitals were the responsible facility in 81% of the missed screen alerts and midwives were involved in 19% of the cases.

There were 506 potential missed cases logged that were not truly missed. There were 101 deceased/palliative cases logged and 116 declines (both higher than last year). There were many cases where the sample was collected and received either the same day as the missed screen alert or after. Of these cases (208), 78 of the samples were batched by the submitter, 98 experienced shipping delays by Purolator, and 28 were both batched and had Purolator shipping delays.

In 2022, there were 179 true missed newborn screen alerts that required follow up by NSO. Of the 179 cases counted as true misses, 101 were cases where a package was lost. Action on the part of NSO resulted in 151 of the 179 (84%) truly missed screens being completed.

1.1.4 AGE AT COLLECTION

Table 5. Age at collection for 2020-2022, initial samples only.

Age at Collection	Number of Initial Samples (2022)	% of Initial Samples (2022)	% of Initial Samples (2021)	% of Initial Samples (2020)
Less than 24 hours	839	0.61%	0.59%	0.66%
24-47 hours (1-2 days)	135,423	98.27%	98.09%	97.48%
48-71 hours (2-3 days)	997	0.72%	0.89%	1.34%
72-168 hours (3-7 days)	397	0.29%	0.32%	0.38%
Greater than 168 hours (7 days)	146	0.11%	0.11%	0.14%

The majority of newborn screening samples are collected between 24-48 hours of age. Greater than 98% of samples are collected by 48 hours of age (Table 5). There has been a positive shift towards samples being collected between 24-48 hours of age following the official change to NSO's recommended age of collection in January 2017.

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1.1.5 UNSATISFACTORY SAMPLES

The unsatisfactory rate decreased in 2022, down to 1.16% compared to 1.44% in 2021. 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 21 samples that were deemed unsatisfactory for both a lab and a data unsat reason. There were 199 unsatisfactory samples that did not require follow up as a repeat sample had already been received or testing of all analytes was able to be completed through two partially saturated samples. There were 1,440 unsatisfactory samples that required follow up.

Table 6. Unsatisfactory samples by reason between 2018-2022.

			2022	2021	2020	2019	2018
SAMPLES	Satisfactory Samples		139,779	145,220	143,333	145,045	144,717
	Unsatisfactory Samples		1,639	2,125	2,332	2,044	2,936
	Unsatisfactory Rate		**1.16%**	**1.44%**	**1.63%**	**1.41%**	**1.99%**
	Samples Collected at <24hrs		514	565	547	575	577
	Unsatisfactory Samples excluding <24hr samples		1,125	1,560	1,785	1,469	2,359
	Unsatisfactory Rate excluding <24hr samples		**0.80%**	**1.06%**	**1.25%**	**1.01%**	**1.60%**
REASONS	Lab Unsat Reasons	Quantity of blood insufficient	639	927	919	710	1,471
		Blood spots appear scratched or abraded	68	142	118	292	531
		Blood spots are supersaturated	21	35	97	176	185
		Blood spots appear clotted or layered	178	217	202	403	639
		Blood spots appear diluted	6	0	<5	<5	5
		Blood spots exhibits serum rings	44	96	82	168	200
		Blood spots are wet and/or discolored	9	9	10	38	<5
		Other	25	24	50	88	62
	Data Unsat Reasons	Blood dot collection paper is expired	49	54	14	12	77
		Insufficient data provided	<5	<5	9	11	29
		Damaged or delayed in transit	0	6	5	45	8
		Delivered to lab > 14 days after collection	81	38	19	8	23
		Sample collected at <24hrs	514	565	697	575	577
		Other/Mislabel	22	22	6	90	47

Of the 514 samples collected at <24 hours, the subsequent samples for these infants indicated a transfusion was given for 141 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).

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1.1.5.1 Repeat Rates for Unsatisfactory Specimens

The majority (~80%) of repeat samples are received within 2 weeks of the initial sample (Table 7). By 6 weeks, 91% of unsatisfactory samples have had screening completed via a repeat sample.

Table 7. Repeats received on unsatisfactory samples from 2020-2022.

Time to receipt of unsatisfactory repeat sample	2022		2021		2020	
Total unsatisfactory samples	**1,440**		**1,951**		**2,332**	
< 1 week	886	61.5%	1,255	64.3%	1,314	56.3%
1 - <2 weeks	264	18.3%	310	15.9%	410	17.7%
2 - <3 weeks	86	6.0%	95	4.9%	155	6.6%
3 - <6 weeks	79	5.5%	103	5.3%	128	5.5%
≥ 6 weeks	17	1.2%	31	1.6%	33	1.4%
Not received	108	7.5%	157	8.0%	292	12.5%

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).

In 2022, NSO performed 718 priority panels (~63.8% of laboratory unsatisfactory samples) (Table 8). These samples are still counted as unsatisfactory (in Table 6), and a repeat is requested. The results of the priority diseases are also reported.

Table 8. Repeat samples for priority panel unsats 2020-2022.

Time to receipt of priority panel repeat sample	2022		2021		2020	
Total priority panels	**718**		**1,030**		**1255**	
< 1 week	397	55.3%	617	58.3%	682	54.3%
1 - <2 weeks	171	23.8%	209	19.8%	278	22.2%
2 - <3 weeks	50	7.0%	57	5.5%	87	6.9%
3 - <6 weeks	39	5.4%	54	5.1%	68	5.4%
≥ 6 weeks	9	1.3%	20	1.9%	15	1.2%
Not received	52	7.2%	73	7.5%	125	10.0%

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There were 14 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.

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.

Table 9. Repeat samples for TLU 2020-2022.

Time to receipt of TLU repeat sample	2022		2021		2020	
Total Test Level Unsats – Routine	**70**		**81**		**74**	
< 1 week	33	47.1%	43	53.1%	28	37.8%
1 - <2 weeks	21	30.0%	20	24.7%	19	25.7%
2 - <3 weeks	7	10.0%	6	7.4%	7	9.5%
3 - <6 weeks	7	10.0%	5	6.2%	9	12.2%
≥ 6 weeks	0	0	<5	<6%	<5	<7%
Not received	<5	<7%	6	7.4%	8	10.8%
Total Test Level Unsats - Urgent	**74**		**69**		**50**	
< 1 week	22	29.7%	28	40.6%	29	58.0%
1 - <2 weeks	33	44.6%	23	33.3%	12	24.0%
≥2 weeks	17	23.0%	16	23.2%	8	16.0%
Not received	<5	<7%	<5	<7%	<5	<10.0%

1.1.6 SCREENING TIMELINESS – RECEIPT AND AGE AT RESULTS

The purpose of the benchmarks was to establish days of age at which samples should be received, analyzed and resulted by the screening program, and screen positive infants should be referred, retrieved, have an initial and full diagnosis established. The goal would be to have 90% of the screened population meet the benchmarks.

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Each cell contains the percentage of infants meeting benchmarks. Cells highlighted in green met the benchmarks. Cells highlighted in yellow had 70-89% of infants achieving benchmarks. Cells highlighted in red had benchmarks <70%.

Initial results refers to results from first tier screening. All infants undergo first tier testing. After interpretation the majority of infants will be screen negative and testing is complete. The second columns of numbers under each year are the age of their final results. There were 136,869 initial samples went through first tier screening in 2022. Of these, 126,764 (92.6%) were screen negative on all assays after first tier. Some infants require additional testing to determine if they are negative or positive. Age at final results is the subset of infants who required additional testing (through second and third screening) and the age that their results are final (either positive or negative).

The percentage of infants meeting the benchmarks decreased across the board this year. This can be directly tied to delays experienced in the shipping of samples to NSO. In May 2022 Purolator moved to a centralized shipping hub. This resulted in delayed shipments during the transition. After the centralized hub was introduced, NSO continued to experience delayed sample receipt. We have met with Purolator managers to strategize ways to improve sample shipments to Ottawa and hope to see improved transit times in 2023.

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 2021 and 2022 (*note that GAMT screening only began in October 2022).

	Screening (Initial Samples) 2022 Only			Screening (Initial Samples) 2021 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	**76%**	**76%**	**96%**	**81%**	**81%**	**98%**
Biotinidase Deficiency	**76%**	**75%**	**96%**	**81%**	**79%**	**97%**
Galactosemia	**76%**	**76%**	**96%**	**81%**	**81%**	**98%**
Mucopolysaccharidosis Type 1	**76%**	**75%**	**96%**	**81%**	**79%**	**97%**
Congenital Adrenal Hyperplasia	**76%**	**76%**	**96%**	**81%**	**81%**	**98%**
Congenital Hypothyroidism	**76%**	**76%**	**96%**	**81%**	**81%**	**98%**
Cystic Fibrosis	**76%**	**75%**	**93%**	**81%**	**81%**	**95%**
Hemoglobinopathies	**76%**	**64%**	**95%**	**81%**	**74%**	**96%**
Severe Combined Immune Deficiency	**76%**	**12%**	**53%**	**81%**	**12%**	**55%**
Spinal Muscular Atrophy	**76%**	**12%**	**55%**	**81%**	**13%**	**58%**

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 10b. Median and 90th centile values for age of receipt of initial samples, and availability of initial and final results, 2021 and 2022.

