NEWBORN SCREENING
ONTARIO

DÉPISTAGE NÉONATAL
ONTARIO

Annual Report 2013

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Calendar Year 2013

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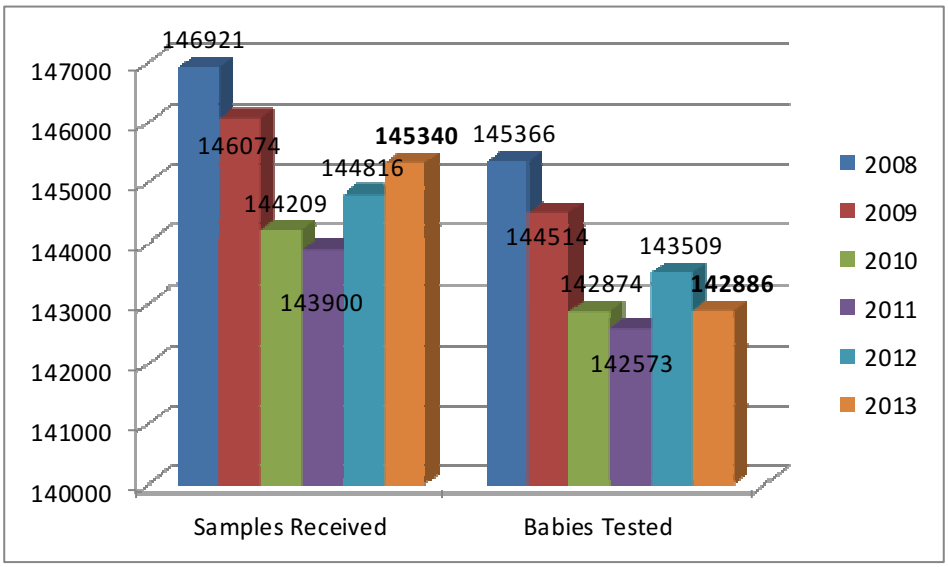
1. Total Samples and Infants Screened

Total Screening Samples Received: 145,340
Estimated Infants Screened: 142,886



This is the total number of samples received for newborn screening purposes only. NSO receives other sample types including monitoring and diagnostic samples, and coroner requests. The number of infants tested assumes that the program's linking and matching algorithms are correct, therefore, this number is an estimate.

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 appears to have been going down over time, although the number of samples received in 2013 increased. NSO's prematurity recommendations may account for some of the increased number of samples.

The unsatisfactory rate in 2013 was 2.14%, down from 2.56% in 2012.

2. Demographics of Screening Samples

2.1 Age at Collection

This table represents the2013 data for age at collection of initial samples only.

Age at Collection	Number of Samples	% of Initial Samples
Less than 24 hours	622	0.44%
24-47 hours	112147	79.73%
48-72 hours	18414	13.09%
1-7 days	139510	99.19%
Greater than 7 days	524	0.37%

Distribution of Age for Initial Samples	Hours (Days)				
	2013	2012	2011	2010	2009
Mode	25 (1)	25 (1)	25 (1)	25 (1)	25 (1)
95th Percentile	81 (3.4)	93 (3.9)	93 (3.9)	94 (3.9)	93 (3.9)
99th Percentile	132 (5.5)	143 (6.0)	143 (6.0)	148 (6.2)	158 (6.6)

2.2 Transfusion Status

Transfused infants should have a repeat sample collected at 4-6 months post transfusion. In the **calendar year** of 2013, 155 (0.11%) initial samples indicated that the baby was transfused prior to the sample being taken. This is lower than in 2012 where 232 samples indicated that the infant was transfused. Overall, of the samples where a repeat sample could be expected, 42.6% of these have completed screening with a repeat sample; however, a number of cases are still open (the date to receive the repeat sample has not passed). In addition, some infants who have had multiple transfusions will be greater than six months old when they are in the right time frame for a repeat newborn screening sample.

Samples received between 4-6 months post-transfusion are sent to NSO without a reminder having been sent to the submitter (ie the submitter has their own tracking system in place). At 6 months submitters receive a reminder by fax that a repeat NBS is required. If the submitter responds to the fax that a health care provider (HCP) has been notified, NSO also sends a letter to the HCP. When the infant is 12 months old, the case is closed with a close case letter to the submitter (and HCP if indicated). If NSO is informed by the submitter that the infant is deceased, the case is closed.

Year	Samples without a repeat			Samples with a repeat			Total	% repeat received	% repeat received (excluding deceased/open cases)
	Close letter	Deceased	Open cases	4-6 mo	6-12 mo	>12 mo			
2011	88	40	0	23	63	13	227	43.6%	52.9%
2012	90	32	0	32	72	6	232	47.4%	55.0%
2013	21	14	54	24	41	1	155	42.6%	75.9%

*2013 data incomplete

2.3 Gestational Age and Birth Weight

In calendar year 2013, **11,135** infants **(7.8%)** were identified as being premature (<37 WGA).

The tables below show the total number of infants by gestational age and weight.

Gestational Age (ww.d)	Number of Infants	% of population
<25	113	0.08
25-27.6	391	0.27
28-32.6	1598	1.12
33-36.6	9033	6.32
Total	**11135**	**7.79**

Birth Weight (g)	Number of Infants	% of population
<1000	474	0.33
1000-1499	851	0.60
1500-2499	7796	5.46
>2500	131585	92.09
Unknown	2180	1.53

3. Unsatisfactory Samples

There were a total of **3215** unsatisfactory samples in the calendar year 2013, and some samples were unsatisfactory for more than one reason. A table on page 5 summarizes the most frequent unsatisfactory reasons, as well as the distribution throughout the year.

Overall the unsatisfactory rate in 2013 was 1.65% (excluding samples that are collected at <24 hours as this is recommended in the case of early discharge). This is lower than the rate for the calendar year 2012, which was 2.11%.

A possible factor in this improvement in the unsatisfactory rate is the availability of the BORN dashboard. Every hospital in Ontario can access their unsatisfactory rates, along with a comparison to the average unsatisfactory rate for other hospitals with the same number of births. Each hospital can access reports containing information about which samples from their institution were unsatisfactory and why, along with reports of the counts of the number of samples they have that are unsatisfactory by reason. This real time data allows institutions to see if there are patterns in the unsatisfactory rates and to address them immediately. NSO continues to prioritize providing feedback to submitters, whether consulting with them by phone or emailing them photos of unsatisfactory samples to help them understand why samples are deemed unsatisfactory.

