Michigan Department of
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MICHIGAN NEWBORN SCREENING PROGRAM

Annual Report 2019

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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 2019, more than 7.4 million infants have been screened with more than 7,000 diagnosed with diseases included in the NBS blood spot panel.

Of the 106,126 infants screened in 2019, the vast majority were Michigan residents and 285 (0.3 %) were diagnosed with a disease. Overall, one infant out of 371 screened was diagnosed with one of the disorders included in the NBS panel (see Table 1 for list of disorders).

Developments occurring in 2019:

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

- The findings from different studies and analyses related to NBS were presented at the:
    - ◊ Michigan Epidemiology Conference in Lansing, Michigan.
    - ◊ Association of Public Health Laboratories (APHL) Newborn Screening Symposium in Chicago, Illinois.

Michigan continued to conduct NBS-related trainings:

- The NBS Follow-up Program held two hospital trainings in Pontiac and Lansing for hospital staff.

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

- Kalamazoo Baby fair
- Lansing Maternal Infant health Summit
- Royal Oak Baby Fair
- Lansing Baby Fair
- Tummy to Toddler Event in Warren
- Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) Spring Conference in Frankenmuth
- AWHONN Fall Conference in Traverse City
- Metro Parent Baby Fair in West Bloomfield
- Livingston County Baby Fair
- A presentation to Grand Valley State University (GVSU) Master’s of Public Health (MPH) students

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) American Public Health Laboratories (APHL) work group
- Quality assurance/Quality control APHL Subcommittee work group

New screening developments:

- The NBS Program started screening for X-linked Adrenoleukodystrophy (X-ALD) in October 2019 and began pilot screening for Spinal Muscle Atrophy (SMA) in November 2019. The NBS Program also continued working towards implementing screening for Guanidinoacetate methyltransferase deficiency (GAMT).

Continuing work:

- NBS lab received a grant from Cure SMA to procure instrumentation for SMA testing.

Listing of Figures & Tables

Figures

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Acronym Key

Acronym	Name
CCHD	Critical Congenital Heart Disease
EBC	Electronic Birth Certificate
FPR	False Positive Rate
MCIR	Michigan Care Improvement Registry
MDHHS	Michigan Department of Health and Human Services
MS/MS	Tandem Mass Spectrometry
NBS	Newborn Screening
NICU	Neonatal Intensive Care Unit
PCP	Primary Care Physician
PPV	Positive Predictive Value
QA	Quality Assurance
SCN	Special Care Nursery

I. Introduction

The Newborn Screening (NBS) Annual Report provides an overview of Michigan's NBS Program, screening performance metrics related to disorders included in the NBS panel, and quality assurance information. This report does not contain any appendices as they have not changed since the last version of this report. All appendices, including the NBS research guidelines, supportive legislation and NBS advisory committees, can be found in previous reports.

This report is intended to provide:

- An introduction and historical account of the development of NBS in Michigan.
- Michigan screening performance metrics.
- Quality assurance information.

What is Newborn Screening?

NBS is the process of early identification of health conditions followed by their subsequent treatment before the onset of disease processes. Successfully screening, confirming and treating newborns with disorders in a timely manner minimizes the risk of long-term sequelae. Depending on the condition, potential outcomes of disorders in the NBS panel include, but are not limited to, brain/neurological damage, intellectual disability, damage to the liver, eyes or spleen or death if not detected early. To prevent these outcomes from occurring, NBS programs test blood spots collected from infants during the first few days of life and refer infants with abnormal screens for appropriate confirmatory testing and medical management.

NBS began in the 1960s when Dr. Robert Guthrie developed the bacterial inhibition assay to diagnose phenylketonuria (PKU) by determining the level of the amino acid phenylalanine in a drop of a baby's blood placed on a strip of filter paper. In 1965, Dr. K. Stanley Read at the Michigan Department of Public Health and Dr. Richard Allen at the University of Michigan introduced NBS for PKU to Michigan and almost immediately turned what had been a devastating, untreatable, genetic disorder into a condition readily manageable by a low protein diet (Figure 1).[1] In 1977, a test for congenital hypothyroidism (CH) was added to the NBS panel, and screening for galactosemia was initiated in 1985. Public Act 14 of 1987 mandated further expansion of screening with the addition of three disorders: biotinidase deficiency, maple syrup urine disease (MSUD), and hemoglobinopathies such as sickle cell disease (SCD). The Act also permitted MDHHS's state laboratory to be the sole testing site and mandated a fee to fund the program. In 1993, another endocrine disorder, congenital adrenal hyperplasia (CAH), was added to the screening panel.

The introduction of tandem mass spectrometry (MS/MS) in 2003 enabled the state laboratory to efficiently screen for a large number of disorders using a single blood spot. This technology replaced Dr. Guthrie's bacterial inhibition assays previously used to detect PKU and MSUD. The first additional disorder screened with this method was medium chain acyl-CoA dehydrogenase deficiency (MCAD), a disorder of fatty acid oxidation that can result in sudden death during periods of fasting. MS/MS technology allowed further expansion of the NBS screening panel in 2004 to include an additional three amino acid disorders: homocystinuria (HCY), citrullinemia (CIT), and argininosuccinic aciduria (ASA).

[1]For more information on the history of PKU and PKU-related NBS Program evaluations conducted in Michigan, see Chapter IV of the 2009 NBS Annual Report.

In 2005, a pilot project was initiated to expand the screening panel to 48 disorders by including the 31 additional MS/MS disorders recommended by the American College of Medical Genetics and Genomics (ACMG) and the March of Dimes. Screening for cystic fibrosis began in Michigan on October 1, 2007, meeting another ACMG recommendation. Hearing screening was also added to the NBS panel in 2007, but this report does not include hearing screening results.[1] Screening for severe combined immunodeficiency (SCID) began on October 1, 2011. Screening for Hemoglobin H disorder began in 2012. Pulse oximetry screening for critical congenital heart disease (CCHD) began in 2014. Information on pulse oximetry screening can be found in a separate annual report[2]. Pompe disease and Mucopolysaccharidosis Type 1 (MPS 1) were added to the panel in 2014 and 2015, respectively. Screening for X-Linked Adrenoleukodystrophy began in October 2019.

Table 1 provides the complete list of disorders currently screened for in Michigan. The highlighted disorders are those that are screened for in Michigan, but no cases have ever been identified and confirmed through NBS. Detailed information about the disorders included in the screening panel, confirmation of diagnoses, and follow-up of positive tests can be found in the Michigan NBS Guide, which is available by clicking on the "Resources for Hospitals and Health Professionals" link on the NBS website.(michigan.gov/newbornscreening).