Category	Screening (Initial Samples) 2022 Only					Screening (Initial Samples) 2021 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	7	43	6	9	4	6	49	6	8
CUD			294	5	8			189	5	7
FAOD			4	4	4			12	5	8
GA1			44	6	8			39	5	7
HCY			48	6	7			42	5	8
IVA			19	5	6			44	5	7
LCHAD/TFP			23	6	9			11	6	9
MCAD			27	5	8			33	5	6
MSUD			18	7	20			28	6	16
PA/MMA			146	6	9			180	6	8
PKU			138	5	7			114	5	7
TYR1			11	7	8			17	6	8
VLCAD			199	6	8			358	5	7
Biotinidase Deficiency			103	6	9			186	6	8
Galactosemia			99	7	9			125	6	9
GAMT			101	10	14					
MPS1H			556	10	20			732	9	18
CAH			605	6	8			525	6	8
CH			770	5	7			915	5	7
Cystic Fibrosis			5,648	9	17			5,820	9	14
Hemoglobinopathies	5	7	105	6	8	5	7	111	7	9
SCID	7	11	949	10	14	7	11	2,377	9	12
SMA	7	10	33	12	23	7	11	106	17	25

The median age (4 days) at receipt remained unchanged between 2021 and 2022, however the 90th centile increased for the majority of conditions screened. There were fewer samples that went on to VLCAD second tier screening in 2022 compared to 2021 (this is discussed further in section 2.5). There were also fewer samples that required more than first tier screening for SMA, MPS1H, and SCID. While the median remained similar for age at initial results, the 90th centile for age at final results increased across many assays.

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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, 2021 and 2022.

	Screening (Initial Samples) 2022 Only					Screening (Initial Samples) 2021 Only				
Category	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	43	50	89	24	26	49	50	75
CUD			294	49	52			189	49	72
FAOD			4	49	51			12	50	106
GA1			44	49	73			39	50	74
HCY			48	49	51			42	49	73
IVA			19	49	73			44	50	74
LCHAD/TFP			23	49	75			11	49	74
MCAD			27	49	57			33	49	72
MSUD			18	51	58			28	49	53
PA/MMA/CblA&B			146	50	99			180	50	98
PKU			138	49	58			114	49	52
TYR1			11	50	76			17	50	73
VLCAD			199	49	72			358	49	73
Biotinidase Deficiency			103	50	74			186	50	74
Galactosemia			99	49	51			125	49	51
GAMT			101	170	199					
MPS1H	25	27	556	151	387	25	27	732	148	345
CAH	24	26	605	51	99	24	26	525	51	98
CH			770	49	73			915	50	74
Cystic Fibrosis			5,648	129	342			5,820	146	248
Hemoglobinopathies	26	73	105	52	121	26	50	111	80	127
SCID	99	149	949	148	218	99	152	2,377	146	176
SMA	99	148	33	218	485	98	150	106	339	511

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1.2 CRITICAL CONGENITAL HEART DISEASE

Submitters submit their Critical Congenital Heart Disease (CCHD) screen results to NSO via a tear off sheet on the standard NSO dried blood spot card. These may come with the dried blood spot, or separately, depending on hospital process. The total number of CCHD cards registered at NSO in 2022 was 140,689 representing 137,520 infants. Including CCHD missed screens in which a card was not received (364) and CCHD missed screens not followed up on as the infant was <33 weeks gestational age, <1500 g, or admitted to Sickkids or CHEO (169), and deceased infants not registered (66), the total number of infants is 138,119, which is lower than the estimated number of infants in Ontario that was derived from the blood spot samples, of 138,318 (Section 1.1.1).

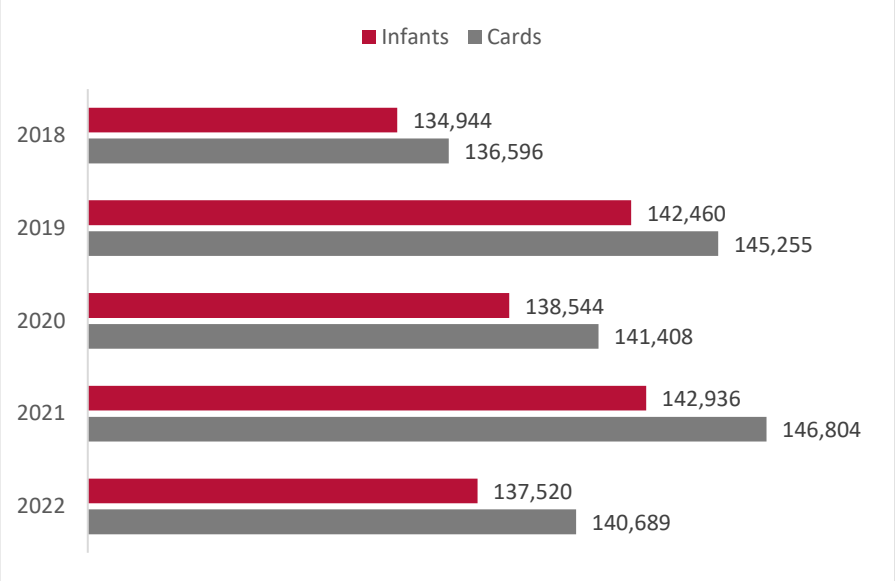

Figure 2. CCHD cards received at NSO and total number of infants between 2018-2022.

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 2022, 7,072 of the requisitions submitted were for screens not done.

Table 12. CCHD cards received.

CCHD Cards received	2022		2021		2020		2019		2018	
Screen Completed	133,617	94.97%	139,264	94.86%	134,834	95.40%	138,775	95.50%	132,134	96.70%
Screen Not Done*	7,072	5.03%	7,540	5.14%	6,574	4.60%	6,480	4.50%	4,462	3.30%
	140,689		146,804		141,408		145,255		136,596	

*NSO began tracking blank cards in 2019 (and continued this practice in 2020), resulting in an increase in 'Screens not Done' for between 2018 and 2019.

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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, 99.13% of the screens were resolved after just one test (most often this would be a pass, but this could also be an immediate referral). Only 0.76% required a second test and 0.11% required three tests to complete the screen.

Table 13. Tests required to complete screen between 2018-2022.

Tests Done	2022		2021		2020		2019		2018	
1 Test	130,639	99.13%	138,050	99.13%	131,592	98.80%	136,935	98.70%	129,967	98.40%
2 Tests	997	0.76%	1,067	0.77%	1,431	1.10%	1,621	1.20%	1,948	1.50%
3 Tests	150	0.11%	147	0.11%	222	0.20%	218	0.20%	219	0.20%
	131,786		139,264		133,245		138,775		132,134	

1.2.2 Screens Not Done

In 2022, CCHD screens were not done on 5.03% 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 2018-2022.

	2022		2021		2020		2019		2018	
'Screen Not Done' cards submitted	7,072		7,540		6,574		6,480		4,462	
Decline/deferred (back page of form not completed)	113	1.60%	106	1.41%	95	1.40%	93	1.40%	78	1.70%
Declined	132	1.87%	139	1.84%	66	1.00%	26	0.40%	26	0.60%
Deferred	441	6.24%	541	7.18%	565	8.60%	542	8.40%	465	10.40%
Infant diagnosed prenatally with heart defect	170	2.40%	178	2.36%	101	1.50%	74	1.10%	58	1.30%
Infant diagnosed with heart defect by physical exam	50	0.71%	70	0.93%	33	0.50%	47	0.70%	58	1.30%
Infant is not appropriate for screening (e.g. NICU > 7 days, on oxygen, IV in right hand, limb anomaly, etc.)	4,336	61.31%	4,745	62.93%	4,725	71.90%	4,732	73.00%	3,735	83.70%
Already done	503	7.11%	514	6.82%	169	2.60%	17	0.30%	8	0.20%
Insufficient information provided/blank card	1,062	15.02%	1,005	13.33%	671	10.20%	704	10.90%	18	0.40%
Other	265	3.75%	242	3.21%	149	2.30%	245	3.80%	16	0.40%

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Of the decline/deferred group (113) where the back of the form was not completed – 89 had a CCHD screen completed and 6 had cards received indicating infant is expected to be in the NICU for > 7 days. Of the decline group (132) – 93 had a CCHD screen completed. In total, 58 families declined CCHD screening (including decline forms received, defer/decline forms, and missed screen notifications). There were 30 families that declined both the CCHD screen and the DBS screen.

