Michigan Department of
Community Health

MICHIGAN NEWBORN SCREENING PROGRAM

Annual Report 2011

Michigan Department of Community Health

MDCH

Rick Snyder, Governor
James K. Haveman, Director

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Acknowledgements

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Executive Summary

The Newborn Screening (NBS) annual report provides an overview of the Michigan NBS Program, target outcomes, screening performance metrics, and quality assurance information.

Since the program began in 1965 with screening for phenylketonuria, over 50 disorders have been added to the screening panel. Through 2011, over 3.5 million infants have been screened with 4,907 diagnosed with diseases included in the NBS panel.

Of the 112,499 infants screened in 2011, the vast majority were Michigan residents and 217 (0.2%) were diagnosed with a disease. Overall, one infant out of 526 screened was diagnosed with one of the 53 disorders included in the NBS panel (see Table 1 for list of disorders).

Developments occurring in 2011:

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 following meetings:
  - ◊ National Immunization Conference (Washington, D.C.)
  - ◊ Florida Partnership for Access to Sickle Cell Services (Hollywood, FL)
  - ◊ CSTE Annual Conference (Pittsburgh, PA)
  - ◊ Michigan Epidemiology Conference (Ann Arbor, MI)
  - ◊ North American Cystic Fibrosis Conference (Anaheim, CA)
  - ◊ Maternal and Child Health Epidemiology Conference (New Orleans, LA)
  - ◊ Newborn Screening and Genetic Testing Symposium (San Diego, CA)

- Variation in Immunoreactive Trypsinogen Concentrations among Michigan Newborns and Implications for Cystic Fibrosis Newborn Screening was published in *Pediatric Pulmonology*.

- Predictors of Insufficient Sweat Production during Confirmatory Testing for Cystic Fibrosis was published in *Pediatric Pulmonology*.

- Clinical validation of cutoff target ranges in newborn screening of metabolic disorders by tandem mass spectrometry: a worldwide collaborative project was published in *Genetics in Medicine*.

MDCH continued to promote NBS Follow-up:

- The NBS Follow-up Program held the third Family Recognition Day on September 24, 2011. Approximately 115 people attended the event at the Frederik Meijer Gardens and Sculpture Park in Grand Rapids.

New capacity was added for NBS:

- The Centers for Disease Control and Preventions awarded Michigan a grant to develop screening for severe combined immunodeficiency disorders (SCID). The aims of the grant are to:
    - ◊ Provide screening for SCID and related disorders for Michigan newborns using T-cell receptor excision circle analysis and optimize testing methodology
    - ◊ Expand the number of laboratory staff with expertise in SCID screening and other molecular screening methods
    - ◊ Provide the necessary training for the public health community about SCID screening
    - ◊ Work cooperatively with the Newborn Screening community to share appropriate data, methods, and protocols with CDC, HRSA, and other interested partners

- The NBS laboratory began screening all Michigan newborns for SCID on October 1, 2011.

Improvements were made to existing processes and procedures:

- A new biotinidase assay was implemented in August 2011. The new assay resulted in significant improvements in the screening performance metrics.

- The percent of specimens deemed "unsatisfactory" increased in 2011. A committee of NBS laboratory and follow-up staff has been created to devise quality improvement strategies to reduce the number of unsatisfactory specimens.

- A new tandem mass spectrometry assay was implemented in January 2011. The new non derivatized assay measures succinylacetone which is the primary marker for Tyrosinemia Type I.

Development and promotion of BioTrust for Health continued:

- The BioTrust for Health consent process was implemented statewide on October 1, 2010. In 2011, approximately 93% of births had a consent form returned. Of the returned forms, 64% had parent consent granted, allowing use of residual dried blood spots in health research.

- The BioTrust for Health Scientific Advisory Board reviewed and approved 4 scientific studies.

- MDCH staff presented information on the BioTrust for Health at 16 community events, 8 college presentations, and 21 events for health professionals including grand rounds, invited presentations, and seminars.

Listing of Figures & Tables

Figures

Tables

Acronym Key

Acronym	Name
ACMG	American College of Medical Genetics
CDC	Centers for Disease Control and Prevention
CHM	Children's Hospital of Michigan
CHMMC	Children's Hospital of Michigan Metabolic Clinic
EBC	Electronic Birth Certificate
FIGLU	Formiminoglutamic acid disorder
FPR	False Positive Rate
HPLC	High Performance Liquid Chromatography
HRSA	Health Resources and Services Administration
MCIR	Michigan Care Improvement Registry
MDCH	Michigan Department of Community Health
MS/MS	Tandem Mass Spectrometry
NBS	Newborn Screening
NICU	Neonatal Intensive Care Unit
PCP	Primary Care Physician
PID	Primary Immunodeficiency Disorders
PPV	Positive Predictive Value
QA	Quality Assurance
QAAC	Quality Assurance Advisory Committee
SCDAA	Sickle Cell Disease Association of America
SCID	Severe Combined Immunodeficiency Disorder
U of M	University of Michigan

I. Introduction

The Newborn Screening (NBS) Annual Report provides an overview of Michigan's NBS Program, target outcomes, screening performance metrics related to disorders included in the NBS panel, and quality assurance information. This report also includes a chapter providing in-depth information on severe combined immunodeficiency disorder (SCID) screening in Michigan (Chapter IV). This chapter contains a brief history and description of SCID, as well as results from the first 3 months of screening in Michigan. This report does not include appendices which have not changed, including the NBS research guidelines, supportive legislation, and NBS advisory committees.[1]

In sum, this report is intended to provide:

- An introduction and historical account of the development of NBS in Michigan
- Michigan screening outcomes
- A detailed account of SCID screening
- Quality assurance information

What is Newborn Screening?

NBS is the process of early identification of health conditions followed by their subsequent timely 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, mental retardation, 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. 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).[2] 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

[1]All of these appendices can be found in previous annual reports, which are available at www.michigan.gov/newbornscreening.
[2]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.

expansion of screening with the addition of three disorders: biotinidase deficiency, maple syrup urine disease (MSUD), and hemoglobinopathies such as sickle cell disease. The Act also designated the state laboratory as the sole testing site and mandated a fee to fund the program to be able to add comprehensive programs for follow-up and medical management. In 1993, 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 detectable from a single blood spot. The first 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).

In 2005, a pilot project was initiated to expand the screening panel to 48 disorders by including the 29 additional MS/MS disorders recommended by the American College of Medical Genetics (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 SCID began on October 1, 2011.

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. Screening for all of these un-detected disorders, except for Citrullinemia Type II and Tyrosinemia Type II and III, began in 2005, so nearly 840,000 infants have been screened for the disorders through 2011, and no cases have been detected. Screening for Citrullinemia Type II began in 2004, meaning approximately 965,000 infants have been screened, and no cases have been identified. Detailed information about the disorders included in the screening panel, confirmation of diagnoses, and follow-up of positive tests can be found in the NBS Procedure Manual available here: www.michigan.gov/newbornscreening.