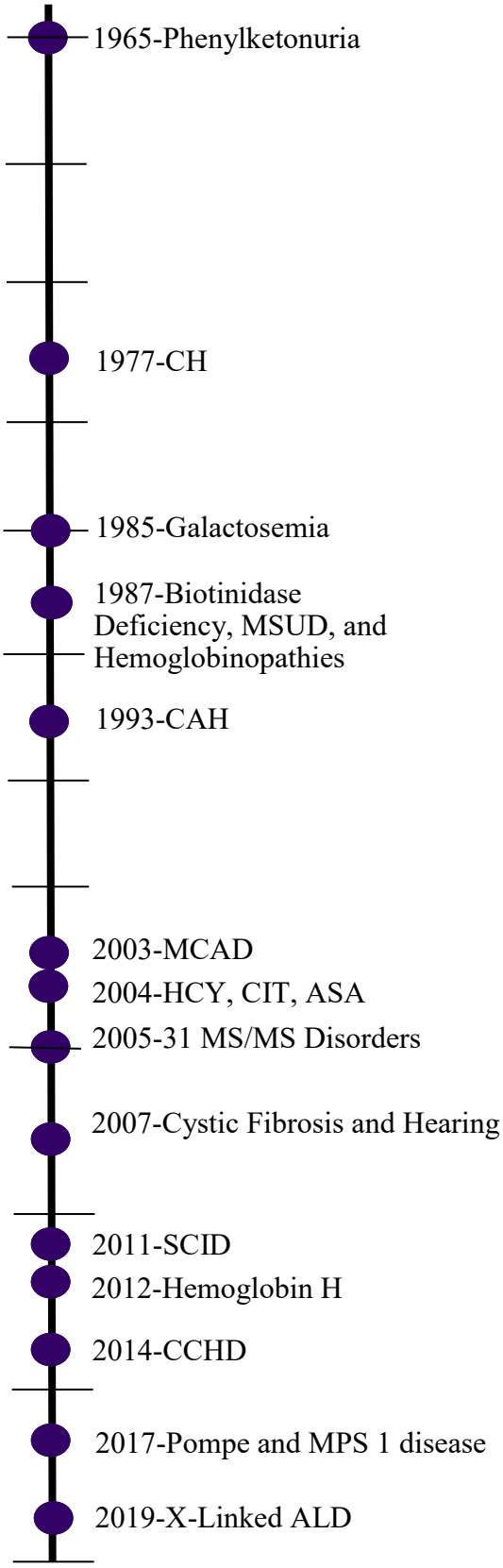

Figure 1. Implementation of Disorders on the NBS Panel, Michigan, 1965-2019

[1]More information about the newborn hearing screening program can be found at michigan.gov/ehdi.
[2] The critical congenital heart disease annual reports can be found in the "Resources for Hospitals and Health Professionals" link on the NBS website (michigan.gov/newbornscreening).

Table 1. Disorders included in the Newborn Screening Blood Spot Panel, Michigan, 2019

Amino Acid Disorders	Organic Acid Disorders
1. Argininemia	30. 2-Methyl-3-hydroxy butyric aciduria
2. Argininosuccinic acidemia	31. 2-Methylbutyryl-CoA dehydrogenase deficiency
3. Citrullinemia	32. 3-Hydroxy 3-methylglutaric aciduria
4. Citrullinemia Type II	33. 3-Methylcrotonyl-CoA carboxylase deficiency
5. Homocystinuria	34. 3-Methylglutaconic aciduria
6. Hypermethioninemia	35. Beta-ketothiolase deficiency
7. Maple syrup urine disease	36. Glutaric acidemia Type I
8. Phenylketonuria	37. Isovaleric acidemia
9. Benign hyperphenylalaninemia defect	38. Methylmalonic acidemia (Cbl A, B)
10. Biopterin cofactor biosynthesis defect	39. Methylmalonic acidemia (Cbl C, D)
11. Biopterin cofactor regeneration defect	40. Methylmalonic acidemia (mutase deficiency)
12. Tyrosinemia Type I	41. Multiple carboxylase deficiency
13. Tyrosinemia Type II	42. Propionic acidemia
14. Tyrosinemia Type III	**Hemoglobinopathies**
Fatty Acid Oxidation Disorders	43. S/Beta thalassemia
15. Carnitine acylcarnitine translocase deficiency	44. S/C disease
16. Carnitine palmitoyltransferase I deficiency	45. Sickle cell anemia
17. Carnitine palmitoyltransferase II deficiency	46. Variant hemoglobinopathies
18. Carnitine uptake defect	47. Hemoglobin H disease
19. Dienoyl-CoA reductase deficiency	**Endocrine Disorders**
20. Glutaric acidemia Type II	48. Congenital adrenal hyperplasia
21. Long-chain L-3-hydroxyl acyl-CoA dehydrogenase deficiency	49. Congenital hypothyroidism
22. Medium/short-chain L-3-hydroxyl acyl-CoA dehydrogenase deficiency	**Other Disorders**
23. Medium-chain acyl-CoA dehydrogenase deficiency	50. Biotinidase deficiency
24. Medium-chain ketoacyl-CoA thiolase deficiency	51. Galactosemia
26. Trifunctional protein deficiency	52. Cystic fibrosis
27. Very long-chain acyl-CoA dehydrogenase deficiency	53. Severe combined immunodeficiency
Lysosomal Storage Disorders	54. T-cell related lymphocyte deficiencies
28. Pompe Disease	55. X-Linked Adrenoleukodystrophy
29. Mucopolysaccharidosis I (MPS I)	

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, #43/#39/42, , #30/#35.