1.2.3 CCHD Missed Screens

In 2022, 494 potential missed screens were identified, significantly fewer than in 2020 when there were 1,297 and 2021 where there were 562. The majority of the alerts were from hospitals (459). The majority of these alerts were due to improper documentation – either the infant was screened but documentation was not sent to NSO (190) or the infant was not suitable for screening and documentation was not sent to NSO (231). There were 64 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 2020-2022.

Category		Total (2022)	Total (2021)	Total (2020)
Non-Missed Screens		430 (87%)	503 (89.5%)	1,163 (89.7%)
True Missed Screens	Missed - infant's health care provider notified	64 (13%)	59 (10.5%)	134 (10.3%)
Grand Total		494	562	1,297

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 (95.78%) of screening is completed by 48 hours of age which is a continued in improvement from previous years.

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Table 16. Age at time of CCHD Screen from 2018-2022

Age at time of CCHD screen	2022		2021		2020		2019		2018	
	Number of screens	%	Number of screens	%	Number of screens	%	Number of screens	%	Number of screens	%
≤48 hours (1-2 days)	128,109	95.88	132,774	95.40	125,382	93.00	128,316	92.40	122,013	92.30
>48-72 hours (2-3 days)	1,377	1.03	1,721	1.20	1,706	1.30	2,571	1.90	3,178	2.40
>72-168 hours (3-7 days)	846	0.63	940	0.70	928	0.70	1,144	0.80	1,147	0.90
Greater than 168 hours (> 7 days)	207	0.15	197	0.10	255	0.20	352	0.30	300	0.20
Not specified	3,080	2.31	3,632	2.60	6,289	4.70	6,391	4.60	5,496	4.20

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 2022 was 1,057, which was 0.75% of the cards received. The most frequent error was incomplete documentation – either of a repeat test done after 1 hour or missing screening values (Table 17). The number of unsatisfactory screens increased in 2019 as NSO started to contact submitters where cards were received with demographic information but no CCHD screening values recorded. With increased submitter education, the unsatisfactory rate decreased in 2020 and has remained below 1%.

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Table 17. Outcomes from unsatisfactory CCHD screen notifications.

	2022	2021	2020	2019	2018
Unsatisfactory Screens	**1,057**	**1,179**	**1,069**	**1,855**	**615**
Baby >7days, no rescreen recommended	42 (4.0%)	39 (3.3%)	65 (6.1%)	49 (2.6%)	31 (5.0%)
Baby in hospital, no screen recommended	185 (17.5%)	203 (17.2%)	253 (23.7%)	566 (30.5%)	33 (5.4%)
Documentation inaccurate or incomplete	653 (61.8%)	723 (61.3%)	574 (53.7%)	865 (46.6%)	297 (48.3%)
Family Declined	0	0	0	3 (0.2%)	0
No action needed	50 (4.7%)	57 (4.8%)	38 (3.6%)	51 (2.7%)	0
Physical exam recommended (screen positive)	<5 (<0.5%)	<5 (<0.5%)	0	<5 (<0.3%)	<5 (<0.5%)
Missed - baby >7 days, no screening recommended	6 (0.6%)	6 (0.5%)	9 (0.8%)	5 (0.3%)	251 (40.8%) (only recorded as rescreen)
Missed - screening recommended	40 (3.8%)	65 (5.5%)	54 (5.1%)	119 (6.4%)	
Rescreen recommended	80 (7.6%)	83 (7.0%)	76 (7.1%)	195 (10.5%)	
Total Screening Forms Submitted	**140,689**	**146,804**	**141,408**	**145,255**	**136,596**
Unsatisfactory Rate	**0.75%**	**0.80%**	**0.76%**	**1.28%**	**0.45%**

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

NSO performed follow up on 1,057 unsatisfactory screens, and in 61.8% of follow up cases the result was amended by the submitter due to incorrect completion of the form. In 7.6% of cases a rescreen was recommended. Through the follow up of unsatisfactory screens NSO was able to follow up with submitters for 120 infants that had not received a proper CCHD screen and needed to be screened (missed) or rescreened.

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

1.3 HEARING

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

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1.3.1 Consent

When risk factor screening for PHL launched, parents/guardians were approached for consent as part of the infant hearing screening process. When the COVID-19 pandemic began in 2020, and all non-essential services were discontinued temporarily, the IHP postponed all audiometric hearing screening and was no longer able to obtain consent for risk factor screening. After careful review and options-analysis with the Ontario Ministry of Health and Ministry of Children Community and Social Services, a decision was made to continue with the risk factor screening without the need for additional consent from the IHP until it became feasible again. This decision was made due to high rate at which approached parents had been consenting and so that babies at high risk for PHL would continue to be identified. All DBS from babies born on or after March 26, 2020, were screened for CMV and genetic risk factors for PHL, and this continued throughout 2022. NSO and the IHP are currently working on an improved workflow and electronic system for when consent is reinstated. It is expected that risk factor screening for PHL will move back to a consented model in late 2023.

Table 18 shows the number of infants screened for CMV and genetic risk factors for PHL. NSO screened 137,842 infants in 2022. Risk factor screening for PHL (CMV and genetics) was completed for 137,737 infants in 2022. All babies that were screened for CMV were also screened for genetic risk factors. This is an improvement from the year previously where there were some samples that were screened for CMV however were not able to be screened for genetic factors. This improvement was facilitated by changes in the GJB2 assay to decrease unsatisfactory samples.

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

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

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2. SCREEN POSITIVES

2.1 TREATMENT CENTRE

2.1.1 Referrals by Treatment Centre

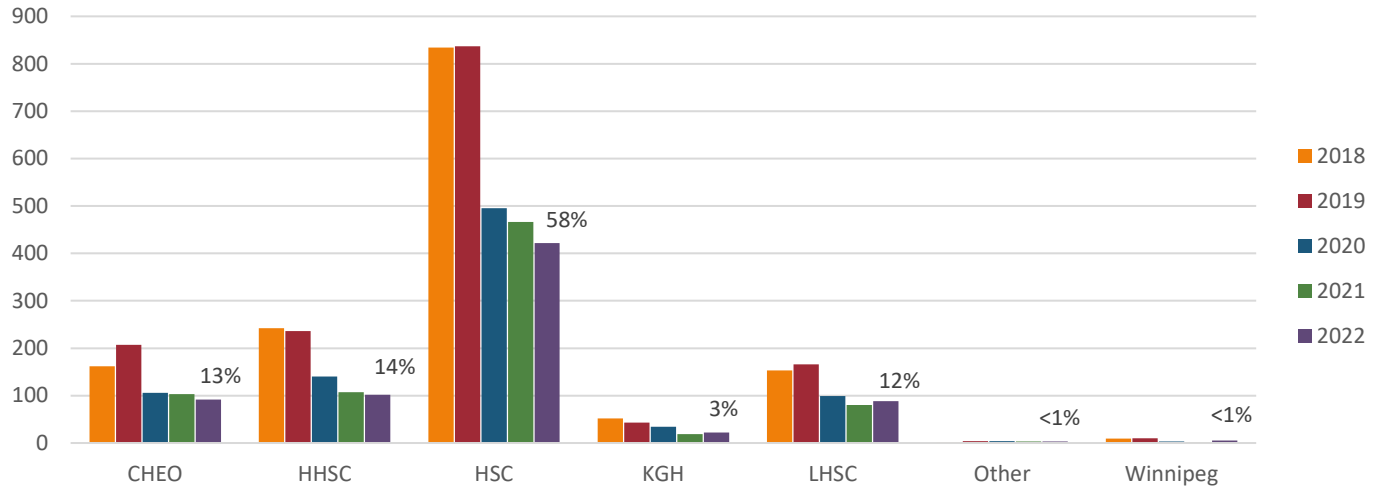

Figure 3a. The total number of referrals by treatment centre between 2018-2022.

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 (Figure 3a). 'Other' represents infants referred to treatment centres outside of Ontario/ Winnipeg, such as Quebec or the USA, or a centre in Ontario that is outside of the standard treatment centres. While the number of referrals have decreased since 2020 onward, the proportion of referrals received by each of the five Ontario regional treatment centres has been relatively unchanged with CHEO, HHSC and LHSC receiving a similar proportion of referrals and HSC receiving approximately 58% of referrals (Figure 3b).

