MICHIGAN DEPARTMENT OF
COMMUNITY HEALTH

MICHIGAN NEWBORN SCREENING PROGRAM

ANNUAL REPORT
2009

Michigan Department of Community Health

MDCH

Jennifer M. Granholm, Governor
Janet Olszewski, Director

Michigan Newborn Screening Program

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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 the screening for phenylketonuria, 49 additional disorders have been added to the screening panel, and millions of infants have been screened with 4,412 being diagnosed with diseases included in the NBS panel.

Of 115,619 infants screened in 2009, 115,292 were Michigan residents and 234 (0.2%) were diagnosed as having a disease.

Developments occurring in 2009:

- The cystic fibrosis (CF) algorithm was modified, so that infants with immunoreactive trypsinogen (IRT) concentrations ≥99.8th percentile and no DNA mutations are monitored, but no longer referred to medical management for confirmatory sweat testing (2/09).

- NBS results became available on the Michigan Care Improvement Registry (MCIR) (07/09).

- A new CAH assay was implemented, which resulted in significant improvements in CAH screening performance metrics (8/09).

- Extensive training and revised schedules for laboratory staff allowed for the complete NBS panel to be provided on Saturdays (9/09).

- The NBS Follow-up Program held regional NBS Hospital Coordinator Trainings around the state.
    - 80% of hospitals sent at least one representative to a training.

- Three manuscripts were prepared and submitted to peer-reviewed journals in 2009:
    - "Newborn Screening Follow-Up Within the Lifespan Context: Michigan's Experience" published in the American Journal of Preventive Medicine (2010).
    - "Predictors of Insufficient Sweat Production during Confirmatory Testing for Cystic Fibrosis" to be published in Pediatric Pulmonology (2010).
    - "Variation in Immunoreactive Trypsinogen Concentrations among Michigan Newborns and Implications for Cystic Fibrosis Newborn Screening" to be published in Pediatric Pulmonology (2010).

- NBS analyses were presented at the National Maternal and Child Health Epidemiology Conference, Pediatric Research Day, and the Region 4 Genetics Collaborative Meeting.

- The Hemoglobinopathy Quality Improvement Committee (HemQIC) was formed.

    - In April 2009, the HemQIC was created by the Michigan NBS Follow-up Program. The Committee meets 4 times a year, and its purpose is to review current MDCH systems for provision of diagnosis, follow-up and treatment services for those with hemoglobinopathies detected by NBS.

- The Metabolic Disorders Quality Improvement Committee (MetdQIC) was formed.

    - In April 2009, the MetdQIC was created by the Michigan NBS Follow-up Program. The Committee meets 4 times per year, and its purpose is to review services (laboratory and clinical) and proposed strategies and policies related to inborn errors of metabolism that may be detected by NBS.

- In June 2009, the Division of Genomics, Perinatal Health and Chronic Disease Epidemiology, where NBS Follow-up is housed, submitted an application to become one of the six sites to implement a Registry and Surveillance System for Hemoglobinopathy (RuSH).

- The Michigan Department of Community Health (MDCH) has led the nation by its successful efforts in coordinating the development of a community-value driven initiative known as the Michigan BioTrust for Health. This is a joint collaboration among MDCH, Wayne State University, Michigan State University, University of Michigan, and the Van Andel Institute that has the following goals:

    - Make residual dried blood spots from NBS more useful for medical and public health research
    - Store residual dried blood spots under conditions that better preserve the samples
    - Let researchers know samples are available
    - Inform and engage the public to assure samples are used in an acceptable manner

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ACRONYM KEY

Acronym[1]	Name
ACMG	American College of Medical Genetics
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
IRT	Immunoreactive Trypsinogen
MCIR	Michigan Care Improvement Registry
MDCH	Michigan Department of Community Health
MIDB	Michigan Inpatient Database
MS/MS	Tandem Mass Spectrometry
NBS	Newborn Screening
NICU	Neonatal Intensive Care Unit
PAH	Phenylalanine Hydroxylase
PCP	Primary Care Physician
PEAC	Pediatric Endocrine Advisory Council
PPV	Positive Predictive Value
QA	Quality Assurance
QAAC	Quality Assurance Advisory Committee
SCDAA	Sickle Cell Disease Association of America
TSH	Thyroid Stimulating Hormone
U of M	University of Michigan

[1] Only those acronyms appearing in the text are presented; disorder acronyms are presented in Table 1

INTRODUCTION

The Newborn Screening (NBS) Annual Report provides an overview of Michigan's NBS Program, target outcomes, screening performance metrics related to conditions included in the NBS panel, and quality assurance information. This report differs from the previously released reports in several ways. First, this is an abridged report in that it does not include appendices which have not changed including the NBS research guidelines, supportive legislation, and website description.[2] Second, this report includes a chapter providing in-depth information on a single NBS condition, phenylketonuria (PKU) (Chapter IV). This chapter includes information on the history of PKU and updates on ongoing PKU-related NBS program evaluation research. In sum, this report is intended to:

- provide an introduction and historical account of the development of NBS in Michigan,
- detail the screening performance targets,
- provide Michigan screening outcomes and explain how they compare to performance targets,
- provide a detailed account of PKU screening in Michigan,
- detail quality assurance information, and
- detail future directions for NBS in Michigan

WHAT IS NEWBORN SCREENING?

NBS is a process of early identification of health conditions followed by their subsequent timely treatment before the onset of disease processes thereby minimizing 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, spleen, stroke, or death if not detected early. To prevent such outcomes from occurring, NBS programs test blood spots collected from infants during the first few days of life and then further monitors for signs of treatable disorders.

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, following Dr. Guthrie's lead, 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. In 1977, a test for congenital hypothyroidism (CH) was added to the NBS panel, and in 1985, screening for galactosemia was initiated. 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. 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, medical management, and quality assurance. 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 was

[2] The 2006, 2007, and 2008 NBS Annual Reports are available at www.michigan.gov/newbornscreening

medium chain acyl-CoA dehyrogenase deficiency (MCAD), a disorder of fatty acid oxidation that can result in sudden death during periods of fasting. This technology allowed further expansion of the NBS screening panel in 2004 to include three other 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 adding the additional MS/ MS disorders recommended by the American College of Medical Genetics (ACMG) and the March of Dimes. Screening for cystic fibrosis began October 1, 2007, thus meeting another recommendation of the ACMG. Hearing screening was also added to the NBS panel in 2007; however, this report does not include hearing screening results.

Table 1 provides the complete list of disorders currently screened for in Michigan. Table 2 provides a list of disorders that are screened for in Michigan, but no cases have ever been identified and confirmed through NBS in Michigan. Screening for all of the disorders listed in Table 2, except for Citrullinemia Type II, began in 2005, so nearly 615,000 infants have been screened for the disorders through 2009, and no cases have been detected. Screening for Citrullinemia Type II began in 2004, meaning approximately 740,000 infants have been screened, and no cases have been detected. Detailed information about the disorders in the screening panel, confirmation of diagnoses, and follow-up of positive tests including algorithms can be found in the NBS Procedure Manual available at: www.michigan.gov/newbornscreening.