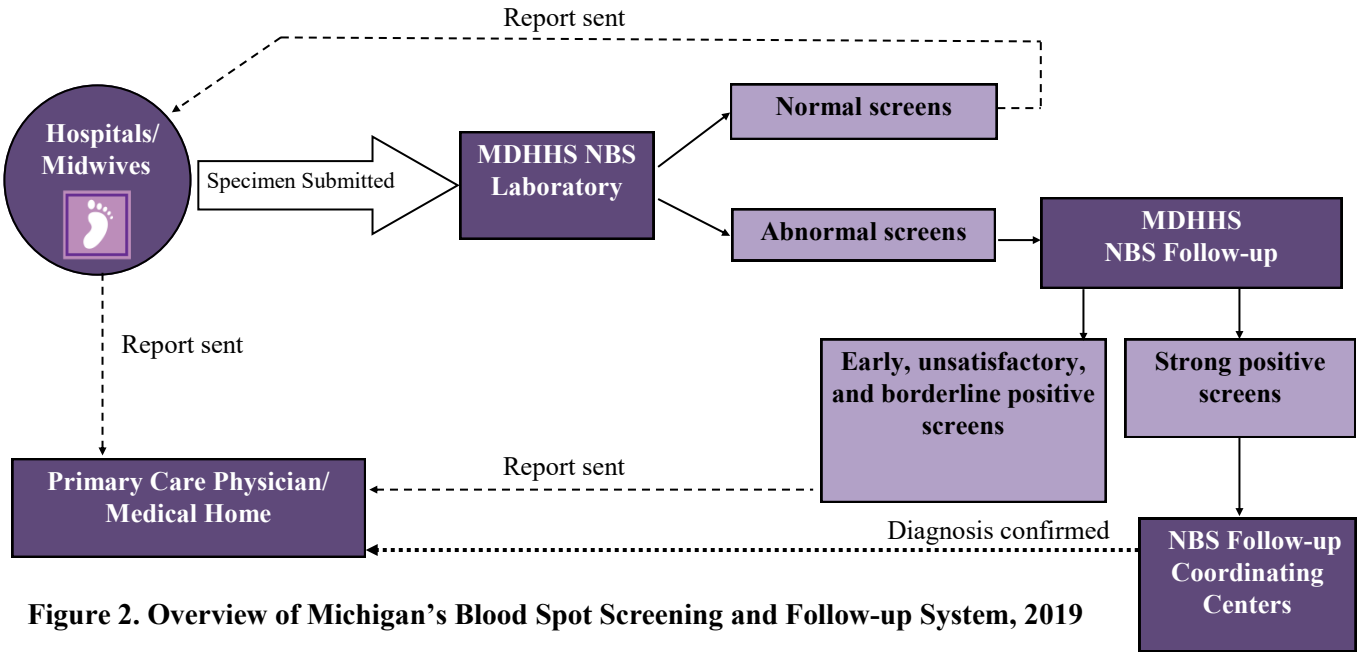

Figure 2. Overview of Michigan's Blood Spot Screening and Follow-up System, 2019

Abbreviations: MDHHS-Michigan Department of Health and Human Services; NBS-Newborn Screening.

HOSPITALS

In 2019, 81 Michigan hospitals had birthing units. Each hospital has a designated NBS Coordinator who helps facilitate the screening process. Hospital coordinators receive a quarterly quality assurance report from the NBS Follow-up Program that includes information on hospital-specific performance indicators compared to the state overall. Hospitals receive periodic site visits by the NBS Nurse Consultant to evaluate the screening process and make recommendations for improvement.

MIDWIVES AND HOME BIRTH ATTENDANTS

There are approximately 83 midwives registered with the NBS Program. Midwives are provided with individual assistance in meeting program standards. Although the number of midwife deliveries is small, they are more prevalent in the Amish and Mennonite communities, which have a higher incidence of several disorders included in the NBS panel.

MICHIGAN DEPARTMENT OF HEALTH AND HUMAN SERVICES

The MDHHS NBS Program includes the NBS Laboratory, the Follow-up Program, and medical management coordinating centers. More detailed descriptions of each entity are included in previous reports available on the NBS website (michigan.gov/newbornscreening).

II. Methods

This section describes the methods used to calculate: a) total number of newborns eligible for screening, b) total number of newborns diagnosed through the NBS process, c) the demographic characteristics of screened newborns, d) screening performance metrics, and e) quality assurance indicators.

TOTAL NUMBER OF NEWBORNS ELIGIBLE FOR SCREENING

Vital statistics data collected by the Vital Records & Health Data Development Section within the Division for Vital Records and Health Statistics at MDHHS was used to determine the total number of live births statewide that were eligible for screening. The number of live births in 2019 (n=106,952) is a preliminary estimate based on the number of births reported by December 2020.

TOTAL NUMBER OF NEWBORNS DIAGNOSED BY NEWBORN SCREENING

The MDHHS laboratory information system (PerkinElmer Life Sciences, Inc.) was used to identify positive cases. Data collected at the coordinating centers and managed by the NBS Follow-up Program was used to determine the total number of cases identified by NBS and to describe the population screened. Cases referred to in this report have the following characteristics: a) they were identified by NBS, b) they were Michigan residents, and c) they were identified and diagnosed through established laboratory and clinical protocols.

DEMOGRAPHIC CHARACTERISTICS OF SCREENED NEWBORNS

The demographic characteristics of screened newborns are presented for Michigan residents screened in Michigan. This report focuses on cases and screening results among Michigan residents only since out-of-state infants born within the state are followed up and diagnosed elsewhere.

Table 2. Screening Performance Indicator Descriptions

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

Table 2 provides a description of screening performance metrics included in subsequent tables. 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 separate tables in this report.

QUALITY ASSURANCE INDICATORS

Quality assurance (QA) data were obtained from NBS cards and information recorded by the state NBS laboratory and coordinating centers. Hospital quarterly reports contain QA indicators that focus on: a) time from birth to specimen collection, b) specimen arrival at the state NBS laboratory by the appropriate day, c) number of specimens that are unsatisfactory, d) number of birth certificates with NBS kit number recorded, and e) number of screened births with BioTrust consent form returned that is completed appropriately, and f) number of errors on the NBS card. Time from birth to start of treatment is another QA indicator used by the NBS Program.

III. Screening Results

DEMOGRAPHIC CHARACTERISTICS OF SCREENED NEWBORNS

This section describes the population of screened infants born in 2019 in terms of race, birth weight, gestational age and birth place (hospital regular nursery, NICU/SCN or non-hospital). These data are helpful in understanding the epidemiology (distribution of disease cases among the population) of the disorders covered in subsequent sections of this report. For example, sickle cell disease is predominantly found in Black populations, so the number of cases will fluctuate with the birth rate of Black populations.

The Michigan NBS Program screened 99.3% of the live births occurring in Michigan in 2019, 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 3). Of the 106,952 live births that occurred in 2019, 337 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 106,615 remaining live births, the linkage algorithm successfully matched newborn screens for 105,675 infants (99.1%). The 940 unmatched records were sent to NBS Follow-up Program technicians for further investigation. This more in-depth follow-up revealed that 213 (22.7%) of the unmatched records were screened. 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, 727 infants (0.7%) born in the state were not screened in Michigan. Of those 727 not screened, 552 (75.9%) were born in a non-hospital setting. Infants were not screened due to parental refusal of screening (n=354), infant expired (n=11), child being screened in another state (n=97), or some other reason for not being screened or reason is unknown (n=265). For all infants without a newborn screen, the NBS Follow-up technicians either contact the NBS coordinator for hospital births or send a parental notification letter for home births. In 2019, 37 infants born in hospitals are known to have missed being screened, and those hospitals were contacted. All 37 were screened after NBS follow up program technicians contacted the hospitals.