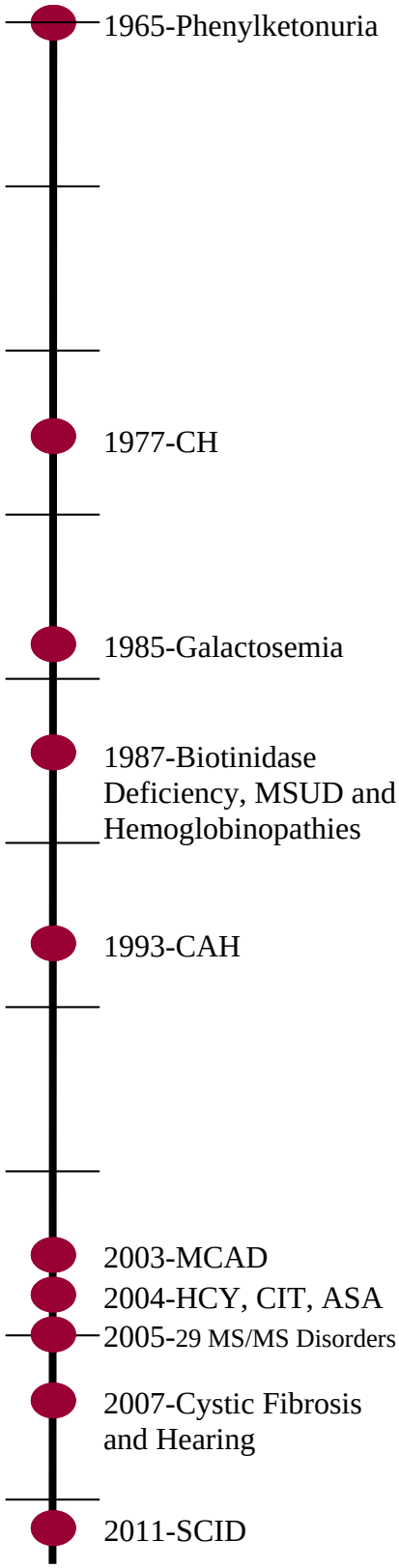

Figure 1. Addition of Disorders to the NBS Panel, Michigan, 1965-2011

[1]More information about the newborn hearing screening program can be found at www.michigan.gov/ehdi.

Table 1. Disorders included in the Newborn Screening Panel, Michigan, 2011

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

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: #2-4, #5-6, #8-11, #13/#14, #15/#17, #21/#26, #29/#36, #41/ #37-39, #25/#35, #30-32/#40, #28/#33, #24/#34.

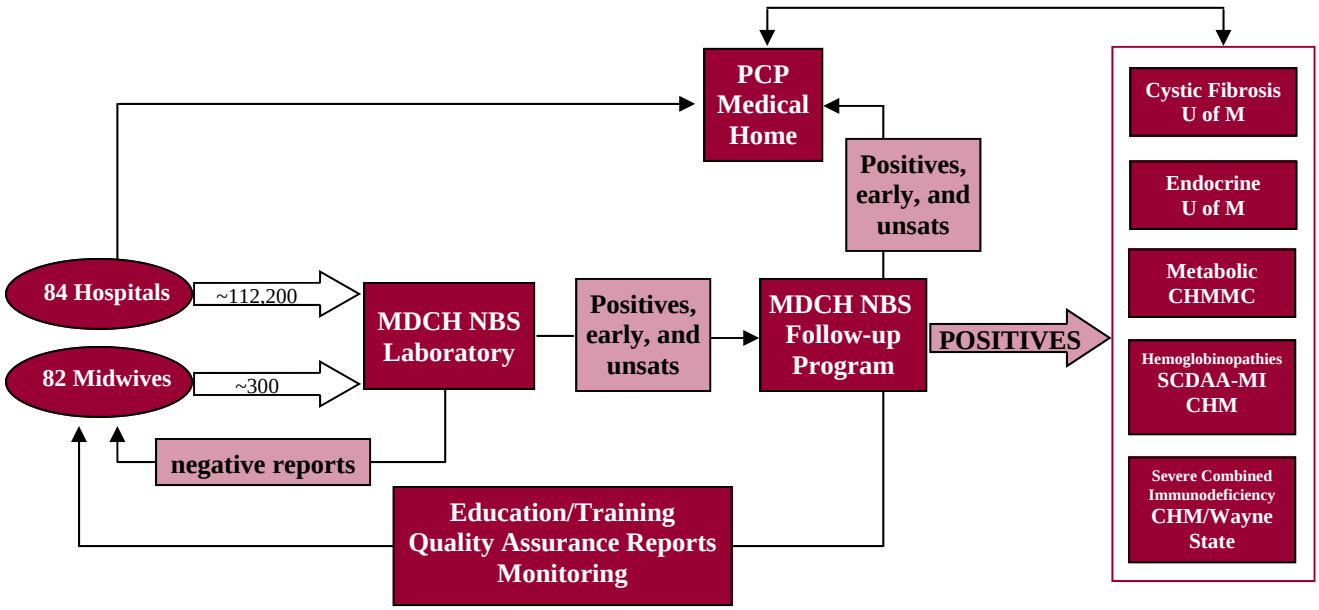

Figure 2. Overview of the Michigan Newborn Screening Program, 2011

Abbreviations: MDCH-Michigan Department of Community Health; NBS-Newborn Screening; PCP-Primary Care Provider; U of M-University of Michigan; CHMMC-Children's Hospital of Michigan Metabolic Clinic; SCDAA-MI-Sickle Cell Disease Association of America-Michigan Chapter; CHM-Children's Hospital of Michigan

HOSPITALS

In 2011, Michigan had 84 hospitals with newborn nurseries. 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 Follow-up Program coordinator or nurse consultant to evaluate the screening process and make recommendations for improvement.

MIDWIVES AND HOME BIRTH ATTENDANTS

There are 82 midwives registered with the NBS Program. Midwives are provided with individual assistance in meeting standards. Although the number of midwife deliveries is small, they often occur in the Amish and Mennonite populations, which have a higher incidence of several disorders included in the NBS panel.

MICHIGAN DEPARTMENT OF COMMUNITY HEALTH

The MDCH NBS Program includes the NBS Laboratory, the Follow-up Program, and five medical management centers. More detailed descriptions of each entity are included in previous reports available on the NBS website (www.michigan.gov/newbornscreening) or by clicking here.

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

We used vital statistics data collected by the Vital Records & Health Data Development Section within the Division for Vital Records and Health Statistics at MDCH to determine the total number of live births statewide eligible for screening. The number of live births in 2011 (n=113,100) is a preliminary estimate as the final files have not been released yet.

TOTAL NUMBER OF NEWBORNS DIAGNOSED BY NEWBORN SCREENING

We used the MDCH laboratory information system (PerkinElmer Life Sciences, Inc.) to identify positive cases. We also used data collected at the medical management centers and managed by the NBS Follow-up Program 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 both Michigan residents and for out-of-state residents screened in Michigan. This report focuses on cases and screening results among Michigan residents. Our reason for focusing on Michigan residents is because out-of-state infants born within the state are followed-up and diagnosed elsewhere.

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.

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 (%)

QUALITY ASSURANCE INDICATORS

Quality assurance (QA) data were obtained from NBS cards and information recorded by the state NBS laboratory and medical management centers. QA indicators included on the hospital quarterly reports prepared by the NBS Follow-up Program include: a) time from birth to specimen collection, b) time from specimen collection to arrival at the state NBS laboratory, c) number of specimens that are unsatisfactory, d) number of envelopes containing specimens with a collection date range of more than two days (i.e., batched envelopes), e) number of birth certificates with NBS kit number recorded, f) number of screened births with BioTrust consent form returned, g) number of non-blank BioTrust consent forms returned out of all returned forms, and h) time from birth to treatment, by disorder. 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 newborns born in 2011 in terms of race, birth weight, gestational age, and birth place (hospital regular nursery, NICU, 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 African Americans, so the number of cases will fluctuate with the birth rate of African Americans.