Table 1: Disorders Included in the Newborn Screening Panel, Michigan, 2009

Amino Acid Disorders	**Organic Acid Disorders**
1. Argininemia (ARG)	26. 2-Methyl 3 hydroxy butyric aciduria (2M3HBA)
2. Argininosuccinic acidemia (ASA)	27. 2-Methyl butyryl-CoA dehydrogenase deficiency (2MBG)
3. Citrullinemia (CIT)	28. 3-OH 3-CH3 glutaric aciduria (HMG)
4. Citrullinemia Type II (CIT II)	29. 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
5. Homocystinuria (HCY)	30. 3-Methylglutaconic aciduria (3MGA)
6. Hypermethioninemia (MET)	31. Beta-ketothiolase deficiency (BKT)
7. Maple syrup disease (MSUD)	32. Glutaric acidemia type I (GA I)
8. Phenylketonuria (PKU)	33. Isobutyryl-CoA dehydrogenase deficiency (IBG)
9. Benign hyperphenylalaninemia (H-PHE)	34. Isovaleric acidemia (IVA)
10. Biopterin cofactor biosynthesis defect (BIOPT(BS))	35. Malonic acidemia (MAL)
11. Biopterin cofactor regeneration defect (BIOPT(REG))	36. Methylmalonic acidemia (Cbl A,B) (MMA)
12. Tyrosinemia Type I (TYR I)	37. Methylmalonic acidemia (Cbl C,D) (MMA)
Fatty Acid Oxidation Disorders	38. Methylmalonic acidemia (mutase deficiency) (MMA)
13. Carnitine:acylcarnitine translocase deficiency (CACT)	39. Multiple carboxylase deficiency (MCD)
14. Carnitine palmitoyltransferase I deficiency (CPT I)	40. Propionic acidemia (PA)
15. Carnitine palmitoyltransferase II deficiency (CPT II)	**Endocrine Disorders**
16. Carnitine uptake defect (CUD)	41. Congenital adrenal hyperplasia (CAH)
17. Dienoyl-CoA reductase deficiency (DERED)	42. Congenital hypothyroidism (CH)
18. Glutaric acidemia type II (GA II)	**Hemoglobinopathies**
19. Long-chain L-3-OH acyl-CoA dehydrogenase deficiency (LCHAD)	43. Hb S/Beta-thalassemia (Hb S/Beta-Th)
20. Medium/short-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency (M/SCHAD)	44. Hb S/C Disease (Hb S/C)
21. Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)	45. Sickle cell anemia (Hb SS)
22. Medium-chain ketoacyl-CoA thiolase deficiency (MCKAT)	46. Variant hemoglobinopathies
23. Short-chain acyl-CoA dehydrogenase deficiency (SCAD)	**Other Disorders**
	47. Biotinidase deficiency (BIO)
24. Trifunctional protein deficiency (TFP)	48. Cystic Fibrosis (CF)
25. Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	49. Galactosemia (GALT)
	50. Hearing*

Note: The following disorders are reported together on the same letter: CIT/CIT II/ASA, HCY/MET, PKU/H-PHE/BIOPT(BS)/BIOPT(REG), CACT/CPT II, LCHAD/TFP, 2MBG/IVA, PA/MMA, HMG/3MGA, SCAD/IBG

**Hearing screening was added to the NBS panel in 2007; however, because hearing screening is conducted by the Early Hearing Detection and Intervention (EHDI) program, this report does not include hearing screening results.*

Table 2: Disorders in the Newborn Screening Panel Never Identified and Confirmed by Newborn Screening, Michigan

Disorder
Amino Acid Disorders
Citrullinemia Type II (CIT II)*
Tyrosinemia Type I (TYR I)**
Argininemia (ARG)
Fatty Acid Oxidation Disorders
Carnitine:acylcarnitine translocase deficiency (CACT)
Carnitine palmitoyltransferase I deficiency (CPT I)
Carnitine palmitoyltransferase II deficiency (CPT II)
Trifunctional protein deficiency (TFP)
Medium/short-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency (M/SCHAD)
Dienoyl-CoA reductase deficiency (DERED)
Medium-chain ketoacyl-CoA thiolase deficiency (MCKAT)
Organic Acid Disorders
3-OH 3-CH3 glutaric aciduria (HMG)
3-Methylglutaconic aciduria (3MGA)
Methylmalonic acidemia (Cbl A,B)
Multiple carboxylase deficiency (MCD)
2-Methyl 3 hydroxy butyric aciduria (2M3HBA)
Malonic acidemia (MAL)
Beta-ketothiolase deficiency (BKT)

**Screening for CIT II began in 2004 (740,000 screens) and for all other disorders in the table in 2005 (615,000 screens).*

***One case of TYR 1 has been diagnosed, but this case was detected clinically and not through established newborn screening algorithms. Therefore, no cases of TYR 1 have been detected by newborn screening in Michigan.*

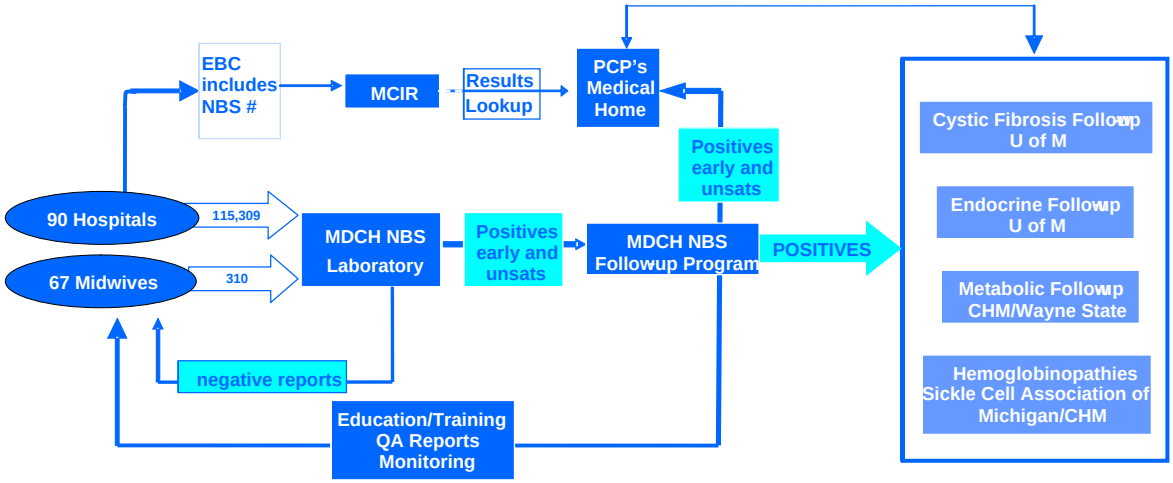

Figure 1: Overview of the Michigan Newborn Screening Program

HOSPITALS

In 2009, Michigan had 90 hospitals with newborn nurseries. Each hospital has a designated NBS coordinator who helps facilitate the screening process by assuring that a) a NBS specimen is properly obtained from all newborns between 24 and 36 hours of age, b) appropriate documentation occurs, and c) all specimens are sent by courier to the NBS laboratory immediately after drying and no later than 24 hours after obtaining the specimens. Each hospital receives a quarterly quality assurance report comparing the number of specimens collected more than 36 hours after birth, specimens arriving at the state laboratory 4 days or more after collection, batched envelopes (i.e., envelopes containing specimens with collection dates spanning more than 2 days), birth certificates with NBS kit number recorded, and unsatisfactory specimens for their hospital with the state average for these indicators. In addition, hospitals receive 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 67 midwives registered with the NBS program. Midwives also receive quarterly quality assurance reports and are provided individual assistance in meeting quality assurance 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 of the NBS disorders screened.