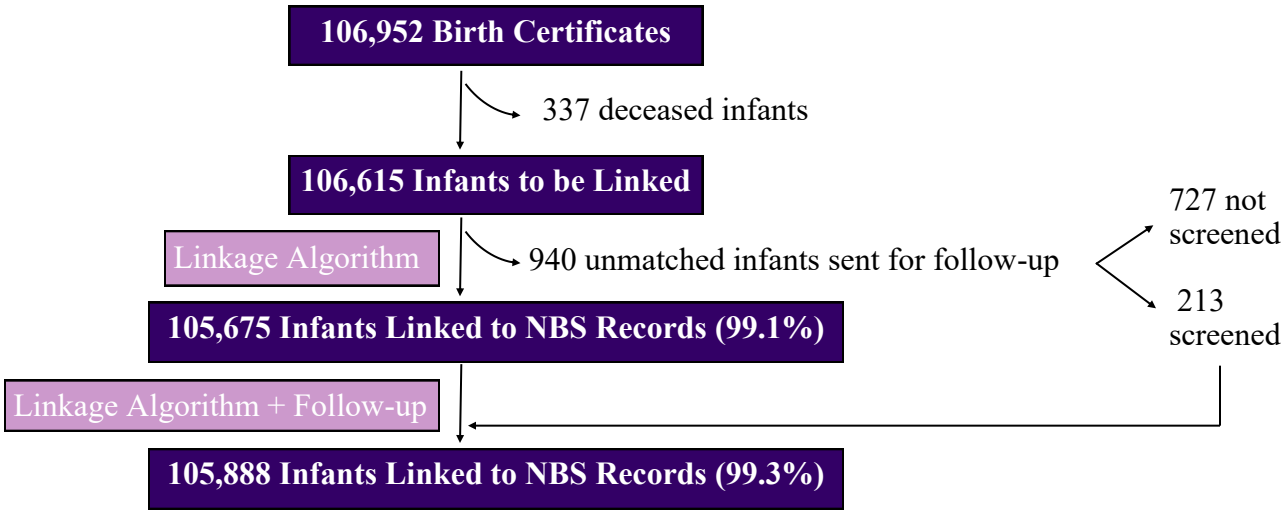

Figure 3. Newborn Screening and Live Births Records Linkage, Michigan, 2019

In total, 106,126 NBS samples were received from infants born in 2019. Of those, 316 (0.3% of screens) belonged to out-of-state residents or were collected out-of-state. Table 3 reports the demographic and perinatal characteristics by race of screened in-state residents born in 2019. This report details the screening results for in-state residents only since non-residents are typically followed in their home state. As indicated in Table 3, the majority of in-state infants screened were white, born in hospital nurseries, term (≥37 weeks gestational age), and of normal birth weight (>2,500 g). Overall, 11.0% of in-state infants screened were admitted to the NICU or special care nursery (SCN), 8.4% were low birth weight (<2,500 grams), and 9.7% were born preterm (<37 weeks gestational age). Black infants were over-represented among NICU, preterm and low birthweight births.

Table 3: Demographics of Infants Screened by Race, Michigan, 2019, Excluding Out-of-State Residents

Race	Column Total		Nursery Type						Birth Weight (g)		Gestational Age (wks.)	
			Regular Hospital		NICU/SCN		Non-Hospital		<2500		<37	
	N	%	N	%	N	%	N	%	N	%	N	%
White	65,225	61.4	57,879	88.7	6,473	9.9	873	1.3	4,318	6.7	5,611	8.7
Black	19,529	18.5	16,185	82.9	3,305	16.9	39	0.2	2,790	14.5	2,715	14.1
Multi-Racial	6,961	6.6	6,251	89.8	654	10.2	56	0.8	588	8.5	659	9.6
Other	7,669	7.3	7,067	92.2	591	7.7	11	0.1	561	7.4	536	7.1
Missing	6,426	6.1	5,756	89.6	652	10.2	18	0.3	553	8.9	622	10.0
Column Total:	105,810	100.0	93,138	88.0	11,675	11.0	997	0.9	8,810	8.4	10,143	9.7

Notes: All percentages are row percentages except for Column Total which is a column percentage. All characteristics are as recorded on the newborn screening card. A total of 1,409 and 1,283 newborns were missing birth weight and gestational age on the card, respectively. Non-hospital nursery type includes home births, births that occurred at birthing centers, and all other births that did not occur at a hospital.

SCREENING OUTCOME INFORMATION

In the following sub-sections, outcome information is provided for the disorders included in the NBS panel in 2019. The total numbers of cases detected both in and through 2019 are presented along with screening performance metrics.

CUMULATIVE DETECTION RATE

Table 4 reports the cumulative detection rate of disorders identified via NBS by classification both in and through 2019. The metabolic disorders detected by 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 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 4: Disorders Identified in Newborns via Newborn Screening, 1965-2019

Type of Disorder Classification (Year Screening Began)	Cases in 2019 (N)	Cases Through 2019 (N)	Cumulative Detection Rate
Galactosemia (1985)	9	219	1:20,436
Biotinidase Deficiencies (1987)	8	360	1:11,667
Amino Acid Disorders (1965)	13	793	1:9,375
Organic Acid Disorders (2005)	9	100	1:17,205
Fatty Acid Oxidation Disorders (2003)	12	287	1:6,903
Congenital Hypothyroidism (1977)	126	2,585	1:1,625
Congenital Adrenal Hyperplasia (1993)	5	175	1:19,002
Sickle Cell Disease (1987)	65	2,097	1:2,003
Hemoglobin H Disease (2012)	4	16	1:55,110
Cystic Fibrosis (2007)	16	322	1:4,165
Primary Immunodeficiencies (2011)	12	120	1:8,214
Lysosomal Storage Disorders (August 2017)	5	17	1:15,297
X-Linked Adrenoleukodystrophy (October 2019)	1	1	1:25,710
Total	285	7,092	-

See Table 1 for a list of all disorders included in each disorder classification.

Figure 4 displays detection rates in 2019 and overall. CH, the most commonly diagnosed disorder, accounted for 44.2% of cases diagnosed in 2019 and 36.5% cumulatively. Sickle cell disease, the second most commonly diagnosed disorder, accounted for 22.8% of cases detected in 2019 and 29.6% detected cumulatively. Cystic fibrosis (CF) was the third most commonly diagnosed disorder in 2019 and accounted for 5.6% of cases detected in 2019 and 4.5% of cases detected cumulatively.

Disorders detected by MS/MS (amino acid, organic acid, and fatty acid oxidation disorders) accounted for 12.0% of cases in 2019 and 16.7% cumulatively. However, PKU, the first disorder screened in Michigan, is now screened by MS/MS, meaning the overall proportion of cases detected by MS/MS is an overestimate because it includes cases detected prior to 2003 when MS/MS screening was initiated. The cumulative detection rate for fatty acid oxidation disorders (4.2%) is an underestimate because MCAD screening began in 2003, while screening for other conditions did not begin until 2005. This means that births included in the denominator from 2003-2005 were not eligible for diagnosis of a fatty acid oxidation disorders other than MCAD leading to an artificially low cumulative detection rate.