NSO currently contacts submitters by fax and/or phone to inform them of unsatisfactory samples, along with mailing an unsatisfactory report. If three weeks have passed and NSO has not received a repeat sample, NSO sends a reminder letter to the submitter informing them that no repeat sample has been received. If another 2 weeks pass and no repeat has been received, NSO sends a letter to the mother/guardian of the infant informing them that a satisfactory sample needs to be collected for their infant. When NSO is informed by the submitter that a family has declined a repeat sample following an unsatisfactory sample, the case is closed and no letter is sent to the family. Unfortunately there currently is no way for NSO to determine the number of families who decline a repeat newborn screen after an unsatisfactory sample.

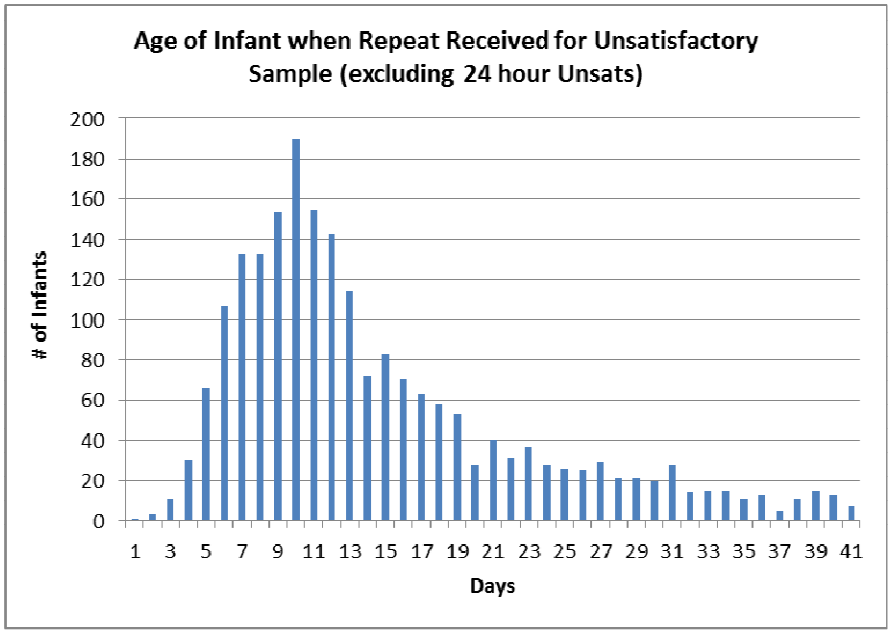
3.1 Quantity of Blood

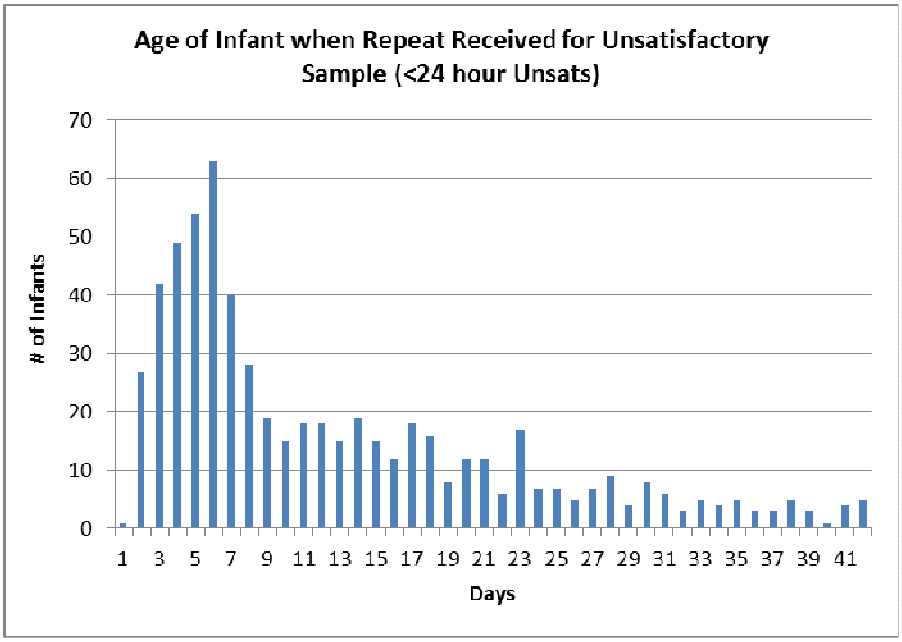
The two main reasons that samples are deemed unsuitable for testing both involve having the right quantity of blood on the filter paper; supersaturated or insufficient quantity of blood. This is consistent with the 2012 data; however, the total number of samples that are unsatisfactory for these reasons decreased. The number of samples that were scratched or abraded also decreased; however there was a slight rise in the number of samples that were clotted or layered.

Quarter	Unsat Samples	Samples collected at <24 hrs of age	% unsats excluding <24 hrs	Lab Unsats				Data unsats			Other
				Quantity of blood insufficient	Blood spots are super-saturated	Blood spots appear scratched or abraded	Blood spots appear clotted or layered	Expired blood spot card	Insufficient data provided	Transport related (delayed, batching)	
Q1 2013	1050	150	2.53%	403 (1.13%)	267 (0.75%)	225 (0.63%)	65 (0.18%)	12 (0.03%)	11 (0.03%)	74 (0.21%)	34 (0.10%)
Q2 2013	770	180	1.55%	344 (0.90%)	155 (0.41%)	150 (0.39%)	32 (0.08%)	13 (0.03%)	14 (0.04%)	16 (0.04%)	39 (0.10%)
Q3 2013	672	215	1.17%	206 (0.53%)	128 (0.33%)	125 (0.32%)	42 (0.11%)	5 (0.01%)	8 (0.02%)	39 (0.10%)	26 (0.07%)
Q4 2013	723	196	1.40%	239 (0.64%)	178 (0.47%)	262 (0.70%)	116 (0.08%)	33 (0.09%)	14 (0.04%)	35 (0.09%)	66 (0.18%)
2013	**3215 (2.14%)**	**741**	**1.65%**	**1192 (0.79%)**	**728 (0.48%)**	**762 (0.51%)**	**255 (0.17%)**	**63 (0.04%)**	**47 (0.03%)**	**164 (0.11%)**	**165 (0.11%)**
2012	3681 (2.56%)	651	2.11%	1215 (0.85%)	1174 (0.82%)	1087 (0.76%)	156 (0.11%)	87 (0.06%)	40 (0.03%)	50 (0.03%)	129 (0.09%)
2011	2927 (2.00%)	711	1.51%	888 (0.61%)	819 (0.56%)	619 (0.42%)	184 (0.13%)	70 (0.03%)	60 (0.04%)	157 (0.10%)	173 (0.12%)
2010	4396 (2.97%)	807	2.42%	1682 (1.14%)	1092 (0.74%)	1275 (0.86%)	604 (0.41%)	200 (0.12%)	164 (0.11%)	272 (0.18%)	461 (0.31%)

3.2 Repeat Rates for Unsatisfactory Samples

The majority (84.28%) of repeat samples required due to an unsatisfactory initial sample are received within 6 weeks of the initial sample. By 3 months, more than 94.34% of unsatisfactory samples have had screening completed via a repeat sample. Repeat samples have not been received for 5.54% of unsatisfactory samples in 2013.