MICHIGAN DEPARTMENT OF COMMUNITY HEALTH

The MDCH NBS program includes the NBS Laboratory, the Follow-up Program, and four medical management centers. The Follow-up Program is responsible for the coordination of the medical management centers. Each component is described in the following sub-sections.

A. NEWBORN SCREENING LABORATORY

Newborn screening is performed within the Division of Chemistry and Toxicology in the Bureau of Laboratories. The laboratory is accredited by CLIA and is directed by Dr. Frances Pouch Downes. The laboratory establishes a newborn reference range for each disorder that maximizes detection rates while minimizing the rate of false positives and false negatives. The laboratory actively participates in HRSA Region 4 initiatives for the standardization of tandem mass spectrometry for screening for metabolic diseases along with the standardization of screening activities for CAH and CH. Testing is performed Monday through Saturday. More than 700 specimens can be analyzed each day for 49 disorders.

B. NEWBORN SCREENING FOLLOW-UP PROGRAM

The NBS Follow-up Program, located in the Division of Genomics, Perinatal Health and Chronic Disease Epidemiology within the Bureau of Epidemiology, oversees short-term and long-term follow-up of infants identified through the screening program. Follow-up starts with referring infants to one of four MDCH-funded medical management centers for rapid diagnosis and treatment. The target is to initiate treatment within the first seven days of life for disorders with an early and severe onset and, when possible, within the first fourteen days of life for all other disorders. Education and training, as well as quality assurance measures, are also responsibilities of the NBS Follow-up Program. These activities are primarily targeted toward hospital staff involved in the NBS process. The Follow-up Program maintains short and long-term follow-up databases for program monitoring and evaluation as well as for assessing the impact of health care services on health outcomes.

C. NEWBORN SCREENING MEDICAL MANAGEMENT CENTERS

The four medical management coordinating centers include the Endocrine Follow-up Program at the University of Michigan Medical Center, the Children's Hospital of Michigan Metabolic Clinic, the Sickle Cell Disease Association of America, Michigan Chapter, and the Cystic Fibrosis Clinic at the University of Michigan.

1. ENDOCRINE FOLLOW-UP PROGRAM, UNIVERSITY OF MICHIGAN MEDICAL CENTER

The Endocrine Follow-up Program in the Department of Pediatrics, University of Michigan, maintains a centralized communication, referral and treatment assessment office that provides follow-up to ensure appropriate diagnostic evaluation and treatment of all infants with positive CH

or CAH screening results.

The overall program is directed by Ram Menon, M.D. Ming Chen M.D., Ph.D. is the director of the Center of Excellence for the Diagnosis and Management of CAH. The Pediatric Endocrinology Advisory Council (PEAC) provides advice to the Michigan NBS Program on screening, diagnosis and medical management of newborns with suspected endocrine disorders.

2. CHILDREN'S HOSPITAL OF MICHIGAN METABOLIC CLINIC

The Children's Hospital of Michigan Metabolic Clinic is responsible for diagnosis and medical management of all newborns with the 42 metabolic disorders detected by NBS. The clinic also provides biochemical and molecular genetic diagnostic laboratory services. The clinic is directed by Gerald Feldman, M.D., Ph.D. while Robert Grier, Ph.D. is the director of the biochemical genetics laboratory.

3. SICKLE CELL DISEASE ASSOCIATION OF AMERICA, MICHIGAN CHAPTER (SCDAA)

The Sickle Cell Disease Association of America provides comprehensive services to all newborns with hemoglobinopathies detected by NBS in Michigan. The SCDAA is located in Detroit and is directed by Wanda Shurney, M.D. The primary responsibilities of the SCDAA are to assure that: (1) all newborns referred with positive sickle cell screening results are appropriately diagnosed, (2) penicillin prophylaxis is initiated, (3) sickle cell counseling and social work services are available, and (4) each newborn has a medical home. In addition to the central office in Detroit the program maintains offices for social workers (patient advocates) in Grand Rapids, Benton Harbor, Pontiac, Flint, Kalamazoo, Lansing, Muskegon, and Saginaw.

4. NEWBORN SCREENING AND COORDINATING PROGRAM FOR CYSTIC FIBROSIS, UNIVERSITY OF MICHIGAN HEALTH SYSTEM

The NBS and Coordinating Program for Cystic Fibrosis is housed within the Department of Pediatrics at the University of Michigan Health System and coordinates with CF centers in Lansing, Grand Rapids, Detroit, and Kalamazoo to provide comprehensive services to all newborns with CF detected by NBS. The CF coordinating center is led by pediatric pulmonologist Samya Nasr, M.D. The CF screening program is advised by a committee including the five CF foundation approved CF clinics' directors.

II: METHODS

This section describes the methods used to calculate: a) total number of newborns in the population to be screened, b) total number of newborns diagnosed through the NBS process and the demographics of those screened, c) screening performance metrics, and d) quality assurance indicators.

TOTAL NUMBER OF NEWBORNS IN THE POPULATION TO BE SCREENED

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 calculate the total number of live births eligible to be screened statewide. The number of live births in 2009 (n=116,315) is a preliminary estimate as the final files have not been released yet.

TOTAL NUMBER OF NEWBORNS DIAGNOSED BY NEWBORN SCREENING & DEMOGRAPHICS OF INFANTS SCREENED

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 had the following characteristics: a) they were identified by NBS, b) they were Michigan residents, and c) they were diagnosed through established clinical and laboratory protocols. Demographics of infants screened are presented both for Michigan residents and, in a separate table, 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 3 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. No NBS test is perfect, but the screening for metabolic disorders by MS/ MS and hemoglobinopathies by high performance liquid chromatography (HPLC) is close. 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 identified by NBS are not included in the performance metrics.

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 include: a) time from birth to specimen collection, b) time from specimen collection to specimen arrival at the State NBS Laboratory, and c) time from birth to treatment of each disorder.

Table 3: Screening Performance Indicator Descriptions

Indicator	Description
Newborns N	The total number of live births *among in-state residents*
Total + (% NICU)	Total number of positive screens (positive = screening value exceeds cutoff) among in-state residents (the percentage of infants in the NICU with positive screens among all positive screens)
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; retest sent to MDCH laboratory)
Confirmed +	A diagnosis of a disorder that has been confirmed among screened Michigan resident infants
False +	A positive screen among screened Michigan resident infants 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 disease divided by the number of infants having positive screens expressed as a percentage (%)

**includes only in-state resident infants in the denominator*

III: SCREENING RESULTS

DEMOGRAPHICS OF INFANTS SCREENED

This section describes the population of infants screened during 2009 in terms of race, birth weight, gestational age, and birth place (hospital nursery, NICU, midwife). 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, thus the number of cases will fluctuate with the birth rate of African Americans.