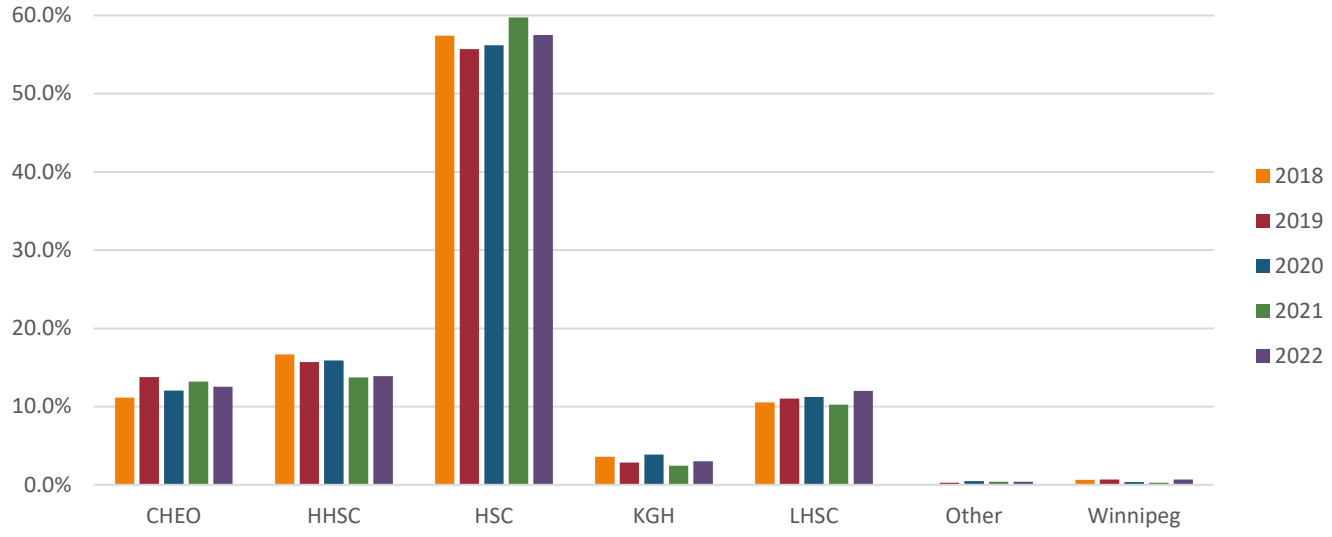

Figure 3b. The percentage of referrals by treatment centre between 2018-2022.

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2.1.2 DBS REFERRALS

In 2022, there were 734 screen positive referrals (Figure 4). This represents ~0.54% of the total number of infants screened by NSO.

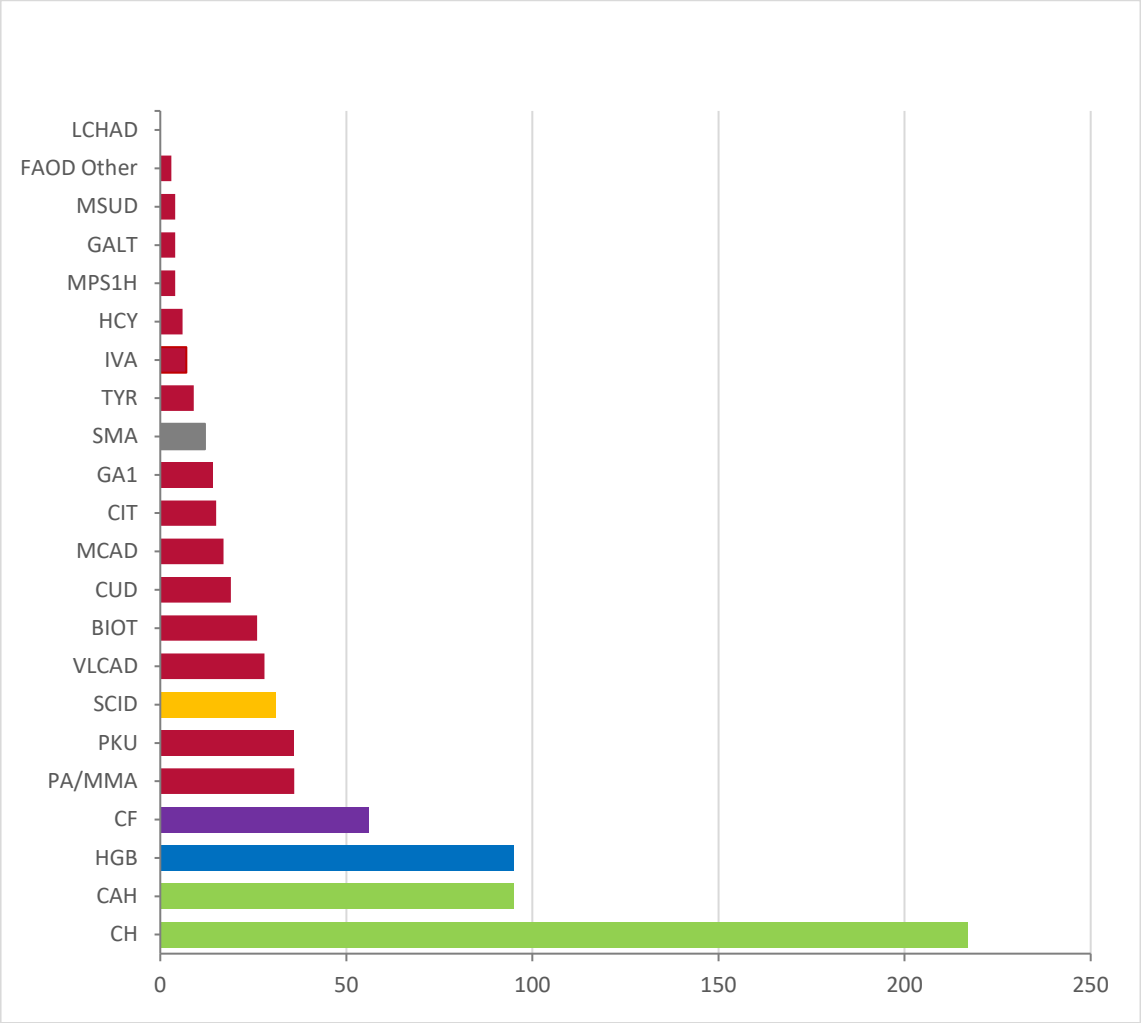

Figure 4. Total number of screen positive referrals by disease in 2022

The number of screen positive infants referred in 2022 decreased slightly from 2021 (780 vs. 734).

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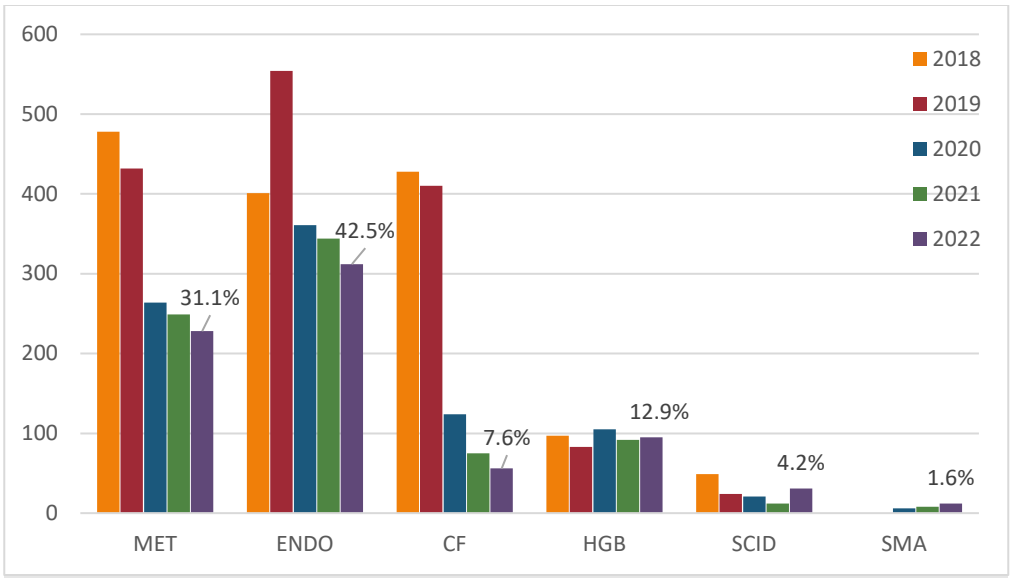

Figure 5. The total number of screen positives by disease grouping between 2018-2022.

The number of screen positive referrals per disease grouping decreased for all referral types except SMA, SCID and Hgb (Figure 5). The CF algorithm changed in March 2020 with the addition of 3rd tier sequencing of the *CFTR* gene and only infants with 2 or more CFTR variants being referred as positive. This accounts for the decrease in CF referrals (discussed more in section 2.3).

