MICHIGAN
Newborn
Screening

Michigan Newborn Screening Program Annual Report 2021

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Executive Summary

The Newborn Screening (NBS) Annual Report provides an overview of the Michigan NBS Program, screening performance metrics and quality assurance information. Since the program began in 1965 with screening for phenylketonuria, more than 50 disorders have been added to the screening panel. Through 2021, more than 7.6 million infants have been screened with more than 7,700 diagnosed with diseases included in the NBS blood spot panel. Of the 102,965 infants screened in 2021, the vast majority were Michigan residents and 302 (0.3%) were diagnosed with a disease. Overall, one infant out of 341 screened was diagnosed with one of the disorders included in the NBS panel (see Page 5 for list of disorders).

Developments occurring in 2021:

Michigan continued to disseminate findings at both the state and national level:

- The findings from different studies and analyses related to NBS were presented virtually at the: Association of Public Health Laboratories (APHL) Newborn Screening and Genetic Testing Symposium.

Michigan continued to conduct NBS-related trainings:

- The NBS Follow-up Program held a virtual educational conference for hospital staff.

NBS follow-up staff presented or participated as an exhibitor at numerous virtual educational events including:

- Livingston County Baby Fair
- Five MDHHS Virtual Baby Fairs
- 2021 Michigan WIC Training and Educational Conference
- 2021 Maternal and Infant Health Summit
- 2021 Newborn Screening Midwife Updates

NBS laboratory personnel and follow-up staff continued to serve on national NBS committees, including:

- Education and Training workgroup for the Advisory Committee on Heritable Disorders in Newborns and Children
- The Clinical Laboratory Standards Institute Document Development Committee
- Critical Congenital Heart Disease (CCHD) Technical Assistance Workgroup
- Health Information Technology (HIT) Association of Public Health Laboratories (APHL) work group
- Quality assurance/Quality control APHL Subcommittee work group

Continuing work:

- The NBS Program continued working towards implementing screening for guanidinoacetate methyltransferase (GAMT) deficiency.

Disorders included on the Newborn Screening Blood Spot Panel, 2021

Amino Acid Disorders

1. Argininemia
2. Argininosuccinic acidemia
3. Citrullinemia
4. Citrullinemia Type II
5. Homocystinuria
6. Hypermethioninemia
7. Maple syrup urine disease
8. Phenylketonuria
9. Benign hyperphenylalaninemia defect
10. Biopterin cofactor biosynthesis defect
11. Biopterin cofactor regeneration defect
12. Tyrosinemia Type I
13. Tyrosinemia Type II
14. Tyrosinemia Type III

Fatty Acid Oxidation Disorders

15. Carnitine acylcarnitine translocase deficiency
16. Carnitine palmitoyltransferase I deficiency
17. Carnitine palmitoyltransferase II deficiency
18. Carnitine uptake defect
19. Dienoyl-CoA reductase deficiency
20. Glutaric acidemia Type II
21. Long-chain L-3-hydroxyl acyl-CoA dehydrogenase deficiency
22. Medium/short-chain L-3-hydroxyl acyl-CoA dehydrogenase deficiency
23. Medium-chain acyl-CoA dehydrogenase deficiency
24. Medium-chain ketoacyl-CoA thiolase deficiency
26. Trifunctional protein deficiency
27. Very long-chain acyl-CoA dehydrogenase deficiency

Lysosomal Storage Disorders

28. Pompe Disease
29. Mucopolysaccharidosis I

Organic Acid Disorders

30. 2-Methyl-3-hydroxy butyric aciduria
31. 2-Methylbutyryl-CoA dehydrogenase deficiency
32. 3-Hydroxy 3-methylglutaric aciduria
33. 3-Methylcrotonyl-CoA carboxylase deficiency
34. 3-Methylglutaconic aciduria
35. Beta-ketothiolase deficiency
36. Glutaric acidemia Type I
37. Isovaleric acidemia
38. Methylmalonic acidemia (Cbl A, B)
39. Methylmalonic acidemia (Cbl C, D)
40. Methylmalonic acidemia (mutase deficiency)
41. Multiple carboxylase deficiency
42. Propionic acidemia