The Michigan NBS program screened 99.5% of the live births occurring in Michigan in 2009; the proportion of live births screened is based on the estimated live births occurring in Michigan in 2009. We note that linkage of NBS records to preliminary live birth records received from the Vital Records & Health Data Development Section and follow-up of unmatched records also indicates that >99% of live births in Michigan were screened in 2009 (Table 4).

Table 4: Newborn Screening & Live Births Records Linkage Results, Michigan, 2009

Birth Year	Total*	Matched	
	N	N	%
2009	115,786	114,659	99.0

*Excluding 529 infants listed as deceased on the live birth record

Of the 1,127 live births records from 2009 that were not successfully matched to NBS records during the initial linkage, 45% (n=504) were screened (Table 5). The live births records did not link to NBS records for these infants. Typically, this failure to link is due to data recording or entry errors. The remaining 55% (n=623) of the infants truly were not screened. Infants may not have been screened for a variety of reasons including: parental refusal of screening, transfer out of state, infant expired, or missed screen. For all infants who were not screened, the NBS Follow-up team either contacts the nurse coordinator for hospital births or sends a parental notification letter for home births. In 2009, 76 infants born in hospitals are known to have been missed by NBS, and hospitals were contacted to obtain a screen. Of the 76 infants, 24 have been screened to date, 20 expired, 8 had parental refusals, 5 were transferred out of state, and the remaining 19 are pending.

Table 5: Follow-up Result for Non-matched Live Births Records, Michigan, 2009

Follow-up Result	N	%
NBS Already Completed	504	44.7
No NBS	623	55.3

There were 327 live births (0.3% of live births screened in Michigan) to out-of-state residents. Tables 6 and 7 report the demographics and perinatal characteristics by race/ethnicity of in-state and out-of-state residents screened in 2009, respectively. This report details further the screening results for in-state residents only. As indicated in Table 6, the majority of in-state infants screened were white, born in hospital nurseries at term (≥37 weeks gestational age), and of normal birth weight (>2500 g). Overall, 11% of infants screened were in the NICU, 8% weighed less than 2,500 g at birth, and 10% were born preterm (<37 weeks gestational age). African Americans were over-represented among NICU, preterm, and low birth weight (<2,500 g) births.

Table 6: Demographics of Infants Screened by Race/Ethnicity, Michigan, 2009, Excluding Out-of-State Residents, N=115,292

Race/ Ethnicity *Missing data: n=10,975*	**Row Total**		**Nursery Type**						**Low Birth Weight** *(missing data: n=12,660)*		**Gestational Age** *(missing data: n=14,162)*	
			Hosp. Nursery^		**Midwife**		**NICU**		**<2500 grams**		**< 37 weeks**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
White	73,247	70.2	65,926	90.0	299	0.4	7,022	9.6	4,823	6.7	6,397	9.0
Black	20,995	20.1	17,370	82.7	2	*	3,623	17.3	2,800	13.5	2,765	13.8
American Indian	527	0.5	489	92.8	0	-	38	7.2	29	5.6	39	7.6
Asian/Pac Islander	2,417	2.3	2,231	92.3	0	-	186	7.7	195	8.2	186	7.9
Middle Eastern	2,338	2.2	2,154	92.1	0	-	184	7.9	156	6.8	171	7.5
Multi-Racial	4,793	4.6	4,299	89.7	8	0.2	486	10.1	374	7.9	437	9.4
Hispanic**	7,719	9.2	7,107	92.1	4	*	608	7.9	466	6.1	574	7.7
Column Total:	*104,317*	*100*	*92,469*	*88.6*	*309*	*0.3*	*11,539*	*11.1*	*8,377*	*8.2*	*9,995*	*9.9*

Note: *percentages expressed in the above table are row percentages across the columns aside from the final row of the table in which column totals and column percentages are expressed. The number 'missing data' for low birth weight and gestational age are indicative of the total number missing race and/or birth weight, gestational age.*

**A rate is not calculated when there are fewer than 6 events, because the width of the confidence interval would negate any usefulness for comparative purposes.*

***Although 'Hispanic' is an ethnic category and not a racial category, most respondents failed to indicate their race when indicating they were of Hispanic ethnicity; thus, we present 'Hispanic' as its own category and not by racial categories. However, the 'Hispanic' row does not contribute to the column totals listed in the bottom row of the above table.*

^Hospital nursery defined as not midwife or NICU.

Table 7: Demographics of Infants Screened by Race/Ethnicity, Michigan, 2009, Out-of-State Residents, N=327

Race/ Ethnicity *Missing data: n=26*	**Row Total**		**Nursery Type**						**Low Birth Weight** *(missing data: n=34)*		**Gestational Age** *(missing data: n=36)*	
			Hosp. Nursery^		**Midwife**		**NICU**		**<2500 grams**		**<37 weeks**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
White	236	78.4	183	77.5	0	-	53	22.5	31	13.5	31	13.7
Black	32	10.6	24	75.0	0	-	8	25.0	5	*	6	19.4
American Indian	1	0.3	1	*	0	-	0	-	0	-	0	-
Asian/Pac Islander	10	3.3	9	90.0	0	-	1	*	0	-	2	*
Middle Eastern	6	2.0	6	100	0	-	0	-	0	-	0	-
Multi-Racial	16	5.3	13	81.3	0	-	3	*	2	*	3	*
Hispanic**	14	6.2	12	85.7	0	-	2	*	1	*	2	*
Column Total:	*301*	*100*	*236*	*78.4*	*0*	-	*65*	*21.6*	*38*	*13.0*	*42*	*14.4*

Note: *percentages expressed in the above table are row percentages across the columns aside from the final row of the table in which column totals and column percentages are expressed. The number 'missing data' for low birth weight and gestational age are indicative of the total number missing race and/or birth weight, gestational age.*

**A rate is not calculated when there are fewer than 6 events, because the width of the confidence interval would negate any usefulness for comparative purposes.*

***Although 'Hispanic' is an ethnic category and not a racial category, most respondents failed to indicate their race when indicating they were of Hispanic ethnicity; thus, we present 'Hispanic' as its own category and not by racial categories. However, the 'Hispanic' row does not contribute to the column totals listed in the bottom row of the above table.*

^Hospital nursery defined as not midwife or NICU.

SCREENING OUTCOME INFORMATION

In the following sub-sections, outcome information is provided for the 49 disorders screened for in 2009. The total number of cases detected both in and through 2009 is presented along with screening performance metric targets and screening performance metrics. The disorders are organized into four categories: metabolic, endocrine, cystic fibrosis and hemoglobinopathy, corresponding to the four medical management programs responsible for diagnosis and medical management.

CUMULATIVE DETECTION RATE

Table 8 reports the cumulative detection rate of disorders identified via NBS by classification both in and through 2009. 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, detectable by enzyme assay screening and not by MS/ MS, 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.