4. Turn Around Times

A number of turnaround times and other quality indicators are monitored to ensure timely and good quality service.

The reasons for using mode, 85th centile, 94th centile are outlined below:

1) The **mode** will primarily reflect samples where at most one weekend interrupts transportation or analysis, and the time at which all tests are completed such that an initial screening determination can be made. For example, a sample which has a screen positive result will have initial results available one working day before the report due to the practice of reanalyzing for confirmation. The mode will reflect better the time at which that initial result is examined for an alert result.

2) The **85th centile** will reflect primarily the turnaround times for samples where at least one weekend interrupts either transportation or analysis, an initial screening result is positive and where analytical QC issues cause a delay in reporting.

3) the **94th centile** will primarily reflect the turnaround times for samples where transportation or analysis is interrupted by a long weekend or by two weekends, while still excluding those initially positive for Cystic Fibrosis where NSO is aiming to introduce a delay in reporting.

Both centiles and the mode will be sensitive to issue such as reporting or data entry delays.

4.1 Transportation Time

Currently the best measurement of transportation time at the sample level is the difference between the date of collection (DOC) and the date the sample is received in the laboratory. Submitting institutions are asked to dry samples for three hours prior to sending via courier to NSO. Most submitters have a scheduled pick up once daily, therefore any samples that are not yet dry and/or packaged for shipment will be delayed by at least 24 hours.

Days in transit (Date of Collection to Receipt of Sample in Laboratory)

Statistic	2013	2012	2011	2010	2009
Average	3.2	3.2	3.3	3.4	4.3
Median	3	3	3	3	4
Mode	2	2	2	2	4
85th Percentile	5	5	5	5	6
94th Percentile	6	6	6	6	7

The reduction in transportation time achieved during 2010 switching to a courier model has been maintained in 2011-2013 with Canpar service. With a consistent mode of 2 it is clear that overnight delivery is the norm for the majority of samples.

4.2 Reporting Times

The turn around times from various points to the printing of a full report are described in the tables below. Screen positive infants may be referred prior to the full report being available, due to ongoing testing.

Date of Collection to Report:

Statistic	2013	2012	2011	2010	2009
Average	7.2	6.8	6.5	6.3	8.6
Median	7	6	6	6	8
Mode	6	6	6	6	7
85th Percentile	10	9	9	8	12
94th Percentile	12	11	11	11	14

For most infants results are available by the time they are a week old. Logically, the time from collection to report is 1-2 days less than the time from birth to report, since most infants are sampled at 24-48 hours of age. These periods include the time for sampling, transportation, and analysis of the sample, and may be impacted by later sampling, batching of samples at the hospital/midwifery practice, delays in transport, or delays in reporting due to further testing or quality issues.

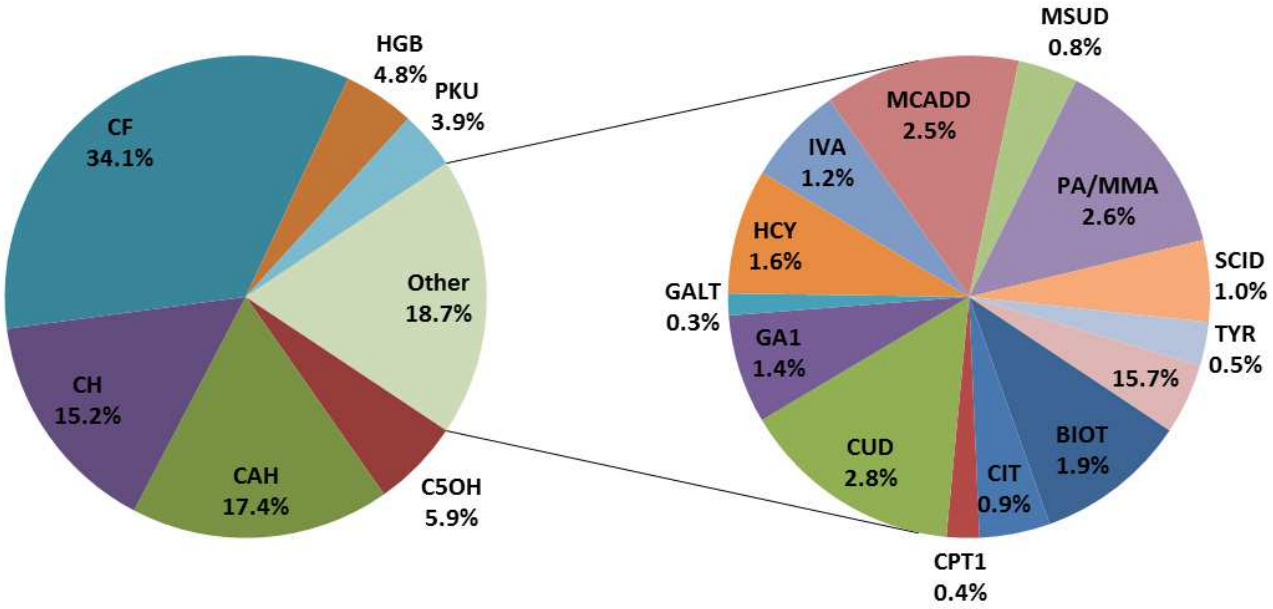
Date of Receipt to Report:

Statistic	2013	2012	2011	2010	2009
Average	4.1	3.3	3.3	2.9	4.3
Median	3	3	2	2	4
Mode	2	3	2	2	2
85th Percentile	6	5	5	5	6
94th Percentile	8	5	7	6	9