The Michigan NBS Program screened 99.6% of the live births occurring in Michigan in 2011, 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 113,100 live births that occurred in 2011, 483 were listed as deceased on the 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 112,617 remaining live births, the linkage algorithm successfully matched newborn screens for 111,687 infants (99.2%). The 970 unmatched records were sent to NBS Follow-up Program technicians for further investigation. This more in-depth follow-up revealed that 490 (50.5%) 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, 480 infants (0.4%) born in the state were not screened. Infants may not have been screened due to parental refusal of screening (n=109), transfer out of state (n=28), infant expired (n=5), or missed screened (n=338). For all infants who were missed, the NBS Follow-up technicians either contact the nurse coordinator for hospital births or send a parental notification letter for home births. In 2011, 42 infants born in hospitals are known to have been missed by NBS, and hospitals were contacted. Of the 42, 21 have been screened to date and the remaining 21 are pending.

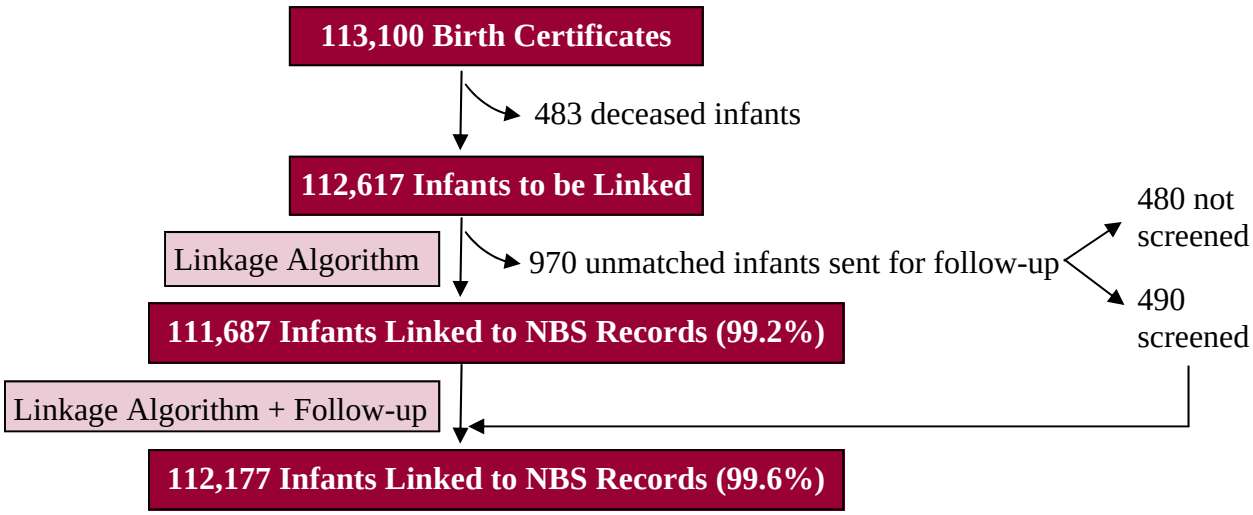

Figure 3. Newborn Screening and Live Births Records Linkage, Michigan, 2011

In total, newborn screens were received for 112,499 infants born in 2011. Of those, 322 (0.3% of screens) belonged to out-of-state residents. Tables 3 and 4 report the demographic and perinatal characteristics by race of in-state and out-of-state residents screened in 2011, respectively. 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% of in-state infants screened were admitted to the NICU, 8% were low birth weight (<2,500 grams), and 10% were born preterm (<37 weeks gestational age). African Americans were over-represented among NICU, preterm, and low birth weight births.

Table 3: Demographics of Infants Screened by Race, Michigan, 2011, Excluding Out-of-State Residents, N=112,177

Race	Column Total		Nursery Type						Birth Weight (g)		Gestational Age (wks)	
			Regular Hospital		NICU		Non-Hospital		<2500		<37	
	N	%	N	%	N	%	N	%	N	%	N	%
White	71,331	63.6	63,806	89.5	6,855	9.6	670	0.9	4,576	6.5	5,915	8.6
Black	20,379	18.2	16,781	82.3	3,591	17.6	7	0.1	2,746	13.6	2,626	13.6
American Indian	407	0.4	368	90.4	38	9.3	*		27	6.7	32	8.1
Asian/Pac Islander	2,465	2.2	2,250	91.3	212	8.6	*		190	7.8	179	7.5
Middle Eastern	3,088	2.8	2,829	91.6	258	8.4	*		235	7.7	226	7.6
Multi-Racial	5,254	4.7	4,703	89.5	514	9.8	37	0.7	431	8.3	482	9.5
Missing	9,253	8.3	8,382	90.6	847	9.2	24	0.3	671	7.5	782	9.2
Column Total:	112,177	100	99,119	88.4	12,315	11.0	743	0.7	8,876	8.1	10,242	9.5

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 1,911 and 4,782 newborns were missing birth weight and gestational age on the card, respectively. Non-hospital nurseries include home births, births that occurred at birthing centers, and all other births that did not occur at a hospital.
**Data suppressed when fewer than 6 events occur*

SCREENING OUTCOME INFORMATION

In the following sub-sections, outcome information is provided for the disorders screened for in 2011. The total numbers of cases detected both in and through 2011 are presented along with screening performance metrics. The disorders are organized into five categories: metabolic, endocrine, cystic fibrosis, hemoglobinopathies, and severe combined immunodeficiency, corresponding to the five medical management programs responsible for diagnosis and treatment.

CUMULATIVE DETECTION RATE

Table 4 reports the cumulative detection rate of disorders identified via NBS by classification both in and through 2011. 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, Michigan Newborn Residents, 1965-2011

Type of Disorder Classification (Year Screening Began)	Cases in 2011 (N)	Cases Through 2011 (N)	Cumulative Detection Rate
Galactosemia (1985)	0	170	1:21,140
Biotinidase Deficiencies (1987)	11	207	1:16,030
Amino Acid Disorders (1965)	15	667	1:9,824
Organic Acid Disorders (2005)	6	49	1:17,117
Fatty Acid Oxidation Disorders (2003)	25	139	1:7,909
Congenital Hypothyroidism (1977)	78	1,798	1:1,846
Congenital Adrenal Hyperplasia (1993)	8	124	1:19,706
Hemoglobinopathies (1987)	61	1,626	1:2,041
Cystic Fibrosis (October 2007)	13	127	1:3,862
Total	217	4,907	-

Notes: Denominators, the number of live births eligible to have been screened, are calculated from the year screening began onward; thus, if screening commenced other than at the start of the year the denominator will be slightly larger than the true denominator. The CF detection rate denominator includes births from October 2007-2011. See Table 1 for a list of all disorders included in each disorder classification.