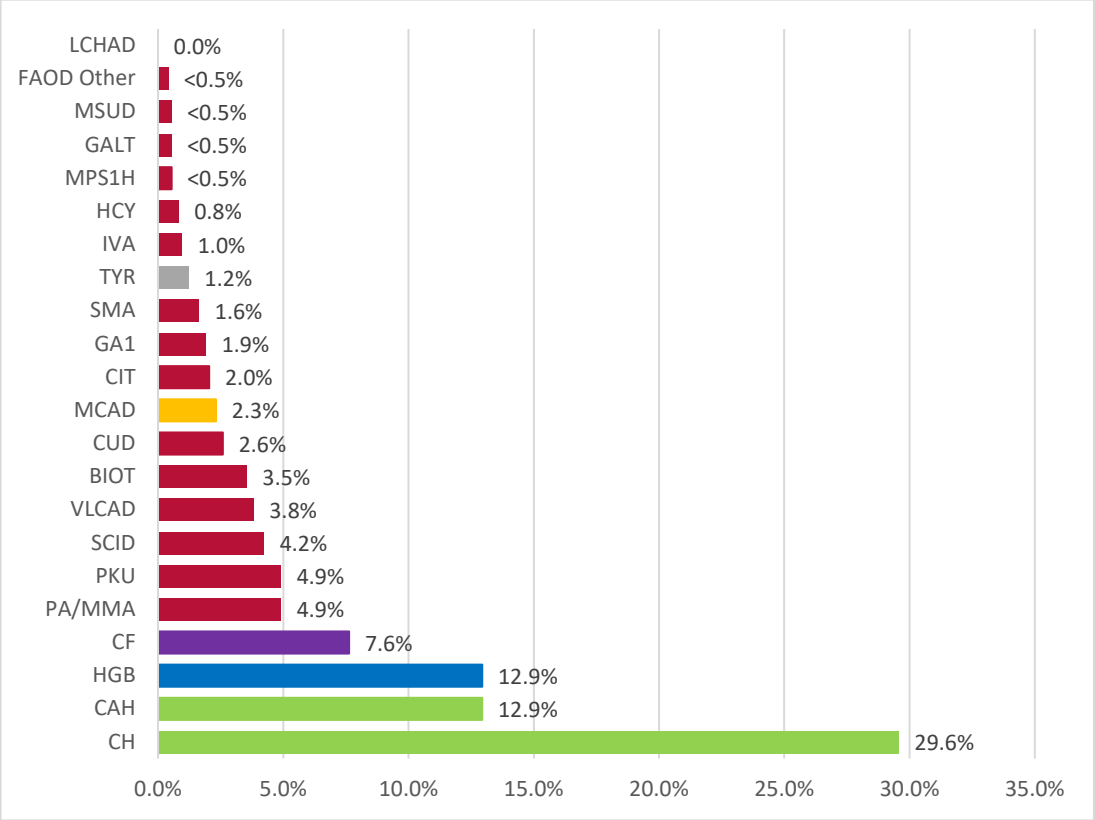

Figure 6. The percentage of screen positive referrals by disorder in 2022.

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Endocrinopathies and Metabolics represent ~43% and ~31% of screen positives respectively (Figures 5 ad 6). SCID screen positive referrals increased in 2022 and now represent 4.2% of total screen positive referrals. The number of Cystic Fibrosis referrals continued to decrease in 2022 and now represent 7.6% of total screen positive referrals. Hemoglobinopathies represent approximately 13% of screen positive referrals, which is unchanged from last year. SMA represents 1.6% of referrals.

2.1.3 Diagnostic Feedback

Approximately 32.2% (236 cases) of diagnostic evaluation report forms (DERFs) remain pending for the referrals made in 2022 as of April 1, 2023. The percentage of pending DERFs is high, however, with the use of preliminary data obtained during confirmation of retrieval and initial diagnosis, an outcome was obtained for 88 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 factors, or sample quality). This information is available earlier than DERF completion and is also a way to incorporate information into data analysis.

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Table 19. The outcome classifications for all referrals in 2022 (DERF data pulled April 1, 2023). 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	38	27	47	32	23	87	<5	217
Congenital Adrenal Hyperplasia	17	15	<5		<5	71	<5	95
Hemoglobinopathies	47	30	48	<5	15		<5	95
Cystic Fibrosis	24	6	26	21	<5			56
Type 1	12		26	<5				27
Type 2	6	<5		7				12
Type 3	6	<5		13	<5			17
SCID	14	13	<5		<5	10	<5	31
SMA	6		12					12
Biotinidase Deficiency	11	4	5	9		8		26
Citrullinemia	7	6	<5	<5	<5	6		15
CUD	6	5	<5		5	7	<5	19
FAO (CPT1, CPT2, and GA2)	<5		<5			<5	<5	<5
Galactosemia	<5			<5	<5	<5		<5
GAMT	0							0
Glutaric Aciduria Type 1	<5	<5	<5		<5	8		14
Homocystinuria	<5	<5			<5	<5		6
Isovaleric Acidemia	<5		<5			5	<5	7
LCHAD	0							0
MCAD	8	<5	9		<5	5		17
MPS1H	<5	<5	<5		<5			<5
MSUD	<5	<5	<5			<5		<5
PA/MMA	15	13			9	12	<5	36
Phenylketonuria	14	8	8	5		15		36
Tyrosinemia	<5	<5			<5	<5	<5	9
VLCAD	12	8	<5	<5	6	8		28
Total No. Positive	**236**	**148**	**174**	**73**	**76**	**252**	**11**	**734**

2.2 HEMATOLOGY

The number of screen positives in 2022 remained consistent with the number of referrals observed in 2021.

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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, 2022)	**61.5%**	**62.3%**	**91.2%**	**9.9%**

2.2.1 Hemoglobin Carriers

Table 21. Hemoglobin carrier requests between 2018-2022.

	2022	2021	2020	2019	2018
Requests from high risk population	23	unknown	23	35	46
Total Requests	**37**	**49**	**32**	**40**	**55**
Number of carriers	13	17	12	16	18

Table 22. Carriers identified in 2022.

HGB Pattern	Carriers Identified
FAC	347
FAD	250
FAE	270
FAS	1,492
FAX	96
Grand Total	**2,455**

In 2022, <0.5% of carriers requested their results. The number of hemoglobin carrier requests remain low compared to the number of carriers. The way hemoglobin carrier requests are logged was changed in 2021. Therefore, the number of requests from high risk populations was unknown for that year. There were 23 requests from high risk populations in 2022.

The NSO-AC struck a task force in 2020 to examine different carrier disclosure models that could be considered in Ontario due to the low uptake in carrier requests. While the task force is looking at Sickle Cell Disease in particular, the modeling could be applied to other conditions screened by NSO, such as Cystic Fibrosis and MPS1H. The task force work will wrap up in 2023.

2.3 Cystic Fibrosis

The number of screen positives in 2022 continued to decrease from 2021. There were 56 referrals this year compared to 75 in 2021. There were 27 Type 1 referrals (genotypes consistent with a high risk of a diagnosis of CF), 12 Type 2 referrals (genotypes consistent with a high risk for a *CFTR* -related disorder NOT meeting CF diagnostic criteria) and 17 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%	5.2%
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%	4.5%
Current (Mar 19, 2020 - Dec 31, 2022) Type 1	98.6%	100.0%	100.0%	1.4%
Current (Mar 19, 2020 - Dec 31, 2022) Type 2	2.1%	100.0%	100.0%	16.1%
Current (Mar 19, 2020 - Dec 31, 2022) Type 3	5.2%	79.3%	79.3%	4.8%
Current (Mar 19, 2020 - Dec 31, 2022) ALL	**42.7%**	**93.3%**	**93.3%**	**6.8%**

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

2.4 ENDOCRINOLOGY

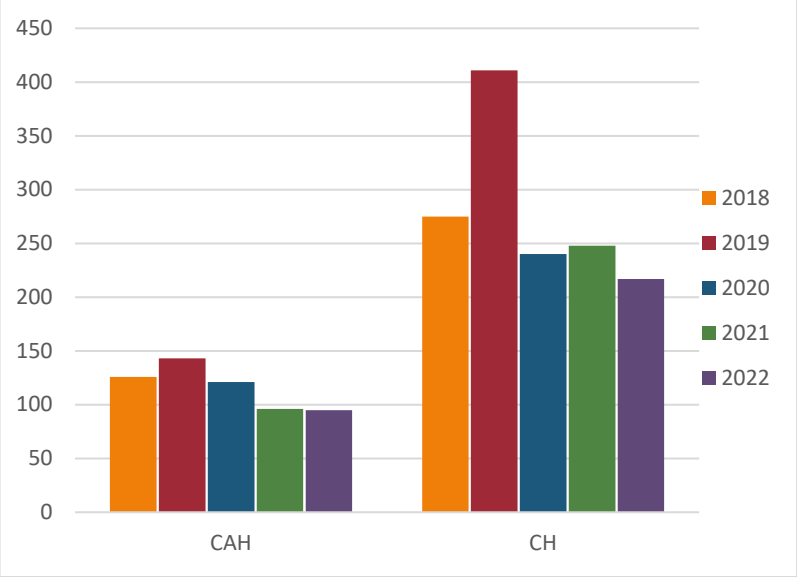

Figure 7. The total number of congenital adrenal hyperplasia and congenital hypothyroidism screen positives between 2018-2022.