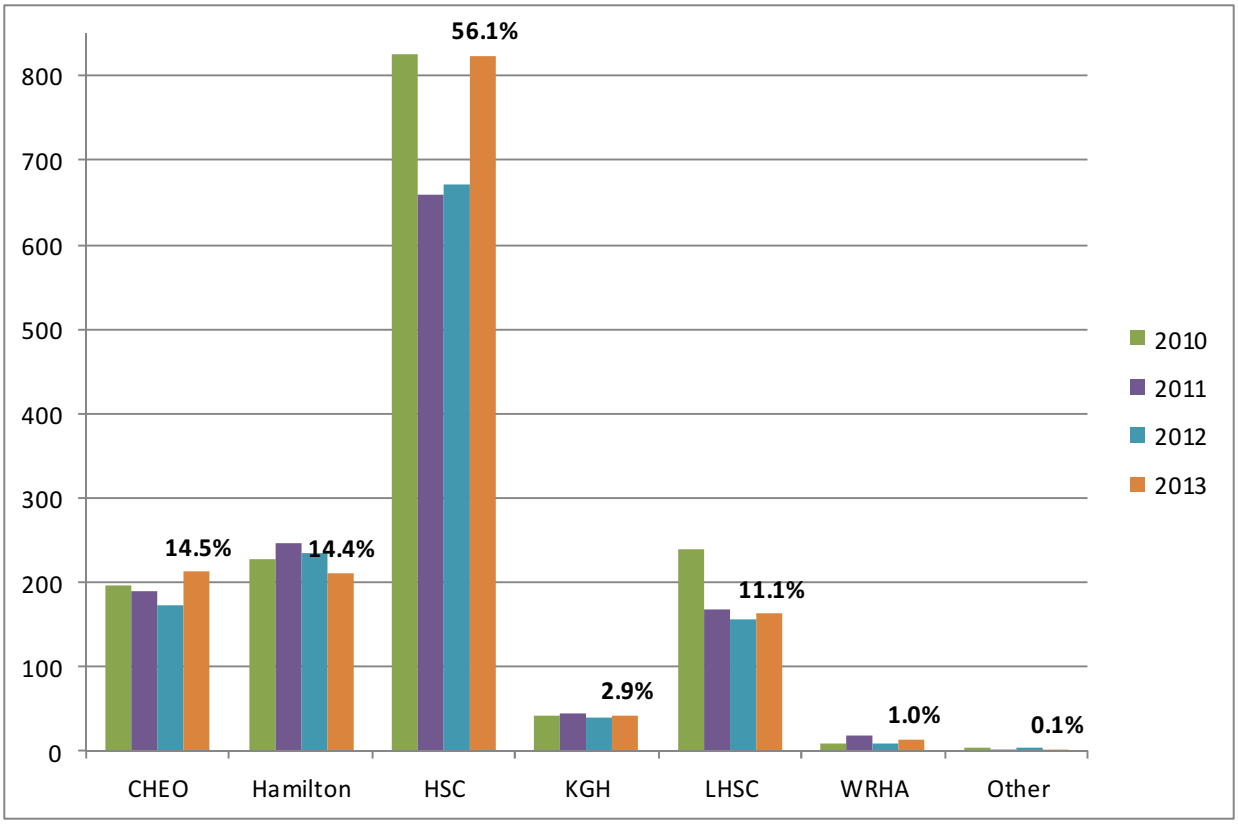
Once a sample is received in the laboratory, the demographic entry must be complete and all test results accepted before a report is available for printing. Due to the batching of reporting for hemoglobinopathies, cystic fibrosis, and SCID (these test results are not accepted on a daily basis) there are some delays in printing the reports. The turn around times for reporting have remained constant over the last four years, with the majority of reports available within 2 days of receipt. Some outliers in turn-around-time reports are due to older children being screened.

5. Screen Positives

In 2013, there were 1466 screen positive referrals, from a total of 1420 infants. This represents 0.99% of the total number of infants screened by NSO. There were 1498 total screen positives but 32 had an elevated TSH in samples taken at <24 hours and were screen negative on repeat sample testing. Cystic fibrosis, endocrinopathies and metabolics each represent approximately 30% of screen positive referrals. Hemoglobinopathies represent approximately 5% of referrals.

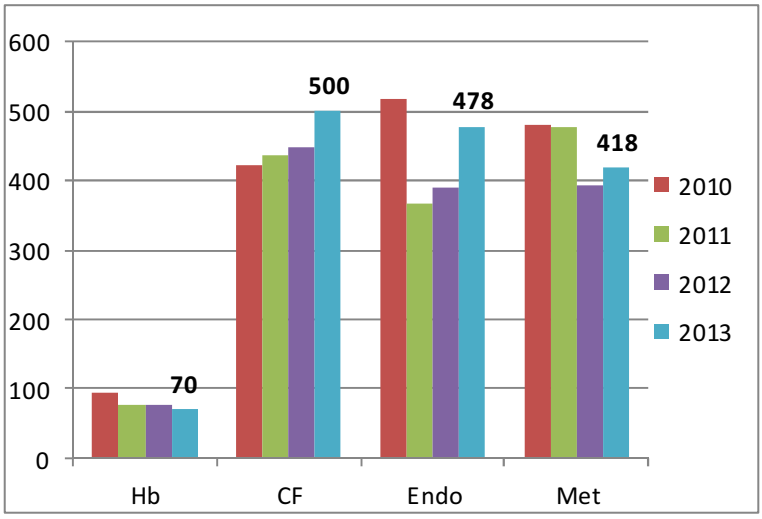


5.1 Referrals by Treatment Centre



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. 'Other' represents Infants referred to treatment centres outside of Ontario/ Winnipeg, such as Quebec or USA, or a centre in Ontario that is outside of the standard treatment centres. The Hospital for Sick Children in Toronto receives approximately half of the screen positive referrals, as is expected given the population of Toronto and surrounding areas

5.2 Referrals by Disorder



5.3 Diagnostic Feedback

Approximately 7.5% of feedback information (DERFs = diagnostic evaluation report forms) was not received or not entered into our electronic record for the referrals made in 2013. This is the lowest incomplete DERF rate in NSO's history.

Of the 1356 referrals on which feedback was received, 175 were classified as true positive. This represents 12.9% of all returned information and provides a true positive rate of 0.1% (~1:822) of all infants screened by NSO. Based on the information available, the positive predictive values are estimated in the table in Section 5.5.

5.4 Classification of True/False Positives

NSO has developed a classification system for true positives to take into account the variability of definitive diagnoses and the impact of variant conditions and incidental findings. The definitions are as follows:

True Positive?	Definition	Example
Yes	confirmed diagnosis of a targeted condition	Classical PKU
No	confirmed to be NOT affected by a target or related disease	Not Affected
Other	lost to follow up; family refused follow up; infant deceased prior to completion of diagnostic evaluation	Deceased

Variant	confirmed diagnosis of a variant of the targeted condition	CF indeterminate or gray zone
Incidental	not affected by target or variant disease but not unaffected; affected with secondary target or other condition; carriers; reason intrinsic to baby or mother that caused the baby to screen positive	Vitamin B12 deficient (PA/MMA screen positive), maternal Grave's disease (CH screen positive)

The category of incidental is a large group – consisting of reasons due to mom and baby. Now that the DERF information is captured in BORN, we have added additional classifications to allow for more useful data extractions in the future.