As indicated in Table 4 and Figure 4, CH and hemoglobinopathies were the most prevalent disorders in 2011, while organic acid disorders and galactosemia were the least prevalent. CF accounted for 6% of cases detected in 2011 and 3% of cases detected cumulatively. The cumulative percentage of CF cases is low compared to the 2011 percentage because screening began recently (October 2007) relative to the other disorders. Disorders detected by MS/MS (amino acid, organic acid, and fatty acid oxidation disorders) accounted for 21% of cases in 2011 and 17% 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 is an underestimate because MCAD screening began in 2003, while other conditions were not screened until 2005. This means that births included in the denominator from 2003-2005 were not eligible for being diagnosed with fatty acid oxidation disorders other than MCAD leading to an artificially low cumulative detection rate. The MS/MS detection rate does not include thirteen cases of formiminoglutamic acid disorder (FIGLU) detected because the disorder is not included in the NBS panel. Galactosemia, including Duarte compound heterozygotes, accounted for 0% of all disorders detected in 2011 and 4% cumulatively. Biotinidase deficiency, including partial biotinidase deficiency, accounted for 5% of all cases detected in 2011 and 4% of all cases detected cumulatively. CAH accounted for 4% all of cases in 2011 and 3% of all cases detected cumulatively.

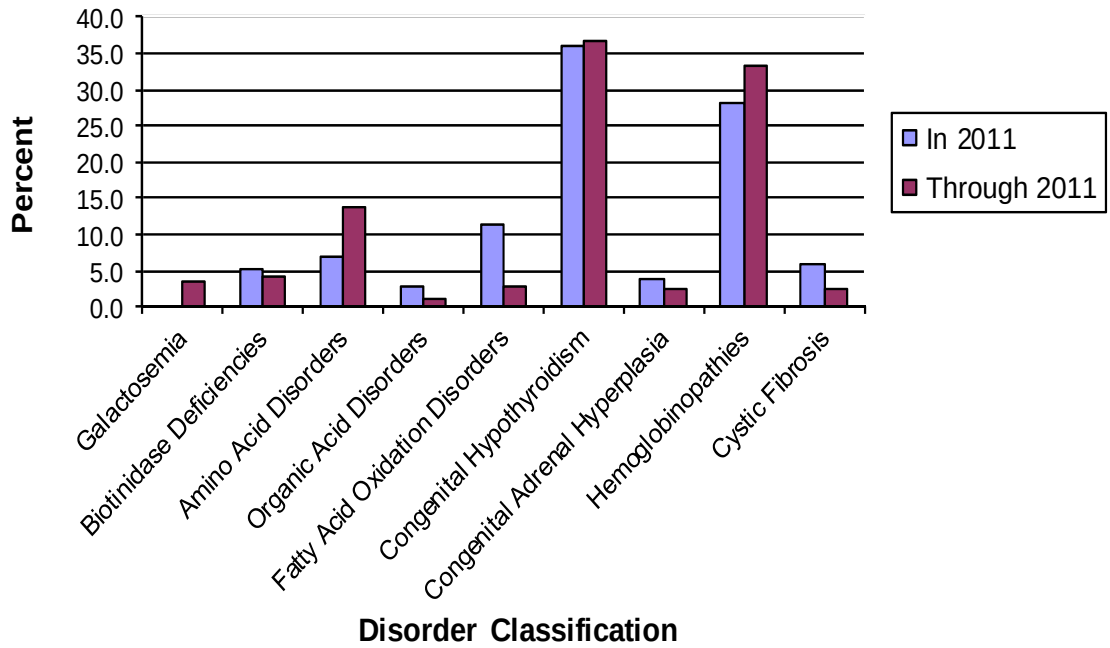

Figure 4. Percent Distribution of Disorders Identified in Newborns via Newborn Screening, Michigan Residents, in 2011 and through 2011

SCREENING PERFORMANCE METRICS

Screening performance metric targets are available in previous reports. Screening performance metrics include the detection rate, false positive rate, and positive predictive value. Table 5 reports screening performance metrics for all disorders in 2011. Performance metrics for individual MS/MS disorders are provided in separate tables (see Tables 7-9).

GALACTOSEMIA, BIOTINIDASE DEFICIENCY & CYSTIC FIBROSIS

No cases of either classic or Duarte D/G variant galactosemia were detected in 2011, resulting in a FPR of 0.003%.

The biotinidase deficiency detection rate (including partial biotinidase deficiency) was 1:10,198; the FPR and PPV were 0.1% and 7%, respectively. Of the eleven cases detected, 10 were partial and 1 was profound. A new assay was implemented in August 2011, which significantly improved screening performance. The FPR rate decreased from 0.2% to 0.01% and the PPV increased from 4% to 46%.

Thirteen cases of cystic fibrosis (CF) were detected in 2011 (detection rate-1:8,629); the associated FPR and PPV were 0.3% and 4%, respectively. Additionally, eight cases of CFTR-related metabolic syndrome were also detected. Chapter IV of the 2008 Annual Report provides more detailed information about CF screening in Michigan.

ENDOCRINE DISORDERS-CH AND CAH

The CH screening FPR was 1%, and the PPV was 8%. The overall detection rate for CH was 1:1,438. Twins who each screened positive for CH had a mother with Graves Disease. Chapter IV of the 2007 Annual Report provides more detailed information about CH screening in Michigan.

The CAH screening FPR was 0.1%, and the PPV was 6%. The overall detection rate for CAH was 1:14,022. Seven of the eight cases detected were salt-wasting.

HEMOGLOBINOPATHIES

Additional hemoglobinopathy screening outcome information is reported in Table 6. Hemoglobinopathy screening differs from screening for the other disorders because the purpose is to identify the presence or absence of abnormal hemoglobins 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, hemoglobinopathies are quite common among African Americans, who accounted for 92% of the cases in 2011. While the overall incidence of hemoglobinopathies is approximately one case per 1,839 screened, the incidence in African Americans is one in 364 screened in Michigan.

Table 5: Screening Results and Performance Metrics, Michigan, 2011

Disorder Type	Total N	Total + N (% NICU)	Confirmed + N	Positive Detection Rate	FPR %	PPV %
Galactosemia	112,177	3 (33.3)			0.003	-
Classic (GG)			0	-		
Duarte (DG)			0	-		
Total			*0*	-		
Biotinidase Deficiency		167 (43.7)			0.14	6.59
Profound			1	1:112,177		
Partial			10	1:11,218		
Total			*11*	*1:10,198*		
Cystic Fibrosis*		300 (18.3)	13	1:8,629	0.26	4.33
Congenital Hypothyroidism		1,030 (28.3)	78	1:1,438	0.85	7.57
Congenital Adrenal Hyperplasias		125 (89.6)			0.10	6.40
Salt wasting			7	1:16,025		
Non-Salt wasting			1	1:112,177		
Total			*8*	*1:14,022*		
Hemoglobinopathies		73 (17.8)	58	1:1,934	0.01	79.45
Amino Acid		46 (15.2)	15	1:7,478	0.03	32.61
Organic Acid		46 (8.7)	6	1:18,696	0.04	13.04
Fatty Acid Oxidation		91 (23.1)	25	1:4,487	0.06	27.47
*MS/MS Disorders Total***		*165 (15.2)*	*46*	*1:2,439*	*0.11*	*27.88*

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).
**Excludes 96 children with high immunoreactive trypsinogen levels, but no DNA mutations*
***SCAD and IBG are screened using the same analyte. Thus, the 18 infants with elevated levels of that analyte are included in the both the organic acid and fatty acid oxidation total positive screens, but counted only once for the MS/MS Disorders total.*

Table 6: Hemoglobinopathy Screening Performance Metrics, Michigan, 2011

Disorder	Newborns (N)	Confirmed + (N)		Positive Detection Rate	
		Total	Among Blacks	Total	Among Blacks
Sickle Cell Anemia	112,177	33	29	1:3,399	1:704
SC Disease		20	19	1:5,609	1:1,074
Sickle β thalassemia		8	8	1:14,022	1:2,551
Total		*61*	*56*	*1:1,839*	*1:364*

Notes: Out of the number of Michigan resident infants screened, total N=112,177, among Blacks N=20,409

MS/MS DISORDERS

The overall FPR for MS/MS disorders was 0.1%. The PPV was 28%, and the detection rate was 1:2,439.