As indicated in the table, CH and the hemoglobinopathies were the most prevalent both in and through 2009, while CAH and organic acid disorders were the least prevalent; however, considering the MS/ MS disorders separately, several have yet to be detected (Table 2). Of note, the MS/MS screening platform allows for multiple disorders to be screened for with a single assay; thus, continuing screening for disorders that have yet to be detected does not significantly increase costs.

Congenital hypothyroidism accounted for 29% of all disorders detected in 2009 and 37% of all cases detected cumulatively. Hemoglobinopathies accounted for 24% of all cases detected in 2009 and 34% of all cases detected cumulatively. CF accounted for 14% of cases detected in 2009 and 2% of cases detected cumulatively. Disorders detected by MS/ MS (amino acid, organic acid and fatty acid oxidation disorders) accounted for 16% of cases in 2009 and 17% cumulatively. However, PKU, the first disorder screened in 1965 in Michigan, is now screened by MS/ MS, meaning the overall proportion of cases detected by MS/ MS is an over-estimate because it includes cases detected by other means 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 disorders other than MCAD leading to an artificially low cumulative detection rate. The MS/ MS detection rate does not include eight cases of formiminoglutamic acid disorder (FIGLU) detected because the disorder is not included in the NBS panel and is not treatable. Galactosemia, including Duarte compound heterozygotes, accounted for 9% of all disorders detected in 2009 and 4% cumulatively. Biotinidase deficiency, including partial biotinidase deficiency, accounted for 6% of all cases detected in 2009 and 4% of all cases detected cumulatively. CAH accounted for 1% all of cases in 2009 and 3% of all cases detected cumulatively.

Table 8: Disorders Identified in Newborns via Newborn Screening, Michigan Newborn Residents, 1965-2009

Type of Disorder Classification (Year Screening Began)	Cases in 2009 (N)	Cases Through 2009 (N)	Cumulative Detection Rate*
Galactosemia (1985)	22	159	1:21,118
Biotinidase Deficiencies (1987)	15	183	1:16,903
Amino Acid Disorders (1965)	19	639	1:9,902
Organic Acid Disorders (2005)	2	27	1:22,736
Fatty Acid Oxidation Disorders (2003)	17	90	1:9,716
Congenital Hypothyroidism (1977)	67	1,619	1:1,911
Congenital Adrenal Hyperplasia (1993)	2	111	1:19,989
Hemoglobinopathies (1987)	57	1,504	1:2,057
Cystic Fibrosis (October 2007)	33	79	1:3,363
Total	234	4,411	-

**Note: 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 for 2007 was calculated by multiplying the average number of births per month by four. Galactosemia includes both classical cases and Duarte variants (DG) since 2004. Biotinidase Deficiency includes both partial and profound biotinidase deficiency. While MCAD, a fatty acid oxidation disorder, began being screened for in 2003 other disorders were not added to the NBS panel until later; thus, the cumulative detection rate artificially low.*

SCREENING PERFORMANCE METRIC TARGETS

Screening performance metric targets are presented in Table 9. Screening performance metrics include the detection rate, false positive rate, and positive predictive value. Performance targets for galactosemia and biotinidase deficiency have not been clearly established. Minimal performance targets that should be achievable by a NBS program but may not be met using current methodologies are provided for these disorders. The purpose of screening for these disorders is the detection of the severe enzyme deficiency in both classic galactosemia and profound biotinidase deficiency. In addition, screening also detects partial enzyme deficiencies associated with Duarte variant forms of galactosemia and partial biotinidase deficiency. Data on Duarte variants and partial biotinidase deficiency are reported for information only. Detection of these disorders is not an objective of the NBS program.

In 2006, Piero Rinaldo, M.D., Ph.D., et al. reported screening performance targets for MS/ MS disorders in *Mental Retardation and Developmental Disability Reviews.*[1] Performance metrics (detection rate, false positive rate (FPR) and positive predictive value (PPV)) provide NBS programs with a method of assessing the screening performance over time for meeting targets established by consensus. Performance targets for MS/ MS screening, based on data reported by Rinaldo et al., are included in Table 9. Performance targets for endocrine disorders, congenital hypothyroidism (CH) and congenital adrenal hyperplasia (CAH) are based on a review of screening performance metrics for CH and CAH for six of the seven states included in the HRSA-sponsored Region 4 Genetics Collaborative.

Hemoglobinopathy screening is done by high performance liquid chromatography (HPLC) and detects the presence of hemoglobins F, A, S, C, D, and E. The most important is hemoglobin S, the hemoglobin responsible for sickle cell conditions. There are no strong or borderline positive categories. The results of screening are virtually identical to the results of the confirmatory isoelectric focusing. There are some disease cases that are re-classified (SS to S/ beta thal) or occasionally to sickle cell trait on confirmatory testing but these changes do not significantly change the FPR and PPV for hemoglobinopathies which are close to 0% and 100%, respectively.

Table 9: Screening Performance Metric Targets

Disorder Category	Disorder	Performance Metric	Performance Target
Galactosemia Classic (G/G)		Detection Rate	1:47,000
		FPR	<0.5%
		PPV	>5%
Biotinidase Deficiency (profound)		Detection Rate	1:109,300 - 1:211,200
		FPR	<0.5%
		PPV	>5 %
MS/MS Disorders		Detection Rate	1:3,000
		FPR	<0.3%
		PPV	>20%
Endocrine Disorders	Congenital Hypothyroidism	Detection Rate	1:2,000 – 1:2,500
		FPR	0.3-0.4%
		PPV	10-15%
	Congenital Adrenal Hyperplasia	Detection Rate	1:15,000 – 1:20,000
		FPR	0.5-0.8%
		PPV	1-2%

SCREENING PERFORMANCE METRICS

Table 10 reports screening performance metrics for all disorders for 2009. Performance metrics for individual MS/ MS disorders are provided in the following section in Tables 13, 14, and 15. Although 11% of infants born in Michigan in 2009 were admitted to a NICU, nearly half (48%) of the positive screens were among these infants. Of positive screens, the percent from infants in NICUs ranged from 93% for CAH to 5% for amino acid disorders.

GALACTOSEMIA, BIOTINIDASE DEFICIENCY, & CYSTIC FIBROSIS

The galactosemia detection rate (including Duarte D/ G variants) was 1:5,241 in 2009. The FPR and PPV were 0.01% and 69%, respectively. However, considering that the purpose of galactosemia screening is to detect classic galactosemia only, we report a detection rate of 1:115,292 for one case identified. The biotinidase deficiency (including partial biotinidase deficiency) detection rate was 1:7,686; the FPR and PPV were 0.11% and 11%, respectively. The FPR and PPV of both galactosemia and biotinidase deficiency meet, and significantly exceed, performance targets of FPR <0.5% and PPV >5%. Thirty-three cases of cystic fibrosis (CF) were detected in 2009 (detection rate-1:3,494); the associated FPR and PPV were 0.3% and 9.0%, respectively. 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 of 0.53% is higher than the target range of 0.3% to 0.4%; the PPV of 9.9% is close to the target range of 10% to 15%. The 2009 detection rate for CH of 1:1,721 is slightly below the target range of 1:2,000 to 1:2,500. The Michigan CH detection rate has had significant fluctuations from year to year with a high of 1:1,101 in 2001 to a low of 1:2,128 in 2006. This is in part related to changes in the screening method; in 2001 the method was changed from a primary T4 to a primary TSH screen and age-adjusted cutoffs were implemented. A second reason is that over time clinical decision-making regarding treatment of suspected hypothyroidism based on marginal increases in serum TSH has changed. Chapter IV of the 2007 Annual Report provides more detailed information about CH screening in Michigan.