Hemoglobinopathies

43. S/Beta thalassemia
44. S/C disease
45. Sickle cell anemia
46. Variant hemoglobinopathies
47. Hemoglobin H disease

Endocrine Disorders

48. Congenital adrenal hyperplasia
49. Congenital hypothyroidism

Other Disorders

50. Biotinidase deficiency
51. Galactosemia
52. Cystic fibrosis
53. Severe combined immunodeficiency
54. T-cell related lymphocyte deficiencies
55. X-linked adrenoleukodystrophy
56. Spinal muscular atrophy

Notes: Highlighted disorders have never been detected in Michigan through NBS. The following disorders are reported together because the same analyte(s) is used for screening: #3/4, #5/#6, #8-11, #13/#14, #15/#17, #21/#26, #31/#37, #32-34/#41, #38-#40/42, and #30/#35.

Screening Performance Indicators

Indicator	Description
Newborns (N)	The total number of screened live births among in-state residents.
Total + (% NICU)	Total number of positive screens among in-state residents (the percentage of infants with positive screens who were admitted to the NICU among all infants with positive screens).
Positive	Screening value exceeds cutoff.
Strong +	Strong positive screen (in most cases considered a medical emergency and referred immediately for diagnostic testing).
Borderline +	Borderline positive screen (not a medical emergency and repeat screen requested).
Confirmed +	A diagnosis of a disorder that has been confirmed.
False +	A positive screen that is not confirmed as a case of a disease included in the NBS panel.
Detection Rate	The number of infants having a confirmed disorder out of the total number of infants screened, depicted as a ratio. One case per 'X' number of infants screened depicted as 1: 'X'.
FPR	False positive rate: the number of infants with false positive screens divided by the total number of infants screened, expressed as a percentage.
PPV	Positive predictive value: the number of infants confirmed with a disorder divided by the number of infants having positive screens, expressed as a percentage.

Screening performance metrics included in subsequent tables are shown above. These indicators are commonly used to assess the performance of screening tests and allow for comparisons both over time and with other screening programs. Ideal screening tests have a high positive predictive value (perfect = 100%) and a low false positive rate (perfect = 0%). A perfect screening test correctly identifies all cases of a disorder with no false positives. Detection rates, the total number of cases identified out of the total number of newborns screened, are based on the total number of screens for in-state residents. Cases are defined as newborns identified with disorders via NBS. Maternal disorders and carriers identified by NBS are not included as confirmed cases in the performance metrics, though they are presented in this report.

Screened Newborns

The Michigan NBS Program screened 99.1% of the live births occurring in Michigan in 2021, as determined by the linkage of NBS records to preliminary live births records received from the Vital Records & Health Data Development Section and follow-up of unmatched records (Figure 1). Of the 104,104 live births that occurred in 2021, 309 were listed as deceased on their birth certificate. Many of these infants are not screened due to their short life spans, so they are excluded from the linkage calculations. Of the 103,795 remaining live births, the linkage algorithm successfully matched newborn screens for 102,540 infants (98.8%). The 1,255 unmatched records were sent to NBS follow-up program technicians for further investigation. This more in-depth follow-up revealed that 281 (22.2%) of the unmatched records were screened in Michigan. For these infants, the linkage algorithm failed to create the match for a variety of reasons, including data recording errors, data entry errors, or name changes due to adoptions.

Overall, 974 infants (0.9%) with a Michigan birth certificate were not screened in Michigan. Of those 974 infants, 84 were screened out of state. Of the remaining 890 infants, 526 were not screened due to parents not permitting the collection of the screen, 21 were not screened due to palliative care or a death after the birth certificate was filed and the reason the screen was not completed is unknown for 343 infants. For all infants without a newborn screen, NBS follow-up staff either contact the NBS coordinator for hospital births or send a parental notification and midwife notification letter for home births.