Screening for lysosomal storage disorders started in August 2017 and accounted for 1.8% of cases diagnosed in 2019, but only 0.24% of cases detected cumulatively. Screening for X-Linked Adrenoleukodystrophy began in October 2019, this accounts for 0.4% of cases diagnosed in 2019, but only 0.01% of cases detected cumulatively.

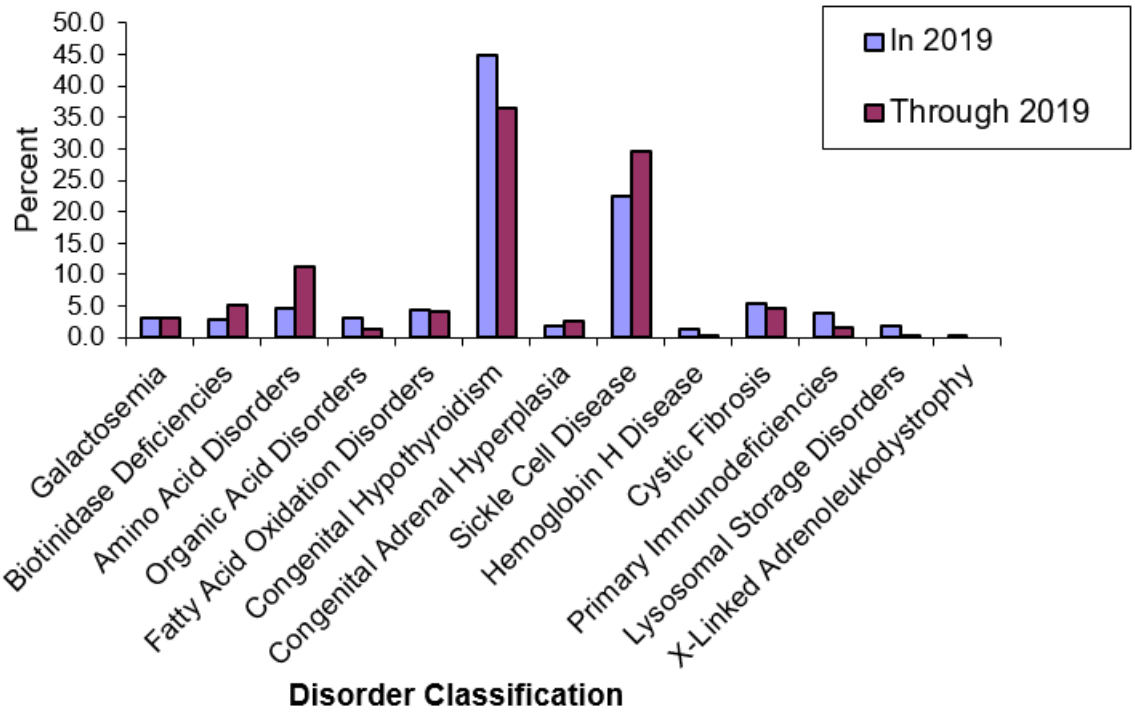

Figure 4. Percent Distribution of Disorders Identified in Newborns via Newborn Screening, Michigan Residents, in 2019 and through 2019

SCREENING PERFORMANCE METRICS

Screening performance metric targets are available in previous annual reports. Screening performance metrics include the detection rate, false positive rate (FPR), and positive predictive value (PPV). Table 5 reports screening performance metrics for all disorders in 2019. Performance metrics for individual MS/MS disorders are provided in separate tables (see Tables 7-9).

GALACTOSEMIA, BIOTINIDASE DEFICIENCY AND CYSTIC FIBROSIS

Four cases of Duarte D/G variant and five cases of classic galactosemia were detected in 2019, resulting in a FPR of 0.003% and PPV of 75%.

The biotinidase deficiency detection rate was 1:13,226. The FPR and PPV were 0.04% and 14.6%, respectively. All 8 cases detected were partial biotinidase cases.

Fifteen cases of CF were detected in 2019 (detection rate-1:7,054). The associated FPR and PPV were 0.3% and 4.7%, respectively. Additionally, eleven cases of CFTR-related metabolic syndrome were detected. Chapter IV of the 2008 Annual Report provides more detailed information describing CF screening in Michigan.

ENDOCRINE DISORDERS-CH AND CAH

One hundred and twenty-six cases of CH were detected in 2019. The CH screening FPR was 1.5%, and the PPV was 7.3%. The overall detection rate for CH was 1:840. Chapter IV of the 2007 Annual Report provides more detailed information describing CH screening in Michigan.

Five cases of CAH were detected in 2019, four were non-salt wasting and one was salt-wasting, The CAH screening FPR was 0.1%, and the PPV was 5.3%. The overall detection rate for CAH was 1:21,162.

HEMOGLOBINOPATHIES

Hemoglobinopathies include sickle cell disease (SCD) and Hemoglobin H disease. Four cases of Hemoglobin H were detected in 2019, resulting in a detection rate of 1:26,453. The Hemoglobin H disease FPR was 0.02% and the PPV was 16.0%.

Additional SCD screening outcome information is reported in Table 6. SCD screening differs from screening for the other disorders because the purpose is to identify the presence or absence of abnormal hemoglobin and not to quantify selected analytes. There is no screening reference range, and the results of screening are essentially considered a confirmatory diagnosis. Confirmatory testing is primarily for differentiating sickling genotypes.

As depicted in Table 6, SCDs are quite common among Black populations, which accounted for 95% of the cases in 2019. While the overall incidence of SCD is one case per 1,628 screened, the incidence in Black populations is one in 320 screened in Michigan.
In addition to sickle cell disease, eight cases of hemoglobin C were identified and one hemoglobin variant was identified.

Table 5: Screening Results and Performance Metrics, Michigan, 2019

Disorder Type	Total N	Total + N (% NICU)	Confirmed + N	Positive Detection Rate	FPR %	PPV %
Galactosemia	105,810	12 (8.3)			0.003	75.0
Classic (GG)			5	1:21,162		
Duarte (DG)			4	1:26,453		
Total			9	1:11,757		
Biotinidase Deficiency		55 (1.8)			0.04	14.6
Profound			0	-		
Partial			8	1:13,226		
Total			8	1:13,226		
Cystic Fibrosis (CF)		319 (35.1)	15	1:7,054	0.3	4.7
Congenital Hypothyroidism (CH)		1,731 (23.1)	126	1:840	1.5	7.3
Congenital Adrenal Hyperplasias (CAH)		94 (95.7)			0.1	5.3
Salt wasting			1	1:105,810		
Non-Salt wasting			4	1:26,453		
Total			5	1:21,162		
Sickle Cell Disease (SCD)		88 (21.6)	65	1:1,628	0.02	73.9
Hemoglobin H Disease		25 (34.6)	4	1:26,453	0.02	16.0
Primary Immunodeficiencies		44 (88.6)			0.03	27.3
SCID			0	-		
Syndromes with T-cell Impairment			3	1: 35,270		
Non-preterm Secondary T-cell Lymphopenias			9	1:13,226		
Total			12	1:8,818		
Lysosomal storage disorders		15 (26.7)	5	1:21,162	0.01	33.3
X-ALD		4 (0.0)	1	1:105,810	.003	25.0
Amino Acid		36 (8.3)	13	1:8,139	0.02	36.1
Organic Acid		24 (20.8)	9	1:11,757	0.02	37.5
Fatty Acid Oxidation		105 (10.4)	12	1:8,181	0.1	11.4
MS/MS Disorders Total		170 (11.5)	34	1:3,112	0.1	20.0

Notes: Maternal cases and carriers identified following an abnormal newborn screen are not included as confirmed cases in the screening performance indicators (i.e., considered false positives).