The number of screen positives for CAH was similar to last year. The number of screen positives for CH decreased compared to 2021 and 2020. There have been no disorder logic changes for either condition in the last few years.

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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)	16.6%	22.2%	22.2%	1.1%
	Current (Jul 4, 2019 - Dec 31, 2022)	**22.5%**	**37.2%**	**37.2%**	**3.9%**
Congenital Adrenal Hyperplasia	Past (Sept 2, 2016 - Jun 11, 2018)	7.0%	7.0%	7.0%	3.0%
	Current (Jun 12, 2018 - Dec 31, 2022)	**5.0%**	**5.4%**	**5.8%**	**5.2%**

2.5 METABOLIC

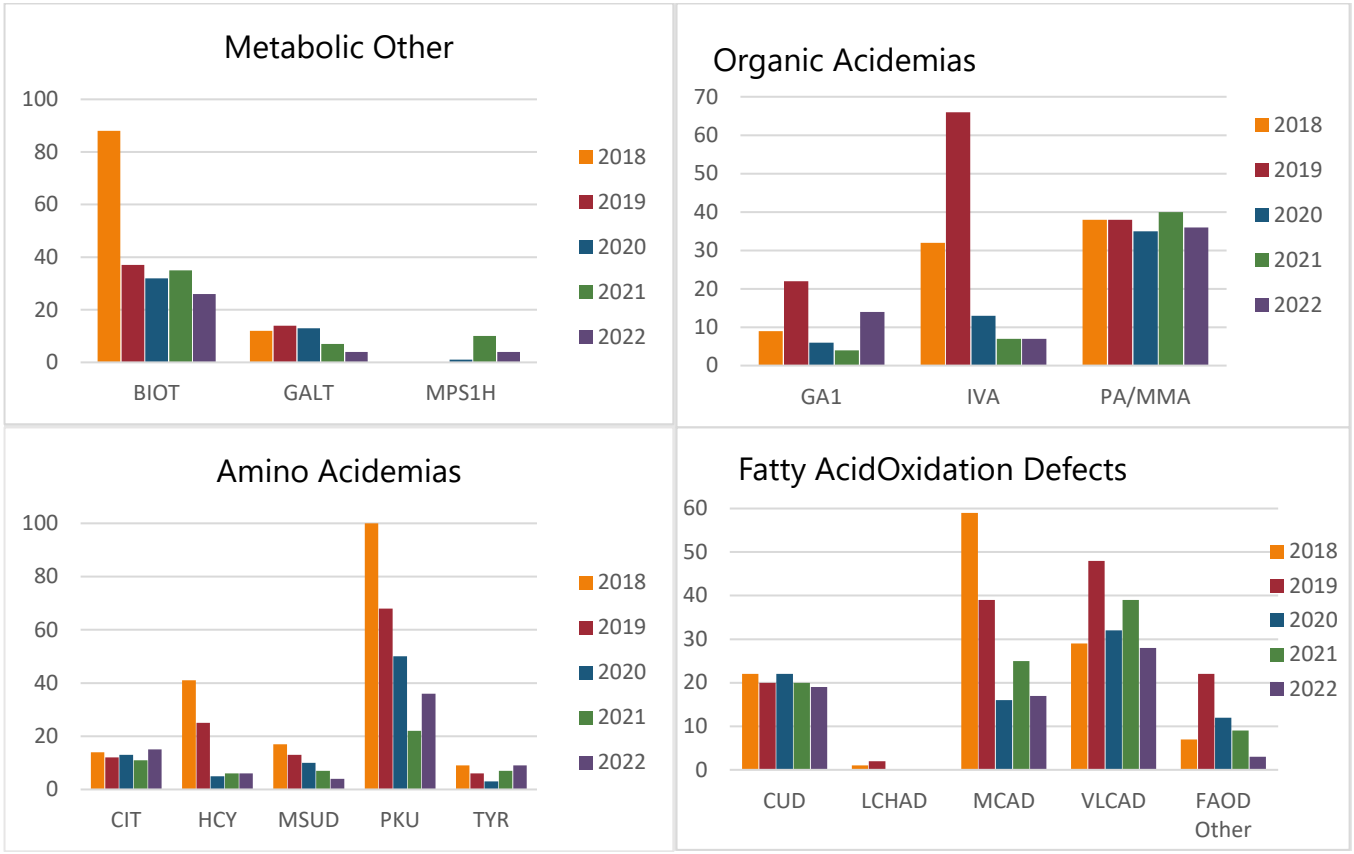

Figure 8. The number of metabolic screen positives between 2018-2022 by disease

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

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

VLCAD had disorder logic change in mid December 2021 with the C14:1 cutoff increasing from 0.65 to 0.75uM. The number of referrals decreased in 2022 as a result of this modification.

CPT1, CPT2, and GA2 referrals are all categorized as FAOD other in the table below. None of these are primary targets of screening but can be identified through the screening process.

The C5 cutoff for IVA was changed from 0.67 to 1.00 on Feb 18, 2020. This resulted in a significant decrease in the number of IVA referrals in 2020 which continued in 2021 and 2022.

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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		**N/A**	**N/A**	**N/A**	**N/A**
Glutaric Aciduria type 1		**9.1%**	**9.1%**	**24.1%**	**2.9%**
Isovaleric Acidemia	Past (until Feb 17, 2020)	3.0%	4.2%	4.2%	0.0%
	Current (Feb 18, 2020 - Dec 31, 2022)	**19.0%**	**19.0%**	**19.0%**	**19.0%**
PA/MMA/CblA/CblB	Past (Feb 16, 2010 - Apr 21, 2013)	3.7%	3.7%	8.3%	0.9%
	Current (Apr 22, 2013 - Dec 31, 2022)	**4.5%**	**4.5%**	**9.6%**	**11.7%**
Fatty Acid Oxidation Defects - Other		**7.8%**	**52.3%**	**52.8%**	**1.5%**
LCHAD/TFP		**81.3%**	**81.3%**	**93.8%**	**0.0%**
VLCAD	Past (until Dec 14, 2021)	7.2%	12.4%	14.2%	3.2%
	Current (Dec 15, 2021 - Dec 31, 2022)	**13.0%**	**26.1%**	**26.1%**	**25.8%**
CUD	Past (until Mar 4, 2014)	5.5%	5.5%	5.5%	0.0%
	Current (Mar 5, 2014 - Dec 31, 2022)	**6.9%**	**6.9%**	**6.9%**	**12.6%**
MCAD	Past (Sep 1, 2016 - Jul 28, 2019))	18.9%	20.3%	21.6%	1.3%
	Current (Jul 29, 2019 - Dec 31, 2022)	**62.5%**	**71.4%**	**71.4%**	**13.8%**
Citrullinemia/ASA		**17.3%**	**21.1%**	**21.1%**	**5.9%**
Homocystinuria	Past (until Jul 28, 2019)	**0.4%**	**0.4%**	**4.0%**	**2.8%**
	Current (Jul 29, 2019 - Dec 31, 2022)	**0.0%**	**0.0%**	**8.3%**	**25.0%**
Phenylketonuria	Past (until Jul 28, 2019)	**14.2%**	**27.4%**	**27.4%**	**1.3%**
	Current (Jul 29, 2019 - Dec 31, 2022)	**22.6%**	**37.7%**	**37.7%**	**13.3%**
MSUD	Past (until Nov 14, 2011)	3.8%	3.8%	3.8%	0.0%
	Current (Nov 15, 2011 - Dec 31, 2022)	**8.2%**	**9.1%**	**9.1%**	**5.0%**
Tyrosinemia	Past (Sep 14, 2009 - Sep 19, 2011)	1.4%	1.4%	1.4%	0.0%
	Current (Sep 20, 2011 - Dec 31, 2022)	**10.3%**	**10.3%**	**13.2%**	**11.1%**
Galactosemia	Past (until Jan 12, 2014)	35.7%	41.4%	41.4%	1.4%
	Current (Jan 13, 2014 - Dec 31, 2022)	**17.0%**	**32.1%**	**32.1%**	**3.5%**
Biotinidase Deficiency	Past (Jan 13, 2014 - Jul 2, 2014)	2.1%	37.5%	37.5%	0.0%
	Current (Jul 3, 2014 - Dec 31, 2022)	**7.4%**	**40.0%**	**40.0%**	**4.2%**
MPS1H		33.3%	33.3%	33.3%	33.3%

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

2.6 IMMUNOLOGY

The number of screen positive referrals for SCID increased from 12 in 2021 to 31 in 2022. There were no algorithm changes in 2022.