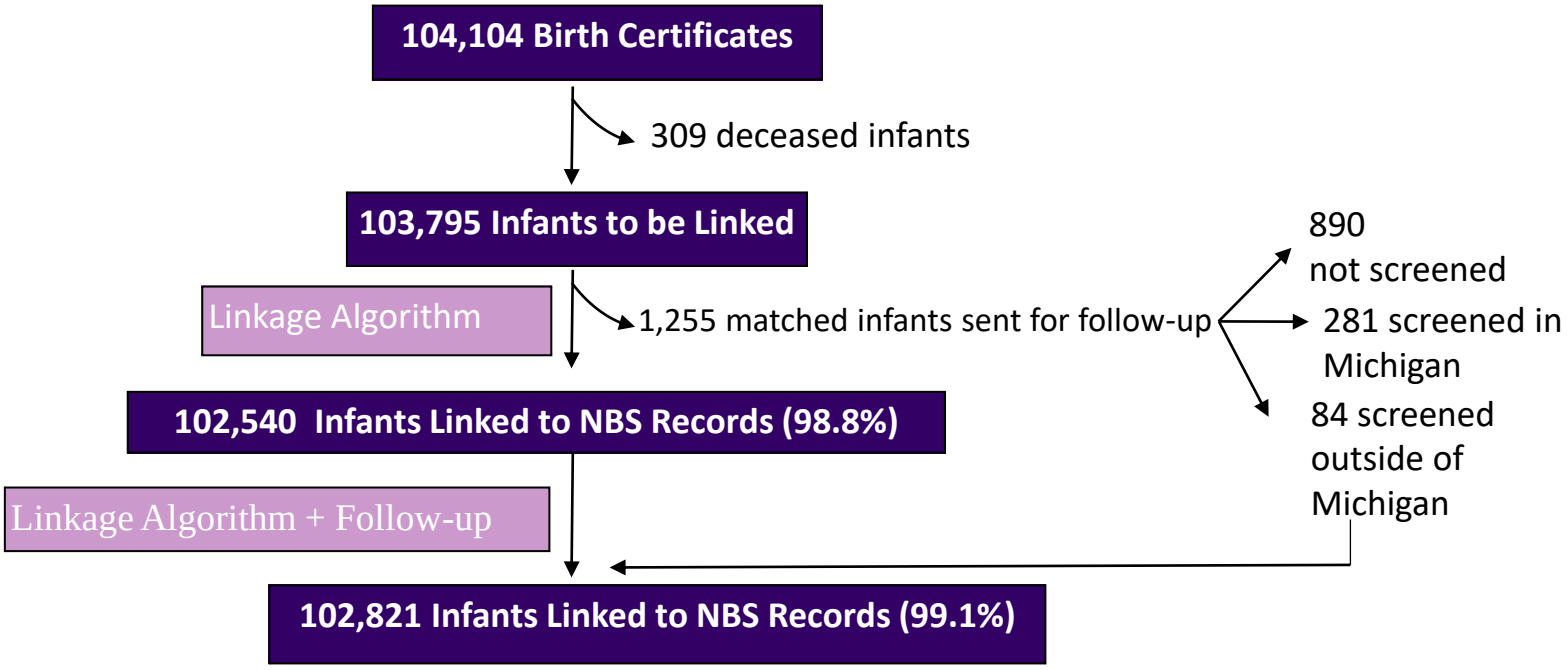

Figure 1. Newborn Screening and Live Births Records Linkage, Michigan, 2021

Screening Outcome Information

In the following subsections, outcome information is provided for the disorders included in the NBS panel in 2021. The total numbers of cases detected both in and through 2021 are presented along with screening performance metrics.