SCREENING PERFORMANCE METRICS-INDIVIDUAL MS/MS DISORDERS

AMINO ACID DISORDERS

Fifteen newborns 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 12,464 newborns screened. As indicated in the table, PKU screening had the highest PPV (64%) among amino acid disorders. Chapter IV of the 2009 Annual Report provides more detailed information about PKU screening in Michigan. Two cases of citrullinemia (CIT) and one case of Maple Syrup Urine Disease were confirmed in 2011. An additional case of CIT and two cases of Hypermethioninemia are probable and included in Table 7, but additional diagnostic confirmatory tests are still pending. One CIT carrier was detected following a positive screen.

ORGANIC ACID DISORDERS

Six newborns were identified with organic acid disorders (Table 8) by MS/MS. Two infants were diagnosed with methylmalonic acidemia (MMA); one infant was diagnosed with 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC); two were diagnosed with 2-Methylbutyryl-CoA dehydrogenase deficiency (2MBG); one was diagnosed with isobutyryl-CoA dehydrogenase deficiency (IVA). The disorders 2MBG and IVA are screened using the same analyte, and their pooled PPV is 67%, the highest of the organic acid disorders. One infant screened positive for PA/MMA, but confirmed with 2MBG following second tier testing. For this report, that positive screen was counted as positive for 2MBG instead of PA/MMA. Of note, in 2011, two maternal cases of 3MCC and three maternal cases of Vitamin B12 Deficiency were detected following their infant's positive screens for 3MCC and PA/MMA, respectively.

FATTY ACID OXIDATION DISORDERS

Twenty-five children were identified with fatty acid oxidation disorders (Table 9); ten medium-chain acyl-CoA dehydrogenase deficiency (MCAD), thirteen short-chain acyl-CoA dehydrogenase deficiency (SCAD), one very long-chain acyl-CoA dehydrogenase deficiency, and one glutaric acidemia type II. Of the disorders detected, MCAD and SCAD had the highest PPV (83% and 72%, respectively). One MCAD carrier was detected following a positive screen.

Table 7: Amino Acid Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2011

Disorder	Newborns N	Total + N	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Phenylketonuria	112,177	14			0.004	64.3
Classic (PKU)			1	1:112,177		
Mild			1	1:112,177		
Benign Hyperphenyl-alaninemia (H-PHE)			7	1:16,025		
Biopterin Cofactor Defects (BIOPT)			0	-		
Total			*9*	*1:12,464*		
Citrullinemia (CIT)/CIT II/ASA		8	3	1:37,392	0.004	37.5
Tyrosinemia I (TYR I)*		1	0	-	0.001	-
Tyrosinemia II-III (TYR II-III)*		11	0	-	0.010	-
Tyrosinemia I-III (TYR I-III)*		1	0	-	0.001	-
Homocystinuria (HCY)/ Hypermethioninemia (MET)		7	2	1:56,089	0.004	28.6
Maple Syrup Disease (MSUD)		4	1	1:112,177	0.003	25.0

*In January 2011, the same analyte was used to detect TYR I-III. After January 2011, a new assay was implemented which allowed for detection of TYR I, separate from TYR II and TYR III.

Notes: Two cases of MET and one case of CIT listed as confirmed positive are probable, but confirmatory diagnostic tests are pending. An additional HCY/MET positive case is still pending.

Table 8: Organic Acid Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2011

Disorder	Newborns N	Total + N	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Isovaleric Acidemia (IVA)/2-Methylbutyryl-CoA Dehydrogenase Deficiency (2MBG)	112,177	3	2	1:56,089	0.001	66.7
3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)		8	1	1:112,177	0.006	12.5
Glutaric Acidemia Type I (GA I)		1	0	-	0.001	-
Propionic Acidemia (PA)/ Methylmalonic Acidemia (MMA)		15	2	1:56,089	0.012	13.3
Multiple carboxylase deficiency (MCD)		1	0	-	0.001	-
Isobutyryl-CoA Dehydrogenase Deficiency (IBG)		18	1	1:112,177	0.015	5.6

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). IBG and SCAD are screened using the same analyte. Thus, the FPR is slightly elevated and the PPV is slightly reduced for IBG since infants confirming with SCAD are considered false positives.

Table 9: Fatty Acid Oxidation Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2011

Disorder	Newborns N	Total + N	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Carnitine Uptake Defect (CUD)	112,177	51	0	-	0.045	-
Short-Chain Acyl-CoA Dehydrogenase deficiency (SCAD)		18	13	1:8,629	0.004	72.2
Carnitine/Acylcarnitine Translocase Deficiency-(CACT)/Carnitine Palmitoyltransferase II Deficiency (CPT II)		1	0	-	0.001	-
Glutaric Acidemia Type II (GA II)		4	1	1:112,177	0.003	25.0
Medium-chain Acyl-CoA Dehydrogenase Deficiency (MCAD)		12	10	1:11,218	0.002	83.3
Very Long-chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)		2	1	1:112,177	0.001	50.0
Long-chain L-3-hydroxy Acyl-CoA Dehydrogenase Deficiency (LCHAD)		3	0	-	0.003	-

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). IBG and SCAD are screened using the same analyte. Thus, the FPR is slightly elevated and the PPV is slightly reduced for SCAD since infants confirming with IBG are 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 10 because their performance metrics have been previously reported. Disorders not detected in 2011 and detected disorders with no borderline positive screens are also excluded from Table 10, 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 10.

Table 10: Screening Performance Metrics (FPR and PPV) among Strong Positive Screens compared to All Positive Screens, Michigan, 2011

Disorder Type	Among All +		Among Strong +	
	FPR	PPV	FPR	PPV
	%	%	%	%
Galactosemia	0.003	-	0.002	-
Biotinidase Deficiency	0.14	6.59	0.007	11.11
Congenital Hypothyroidism (CH)	0.85	7.57	0.128	24.21
Congenital Adrenal Hyperplasia (CAH)	0.10	6.40	0.025	20.00
Phenylketonuria (PKU)	0.004	64.29	0.0	100.0
Homocystinuria (HCY)/ Hypermethio-ninemia (MET)	0.004	28.57	0.004	20.00
Propionic Acidemia (PA) / Methylmalonic Acidemia (MMA)	0.01	13.33	0.010	15.38
3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)	0.001	12.50	0.002	33.33
Very Long-Chain Acyl-CoA Dehydro-genase Deficiency (VLCAD)	0.001	50.00	0.0	100.0
Glutaric Acidemia Type II (GA II)	0.003	25.00	0.002	33.33
Isovaleric Acidemia (IVA)/2-Methylbutyryl-CoA Dehydrogenase De-ficiency (2MBG)	0.001	66.67	0.001	50.0
Maple Syrup Urine Disease (MSUD)	0.003	25.00	0.0	100.0
Tyrosinemia (TYR I)	0.01	-	0.001	-
Cystic Fibrosis (CF)	0.26	4.33	0.004	70.59

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

The FPR for biotinidase is reduced nearly 20-fold, and the PPV is increased approximately 2-fold among strong positive screens relative to all positive screens.