PRIMARY IMMUNODEFICIENCIES

In total, 12 cases of primary immunodeficiencies (PID) were identified, resulting in FPR of 0.03% and PPV of 27.3%. Of the 12 cases, three had syndromes with T-cell impairment, and nine had non-preterm secondary T-cell lymphopenias. Chapter IV of the 2011 Annual Report provides more detailed information about PID screening in Michigan.

MS/MS DISORDERS

In total, 33 disorders were detected by MS/MS. The overall FPR for MS/MS disorders was 0.1%. The PPV was 20%, and the detection rate was 1:3,112.

SCREENING PERFORMANCE METRICS-INDIVIDUAL MS/MS DISORDERS

AMINO ACID DISORDERS

Thirteen infants were identified with amino acid disorders (Table 7) by MS/MS. Phenylketonuria (PKU) was the most frequent amino acid disorder identified, found in one of every 9,619 newborns screened (11 newborns total). Chapter IV of the 2009 Annual Report provides more detailed information about PKU screening in Michigan. One case of HCY and one case of ASA was also identified.

ORGANIC ACID DISORDERS

Nine infants were diagnosed with an organic acid disorder in 2019. Six infants were diagnosed with Propionic acidemia/Methylmalonic acidemia (PA/MMA). One was diagnosed with 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC). One was diagnosed with Glutaric acidemia Type I (GA1) and one was diagnosed with Isovaleric acidemia (IVA).

FATTY ACID OXIDATION DISORDERS

Twelve newborns were identified with organic acid disorders (Table 9) by MS/MS. Eight were diagnosed with medium-chain acyl-CoA dehydrogenase deficiency (MCAD), two were diagnosed with Carnitine uptake defect (CUD), one was diagnosed with Carnitine palmitoyltransferase II deficiency (CPT II) and one was diagnosed with very long-chain acyl-CoA dehydrogenase deficiency (VLCAD).

LYSOSOMAL STORAGE DISORDERS

Eleven infants were identified with lysosomal storage disorders (Table 10); eight with Pompe disease and three with Mucopolysaccharidosis Type 1 (MPS 1). The overall PPV for LSDs was 73.3% and the false positive rates was 0.004%. For Pompe disease, the PPV was 80.0 and for MPS 1 the PPV was 60.0%. The false positive rate was 0.002% for Pompe and 0.002% for MPS 1.

Table 6: Hemoglobinopathy Screening Performance Metrics, Michigan, 2019

Disorder	Newborns (N)	Confirmed + (N)		Positive Detection Rate	
		Total	Among Black Populations	Total	Among Black Populations
Sickle Cell Anemia	105,810	42	39	1:2,581	1:502
SC Disease		12	11	1:9,619	1:1,778
Sickle β thalassemia		10	10	1:10,581	1:1,956
SD Disease		1	1	1:105,810	1:19,563
Total		65	61	*1:1,628*	1:320

Notes: Out of the number of Michigan resident infants screened, total N=105,810, among black populations N=19,563

Table 7: Amino Acid Disorders Detected by Tandem Mass Spectrometry, Screening Performance Metrics, Michigan, 2019

Disorder	Newborns N	Total + N	Con-firmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Phenylketonuria	105,810	18			0.01	73.3
Medically treated (PKU)			4	1:26,453		
Benign Hyperphenyl-alaninemia (H-PHE)			7	1:15,116		
Total			11	1:9,619		
Citrullinemia (CIT)/CIT II		1	0	-	0.001	0.0
Tyrosinemia I (TYR I)		2	0	-	0.002	0.0
Tyrosinemia II/III (TYR II/III)		6	0	-	0.01	0.0
Homocystinuria (HCY)		1	1	1:105,810	0.001	100.0
Argininemia (ARG)		2	0	-	0.002	0.0
Maple Syrup Urine Disease (MSUD)		5	0	-	0.005	0.0
Argininosuccinic acidem-ia (ASA)		1	1	1:105,810	0.0	100.0

Table 8: Organic Acid Disorders Detected by Tandem Mass Spectrometry, Screening Performance Metrics, Michigan, 2019

Disorder	Newborns N	Total + N	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)	105,810	4	1	1:105,810	0.003	25.0
Glutaric Acidemia Type I (GA I)		2	1	1:105,810	0.001	50.0
Propionic Acidemia (PA)/ Methylmalonic Acidemia (MMA)		15	6	1:17,636	0.01	40.0
Isovaleric acidemia (IVA)		3	1	1:105,810	0.002	33.3

Notes: Maternal cases and carriers identified following an abnormal newborn screen are not included as confirmed cases in the screening performance indicators (i.e., considered false positives).

Table 9: Fatty Acid Oxidation Disorders Detected by Tandem Mass Spectrometry, Screening Performance Metrics, Michigan, 2019

Disorder	Newborns N	Total + N	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Carnitine Uptake Defect (CUD)	105,810	87	2	1:52,905	0.08	2.3
Medium-chain Acyl-CoA Dehydrogenase Deficiency (MCAD)		10	8	1:13,226	0.002	80.0
Very Long-chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)		2	1	1:54,722	0.001	50.0
Carnitine palmitoyltransferase II deficiency (CPT II)		4	1	1:108,277	0.003	25.0
Glutaric acidemia Type II (GA II)		2	0	-	0.002	0.0

Maternal cases and carriers identified following an abnormal newborn screen are not included as confirmed cases in the screening performance indicators (i.e., considered false positives).

Table 10: Lysosomal Storage Disorders, Screening Performance Metrics, Michigan, 2019

Disorder	Newborns N	Total + N	Confirmed + (N)	Positive Detec-tion Rate	FPR (%)	PPV (%)
Pompe disease	105,810	10	5	1:21,162	0.005	50.0
Mucopolysaccharidosis Type 1 (MPS 1)		5	0	-	0.005	0.0

Notes: Maternal cases and carriers identified following an abnormal newborn screen are not included as confirmed cases in the screening performance indicators (i.e., considered false positives).