While the detection rate for CAH of 1:57,646 is lower than the target range of 1:15,000 to 1:20,000, this is not unusual for a rare disorder in any single year. Of note, the cumulative CAH detection rate of 1:19,989 is within the target range; however, the PPV of 0.32% is well below the already low PPV target of 1-2%, and the FPR of 0.53% is within the target FPR of 0.5-0.8%. One case of salt-wasting CAH and one case of non-salt-wasting CAH were detected among 620 positive screens in 2009. The large number of strong positive screens relative to the small number of confirmed cases reflects a problem in the CAH screening methodology. Specifically, the method is susceptible to stress-related false positives (high 17-OHP) for premature newborns. The high 17-OHP is due also to cross-reactivity of other steroids with the antibody used in the assay. The poor performance of primary 17-OHP screening led to the development of a second tier screen. Second tier screening involves evaluation by the Mayo Laboratory of the steroid profile (sum of 17-OHP + androstenedione/ cortisol) by MS/ MS for newborns with an initial positive 17-OHP. The use of the second tier screening resulted in increased PPV and decreased FPR. However, second tier screening for CAH is still being evaluated. Additionally, a new assay for CAH was implemented in August 2009. This new assay resulted in a dramatic improvement in screening performance metrics. After the introduction of the assay, the FPR for CAH decreased from 0.83% to 0.09%, a 9-fold difference; the PPV increased from 0.2% to 2.1%, a 10.5-fold difference. Based on the CAH screening performance improvements due to the new assay, we anticipate meeting the FPR and PPV targets in 2010.

Table 10: Screening Results and Performance Metrics, Michigan, 2009

Disorder Type	Total N	Total + N (% NICU)	Confirmed + N	Positive Detection Rate	FPR %	PPV %
Galactosemia Classic (GG)	115,292	32 (15.6)	1	1:115,292	0.01	68.75
Duarte (DG)			21	1:5,490		
Total			*22*	*1:5,241*		
Biotinidase Deficiency		139 (30.2)	3	1:38,431	0.11	10.79
Profound						
Partial			12	1:9,608		
Total			*15*	*1:7,686*		
Cystic Fibrosis		366† (14.8)	33	1:3,494	0.29	9.02
Congenital Hypothyroidism (CH)		675 (33.6)	67	1:1,721	0.53	9.93
Congenital Adrenal Hyperplasias (CAH) Salt wasting		612 (92.5)	1	1:115,292	0.53	0.33
Non-Salt wasting			1	1:115,292		
Total			*2*	*1:57,646*		
Hemoglobinopathies		70 (21.4)	57	1:2,023	0.01	81.43
Amino Acid*		65 (4.6)	19	1:6,068	0.04	29.23
Organic Acid*		43 (20.9)	2	1:57,646	0.04	4.65
Fatty Acid Oxidation*		47 (14.9)	17	1:6,782	0.03	36.17
*MS/MS Disorders Total***		*148 (10.8)*	*38*	*1:3,034*	*0.10*	*25.68*

Note: *Maternal cases detected are not included in this table.*

†Excluding 141 infants with IRT concentrations ≥99.8th percentile and no DNA mutations

**Detected by MS/MS*

***SCAD and IBG are screened using the same analyte. Thus, the 7 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.*

HEMOGLOBINOPATHIES

Hemoglobinopathy screening outcome information is reported in Table 11. Hemoglobinopathy screening differs from screening for the other disorders. The purpose of hemoglobinopathy screening is to identify the presence or absence of abnormal hemoglobins and not to quantify selected analytes as with other screening tests. 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 11, hemoglobinopathies are quite common among African Americans, who accounted for 100% of the cases in 2009. While the overall incidence of hemoglobinopathies is approximately one case per 2,023 screened, the incidence in African American infants is one in 368 screened in Michigan.

Table 11: Hemoglobinopathy Screening Performance Indicators, Michigan, 2009

Disorder	Newborns (N)	Confirmed + (N)		Positive Detection Rate	
		Total	Among Blacks	Total*	Among Blacks*
Sickle Cell Anemia	115,292	34	34	1:3,391	1:618
SC Disease		18	18	1:6,405	1:1,166
Sickle β thalassemia		5	5	1:23,058	1:4,199
Total		*57*	*57*	*1:2,023*	*1:368*

**Out of the number of Michigan resident infants screened, total N=115,292, among Blacks N=20,995*

MS/MS DISORDERS

The overall FPR for MS/MS of 0.1% is within the target of less than or equal to 0.3%. The detection rate of 1:3,116 and PPV of 26% are near and exceed the target metrics of 1:3,000 and 20%, respectively. In 2007, the MS/ MS disorders did not meet the target metrics. This improvement is likely due to changes in disease profiles and refinements in laboratory cut-offs in order to identify all true cases, while minimizing the number of false positives. Others have noted until there is uniformity of testing, aggregate performance metrics are less informative than those of specific conditions explaining our presentation of disorder specific performance metrics in subsequent tables.[1]

SCREENING PERFORMANCE METRICS – INDIVIDUAL MS/MS DISORDERS

AMINO ACID DISORDERS

Nineteen amino acid disorders (Table 12) were detected by MS/ MS. PKU is the most frequent amino acid disorder identified, found in one of every 7,686 newborns screened. As indicated in the table, PKU screening had the second highest PPV (63%) among amino acid disorders, following HCY/ MET. The FPR for PKU screening of 0.008% reflects the very high sensitivity of MS/ MS screening for this disorder. One case of homocystinuria, one case of hypermethioninemia, and two cases of citrullinemia were confirmed in 2009.

Although 19 infants had positive screens for Tyrosinemia Type I (TYR I), no infants were confirmed with the disease. No true cases of TYR I have been confirmed in Michigan through NBS. The current PerkinElmer MS/ MS screening kit uses the analyte tyrosine to test for TYR I. However, tyrosine is a late rising marker for TYR I. Specimens with elevated levels of tyrosine are sent to the Mayo Laboratory for testing of succinylacetone (SUAC), an early marker for TYR I. Specimens with TYR II, III and transient TYR can be detected by elevations of tyrosine in the first 24-36 hours of life. If the initial specimen has elevated tyrosine, this is most likely due to transient TYR, a fairly common occurrence, and tyrosine levels return to normal or begin to fall after the first few weeks of life. If the second or third screen indicates that tyrosine levels are falling, then transient TYR is assumed to be the cause of the initial elevation. If tyrosine levels continue to rise, then TYR Types I, II or III must be ruled out by referral for further diagnostic testing. In 2009, the algorithm for TYR was changed to request a repeat specimen if tyrosine was elevated. This modification was made to allow for the potential detection of TYR II and III, in addition to TYR I.