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

Additional information	PPV (Primary)	PPV (Primary + Variant)	PPV (Primary + Variant + Secondary)	% of Outcomes Unknown
Past (Jan 6, 2020 - Feb 28, 2021)	30.8%	30.8%	30.8%	30.4%
Current (Mar 1, 2021 - Dec 31, 2022)	**20.0%**	**20.0%**	**20.0%**	**41.5%**

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

2.7 NEUROLOGY

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

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	9
24-48 hours	133
> 48 hours	<5
Not available	<5
Grand Total	**148**

There were 148 CCHD screen positives in 2022, most of which were screened within 24-48 hours. There were nine screens performed at <24 hours of age. Of the 6 true positives, they were all screened between 24-29 hours of age.

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

Definitive Diagnosis Categorization	2022	2021	2020	2019	2017-2018*	Cumulative
Primary target	6	9	11	15	12	53
Secondary target	61	69	48	36	63	277
Incidental Finding	31	38	47	44	55	215
Not affected	49	51	90	72	142	404
Lost to follow up	<5	0	<5	0	0	<5
Grand Total	**148**	**167**	**197**	**167**	**272**	**951**

*CCHD screening was implemented in 2017 and submitters continued to roll out screening through 2018. 2019 marked the first full year of screening.

Of the 148 screen positives received in 2022, 6 were diagnosed with a critical congenital heart defect, 92 had a secondary CHD target or were diagnosed with an incidental finding such as pulmonary disease or infection, and 49 were found to be not affected.

2.8.1 CCHD Definitive Diagnosis Data and Positive Predictive Values

In 2022, the Positive Predictive Value (PPV) for CCHD screening was 4.08% for primary targets and 45.58% for primary and classical secondary target diseases. Cumulatively since the beginning of the program, the PPV is 5.58% for primary targets, and 34.77% for primary and classical secondary target diseases. Of the 949 screen positives since the initiation of CCHD screening (the lost to follow up DERFs have been excluded from analysis), 404 (42.57%) have been determined to be not affected after diagnostic follow up.

Table 30. PPV calculations for CCHD Screen Positives (yearly 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
2017-18	4.40%	27.60%	272	12	63	55	142	0
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
Cumulative	5.58%	34.77%	951	53	277	215	404	<5

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2.9 HEARING

CMV screening is performed using a real-time PCR assay and specimens where CMV is detected are reported as screen positive. Genetic screening is performed using mass array technology for a panel of selected mutations in the genes *GJB2/6* and *SLC26A4*, and infants with 2 or more mutations in the same gene are considered screen positive. The referral care pathways are summarized in the 2020 NSO Annual Report.

Table 31. Number of risk factor screen positive babies in 2022

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

The table above shows the number of risk factor screen positive infants for the last three years. In 2022, there were 190 CMV screen positive infants. The CMV screen positive rate was 0.13%. This is an increase in 50 cases from the year previously. Given there were no changes to our screening protocols it is difficult to determine what contributed to this increase, however it is possible that the loosening of COVID-19 restrictions played a role. We are aware of 5 cases of cCMV that were ascertained clinically but missed through screening (i.e. false negatives) in 2022.

There were 37 infants with genetic screen positive results in 2022. The referral rate has remained consistent since the introduction of reflexive testing for the *GJB2* p.(V37I) mutation in October 2020. There were only a few *SLC26A4* screen positives in 2022. This is not unexpected; it is well known that *SLC26A4*-related PHL is less common than *GJB2/6*-related PHL. We are not aware of any missed cases of PHL involving the mutations included on the screening panel. We continue to evaluate the frequency of mutations screened in our population and they are as expected.

2.9.1 CMV screen positive referrals and outcomes

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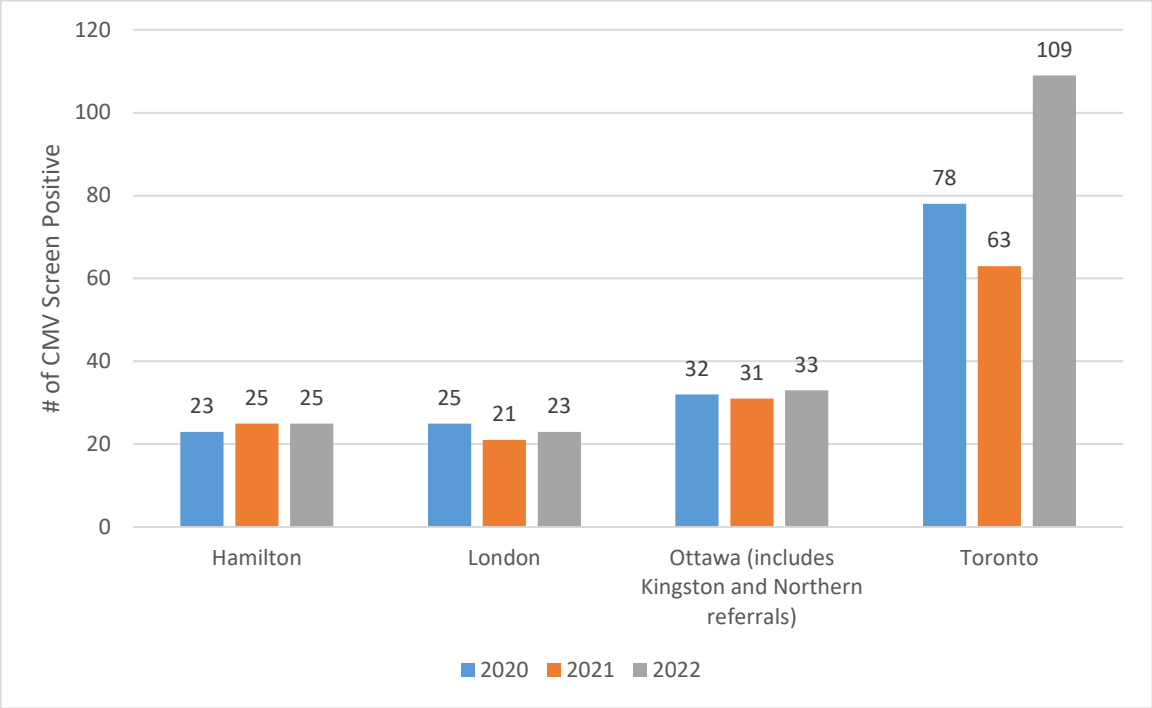

Figure 9. CMV screen positives by referral region

Figure 9 shows the breakdown of CMV screen positive referrals by region. As expected, Toronto received the largest number of CMV referrals (109/190, 57%), followed by Ottawa (33/190, 17%) Hamilton (25/190, 13%) and London (23/190, 12%). The Ottawa referral region includes the following areas; Ottawa, Kingston and Northern Ontario. This distribution is similar to that observed in 2021; however, there was an overall increase in 50 referrals, with Toronto receiving the highest increase in referrals.

The majority of CMV screen positive infants were referred to a community pediatrician for their initial assessment (169/190, 89%). The remaining infants were referred directly to ID for their initial assessment (21/190, 11%). This proportion was similar to that observed in 2021, where 81% were seen for their initial assessment by community pediatricians and 19% 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 2022**	**GRAND TOTAL 2021**	**GRAND TOTAL 2020**
Detected	156	8	164	<5	<5	6	170	120	159
Borderline	13	7	20				20	20	*
TOTAL	169 (92%)	15 (8%)	184	<5	<5	5	190	140	159

*The category of borderline result was introduced in 2021

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The table above summarizes the urine CMV PCR results in 2022. Urine CMV PCR results are available for 184 (97%) of the screen positive infants. Of these, 169 (92%) had positive/detected results. There were 15 cases (8%) 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. To date, false positive newborn screening results, false negative urine diagnostic lab results, and contaminated blood spot cards have all been observed in such cases, and they have been difficult to resolve.

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 2022 showed that 35% of borderline screen positives had negative urine CMV PCR results as compared to 5% of robust screen positives. This is in comparison to 2021 data that showed 17% of borderline screen positives cases had negative urine CMV PCR results as compared to 8% of robust screen positives. This suggests that a borderline result at NSO is more likely to result in a negative urine CMV PCR result but is not entirely predictive on its own. NSO is working to further streamline the evaluation of cases with negative urine CMV PCR with Public Health Ontario (PHO). This project will involve all urine samples being sent to PHO for initial testing and then further testing being done on all samples where the urine CMV PCR result is negative. The goal of this project is help to better understand and classify infants whose urine CMV PCR sample is negative.

Of the CMV screen positive infants with positive confirmatory urine CMV PCR results, 85% (143/169) were deemed to have asymptomatic cCMV infection and 12% (21/169) 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 consistency with what has been described in the literature. None of the asymptomatic infants are being treated.