SCREENING PERFORMANCE METRICS AMONG STRONG POSITIVE SCREENS

This section provides screening performance metrics (FPR and PPV) among strong positive screens relative to those among total positive screens (strong and borderline positives). Disorders lacking a borderline positive category are not reported in Table 11 because their performance metrics have been previously reported in Tables 5-10. Disorders not detected in 2019 and detected disorders with no borderline positive screens are also excluded from Table 11, as there would be no change in screening performance overall compared to strong positive screens only.

Performance metrics among strong positive screens are particularly useful clinically in that they report the risk of a strong positive being a true case (PPV) or a false positive (FPR). When evaluating the significance of a strong positive screen, the performance metrics below should be considered. As indicated in Table 10, the FPRs and PPVs among strong positive screens are significantly improved relative to the overall screening performance metrics among all positive screens. Maternal cases and carriers identified through NBS are not included in Table 11.

Table 11: Screening Performance Metrics (FPR and PPV) among Strong Positive Screens compared to All Positive Screens, Michigan, 2019

Disorder Type	Among All +		Among Strong +	
	FPR	PPV	FPR	PPV
	%	%	%	%
Congenital Hypothyroidism (CH)	1.5	7.3	0.2	24.0
Congenital Adrenal Hyperplasia (CAH)	0.1	5.3	0.01	18.8
Phenylketonuria (PKU)	0.004	73.3	0.00001	90.0
Galactosemia	0.003	75.0	0.0	100.0
Cystic Fibrosis (CF)	0.3	4.7	0.004	71.4
Primary Immunodeficiency (PID)	0.03	27.3	0.01	43.5
Biotinidase Deficiency	0.04	14.6	0.00005	50.0
Carnitine uptake defect (CUD)	0.1	2.3	0.002	16.7

The FPR for CH is reduced approximately eight-fold for strong positive screens, and the PPV is increased approximately three-fold compared to all positives. Among strong positive screens for metabolic disorders, galactosemia had the best screening performance metrics, with a 100% PPV and a 0% FPR. Although cystic fibrosis does not have a strong positive category, children with compound heterozygote or homozygote DNA mutations were considered “strong positive” in Table 11. The FPR decreased 75-fold and the PPV increased from 5% to 71% when excluding children with a heterozygote DNA mutation. For PID, the PPV increased from 27% to 44% for strong positive screens compared to all positive screens. Overall, strong positive screens are far less likely to be false positives and far more likely to be indicative of true disease compared to positive screens overall (i.e., both strong and borderline).

CARRIERS, MATERNAL DISORDERS AND OTHER DISORDERS DETECTED

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 2019, a total of 3,197 infants were identified as carriers of a disease included in the NBS panel, following an abnormal screen (Table 12). The majority of these infants (n=2,898) had a hemoglobin trait. Almost 300 infants (n=294) were cystic fibrosis carriers, two were identified as Pompe carriers, one was identified as a Biotinidase deficiency carrier, one was identified as an IVA carrier and one was identified as a GA1 carrier.

Table 12: Carriers Identified from Newborn Screening, Michigan, 2019

Disorder	**N**
Hemoglobin Traits	2,898
Cystic fibrosis (CF)	294
Pompe disease	2
Biotinidase deficiency	1
Isovaleric Acidemia (IVA)	1
Glutaric Acidemia 1 (GA1)	1

Notes: All of these infants were identified following an abnormal screen. Not all carriers will have abnormal screens, so not all carriers will be detected through newborn screening.

MATERNAL DISORDERS IDENTIFIED FROM NEWBORN SCREENING

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 2019.

IV. Quality Assurance Information

This section includes quality assurance (QA) information about NBS specimen characteristics and indicators included in the quarterly reports that are distributed to hospitals.

SPECIMEN CHARACTERISTICS

Table 13 reports specimen characteristics by nursery type where the specimen was collected. Although 11% of infants were admitted to the NICU or SCN, 47% and 21% of strong and borderline positive screens were received from infants in the NICU, respectively. Isolated elevations of one or more amino acids and/or acyl-carnitines were also more prevalent among specimens received from infants in the NICU; these elevations are commonly associated with infants receiving total parenteral nutrition or transfusions, or low birth weight or preterm infants. While the overall number of unsatisfactory specimens was greatest among hospital nurseries, the proportion of unsatisfactory specimens was greatest among non-hospital samples (6.2%). Early (collected before 24 hours of life) and transfused specimens were more common among infants from the NICU (8.3%, 0.7%, respectively), while late specimens (collected after six days of life) were most common among non-hospital deliveries (9.1%). The NBS Follow-up Program tracks all strong and borderline positive, isolated elevation, unsatisfactory, early, and transfused specimens; approximately 6,500 specimens required follow-up in 2019.

Table 13: Specimen Characteristics by Nursery Type, Michigan, 2019

Indicator	Type of Birth					
	Regular Nursery		NICU/SCN		Non-Hospital	
	N	%	N	%	N	%
Strong Positive Specimens	189	0.2	175	1.5	6	0.6
Borderline Positive Specimens	1,364	1.5	364	3.1	8	0.8
All Positive Specimens*	1,937	2.1	621	5.3	18	1.3
Isolated elevations of amino acids and acyl-carnitines	11	0.0	495	4.2	0	0.0
Unsatisfactory Specimens	1,654	1.8	470	4.0	62	6.2
Late (>6 days) Specimens	35	0.0	18	0.2	90	9.1
Early (<1 day) Specimens	251	0.3	968	8.3	3	0.3
Transfused Specimens	2	0.0	71	0.7	1	0.1
Specimens Missing Demographics **	1,285	1.4	140	1.2	13	1.3
Total Births Screened	93,138	88.0	11,675	11.0	997	0.9

**Includes all strong and borderline specimens plus specimens positive for cystic fibrosis or hemoglobinopathies.*
***Defined as missing race, specimen collection time, or birth weight.*
Notes: Percentages expressed in the above table are column percentages, except for Total Births Screened which is a row percentage.

PERFORMANCE INDICATORS

During 2019, the hospital quarterly reports included six indicators related to blood spot screening. Table 14 lists the indicators and the performance goal for each indicator.

Table 14: Indicators and Performance Goals for Newborn Screening, Michigan, 2019

Measure	Performance Goal
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 for Health Consent Forms	At least 90% of specimens have a returned BioTrust for Health consent form that is completed appropriately
NBS card with incorrect demographics	Less than 1% of specimens have errors in the birth date/ time and/or specimen collection date/time on the NBS card

Table 15 lists the statistics for each performance measure and whether the goal was met, by nursery type. For late screens, regular nurseries and NICU/SCN nurseries met the goal. Of note, more than 50% of non-hospital births had screens collected more than 36 hours after birth. Timely collection of specimens is critical for ensuring prompt screening and referral to medical management. Receipt by appropriate day is a measure based on specimen collection time and each hospital's courier pickup days and times. Any specimen collected more than five hours before the designated pickup time for that day should be sent out the same day and received in the state laboratory the next day. For appropriate day, regular nurseries met the goal with 92.2% of specimens arriving on or before the appropriate day. NICUs had 86.9% of specimens arrive by the appropriate day and thus did not meet the goal of 90%.