ORGANIC ACID DISORDERS

Two organic acid disorders (Table 13) were detected by MS/MS; both were methylmalonic acidemia. The detection rate for organic acid disorders fluctuates due to the small number of confirmed cases; the detection rate was 1:41,171 in 2007, 1:9,944 in 2008, and 1:57,646 in 2009. We will continue to monitor the detection rate closely. Of note, in 2009 one maternal case of 3MCC and one maternal case of Vitamin B12 Deficiency were detected for infants who screened positive for 3MCC and PA/MMA, respectively.

FATTY ACID OXIDATION DISORDERS

Seventeen fatty acid oxidation disorders (Table 14) were detected (one CUD, five SCAD, nine MCAD, and two VLCAD). Three of the four detected disorders had PPV greater than or equal to 66.7%. CUD had the lowest PPV at 8.3%. However, two of the infants who screened positive, but were not diagnosed with CUD, had mothers diagnosed with CUD.

Table 12: Amino Acid Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2009

Disorder	Newborns N	Total + N	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Phenylketonuria Classic (PKU)	115,292	24	6	1:19,215	0.008	62.5
Mild			3	1:38,431		
Benign Hyperphenyl-alaninemia (H-PHE)			6	1:19,215		
Biopterin Cofactor Defects (BIOPT)			0	-		
Total			*15*	*1:7,686*		
Argininemia (ARG)		3	0	-	0.003	-
Citrullinemia (CIT)/CIT II/ASA		10	2	1:57,646	0.007	20.0
Tyrosinemia (TYR I)		19	0	-	0.017	-
Homocystinuria (HCY)/ Hypermethioninemia (MET)		2	2	1: 57,646	0.0	100.0
Maple Syrup Disease (MSUD)		7	0	-	0.006	-

Table 13: Organic Acid Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2009

Disorder	Newborns N	Total + N	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)	115,292	1	0	-	0.001	-
Glutaric Acidemia Type I (GA I)		4	0	-	0.003	-
Propionic Acidemia (PA)/ Methylmalonic Acidemia (MMA)		30	2	1:57,646	0.024	6.7
3-OH 3-Methyl Glutaric Aciduria (HMG)/ 3-Methylglutaconic aciduria (3MGA)		1	0	-	0.001	-
Isobutyryl-CoA dehydrogenase deficiency (IBG)		7	0	-	0.006	-

Note: Maternal cases identified following an abnormal newborn screen are not included in the PPV calculation. In 2009, one maternal 3MCC case and one maternal Vitamin B12 Deficiency case were identified following abnormal newborn screens for 3MCC and PA/MMA, respectively.

Table 14: Fatty Acid Oxidation Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2009

Disorder	Newborns N	Total + N	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Carnitine Uptake Defect-(CUD)	115,292	12	1	1:115,292	0.010	8.3
Short-Chain Acyl-CoA Dehydrogenase deficiency (SCAD)		7	5	1:23,058	0.002	71.4
Carnitine Palmitoyltransferase I Deficiency (CPT I)		1	0	-	0.001	-
Carnitine/Acylcarnitine Translocase Deficiency-(CACT)/Carnitine Palmitoyltransferase II Deficiency (CPT II)		10	0	-	0.009	-
Glutaric Acidemia Type II (GA II)		1	0	-	0.001	-
Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)		10	9	1:12,810	0.001	90.0
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)		3	2	1:57,646	0.001	66.7
Medium-Chain Ketoacyl-CoA Thiolase Deficiency (MCKAT)		2	0	-	0.002	-
Medium/Short-chain L-3-hydroxy Acyl-CoA Dehydrogenase Deficiency (M/SCHAD)		1	0	-	0.001	-

Note: Maternal cases identified following an abnormal newborn screen are not included in the PPV calculation. In 2009, two maternal CUD cases were identified following abnormal newborn screens for CUD.

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 plus borderline positive). Disorders lacking a borderline positive category are not reported in Table 15 because their performance metrics have been previously reported. Disorders not detected in 2009 and detected disorders with no borderline positive screens are also not reported in Table 15, as there would be no change in screening performance.

Performance metrics among strong positives 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, the performance metrics below should be considered. As indicated in Table 15, the FPRs and PPVs among strong positives are significantly improved relative to the overall screening performance metrics among all positives. Maternal cases found through NBS are not included in Table 15.

Table 15: Screening Performance Metrics (FPR and PPV) among Strong Positive Screens, 2009

Disorder Type	Among All +		Among Strong +	
	FPR	PPV	FPR	PPV
	%	%	%	%
Galactosemia	0.01	68.75	0.001	83.33
Biotinidase Deficiency	0.11	10.79	0.005	40.00
Congenital Hypothyroidism (CH)	0.53	9.93	0.112	26.29
Congenital Adrenal Hyperplasia (CAH)	0.53	0.33	0.217	0.79
Phenylketonuria (PKU)*	0.01	62.50	0.0	100.0
Propionic Acidemia (PA) / Methylmalonic Acidemia (MMA)*	0.02	6.67	0.007	20.00
Citrullinemia/ASA (CIT/ASA)*	0.007	20.00	0.006	22.22

*MS/MS disorders

The FPR for galactosemia is reduced 10-fold and the PPV is increased 1.2-fold among strong positive screens relative to all positive screens. The reduction in the FPR among strong positives for biotinidase deficiency is large, representing a 22-fold decrease, while the PPV increased nearly 4-fold.

The FPR for CH is reduced nearly 5-fold for strong positives, and the PPV increased approximately 3-fold. The FPR and PPV for CAH are decreased and increased respectively by 1.5-fold and nearly 2.5-fold among strong positives, respectively.

Among MS/ MS disorders, the FPR and PPV decreased and increased 3-fold, respectively for PA/ MMA. Since nearly all positive screens for CIT/ASA were strong positives, the FPR and PPV improved only slightly among strong positive screens. All strong positives PKU were confirmed with disease, so the PPV among strong positives for these two disorders was 100% and the FPR was 0%.

In sum, strong positive screens are far less likely to be false positive and far more likely to be indicative of true disease.

CARRIERS DETECTED AND MATERNAL DISORDERS

Although the overarching goal of NBS is to detect disorders in the newborn, 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 specific 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, or carrier. NBS will only detect carriers or maternal disorders following an abnormal screen. Thus, NBS will not identify all carriers or all maternal disorders.

In 2009, a total of 3,139 infants were identified as carriers of a disease included in the NBS panel, following an abnormal screen (Table 16). The majority of these infants (n=2,814) had sickle cell trait. Over 300 (n=322) infants were cystic fibrosis carriers, 2 infants were citrullinemia carriers, and 1 infant was identified as a biotinidase carrier.

Table 16: Carriers Identified from Newborn Screening, Michigan, 2009*

Disorder	N
Biotinidase	1
Citrullinemia	2
Cystic fibrosis	322
Sickle Cell Trait	2,814

**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.*

Besides the confirmatory diagnostic testing for infants, the medical management centers also offer diagnostic testing for mothers. Since mothers may have the disease, they could possibly be identified through NBS for a few disorders.