The FPR for CH is reduced nearly 7-fold for strong positive screens, and the PPV is increased approximately 3-fold. The FPR and PPV for CAH are decreased and increased by 4-fold and 3-fold, respectively, among strong positives.

Among MS/MS disorders, all six strong positives for PKU, the one strong positive for VLCAD, and the one strong positive for MSUD were confirmed with disease, meaning the PPV among strong positives was 100% and the FPR was 0%. Since nearly all positive screens for HCY, PA/MMA, GAII, and IVA were strong positives, the FPR and PPV improved only slightly among strong positive screens.

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 57-fold and the PPV increased from 4% to 71% when excluding children with a heterozygote DNA mutation.

In sum, 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 AND MATERNAL 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 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 2011, a total of 3,078 infants were identified as carriers of a disease included in the NBS panel, following an abnormal screen (Table 11). The majority of these infants (n=2,817) had sickle cell

Table 11: Carriers Identified from Newborn Screening, Michigan, 2011

Disorder	N
Citrullinemia	1
Cystic fibrosis	259
Medium-chain Acyl-CoA Dehydrogenase Deficiency (MCAD)	1
Sickle Cell Trait	2,817

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.

trait. Over 250 infants (n=259) were cystic fibrosis carriers, one infant was a citrullinemia carrier, and one was identified as a MCAD carrier.

Besides the confirmatory diagnostic testing for infants, the 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.

In 2011, ten maternal disorders were identified following an infant's positive NBS (Table 12). Two infants with a strong positive screen for 3MCC were confirmed normal, but the disorder was identified in the mothers. Three mothers were confirmed with Vitamin B12 deficiency following their infant's positive screen for PA/MMA. Two mothers with Graves Disease had infants screen positive for congenital hypothyroidism. Following positive screens for CUD, two mothers were identified with CUD and one mother confirmed with GA I.

Table 12: Maternal Disorders Identified from Newborn Screening, Michigan, 2011

Maternal Disorder	N
3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)	2
Grave's Disease	2
Vitamin B12 Deficiency	3
Carnitine Uptake Defect (CUD)	2
Glutaric Acidemia Type I (GA I)	1

Notes: These maternal disorders were identified following or caused their infant's abnormal screen. Not all infants of women with disorders will have abnormal screens, so not all maternal disorders will be detected through newborn screening.

IV. Severe Combined Immunodeficiency Screening in Michigan

This section provides a detailed account of severe combined immunodeficiency disorder (SCID) including: 1) an overview of SCID, 2) the status of NBS for SCID in the United States, 3) the status of NBS for SCID in Michigan, and 4) a summary of the first three months of SCID screening in Michigan.

OVERVIEW OF SCID

SCID is a group of inherited disorders that are characterized by absent T and B-cell function. SCID subtypes are defined by the presence or absence of B-cells and NK-cells (Figure 5). While classic SCID cases have no T-cells, cases of variant SCID have T-cells present at reduced levels. People with classic SCID may experience recurrent, severe opportunistic infections, chronic diarrhea, and failure to thrive.

Treatment options for SCID include care to prevent infection, gene therapy, enzyme replacement, and hematopoietic stem cell transplant (HSCT). Minimizing time from birth to the HSCT is key since thymic output and T-cell reconstitution are significantly improved for those with early HSCT compared to those with late HSCT.[1] A study involving siblings found a 40% survival rate among children diagnosed with SCID at an average age of 4.5 months compared to a 90% survival rate among their siblings diagnosed at birth.[2] Another study with patients diagnosed before and after 3.5 months found that earlier diagnosis resulted in significant improvements in survival and decreased likelihood of health problems.[3]

The incidence of SCID is estimated at one case per 65,000-100,000 live births per year[4], meaning approximately 100 cases are born every year in the United States[5]. Without therapy, patients with SCID rarely survive to their first birthday and SCID has universal mortality by two years of life. Due to the extremely low likelihood of survival beyond infancy without treatment and the improved success seen with earlier treatment, NBS for SCID is vitally important.

1. Myers LA, Patel DD, Puck JM, Buckley RH. Hematopoietic stem cell transplantation for severe combined immunodeficiency in the neonatal period leads to superior thymic output and improved survival. Blood 2002;3:872-8.
2. Brown L, Xu-Bayford J, Allwood Z, Slatter M, Cant A, Davies EG, Veys P, Gennery AR, Gaspar HB. Neonatal diagnosis of severe combined immunodeficiency leads to significantly improved survival outcome: the case for newborn screening. Blood 2011;117:3243-6.
3. Railey MD, Lokhnygina Y, Buckley RH. Long-term clinical outcome of patients with severe combined immunodeficiency who received related donor bone marrow transplants without pre-transplant chemotherapy or post-transplant GVHD prophylaxis. J Pediatr 2009;155:834-40
4. Yee A, De Ravin SS, Elliott E, Ziegler JB. Severe combined immunodeficiency: A national surveillance study. Pediatr Allergy Immunol 2008;19:298–302.
5. Puck J. Population-Based Newborn Screening for Severe Combined Immunodeficiency: Steps Toward Implementation. Journal Allergy Clin Immunol 2007;120:760-8.

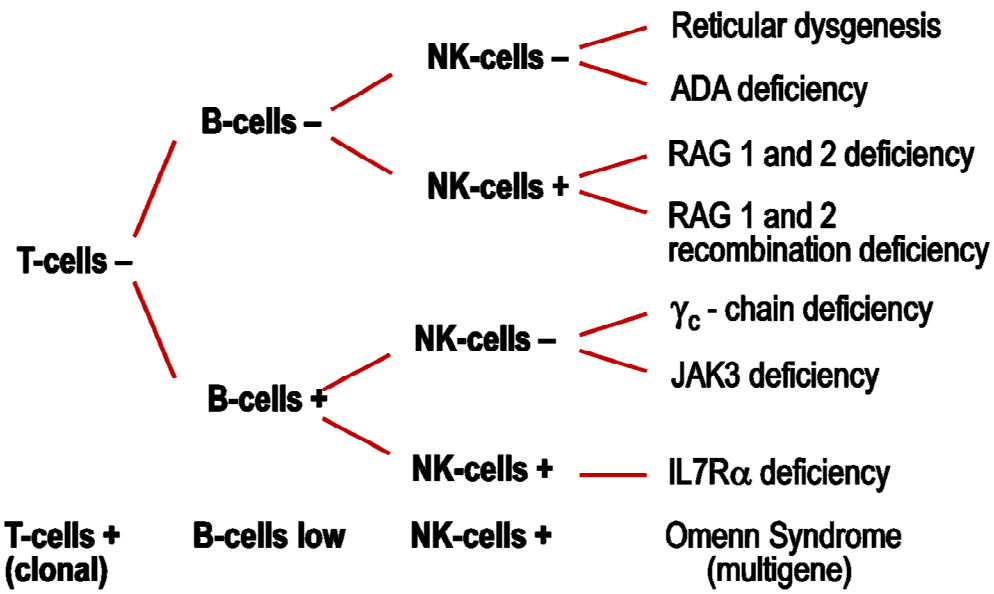

Figure 5. SCID Subtypes

HOW IS SCID IDENTIFIED THROUGH NBS?