Table 1 reports the cumulative detection rate of disorders identified via NBS by classification both in and through 2021. The metabolic disorders detected by Tandem Mass Spectrometry (MS/MS) are grouped by category (amino acid, organic acid and fatty acid oxidation disorders). Two metabolic disorders, galactosemia and biotinidase deficiency, are detectable by enzyme assay screening rather than MS/MS and are listed separately. The galactosemia cumulative detection rate includes both Duarte compound heterozygotes (D/G) and classic galactosemia (G/G). However, only D/G cases that have been detected since 2004, the year that the Children's Hospital of Michigan Metabolic Clinic (CHMMC) began short-term treatment of this disorder, are included in the cumulative detection rate. Similarly, the biotinidase deficiency cumulative detection rate includes both partial and profound biotinidase deficiency. Treatment of partial biotinidase deficiency did not begin until 2000.

Table 1: Disorders Identified in Newborns via Newborn Screening, Michigan, 1965-2021

Disorder Type	Cases in 2021 (N)	Cases Through 2021 (N)	Detection Rate (1:X)[1]
Galactosemia (1985)	6	228	20,620
Biotinidase Deficiencies (1987)	11	388	11,130
Amino Acid Disorders (1965)	12	816	20,620
Organic Acid Disorders (2005)	8	116	15,895
Fatty Acid Oxidation Disorders (2003)	11	305	6,725
Congenital Hypothyroidism (1977)	144	2,850	1,551
Congenital Adrenal Hyperplasia (1993)	1	185	18,052
Sickle Cell Disease (1987)	39	2,208	1,935
Hemoglobin H Disease (2012)	8	25	51,641
Cystic Fibrosis (2007)	23	371	3,843
Primary Immunodeficiencies (2011)	16	150	7,389
Lysosomal Storage Disorders (2017)	11	35	10,675
X-Linked Adrenoleukodystrophy (2019)	3	5	63,830
Spinal Muscular Atrophy (2020)	9	21	9,898
Total	*302*	*7,703*	-

[1]Data interpretation: The detection rate reflects the number of infants screened per confirmed case. For example, one in every 20,620 infants screened for Galactosemia between 1985 and 2021 have the disorder.

Screening Performance Indicators

Table 2 reports screening performance metrics for all disorders in 2021. Screening performance metrics include the detection rate, false positive rate (FPR), and positive predictive value (PPV).

Table 2: Screening Results and Performance Metrics, Michigan, 2021, Screened N=102,678

Disorder Type	Positives (N)	Confirmed cases (N)	Detection Rate (1:X)[1]	FPR (%)	PPV (%)
Galactosemia	13	6	17,113	0.01	46.2
Biotinidase Deficiencies	41	11	9,334	0.03	26.8
Amino Acid Disorders	32	12	7,898	0.02	37.5
Organic Acid Disorders	19	8	12,835	0.01	42.1
Fatty Acid Oxidation Disorders	86	11	9,334	0.07	12.8
Congenital Hypothyroidism	2,102	144	713	1.91	6.9
Congenital Adrenal Hyperplasia	91	1	102,678	0.09	1.1
Sickle Cell Disease	48	39	2,633	0.01	81.3
Hemoglobin H Disease	21	8	12,835	0.01	38.1
Cystic Fibrosis[2]	349	23	4,464	0.32	6.6
Primary Immunodeficiencies	65	16	6,417	0.05	24.6
Lysosomal Storage Disorders	25	11	10,268	0.01	44.0
X-Linked Adrenoleukodystrophy	14	3	34,226	0.01	21.4
Spinal Muscular Atrophy	9	9	11,409	0.00	100.0

[1] Data interpretation: The detection rate reflects the number of infants screened per confirmed case. For example, one in every 17,1113 infants screened in 2021 for Galactosemia have the disorder.
[2] One CF case was not detected by NBS; this case is not included in case counts. In addition, 15 CF related metabolic syndrome (CRMS) cases were also detected through screening, these cases are also not included in case counts.

A breakdown of amino acid disorders can be found in Table 3, a breakdown of organic acid disorders can be found in Table 4, a breakdown of fatty acid oxidation disorders can be found in Table 5, a breakdown of sickle cell disorders can be found in Table 6 and a breakdown of lysosomal storage disorders can be found in Table 7.