Very few 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, 11 (52%) infants had PHL identified at the initial diagnostic audiology assessment. The importance of ongoing hearing surveillance must be underscored for all CMV screen positive infants as there is there is risk of developing PHL for both asymptomatic (~10%) and symptomatic (~30%) cases. It will be important to review IHP outcome information from audiologic surveillance to learn what proportion of infants develop non-congenital PHL and at what age to better understand any predictors.

2.9.2 Genetic screen positive outcomes

In 2022, there were no genetic screen positive infants from the following IHP regions: Simcoe Muskoka-Parry Sound, Thunder Bay, or Kenora Rainy River, and Essex Kent received their first genetic screen positive referral. Referral numbers remained relatively consistent across IHP regions, except for Central West, which saw an increase in referral numbers.

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Table 33. Genetic screen positive results and PHL interventions

	Genotype Class			
Intervention	P/P Genotype	P/V37I genotype	TOTAL 2022	TOTAL 2021
CI candidate	11	<5	11	8
Amplification	5	<5	9	9
Monitoring+	<5	6	6	9
Surveillance**	<5	10	11	6
TOTAL	17	20	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 17 infants with panel/panel genotypes, a slight increase from 2021 where there were 13, despite any changes in the mutation panel. As expected, most of these infants were found to have PHL at their initial diagnostic audiology assessment.

There were 20 infants with panel/V37I genotypes. About 50% of these infants had some degree of PHL noted at their initial diagnostic audiology assessment and the degree of hearing loss observed was never in the severe-profound range. Most observed were results showing a minimal or slight PHL warranting close monitoring, or permanent hearing loss in the mild-moderate range. It will be important to collect audiology outcome data over time to see if hearing loss develops in the children with normal hearing at birth, or if there is progression in the group of children with PHL.

As risk factor screening for PHL continues, we will focus our efforts in the following areas:

- Development and implementation of an improved workflow for obtaining consent for risk factor screening, with electronic transfer of information between NSO and the IHP.
- Updating protocols to get more definitive diagnoses for CMV screen positives with negative urine CMV PCR results.
- Evaluation of the genetic screening panel and consideration of the addition of the *GJB2* p.(V37I) mutation on the first-tier screening panel.
- Recruitment of additional pediatricians that would like to participate in this program as well as engagement of pediatricians already involved
- Involvement in a research study seeking to identify the clinical utility and accuracy of dried saliva spots in identifying CMV after birth

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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 2022, NSO received 6,634 samples from 2,202 patients. Monitoring samples accounted for 1,288 of the samples received. Screen positive follow up accounted for 549 of the 6,634 samples.

3.2 MOLECULAR

NSO performs molecular diagnostic testing for targets of newborn screening, mitochondrial conditions, progressive external ophthalmoplegia optic atrophy, and rhabdomyolysis. The number of requests have increased annually, with 484 samples received in 2020, 532 in 2021 and 795 in 2022. Of the 795 samples received in 2022, 142 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

NSO receives post mortem samples at the request of the coroner's office. The sample types collected and sent can include blood, bile and whole blood/DNA. The samples are typically run for inborn errors of metabolism. It is a service for the coroner's office in their review of what caused the infant/child's death but also serves as a quality review for NSO to ensure that no cases were missed. In 2022, NSO received 209 post mortem case requests.

3.3.2 DISCREPANT RESULTS

3.3.2.1 Dried Blood Spot

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.

3.3.2.2 CCHD

NSO tracks missed CCHD cases. These can include cases that were screened and were negative, were screened and were positive but CCHD not identified through the screening process, or cases where the infant wasn't screened (missed screening) but presented clinically later. When notified about a case, NSO follows up with the birth hospital and responsible health care provider(s) to understand the clinical steps taken. NSO then follows up with the cardiology surgical sites to obtain an outcome history. NSO reviews the case with the birth centre/ responsible health care provider(s) to educate where applicable and discuss anything that could be improved for future screens.

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3.4 RESEARCH

NSO's research program focuses on developing novel laboratory methods and clinical biomarkers, most recently using metabolomics and genomics, studying policy, and clinical research in newborn screening. NSO is involved in approximately 25 research projects, 10 of which are led by NSO. NSO's involvement varies depending on the project, such as secondary use of NSO data and data analysis, secondary use of NSO samples, testing of external samples, review and analysis of screening data, interviews and surveys of collaborators.

A research study is currently underway examining the effect of differential holding of parenteral nutrition on levels of amino acids used as biomarkers for newborn screening. The study is investigating whether there is a difference between target amino acid levels after holding TPN administration for 1 hour (modified screening protocol) and 3 hours (current screening protocol) within individual participants. In July 2022, NSO starting receiving an additional sample for consented patients at the 1 hour timepoint for comparison. 72 samples have been collected and tested to date.

In 2022, NSO completed their research initiative funded by the Bill & Melinda Gates Foundation which assessed the implementation of a gestational age estimation model using newborn dried blood spots AND the feasibility and outcomes of newborn screening in low resource settings. From April 2019 to January 2022, NSO received and tested 6476 umbilical cord and heel prick dried blood spot samples from babies born in low-resource settings (Bangladesh = 2103, Zambia = 862, Kenya = 2103, Zimbabwe = 1161). Across the 4 sites, 16 screen positive alerts were issued and DERFs completed for 3 diseases (CH, HGB, MCADD).

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Appendix A: Classifications of Diagnostic Categories

NSO has developed a diagnostic outcome classification system for screen 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 diagnostic outcome classification for screen positives.

Classification	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 screen positive diagnostic outcome categories.

Screen Positive Diagnostic Outcome Categories	
Generic	Detailed
Not Affected	Not Affected
Primary	Primary Target – Classic
Variant	Primary Target – Variant or Indeterminate
Incidental	Secondary Target – Classic
	Secondary Target – Variant or Indeterminate
	Untargeted Disease
	Persistent Laboratory Abnormalities
	Carrier
	Maternal Disease
	Maternal Persistent Laboratory Abnormalities
Other	Lost to Follow Up
	Deceased
	Other
Twin	Twin (Screen Negative)

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Appendix B: Disease Prevalence and PPV for High PPV Referrals

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

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

Diseases	Date Screening Initiated	% of Outcomes Unknown	Disease Prevalence of Primary Targets	Positive Predictive Value (PPV) for High PPV Referrals
Congenital Hypothyroidism (CH)	4-Apr-06	1.5%	1 in 2,069	86%
Congenital Adrenal Hyperplasia (CAH)	14-May-07	1.6%	1 in 20,854	29%
Sickle Cell Disease	24-Nov-06	5.0%	1 in 2,824	94%
Cystic Fibrosis (CF)	9-Apr-08	1.1%	1 in 4,624	83%
Severe Combined Immune Deficiency (SCID)	12-Aug-13	9.1%	1 in 58,615	33%
Glutaric Aciduria type 1 (GA1)	9-Aug-06	2.9%	1 in 138,802	100%
Guanidinoacetate Methyltransferase Deficiency (GAMT)	17-Oct-22	N/A	Unknown	Unknown
Isovaleric Acidemia (IVA)	9-Aug-06	0.9%	1 in 157,309	54%
Propionic Acidemia (PA)	9-Aug-06	5.6%	1 in 214,512	33%
Methylmalonic Acidemia (MMA)			1 in 168,545	
Cobalamin A Deficiency			1 in 1,179,818	
Cobalamin B Deficiency			1 in 1,179,818	
Long-chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHAD)	9-Aug-06	0.0%	1 in 196,636	88%
Trifunctional Protein Deficiency (TFP)			1 in 2,359,635	
Very-long-chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)	9-Aug-06	4.8%	1 in 76,117	62%
Carnitine Uptake Defect (CUD)	9-Aug-06	4.9%	1 in 87,394	21%
Medium-chain Acyl-CoA Dehydrogenase Deficiency (MCADD)	4-Apr-06	2.1%	1 in 15,440	88%
Citrullinemia (CIT)	9-Aug-06	5.9%	1 in 124,191	42%
Argininosuccinic Acid Lyase Deficiency (ASA)			1 in 181,510	
Cystathionine beta-synthase (CBS) deficiency	9-Aug-06	4.2%	1 in 1,179,818	Unknown
Phenylketonuria (PKU)	4-Apr-06	2.7%	1 in 16,497	65%
Maple Syrup Urine Disease (MSUD)	9-Aug-06	2.9%	1 in 131,091	22%
Tyrosinemia type 1	9-Aug-06	5.1%	1 in 262,182	71%
Galactosemia (GALT)	19-Feb-07	2.7%	1 in 50,768	21%
Biotinidase Deficiency (BIOT)	19-Feb-07	2.5%	1 in 55,721	18%
Mucopolysaccharidosis type 1 Hurler (MPS1H)	27-Jul-20	33.3%	1 in 113,914	Unknown
Spinal Muscular Atrophy (SMA)	13-Jan-20	0.0%	1 in 16,137	100%

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

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