None of the groups met the goal for unsatisfactory specimens for 2019. For recording of the NBS card number on birth certificates, regular nurseries met the goal, while non-hospital births did not meet the goal. Birth certificates coming from regular nurseries were more than twice as likely to have the NBS kit number recorded than certificates for non-hospital births. Although none of the nursery types met the BioTrust for Health measure, regular nurseries were very close; 89.5% of regular nursery births had a BioTrust for Health consent form returned that was appropriately completed compared to approximately 66% of NICUs/SCNs and 69% of non-hospital births.

The metric regarding data accuracy aims for less than 1% of specimens to have errors in the birth or collection date/time fields or any other demographic on the card such as birthweight or gestational age. When an error is suspected the NBS lab calls hospitals or the birth attendants to verify the information on the NBS card. Non-hospital births had the highest percentage of errors with 7.6% of cards having errors, while regular baby nurseries had 2.4% of cards with errors and NICUs/SCNs had 2.8% of cards with errors.

Table 15: Measures for Newborn Screening, by Nursery Type, Michigan, 2019

Measure	Nursery Type	N	%	Met Goal?
Late Screens: Less than 2% of screens collected greater than 36 hours after birth	Regular	796	0.9	Yes
	NICU/SCN	182	1.6	Yes
	Non-hospital	561	53.9	No
Appropriate Day: Greater than 90% of screens arrive in state laboratory on or before the appropriate day	Regular	85,931	92.2	Yes
	NICU/SCN	10,138	86.9	No
	Non-hospital*	NA		
Unsatisfactory Screens: Less than 1% of screens are unsatisfactory	Regular	1,654	1.8	No
	NICU/SCN	470	4.0	No
	Non-hospital	62	6.2	No
NBS Card Number: Greater than 95% of electronic birth certificates have the NBS card number recorded	Regular	91,097	93.3	No
	NICU/SCN**	-	-	-
	Non-hospital	416	40.9	No
Returned BioTrust for Health Consent Forms Completed Appropriately: At least 90% of specimens have a returned consent form that is completed appropriately	Regular	83,395	89.5	No
	NICU/SCN	7,693	65.9	No
	Non-hospital	688	69.0	No
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	Regular	2,231	2.4	No
	NICU/SCN	328	2.8	No
	Non-hospital	76	7.6	No

*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.
**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.

SCREENING TURN-AROUND TIME

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.

TIME TO TREATMENT

Table 16 reports the time to treatment for disorders other than hemoglobinopathies and cystic fibrosis. Penicillin prophylaxis, the treatment for hemoglobinopathies, is initiated later than treatment for other disorders and is reported in a separate table (Table 17). As indicated in Table 16, time to treatment ranged from two to 97 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.

GALACTOSEMIA

All five classic galactosemia cases were treated within the first week of life.

BIOTINIDASE DEFICIENCY

No cases of profound Biotinidase were identified in 2019. The treatment start date ranged from four to 17 days after birth for the eight partial Biotinidase deficiency cases.

MS/MS DISORDERS

All four medically treated PKU cases were treated in the first week of life.

Four of the nine infants identified with an organic acid disorder started treatment within the first week of life, the other five cases began treatment in the second week of life.

All 12 infants with fatty acid oxidation disorders were treated within the first week of life.

ENDOCRIN DISORDERS

The salt-wasting form of CAH is life-threatening in the first few weeks of life. The one infant identified with salt-wasting CAH was treated on the eighth day of life.

The target for CH is treatment by 14 days of life for newborns with initial TSH values greater than 50 (i.e., strong positives). Of the 61 CH cases with a strong positive screen, 49 (80.3%) were treated by the 14th day of life.

Table 16: Time to Treatment of Amino Acid Disorders, Organic Acid, Fatty Acid Oxidation, and Endocrine Disorders, Michigan, 2019

Disorder		Total	Treatment Time (days from birth)			Treatment Time Range (days)
			N			
		N	1-7	8-14	>14	
Galactosemia	Classic (GG)	5	5			2-4
Biotinidase Deficiency	Partial	8	5	0	3	4-17
Amino Acid Disorders	PKU-medically treated	4	4			4-5
	ASA	1	1			4
	HCY	1	0	1		12
	Total	6	5	1		4-12
Organic Acid Disorders	3MCC	1	0	1		13
	PA/MMA	6	3	3		2-12
	GA1	1	1			4
	IVA	1	0	1		12
	Total	9	4	5		2-13
Fatty Acid Oxidation Disorders	MCAD	8	8			2-4
	VLCAD	1	1			4
	CUD	2	2			4-7
	CPT II	1	1			4
	Total	12	12			2-7
Endocrine Disorders	CH– Strong[1]	61	32	17	11	4-42
	CH– Borderline	65	6	16	44	5-97
	CAH– Salt Wasting	1	0	1		8
Total		167	67	36	50	2-97

Notes: Disorders that do not require treatment are excluded from the table. Time to treatment categories for CH are based on the results of the first screen. Infants who screened borderline or inconclusive on their first screened required a repeat screen before referral to medical management.
[1]One infant who had an initial CH-strong screen and confirmed with CH was missing a treatment start date.

HEMOGLOBINOPATHIES

Table 17 reports the time to treatment among newborns with hemoglobinopathies. The target is to initiate penicillin prophylaxis by four months of life (120 days). Of the 62 cases with a known penicillin initiation date, 87.1% were treated with penicillin within the first four months, 9.7% began treatment between four and five months of life and 3.2% began treatment after five months of life.

Table 17: Time to Penicillin Initiation for Sickle Cell Disorders, Michigan, 2019

Disorder	Penicillin Prophylaxis Initiation Time		
	< 120 days	**120-149 days**	**> 150 days**
Sickle Cell Disorders*	54 (87.1)	6 (9.7%)	2 (3.2%)

*Three cases were missing a penicillin initiation date.

V. Conclusions

NBS is a critical public health program that protects the lives of our state's newest residents. The NBS Laboratory screened 106,126 infants born in 2019, and the NBS Follow-up Program tracked approximately 6,500 strong and borderline positive, isolated elevation, unsatisfactory, early, and transfused specimens; newborns with strong positive screening results were immediately referred to the appropriate NBS follow-up coordinating center for evaluation. A total of 285 newborns were identified with a disorder by NBS in 2019, as well as 3,197 carriers. Since blood spot screening began in Michigan in 1965, 7,093 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.