True Positive Categories	
Not Affected	➔ No
Primary Target	➔ Yes
Primary Target – Variant or Indeterminate	➔ Variant
Secondary Target	➔ Incidental
Secondary Target – Variant or Indeterminate	
Untargeted Disease	
Persistent laboratory anomalies	
Carrier	
Maternal Disease	
Maternal persistent laboratory abnormalities	
Lost to follow up	➔ Other
Deceased	
Other	
Twin (screen negative)	➔ Twin

5.5 Positive Predictive Values

Current & Previous Method PPV Data (2006-2013)

Hemoglobinopathies

Disease	Current PPV			Previous PPV		
	Total No. Positive	PPV (yes)	PPV (yes + variant)	Total No. Positive	PPV (yes)	PPV (yes + variant)
Hemoglobinopathies	260	70.9%	71.3%	353	59.9%	59.9%

In October 2010 Hemoglobinopathies reporting changed and NSO stopped reporting out "Other" hemoglobin patterns.

Cystic Fibrosis

Disease	Current PPV		
	Total No. Positive	PPV (yes)	PPV (yes + variant)
Cystic Fibrosis			
Category A	131	99.2%	100.0%
Category B	1932	1.6%	5.1%
Category C	474	0.5%	0.9%
Total	2537	6.2%	9.0%

Endocrine Diseases

Congenital Hypothyroidism

Disease	Current PPV		
	Total No. Positive	PPV (yes)	PPV (yes + variant)
Congenital Hypothyroidism			
Referred	1413	43.5%	43.6%
< 24 hrs	183	0.5%	0.5%
Total	1596	38.4%	38.5%

Congenital Adrenal Hyperplasia

Disease	Current PPV			Previous PPV		
	Total No. Positive	PPV (yes)	PPV (yes + variant)	Total No. Positive	PPV (yes)	PPV (yes + variant)
Congenital Adrenal Hyperplasia	324	3.9%	3.9%	248	5.1%	5.1%

CAH disorder logic changed on August 9, 2012 to only reporting out samples as screen positive with a positive steroid profile. From December 20, 2010-August 9, 2012, all samples with an initial critical 17OHP on immunoassay as well as all samples with a positive steroid profile were referred out. From the initiation of CAH screening in 2007 to December 20, 2010 all samples with a critical or intermediate immunoassay 17 OHP were referred out (PPV 4.5%, 244 total screen positives).

Metabolic Diseases

Amino Acidopathies, Organic Acidemias & Fatty Acid Oxidation Defects

Disease	Current PPV			Previous PPV		
	Total No. Positive	PPV (yes)	PPV (yes + variant)	Total No. Positive	PPV (yes)	PPV (yes + variant)
Amino Acidopathies						
Citrullinemia	96	19.0%	20.2%			
Phenylketonuria	386	18.4%	34.9%			
MSUD	18	16.7%	16.7%	86	2.7%	2.7%
Tyrosinemia	24	15.8%	15.8%	70	1.5%	1.5%
Homocystinuria	86	0.0%	0.0%			
Organic Acidemias						
Glutaric Aciduria type 1	111	8.4%	8.4%			
PA/MMA	20	0.0%	0.0%	218	3.4%	3.4%
Isovaleric Acidemia	182	1.8%	2.4%			
C5OH	442	5.9%	5.9%			
Fatty Acid Oxidation Disorders						
CUD	292	5.5%	5.5%			
CPTI	59	5.4%	37.5%			
CPTII	29	3.4%	3.4%			
LCHAD	9	77.8%	77.8%			
MCADD	223	26.9%	34.8%			
VLCAD	151	9.2%	16.2%			

MSUD disorder logic was updated on Nov 15, 2011. The Leucine to Alanine ratio cutoff was set to 1.0 and the cutoff for Leu remained unchanged at 300 uM.

Tyrosinemia disorder logic was updated on September 14, 2009, with the introduction of SUAC as the primary marker. The SUAC cutoff was raised from 3.5 to 5.0 on September 20, 2011.

*The "Current PPV" for PA/MMA reflects April 22, 2013- December 31, 2013 (MCA added, see Section 6.3). The previous PPV reflects Feb 16, 2010-April 22, 2013. Prior to that the PPV for PA/MMA (using C3 as the only marker) was 3.7% (226 total screen positives).

Galactosemia & Biotinidase Deficiency

Disease	Current PPV		
	Total No. Positive	PPV (yes)	PPV (yes + variant)
Galactosemia	72	38.6%	41.4%
Biotinidase Deficiency	235	6.0%	28.9%

SCID*

Disease	Current PPV		
	Total No. Positive	PPV (yes)	PPV (yes + variant)
SCID	15	0.0%	0.0%

*The PPV for SCID reflects less than a full year's data as SCID screening began on August 12, 2013.

The current PPVs are for current disorder logics.

The PPV for yes is calculated using our classification of 'yes' in the numerator and the sum of 'yes', 'variant', 'incidental' and 'no' in the denominator. 'Other' is excluded as follow up data is not known. The PPV including yes plus variant is calculated with the addition of 'variant' in the numerator.

Variant is particularly important in CF = indeterminate or gray zone where there are borderline sweat results and 1 or more CFTR mutations identified, biotinidase deficiency (partial biot def), PKU variant = mild hyperphe (Phe = 120-600) and mild PKU (Phe = 600-1200), and CPT1 deficiency with the Inuit common mutation (which is questionable as to whether or not it is associated with disease). Therefore, our PPVs are higher when these primary disease variants are taken into account.

There were only 5 conditions in which there have been disorder logic updates: CAH, Hemoglobinopathies, PA/MMA, Tyrosinemias, and MSUD.

With the change in disorder logic, the PPV for Hemoglobinopathies has increased form 59.9% to 71.3%. Of note, the PPV calculation is performed with incidental in the denominator. Incidentals are non-targeted conditions, such as beta thalassemia, EE disease, etc. So while they are diseases, they are not the targeted conditions.

Action Item: To further improve the PPV of a Hemoglobinopathy screen positive, NSO will be examining the reporting of hemoglobin patterns not in keeping with normality or a specific diseases (for example, the presence of two variant hemoglobins and a low hemoglobin A) to determine which are unlikely to be associated with disease and thus should not constitute a screen positive.

For tyrosinemia, the previous cutoff was too close to the detection limits. With the new cutoffs, the PPV has risen to 15.8% (which includes type 1 as well as other types of tyrosinemia). The initial positive rate has also decreased which is reflected in the current PPV.

The new disorder logic for MSUD improved the PPV from 2.7% to 16.7%, as well as decreasing the number of initial positives for MSUD.