T-cells are created from pluripotent hematopoietic stem cells in the bone marrow that migrate to the thymus to mature. Maturation of T-cells depends on several steps, including rearrangement of particular regions of the T-cells. During this rearrangement, T-cell receptor excision circles (TRECs) are generated. Since TRECs are created during T-cell maturation, no or low levels of TRECs in blood may indicated severe T-cell impairment and possible SCID.

Prior to NBS for SCID, Children's Hospital of Michigan (CHM) had seven SCID cases diagnosed in ten years and suspected that some children with SCID died before the disease was recognized and the cause of death was misclassified as pneumonia or sepsis. CHM staff reviewed records and found 285 cases of interest, which was defined as death before one year of age with an infectious cause occurring in the 10-year study period. MDCH NBS Program staff retrieved the NBS cards for the cases of interest. Some cards were damaged and excluded from future work, but the remaining cards had TREC analysis performed by University of California-San Francisco collaborators. A total of 45 cases had low TRECs. After DNA extraction from the cards, two cases had SCID confirmed with a third suspicious case that could not be confirmed. This pilot study demonstrated that blood from the NBS card could be used for a TREC assay.

Table 13: Screening Results from SCID Pilot*

State	Screened	Positive	SCID	SCID Variant	Non SCID
CA	358,000	46	5	6	3
LA	31,464	8	0	0	1
MA	161,707	28	1	0	14
NY	136,635	223	4	0	12
WI	243,707	50	4	0	7
PR	29,115	8	0	0	3
Navajo Nation	1297	1	0	0	0

*Obtained from: http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendations/correspondence/combinedimmunodeficiency.pdf. Positive defined as cases referred for medical management.

NBS FOR SCID IN THE UNITED STATES AND MICHIGAN

SCID was added to the recommended panel of NBS disorders by Kathleen Sebelius, Secretary of the United States Department of Health and Human Services (DHHS), in May 2010. Seven states, one territory, and the Navajo Nation participated in a NBS pilot for SCID and reported results to DHHS in May 2011 (Table 13).

When SCID was listed as under consideration for additional to the uniform NBS panel, the Michigan NBS Program formed an advisory committee for SCID. Three hospitals in the state had the clinical knowledge and expertise to perform HSCT. These three hospitals, CHM, University of Michigan Hospital, and Helen DeVos Children's Hospital, became the three referral centers. Additionally, CHM became the coordinating center for NBS for SCID. The chair of the advisory committee, along with others, presented on NBS for SCID at the 2010 NBS Quality Assurance Advisory Committee. The Quality Assurance Advisory Committee is the legislatively-appointed group that recommends adding disorder to Michigan's NBS panel and approves fee changes beyond those associated with changes in the Detroit consumer price index. The committee decided to increase the NBS fee by $7 and added SCID and other T-cell lymphocyte deficiencies to the panel effective October 1, 2011.

Using advice and algorithms from other states as a guide, Michigan created its own NBS method for SCID. The TREC assay is run at the NBS laboratory with β-actin as a control marker. If β-actin is low, then the result is "inconclusive", meaning the DNA failed to amplify. If the β-actin is normal, then the result depends on the TREC level. Samples with absent or low TRECs have screened positive for SCID. Samples with high TRECs are considered normal.

When a full-term infant has a positive screen for SCID, the baby's primary care provider is notified immediately. The nurse coordinator at the Primary Immune Deficiency clinic at CHM, the SCID medical management center, works with the family and provider to arrange for confirmatory testing at one of the three referral centers in Michigan. The confirmatory testing is flow cytometry that tests for B, T, and NK cell markers. When a low birth weight infant has a positive screen for SCID, a repeat NBS is drawn at 14 days (or 30 days for an extremely low birth weight infant).

FIRST THREE MONTHS OF SCREENING

Michigan's NBS Program began screening all newborns for SCID on October 1, 2011. In the first three months of screening, 70 infants had a positive screen. Of those infants, 64 (91%) were in the NICU. Twenty-seven children with a positive screen had normal flow cytometry results, 26 had normal results on a repeat NBS, 10 expired, and 7 infants were diagnosed with an immune deficiency other than SCID. Five children had secondary immune deficiencies following a thymectomy, one child had secondary transient T-cell lymphocyte deficiency secondary to chylothorax, and one child had T-cell related lymphocyte deficiency. No SCID cases were detected, resulting in a FPR of 0.26% and a PPV of 0% for SCID. However, the PPV of screening was 10% for detecting all immune deficiencies.

FUTURE DIRECTIONS

Based on the first three months of screening (n=27,159), Michigan appears to have a slightly higher FPR for SCID compared to the rates seen in the DHHS pilot for SCID. There are several possible reasons for the higher rate that the NBS Program will be exploring in the future. A conservative approach for the assay cutoffs was used in Michigan until more experience was obtained; thus, Michigan did not have a borderline category and all positives were referred for medical management. Since the overwhelming majority of infants who screen positive for SCID are in the NICU, rates of preterm birth and low birth weight babies will affect the FPR. For example, if Michigan has more preterm and low birth weight babies compared to other states screening for SCID, then the FPR rate may be higher in Michigan due to the increased likelihood of SCID false positive screens among those vulnerable populations. The collection method for

blood spots (sampling from indwelling catheters vs. heel stick) may affect the results, and the Michigan PID Quality Improvement Research Subcommittee plans to conduct an evaluation study to learn more. Modification of the SCID screening assay to reduce the interference of heparin from indwelling catheters is also under investigation. Finally, the algorithm will be carefully examined to determine whether it should be modified to reduce the number of false positives.

Acknowledgements: Thank you to Joan Ehrhardt, Dr. Elizabeth Secord, and the PID Quality Improvement Committee members for assisting with this chapter.

V. 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 14 reports specimen characteristics by nursery type where specimen was collected. Although 11% of infants were admitted to the NICU, 49% and 30% 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 (5.8%). Early and transfused specimens were more common among infants from the NICU, while late specimens, those collected after six days of life, were most common among non-hospital deliveries. The NBS Follow-up Program tracks all strong and borderline positive, isolated elevation, unsatisfactory, early, and transfused specimens; approximately 5,500 specimens required follow-up in 2011.

Table 14: Specimen Characteristics by Nursery Type, Michigan, 2011

Indicator	Type of Birth					
	Regular Nursery		NICU		Non-Hospital	
	N	%	N	%	N	%
Strong Positive Specimens	157	0.16	153	1.24	3	0.40
Borderline Positive Specimens	816	0.82	355	2.88	6	0.81
All Positive Specimens*	1,282	1.29	638	5.18	13	1.75
Isolated elevations of amino acids and acyl-carnitines	60	0.06	518	4.21	0	-
Unsatisfactory Specimens	1,362	1.37	413	3.35	43	5.79
Late (>6 days) Specimens	68	0.07	37	0.30	43	5.83
Early (<1 day) Specimens	323	0.33	752	6.12	8	1.08
Transfused Specimens	3	0.00	136	1.26	0	-
Specimens Missing Demographics **	9,790	9.88	1,014	8.23	66	8.88
Total Births Screened	99,119	88.4	12,315	11.0	743	0.7

**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 2011, the quarterly reports included seven indicators. Table 15 lists the indicators and the performance goal for each indicator.