For some disorders, infants receive further classification upon diagnosis. Of the six cases of galactosemia, two confirmed with classic galactosemia and four confirmed with Duarte galactosemia. Of the 11 cases that confirmed with Biotinidase deficiency, 10 confirmed with partial biotinidase deficiency and one confirmed with profound biotinidase deficiency. Only one case of CAH confirmed, and this case was a salt wasting case. No non-salt wasting cases were diagnosed in 2021. Of the 17 newborns with primary immunodeficiencies, one confirmed with SCID, three confirmed with Syndromes of T-cell impairment, and 13 confirmed with T-cell lymphopenias. No cases of ADA SCID were detected in 2021.

Screening Performance Indicators

Table 3: Amino Acid Disorders Screening Performance Metrics, Michigan, 2021, Screened N=102,678

Disorder	Total Positives (N)	Confirmed Cases (N)	Detection Rate (1:X)[1]	FPR (%)	PPV (%)
Phenylketonuria (PKU) Total	11	8	12,835	0.003	72.7
Medically treated PKU	-	2	51,339	-	-
Hyperphenylalaninemia	-	6	17,113	-	-
Citrullinemia (CIT)/CIT II	3	1	102,678	0.002	33.3
Tyrosinemia I (TYR I)	7	2	51,339	0.005	28.6
Tyrosinemia II/III (TYR II/III)	6	0	-	0.006	0.0
Maple Syrup Urine Disease (MSUD)	2	0	102,678	0.002	0.0
Homocystinuria (HCY)	2	0	-	0.002	0.0
Argininemia	1	1	102,678	0.000	100.0

[1] Data interpretation: The detection rate reflects the number of infants screened per confirmed case. For example, one in every 12,835 infants screened for Phenylketonuria in 2021 have the disorder.

Table 4: Organic Acid Disorders Detected Screening Performance Metrics, Michigan, 2021, N=102,678

Disorder Type	Positives (N)	Confirmed cases (N)	Detection Rate (1:X)[1]	FPR (%)	PPV (%)
3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)	7	4	25,670	0.003	57.1
Glutaric Acidemia Type I (GA1)	2	1	102,678	0.001	50.0
Proprionic Acidemia/Methylmalonic acidemia (PA/MMA)	8	2	51,339	0.006	25.0
2-Methyl-3-hydroxy butyric aciduria/Isovaleric acidemia (2MBG/IVA)	2	1	102,678	0.001	50.0

[1] Data interpretation: The detection rate reflects the number of infants screened per confirmed case. For example, one in every 25,670 infants screened for 3MCC in 2021 have the disorder.

Table 5: Fatty Acid Oxidation Disorders Screening Performance Metrics, Michigan, 2021, N=102,678

Disorder Type	Positives (N)	Confirmed cases (N)	Detection Rate (1:X)[1]	FPR (%)	PPV (%)
Carnitine uptake defect (CUD)	65	0	-	0.063	0.0
Carnitine palmitoyltransferase II deficiency (CPT II)	5	2	51,339	0.003	40.0
Glutaric acidemia Type II (GA II)	3	0	-	0.003	0.0
Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)	8	6	17,113	0.002	75.0
Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	5	3	34,226	0.002	60.0

[1] Data interpretation: The detection rate reflects the number of infants screened per confirmed case. For example, one in every 51,339 infants screened for CPT II in 2021 have the disorder.