The new disorder logic for PA/MMA including a second tier test for methylcitrate began on April 22, 2013. Since the implementation of this change, the number of screen positives for PA/MMA has decreased. Because no infant has been identified with PA/MMA since this change the current PPV is 0%; however we anticipate that with more data the PPV will be higher than the previous PPV of 3.4%.

For CAH, the PPV has decreased and the number of referrals increased in 2013, which was not expected. Further analysis of the CAH showed the following:

Disease	**2013 Data**			
	2013 Initial Positive	2013 DERFs Pending	PPV (yes)	PPV (yes + variant)
CAH				
<37 wks	227	10	1.4%	1.4%
>37 wks	23	1	31.8%	31.8%

Initial CAH immunoassay results determine which samples go on to second tier steroid profile testing, and those results are dependent on birth weight stratified cutoffs. When examining the CAH screen positives by birth weight category it is clear that infants less than 1500 grams are most likely to have a false positive for CAH.

BW (g)	**2013 Data**			
	2013 Initial Positive	2013 DERFs Pending	PPV (yes)	PPV (yes + variant)
<1000	32	5	0.0%	0.0%
1000-1499	40	5	0.0%	0.0%
1500-2499	113	5	1.9%	1.9%
≥2500	71	4	10.6%	10.6%

It is well established in the newborn screening community that preterm infants are more likely to have a false positive for CAH. Our data shows that the PPV for a CAH screen positive is 1.4% in a preterm (<37 weeks GA) infant vs a PPV 31.8% in a term infant.

BW (g)	17OHP IA Cutoff	2013 Data			
		2013 Initial Positive	2013 DERFs Pending	PPV (yes)	PPV (yes + variant)
1500-2499	Intermediate	104	5	0.0%	0.0%
	Critical	8	0	25.0%	25.0%
≥2500	Intermediate	59	1	0.0%	0.0%
	Critical	12	3	77.8%	77.8%

NSO reports out both intermediate and critical immunoassay 17OHP levels when the steroid profile is positive. When the screen positive data is broken down by Intermediate vs. Critical positives, it shows that screen positives with an Intermediate 17OHP value have a PPV of 0%, whereas screen positives with a Critical 17OHP value have a PPV of 25% in infants who are 1500-2499 grams and 77.8% in infants who are ≥2500 grams.

Action Item: NSO will be examining the potential of using birth weight specific 17OHP LC MS/MS cutoffs to improve the specificity of the CAH screen and improve the PPV.

6. New and Ongoing Initiatives

6.1 Monitoring and Diagnostic Testing

NSO continues to offer a variety of diagnostic and monitoring services. In the first year of offering (2011), NSO received 158 diagnostic or monitoring samples from 50 different individuals. In 2012, 327 diagnostic or monitoring samples from 67 individuals were received. In 2013, 612 samples from 281 patients were received. SCID diagnostic testing was added in 2013 and 29 samples on 28 patients were received for this purpose. In addition, NSO began hemoglobin screening on cord blood samples for Canadian Blood Services on April 19, 2013. One hundred and sixty samples on 160 individuals were received for this purpose.

NSO also receives coroner samples, in the form of dried blood spots and bile samples. In 2013, NSO received 279 samples from 194 patients.

Sample Type	Samples	Patients
Coroner samples	279	194
Monitoring/Diagnostic samples	612	281

6.2 Preterm and/or Very Low Birth Weight Recommendations

NSO released recommendations for significantly preterm (<33 weeks Gestation Age) and/or Very Low Birth Weight (<1500 grams) on January 23, 2013. Significantly premature or very low birth weight Infants may have a delayed rise in TSH even if they have Congenital Hypothyroidism (CH). As NSO uses elevation of TSH as the screening marker for CH, there is an increased risk of a false negative result (missed case) if these Infants are screened only once in the early neonatal period.

Significantly premature (<33 WGA) or very low birth weight (<1500g) Infants should have:

1) A first newborn screening sample collected between 24 and 72 hours of age.

2) A second sample collected at 3 weeks of age or when the baby is being discharged home from the hospital, whichever comes first.

   2.1) If the baby is discharged home prior to 3 weeks of age from a hospital with a robust tracking system to ensure follow-up, an outpatient appointment between 3 and 4 weeks of age can be arranged without the need for a blood draw prior to discharge.

   2.2) If the baby is discharged home with the second sample collected before 3 weeks of age consideration should be given to having a third sample arranged as an outpatient between 3 and 4 weeks of age.

3) If the baby is being transferred to another hospital after 3 weeks of age, the hospital receiving the baby should confirm that the second sample was taken prior to transfer. If it was not taken, the receiving

hospital should take the second sample as soon as possible after the baby arrives. The receiving hospital can also call NSO to inquire whether a second sample was received.

6.3 Second Tier Testing for PA/MMA

Implemented: April 22, 2013.

Newborn Screening Ontario (NSO) updated the disorder logic for newborn screening for Propionic and Methylmalonic acidemia (PA/MMA) by adding a second tier Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) assay for methylcitrate (MCA). Therefore, a baby would only be reported as screen positive for PA/MMA if the MS/MS C3 and C3/C2 ratio exceed the current cutoffs and:

1. MCA exceeds 0.7 µM, OR
2. MCA exceeds 0.5 µM AND C3/C2 ratio exceeds 0.23.

It is anticipated that the initial positive rate will decrease by ~65% and the specificity of newborn screening for PA/MMA will improve.