Table 15: Indicators and Performance Goals for Newborn Screening, Michigan, 2011

Measure	Performance Goal
Late Screens	Less than 2% of screens collected greater than 36 hours after birth
Courier Time	Greater than 90% of screens arrive in state laboratory less than or equal to 4 days after collection
Unsatisfactory Screens	Less than 1% of screens are unsatisfactory
Batching	Less than 2% of envelopes are batched*
NBS Card Number	Greater than 95% of electronic birth certificates have the NBS card number recorded
Returned BioTrust for Health Consent Forms	At least 95% of specimens have a returned BioTrust for Health consent form
Non-blank BioTrust for Health Consent Forms	At least 90% of returned BioTrust for Health consent forms are not blank

*Batched envelopes are those containing specimens with a collection date range of more than 2 days.

Table 16 lists the statistics for each performance measure and whether the goal was met, by nursery type. For late screens, none of the three nursery types met the goal, but regular nurseries were closest to meeting the goal with just over 2.5% of screens being collected more than 36 hours after birth. Of note, nearly 60% 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. For courier time, both regular nurseries and NICUs met the goal, with over 98% of specimens received in the state laboratory within four days of collection. Non-hospital births did not meet the goal. None of nursery types met the goal for unsatisfactory specimens for 2011, with nearly 6% of non-hospital births having an unsatisfactory specimen. Both NICUs and non-hospital births met the batching goal, while regular nurseries did not. For recording of the NBS card number on birth certificates, neither regular nurseries nor non-hospital births met the goal. However, birth certificates coming from regular nurseries were approximately 9 times more likely to have the NBS kit number recorded than certificates coming from non-hospital births. Although none of the nursery types met either BioTrust for Health measure, regular nurseries were the closest; 94% of regular nursery births had a BioTrust for Health consent form returned and 83% of those returned forms had parental response recorded.

Table 16: Measures for Newborn Screening, by Nursery Type, Michigan, 2011

Measure	Nursery Type	N	%	Met Goal?
Late Screens	Regular	2,533	2.6	No
	NICU	635	5.2	No
	Non-hospital	436	59.1	No
Courier Time	Regular	98,043	99.1	Yes
	NICU	12,075	98.4	Yes
	Non-hospital	606	83.1	No
Unsatisfactory Screens	Regular	1,362	1.4	No
	NICU	413	3.4	No
	Non-hospital	43	5.8	No
Batching	Regular	537	2.4	No
	NICU	100	1.6	Yes
	Non-hospital	3	0.4	Yes
NBS Card Number	Regular	96,602	93.6	No
	NICU*	NA		
	Non-hospital	116	10.0	No
Returned BioTrust for Health Consent Forms	Regular	93,022	93.9	No
	NICU	10,359	84.1	No
	Non-hospital	587	79.0	No
Non-blank BioTrust for Health Consent Forms	Regular	77,078	82.9	No
	NICU	7,265	70.1	No
	Non-hospital	383	65.3	No

*Recording of NBS card number is not a performance measure for NICUs since the birth hospital is asked to draw the NBS card 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

target for other disorders varies.

TIME TO TREATMENT

Table 17 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 18). As indicated in Table 17, time to treatment ranged from 1 to 163 days after birth among all disorders. Limiting factors in the screening and diagnostic process for some disorders such as partial biotinidase deficiency and CH affect the ability to meet treatment targets. These disorders often require one or more retests before being referred for confirmatory diagnosis. For that reason, CH is presented separately by initial screening result (strong or borderline) in the table.

BIOTINIDASE DEFICIENCY

The sole case of profound biotinidase deficiency was treated on the fourth day of life. The majority (80%) of cases of partial biotinidase deficiency were treated in the second week of life; the remaining two cases were treated after the second week of life.

MS/MS DISORDERS

The majority of PKU cases were hyperphenylalaninemia which does not require treatment. The one classic PKU case was treated on the tenth day of life and the one mild PKU case on the fifth day. Both cases of CIT were treated in the first week of life. The MSUD case was positive for the first time on a repeat screen and was diagnosed with mild MSUD. Thus, the child was not treated until 33 days of life, but treatment was initiated within 7 days of the screen being received by the NBS laboratory.

Four of the 6 cases of organic acid disorders had treatment started before twelve days of life. The remaining two cases (one MMA and one 2MBG) were both treated on the fifteenth day of life. Both infants identified with 3MCC and IBG had treatment initiated within the first week of life.

Of the 25 infants with fatty acid oxidation disorders and a treatment start date, 24 were treated within the first week of life. The remaining MCAD case was treated on the sixteenth day of life, which was within one day of the screen being received by the NBS laboratory.

ENDOCRINE DISORDERS-CAH AND CH

The salt-wasting form of CAH is life-threatening in the first few weeks of life. All seven salt-wasting cases of CAH were treated within the first two weeks of life. One case of non salt-wasting CAH had treatment started on 124 days of life due to confusion over maternal issues causing the elevation vs. true disease.

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 CH cases with a strong positive screen, 38 (83%) were treated by the 14th day of life.

Table 17: Time to Treatment of Amino Acid Disorders, Organic Acid, Fatty Acid Oxidation, and Endocrine Disorders, Michigan, 2011

Disorder		Total	Treatment Time (days from birth) N			Treatment Time Range (days)
		N	1-7	8-14	>14	
Biotinidase Deficiency	Partial	10		8	2	11-23
	Profound	1	1			4
Amino Acid Disorders	PKU					
	Classic	1		1		10
	Mild	1	1			5
	CIT	2	2			2-6
	MSUD	1			1	33
	Total	*5*	*3*	*1*	*1*	*2-33*
Organic Acid Disorders	PA/MMA	2	1		1	3-15
	3MCC	1	1			4
	2MBG	2		1	1	12-15
	IBG	1	1			3
	Total	*6*	*3*	*1*	*2*	*3-15*
Fatty Acid Oxidation Disorders	SCAD	13	13			3-7
	MCAD	10	9		1	1-16
	VLCAD	1	1			4
	GAII	1	1			5
	Total	*25*	*24*		*1*	*3-16*
Endocrine Disorders	CH					
	Borderline	32		4	28	8-163
	Strong	46	24	14	8	1-47
	CAH					
	Salt-wasting	7	2	5	0	1-11
	Non salt-wasting	1			1	124

Notes: Disorders that do not require treatment are excluded from the table.

HEMOGLOBINOPATHIES

Table 18 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 57 cases having a penicillin start date reported, 84% were treated with penicillin within the first four months, 9% began treatment between four and five months of life, 5% began treatment between five and six months, and 2% began treatment beyond six months of age.

Table 18: Time to Penicillin Initiation for Sickle Cell Disorders, Michigan, 2011

Disorder	Penicillin Prophylaxis Initiation Time			
	< 120 days	**120-149 days**	**150-179 days**	**≥ 180 days**
Sickle Cell Disorders*	48 (84.2%)	5 (8.8%)	3 (5.3%)	1 (1.8%)

*4 cases missing penicillin initiation date

VI. Conclusions

NBS is a critical public health program protecting the lives of our State's newest residents. The NBS Laboratory screened 112,499 infants born in 2011, and the NBS Follow-up Program tracked approximately 5,500 strong and borderline positive, isolated elevation, unsatisfactory, early, and transfused specimens; newborns with strong positive screening results were immediately referred to the appropriate medical management center for evaluation. A total of 217 newborns were identified with a disorder by NBS in 2011. Since NBS began in Michigan in 1965, 4,907 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.