Table 6. Hemoglobinopathy Screening Performance Metrics, Michigan, 2021, Screened N=102,678

Disorder	Total Confirmed cases	Total Confirmed cases among black populations	Detection Rate (1:X)[1]	Detection Rate among black populations (1:X)[2]
Sickle Cell Anemia	21	18	4,889	979
SC Disease	13	11	7,898	1,601
Sickle β thalassemia	5	4	20,536	4,403
Total	39	33	2,633	534

[1] Data interpretation: The detection rate reflects the number of infants screened per confirmed case. For example, one in every 2,633 infants screened for sickle cell disease in 2021 have the disorder.
[2] Data interpretation: The detection rate among black populations reflects the number of black infants screened per confirmed case. In 2021, there were 17,613 black infants screened. For example, one in every 534 black infants screened for sickle cell disease in 2021 have the disorder.
Note: Six cases of Hemoglobin C and two cases of Hemoglobin C thalassemia plus were also detected.

Table 7: Lysosomal Storage Disorders, Screening Performance Metrics, Michigan, 2021, Screened N=102,678

Disorder	Positives (N)	Confirmed cases (N)	Detection Rate (1:X)[1]	FPR (%)	PPV (%)
Pompe Disease	12	9	11,409	0.003	75.0
MPS1	13	2	51,339	0.011	15.4

[1] Data interpretation: The detection rate reflects the number of infants screened per confirmed case. For example, one in every 11,409 infants screened for Pompe Disease in 2021 have the disorder.

Carriers and Maternal Disorders

Although the overarching goal of NBS is to detect disorders in newborns, carriers and maternal disorders are also identified. For disorders in the NBS panel, carriers have one normal gene and one mutated gene and typically do not display any clinical symptoms. On a routine basis, the NBS Follow-up Program refers all newborns with positive screens to the appropriate medical management coordinating center that will follow-up to determine the final diagnosis: no disease, disease, carrier, or maternal disorder. NBS will only detect carriers or maternal disorders following an abnormal screen. Thus, NBS will not identify all carriers or all maternal disorders.

In 2021, a total of 2,797 infants were identified as carriers of a disease included in the NBS panel, following an abnormal screen (Table 8). Besides confirmatory diagnostic testing for infants, medical management centers also offer diagnostic testing for mothers. Since mothers may have the disease rather than the infant, they could possibly be identified through NBS for a few disorders. No maternal cases were detected in 2021.

Table 8: Carriers Identified from Newborn Screening, Michigan, 2021

Disorder	N
Hemoglobin Traits	2,496
Cystic fibrosis (CF)	296
MCAD deficiency	2
MPS 1	2
Pompe Disease	1

Time to Treatment

Turn-around time in NBS refers to the time from birth to initiation of treatment. The target turn-around time for initiating treatment for the early-onset life-threatening disorders (CAH, galactosemia and disorders detected by MS/MS) is no later than the seventh day of life. The goals for other disorders vary. Table 9 reports the time to treatment for disorders other than hemoglobinopathies and cystic fibrosis. As indicated in Table 9, time to treatment ranged from zero to 189 days among all disorders. Since borderline positive screens require one or more retests before being referred for confirmatory testing, CH is presented separately by initial screening result (strong or borderline) in the table.

Table 9: Time to Treatment, Michigan, 2021

Disorder	Total confimed	Treated on 1-7 days of Life	Treated on 8-14 days of life	Treated >14 days of life	Treatment Time Range (days)
Spinal Muscular Atrophy	9		1	8	13-38
Classic Galactosemia	2	2			0-4
Biotinidase Profound	1	1			6
Biotinidase Partial	10	5	3	2	4-77
Medically treated (PKU)	2	1	1		6-14
Citrullinemia (CIT)/CIT II	1	1			3
Tyrosinemia I (TYR I)	2	2			4
Argininemia	1	1			4
3MCC	4	4			3-5
Glutaric Acidemia Type I	1	1			5
Proprionic Acidemia(PA) /MMA	2	1	1		6-8
2MBG	1		1		12
CPT II	2	2			0-7
MCAD	6	6			2-5
VLCAD	3	3			2-6
MPS1	2			2	53-61
Pompe Disease- classic infantile onset	1	1			1
CH– Strong	71	33	13	25	3-78
CH– Borderline	73	8	13	52	6-189
CAH– Salt Wasting	1	1			3
Total	*195*	*73*	*33*	*89*	*0-189*

Table 10 reports the time to treatment among newborns with hemoglobinopathies. The target is to initiate penicillin prophylaxis by four months of life (120 days).