6.4 Missed Screens

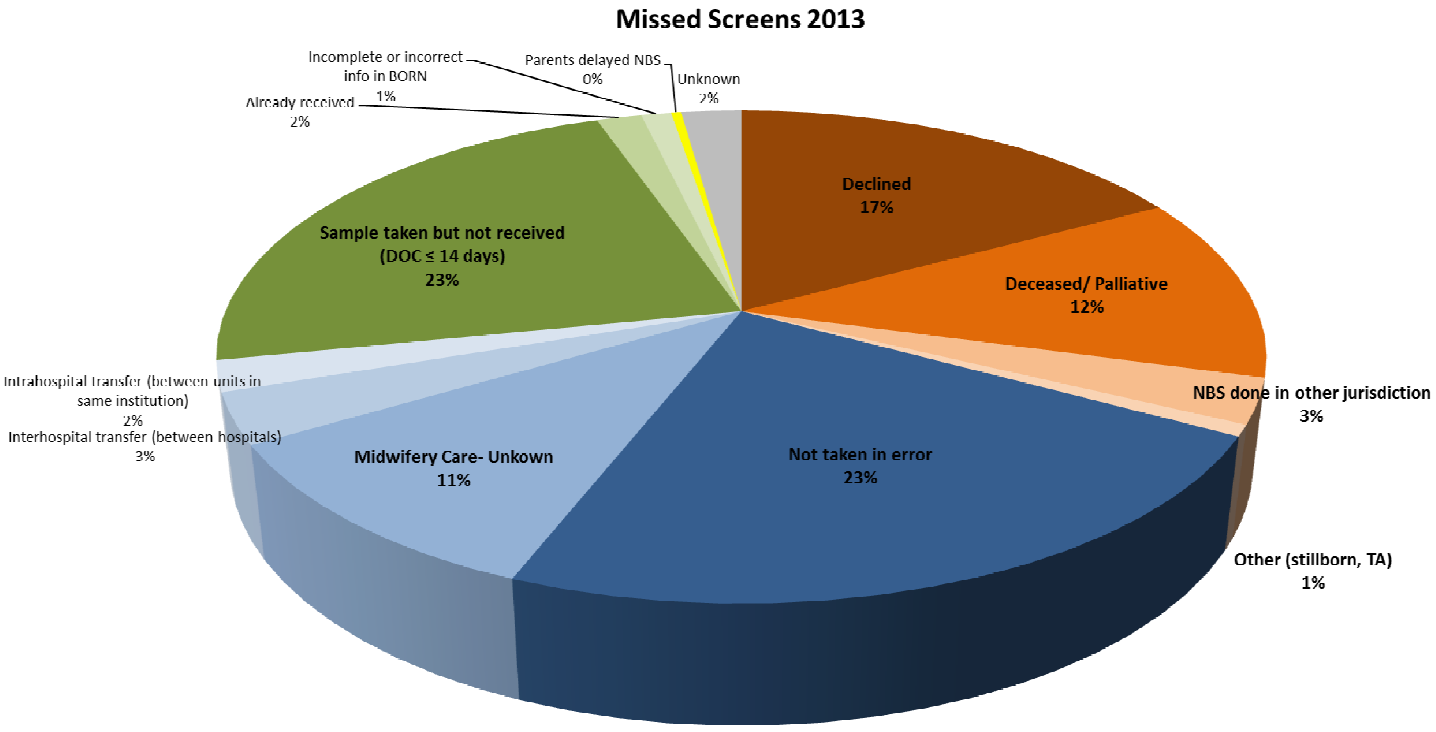
Beginning in January 2012, NSO began sending HL7 messages containing real time demographic information and laboratory results for NSO samples to BORN for inclusion in the registry data. Thus 2013 was the first complete year for the identification of missed screens (ie. Infants born in Ontario but no NSO sample was received by 14 days of age).

The data regarding these infants is attached, and indicates that in 2013 223 infants truly had missed newborn screens (indicated in blue on the pie chart below). Following the notification from NSO, the birthing hospital or midwifery practice involved with the family was able to ensure that the newborn screen was completed for 167 of the 223 infants (75%).

In 139 cases, a newborn screening sample had already been collected- for 6 infants the information in BORN was incorrect or incomplete, for 9 infants the sample was already received but there were problems with NSO's data, and for 124 infants there was a delay in either sample collection or sample transportation. In 23 cases, the Potential Missed Screen Alert was initiated the same day that the sample arrived at NSO.

For 175 infants, a newborn screening sample would not be expected (indicated in orange on the pie chart below). In 93 of cases families declined the newborn screen, in 66 cases the infant was deceased or in palliative care, and for 16 cases the newborn screen was done in another jurisdiction.

In addition, there were 321 cases in which a missed screen alert should have been issued as an infant was greater than 14 days and no newborn screening sample was received; however this did not happen because BORN entry was not completed for these infants.



In 93 (11%) missed screen alerts a sample will never be obtained because the parents have declined the screening test. While a minority (34%) of infants are in midwifery care, 67 (72%), of the declines were from Infants in midwifery care, consistent with 2012 data (see graph below).

Of the alerts, 186 (34%) had midwifery (MW) involvement, while only 10% of births in Ontario are under midwifery care.

6.5 Severe Combined Immune Deficiency

Screening for Severe Combined Immune Deficiency (SCID) was approved by the Ministry of Health and Long Term Care in November 2012 and was launched on August 12, 2013. Ontario became the first province in Canada to screen all newborns for this life-threatening disease. NSO partnered with the Ministry of Health to formally launch SCID screening in an event that received local, provincial, and national news coverage.

6.6 Newborn Screening Manual

NSO launched the first edition of the "Newborn Screening Manual: A guide for newborn care providers" for health care providers in December 2013. This manual provides all the information that front line health care providers need to successfully take a newborn screening sample. NSO is distributing the manual free of charge to all centres in Ontario that take newborn screening samples, as well as providing it in PDF format on the NSO website.

6.7 Infant Hearing Program

Collaboration between the Ministry of Children and Youth Services' (MCYS) Infant Hearing Program (IHP) and NSO was established in 2012 to explore ways in which newborn screening dried blood spots could be tested for common infectious and genetic causes of hearing loss. Goals of this initiative include enhancing the current ascertainment of children at risk for permanent hearing loss in Ontario and introducing an etiologic component to infant hearing screening.

The bulk of the work for phase 1 of this project took place during 2013, and was completed in March of 2014. This phase explored the development of screening techniques to determine the birth prevalence of congenital cytomegalovirus (cCMV) and frequency of genetic mutations in the common hearing loss-associated genes.

To generate this information, NSO tested 10,000 historical, anonymized dried blood samples for cCMV (the leading environmental cause of hearing loss) and several mutations in the GJB2, GJB6, SLC26A4 and MT-RNR1 genes. In addition, as part of Phase 1, an assessment of potential clinical practice and workflow considerations were studied using the current system as a baseline to identify areas in which possible changes would be required to undertake an integrated approach to screening for permanent hearing loss.

Based on the results of Phase 1, NSO is moving forward to collaborate with MCYS on Phase 2 of this project. Phase 2 will map out critical issues in terms of development and deployment of an integrated screening program for permanent hearing loss and address key lab issues related to DNA screening.

6.8 Canadian Newborn and Childhood Screening Symposium

NSO hosted the 2013 Canadian Newborn and Child Screening Symposium on April 11-12, 2013, in Ottawa, Ontario. NSO has hosted annual symposia, since 2008 to gather together specialists from the different treatment centres in Ontario and Winnipeg for advice and the development of practice guidelines. For the first

time, in response to participant feedback and a growing interest from other provincial programs, NSO reinvented the 2013 symposium for a national audience.

The first day of the conference focused on disease specific workshops where attendees could share challenges and successes. These workshops were led by disease specialists from across Canada, who moderated discussion about disease specific issues and practices. Themes also emerged about challenges that span the different specialties, such as the disclosure of carrier information, which were highlighted in a combined specialty panel discussion. The first day ended with dinner and a key note presentation by Dr. Guy Van Vliet.