Table 10: Time to Penicillin Initiation for Sickle Cell Disorders, Michigan, 2021

Disorder	Total Confirmed	Penicillin Prophylaxis Initiated < 120 days	Penicillin Prophylaxis Initiated 120-149 days	Penicillin Prophylaxis Initiated > 150 days
Sickle cell disorder	39	32	2	3

NBS Performance measures

The Michigan NBS Program prepares quarterly hospital reports to evaluate how hospital are performing on key NBS indicators and highlight areas for improvement. During 2021, the hospital quarterly reports included six indicators related to blood spot screening. Those indicators are displayed below:

Late Screens:	Less than 2% of screens collected greater than 36 hours after birth.
Appropriate Day:	Greater than 90% of screens arrive in state laboratory on or before the appropriate day.
Unsatisfactory Screens:	Less than 1% of screens are unsatisfactory.
NBS Card Number:	Greater than 95% of electronic birth certificates have the NBS card number recorded.
Returned BioTrust Consent Forms	At least 90% of specimens have a returned consent form that is completed appropriately.
NBS card with incorrect dates/times:	Less than 1% of specimen have errors in their birth date/ time and/or collection date/time on the NBS card.

Table 11 lists the statistics for each performance measure and whether the goal was met by nursery type. Nursery type includes regular baby nurseries, the neonatal intensive care and special care nurseries (NICU/SCN), and non-hospital births.

Table 11: Measures for Newborn Screening, by Nursery Type, Michigan, 2021

Measure by Nursery Type	N	%	Met Goal?
Late Screens: Regular	400	0.5	Yes
Late Screens: NICU/SCN	158	1.4	Yes
Late Screens: Non-hospital	783	51.3	No
Appropriate Day: Regular	83,838	92.4	Yes
Appropriate Day: NICU/SCN	10,132	88.5	No
Appropriate Day: Non-hospital[1]	NA	NA	NA
Unsatisfactory Screens: Regular	904	1	No
Unsatisfactory Screens: NICU/SCN	222	1.9	No
Unsatisfactory Screens: Non-hospital	44	2.9	No
NBS Card Number: Regular	90,469	98	Yes
NBS Card Number: NICU/SCN[2]	-	-	-
NBS Card Number: Non-hospital	1,597	76.9	No
Returned BioTrust Consent Forms: Regular	80,731	90	Yes
Returned BioTrust Consent Forms: NICU/SCN	7,342	64	No
Returned BioTrust Consent Forms: Non-hospital	1,134	74	No
NBS card with incorrect dates/times: Regular	2,130	2.4	No
NBS card with incorrect dates/times: NICU/SCN	373	3.3	No
NBS card with incorrect dates/times: Non-hospital	95	6.2	No

[1]*Receipt by appropriate day is not calculated for non-hospital births because they do not have a designated courier pick-up time for each day like birthing facilities have.*

[2]*Recording of NBS card number is not a performance measure for NICUs since the birth hospital is asked to draw the NBS specimen before transferring the infant to the NICU. Infants transferred to NICUs (as recorded on the birth certificate) are not included in the performance measure for regular nurseries.*

Conclusion

NBS is a critical public health program that protects the lives of our state's newest residents. The NBS Laboratory screened 102,965 infants born in 2021, and the NBS Follow-up Program tracked approximately 7,000 positive, isolated elevation, unsatisfactory, early, and transfused specimens. Newborns with strong positive screening result were immediately referred to the appropriate NBS follow-up coordinating center for evaluation. A total of 302 newborns were identified with a disorder by NBS in 2021, as well as 2,797 carriers. Since blood spot screening began in Michigan in 1965, 7,703 newborns have been diagnosed and treated. We are continuing to both expand and refine the NBS Program in order to better protect the health of infants born in Michigan.

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