The second day of the two day conference attracted a broader audience for poster sessions, abstract presentations, and invited speakers. The main themes of the second day were screening for Severe Combined Immune Deficiency (SCID) and developmental delay. Dr. Alex Kemper from Duke University School of Medicine in North Carolina opened the day with a summary of the newborn screening review process in the United States. He was followed by Dr. John Cairney from McMaster University in Hamilton, who spoke about early infancy/ childhood screening for developmental delay and the application of tools in Ontario. These talks were complimented by six abstract presentations of diverse work related to novel screening techniques, educational initiatives, and research. Dr. Mei Baker from the Wisconsin Newborn Screening Program and Dr. Francis Lee from the Center for Disease Control in Atlanta spoke in the afternoon about their pioneering work on SCID screening in the US.

The success of the conference was due in part to the diversity of the participants, with attendees from across Canada and the United States, from various specialties and training backgrounds. The feedback from the attendees was positive and NSO is planning for the 2014 Canadian Newborn and Child Screening Symposium which will occur along with the 2014 Garrod Symposium in Ottawa in the spring.

6.9 Public/ Parent Education Activities

In partnership with the Ministry of Health, a new version of the "Newborn Screening and Your Baby: A healthier start leads to a healthier life" pamphlet was produced and released. The pamphlet was translated into additional languages (now in 20 languages). NSO also partnered with the MOH to update the newborn screening DVD, which is also now available in 20 languages and each video is also hosted on the NSO YouTube channel. NSO is currently working with the MOH to update the newborn screening poster.

6.10 Exploration

NSO has also been involved in a number of research projects:

A shared understanding? Attitudes and experiences of stakeholders to newborn screening consent practices and implications for policy and practice
The overall aim of this project is to inform NBS policy and practice regarding consent processes for NBS in Canada. Interviews and surveys with key stakeholders (parents, healthcare professionals, and policy decision-makers) will be done to explore their attitudes towards consent for newborn screening and the impact of these attitudes on experiences of the consent process.

Ensuring Effective Newborn Screening: The Case of Cystic Fibrosis
This study will examine NBS for CF in Ontario as a case study to ensure a fulsome assessment of the health service and familial implications of expanded NBS in the Canadian context, and generate evidence to support planning and policy development.

Measuring purines and adenosine deaminase activity in neonatal dried blood spots to improve screening for severe combined immunodeficiency
Two genetic defects of the purine salvage pathway account for two immunodeficiencies that result in SCID: adenosine deaminase (ADA) deficiency and purine nucleoside phosphorylase (PNP) deficiency. As part of NSO's quality improvement initiatives, a novel technique was developed to improve newborn screening for SCID that will be able to identify ADA and PNP deficiencies. The purpose of this study is to review the validation data, as well as the performance of screening for ADA and PNP deficiencies, including the cutoff values.

Measuring methylcitrate in neonatal dried blood spots to improve screening for Propionic acidemia and Methlymalonic acidemias
As part of NSO's quality improvement initiatives, a novel technique was developed to improve newborn screening for PA and MMA. Methylcitrate (MCA), a pathognomonic hallmark of disorders of C_3 metabolism, is not detectable by the current newborn screening method of tandem mass spectrometry (MS/MS). NSO developed a novel approach of liquid chromatography (LC) – MS/MS to determine levels of MCA in DBS samples. The purpose of this study is to review the validation data described above, as well as the performance of screening for PA/MMA pre- and post- implementation of the new screening algorithm, including the cutoff values.

Ontario Newborn Screening Program Database Review
Using the Newborn Screening Ontario database, we continue to analyze screening performance and outcome for all screening target diseases on an ongoing basis.

Transient Elevation of the 17-OH-Progesterone in Newborn Screening for Congenital Adrenal Hyperplasia: Are there any early Biochemical Predictors for Later Resolution?
We propose investigating the prevalence and the clinical course of infants with indeterminant 17-OHP status identified by CAH NBS in Ontario from May 2007 until May 2012. The primary objective is to investigate the prevalence, clinical and biochemical characteristics and the outcome of infants with indeterminant 17-OHP level in the Ontario CAH NBS program.

Descriptive Epidemiology and Health Services Impact of Inborn Errors of Metabolism in an Ontario Newborn Cohort
The purpose of this study is to evaluate the performance (positive predictive value, false positive rate) of newborn screening for inborn errors of metabolism (IEM) in Ontario, to determine the prevalence of IEM in an Ontario newborn cohort and to describe patterns of health services use among newborns with different IEM, relative to one another and to an unaffected birth cohort over the first years of life.

Newborn Screening of Glutaric Aciduria Type 1 in the Oji-Cree Community: A Pilot Comparing a Novel Dried Urine Spot Metabolite System with the Established Molecular Analysis System
We recently developed a novel LC-MS/MS method for the determination of 3HGA in dried urine spots. Further, we also evaluated the determination of C_5DC in DUS using a combination of the method for liquid urine analysis and the routine method used for DBS analysis, an approach that has not been reported. These two markers are permanently elevated in GA1 in urine regardless of biochemical phenotype and form an innovative

new approach to GA1 screening. The main objective of this study is to demonstrate the feasibility of DUS screening as a means of identifying babies at risk of GA1 and to define the cost for DUS screening and compare with the existing method.

Emerging Team in Genomics Screening – Newborn Screening Project
There is uncertainty about the educational needs of parents and about the impact of different information on parental attitudes regarding newborn screening. The objectives of this study it to measure the decisional conflict that expecting mothers experience when provided with information about NBS, to ascertain which specific messages about NBS procedures or policies are most strongly associated with decisional conflict, to ascertain whether specific messages are associated with participating in NBS.

6.11 Ontario Laboratory Information System

The Ontario Laboratory Information System (OLIS) is an "information system that connects hospitals, community laboratories, public health laboratories and practitioners to facilitate the secure electronic exchange of laboratory test orders and results". NSO is working towards sending screen positive and screen negative results to OLIS so that submitters and community healthcare providers can access these results electronically. The anticipated go-live is the Fall of 2014. In addition, NSO is working with several sites to pilot electronic test requests for newborn screening via OLIS. At this time, results for samples that are unsatisfactory for testing will continue to be paper-based only.

6.12 Laboratory Move & Address Change

NSO began the move to its new Laboratory space in December 2013. With this move NSO took on its own lab license and has a new address:

Newborn Screening Ontario
415 Smyth Road
Ottawa ON
K1H 8M8

6.13 Social Media

NSO is active on social media including:

Twitter:	@NBS_Ontario
YouTube:	https://www.youtube.com/user/NBSOntario
Google+:	https://plus.google.com/104433650961217875289/about