In 2009, 4 maternal disorders were identified following a positive NBS (Table 16). One infant with a strong positive screen for 3MCC was confirmed normal, but the disorder was identified in the mother. Two mothers were identified with CUD after their infants had borderline positive screens. Following an infant's strong positive screen for propionic acid/ methylmalonic acid, the mother was confirmed with vitamin B12 deficiency.

Table 17: Maternal Disorders Identified from Newborn Screening, Michigan, 2009*

Maternal Disorder	N
3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)†	1
Carnitine update defect (CUD)	2
Vitamin B12 deficiency	1

**All of these mothers were identified following 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.*
†This mother was confirmed with 3MCC after birth of a child in 2008. Her child born in 2009 also had a positive screen for 3MCC.

IV: PHENYLKETONURIA SCREENING IN MICHIGAN

This section provides a detailed account of phenylketonuria (PKU) screening including: 1) an overview of PKU, 2) early history of PKU and maternal PKU, 3) the history of NBS for PKU in the United States, 4) the history of NBS for PKU in Michigan, and 5) PKU screening program evaluation studies in Michigan.

OVERVIEW OF PKU

PKU is an autosomal recessive disease affecting the conversion of phenylalanine to tyrosine. Phenylalanine is an amino acid, one of the building blocks of proteins, and is present in many foods. If a newborn with PKU does not receive prompt diet-treatment, phenylalanine levels in blood increase, causing brain damage and mental retardation.

Phenylalanine hydroxylase (PAH) is the enzyme involved in the catabolism of excess phenylalanine. PKU is caused by a deficiency in PAH. Mutations of the PAH gene can disrupt either the PAH structure or function, resulting in varying degrees of deficiency. Approximately 560 mutations have been found in patients with PKU or hyperphenylalaninemia and added to the mutation database for PAH.[2] The degree of PAH deficiency is used to differentiate classic PKU, mild PKU, and hyperphenylalaninemia.[3]

In classic PKU, the PAH enzyme is completely or nearly completely deficient. This is the most severe form of PKU. People with classic PKU have blood phenylalanine levels greater than 20 mg/dl when not on a phenylalanine-restricted diet and typically tolerate less than 250–350 mg of dietary phenylalanine a day. Mild PKU is a less severe form of PKU that may still cause mental retardation if not managed with a restricted diet. People with mild PKU have blood phenylalanine levels of 10-20 mg/ dl when not on a phenylalanine-restricted diet and tolerate about 350–400 mg of dietary phenylalanine a day. People with hyperphenylalaninemia have blood phenylalanine levels of 2-10 mg/ dl and typically do not require diet-treatment. A normal blood phenylalanine level is 1-2 mg/ dl. The goal of PKU treatment is to maintain a phenylalanine blood level between 2-6 mg/ dl throughout life for females, 2-6 mg/ dl for males between birth and 12 years of age, and 2-10 mg/dl for males over 12 years of age.

People with PKU are placed on a low phenylalanine diet. If placed on treatment early and the diet is followed, affected people can expect normal development and a normal life span. However, if PKU is not treated and low phenylalanine blood levels are not maintained, people with PKU may suffer from growth failure, microcephaly, seizures, and mental impairment.

PKU can occur in all individuals, but the incidence of PKU differs among races and regions. A study in southeast England found the birth prevalence of PKU was highest for whites (1.14 per 10,000), lower for Asians (0.29 per 10,000), and lowest for blacks (0.11 per 10,000).[4] The incidence of PKU ranges from a low of 1:200,000 in Finland to a high of 1:2,600 in Turkey.[5]

EARLY HISTORY OF PKU DIAGNOSES

In 1934, a persistent Norwegian mother brought her two impaired children to Dr. Asbjørn Følling for an examination.[6] She had taken her children to many doctors, but no one had been able to determine what

caused her children's intellectual impairment. Følling noted that the children suffered from mental retardation, but no other clear signs of disease. After addition of ferric chloride to the children's urine (a test used to check for ketones in the urine of people with diabetes), the urine turned deep green. This reaction puzzled Følling since he had never seen this happen before or read about it in the literature. Følling asked the mother to stop all of her children's medications, thinking that they may have caused the unusual reaction with the ferric chloride. He then repeated the urine test and found the same result. From this, he concluded that the children had a substance in their urine that was not found in urine from an average person. Through a series of chemical analyses, including extraction, purification, combustion, and oxidation, Følling was able to determine the substance's melting point and hypothesize that the substance was phenylpyruvic acid. Through another melting point experiment, Følling confirmed that these children were excreting phenylpyruvic acid in their urine. To determine whether people with mental impairment also excreted phenylpyruvic acid in their urine, he collected urine samples from 430 patients at local institutions. He found the green color in 8 of the 430 samples. Følling noted similarities in complexion, body shape, gait, and intellectual abilities in these 8 people. He went on to conduct family studies and determined that the characteristics fit the model of a recessive autosomal disease. Følling published his findings in 1934 and called the disease 'imbecellitas phenylpyruvia'.[7] Følling also found high levels of phenylalanine in the children's urine, so he postulated that they could not break down phenylalanine. He recommended limiting protein intake as a way to reduce phenylalanine in the diet for this disorder.

In 1935, Dr. Lionel Penrose recommended changing the name of the disease to phenylketonuria (PKU) because of the "phenylketone", phenylpyruvic acid, in the urine. Dr. George Jervis, the first American physician to study PKU, found that PKU was caused by errors in the functioning of the enzyme PAH.[8] Several researchers including Dr. Horst Bickel developed a protein substitute drink that was low in phenylalanine.[9] This drink was given to a young child, and the child's mental development and behavior improved. In 1957, Dr. Willard Centerwall created the "Wet Diaper" test for PKU. This test could identify increased levels of phenylpyruvic acid and diagnose PKU, but it was not accurate until the child was several weeks old.

MATERNAL PKU

Maternal PKU, defined as a pregnant woman with PKU, was first identified in 1957. Maternal PKU syndrome is potentially harmful to the fetus if the mother's blood phenylalanine levels are not being monitored and controlled. Mothers with uncontrolled PKU are at increased risk for having newborns with intrauterine growth retardation, facial dysmorphism, microcephaly, congenital heart disease, and developmental delay.[10,11] A dose-response relationship appears to exist, so women with higher phenylalanine levels have higher risk of adverse fetal outcomes.[12] Recognizing the importance of learning more about pregnancy outcomes and development of children born to mothers with PKU, Dr. Rich Koch and others started the International Maternal PKU Study. This study included women with PKU in the United States, Canada, and Germany and has allowed for much deeper exploration of maternal PKU and fetal outcomes.

HISTORY OF NEWBORN SCREENING FOR PKU

Dr. Robert Guthrie paved the way for NBS for PKU in 1960 when he developed a filter paper screening test for PKU that was inexpensive, accurate, and effective on newborns.[13] In the early 1960's, Guthrie coordinated a trial of NBS for PKU in 29 states.[14] Approximately 400,000 infants were screened using the

Guthrie Test. In 1963, Massachusetts became the first state to make NBS for PKU mandatory by law. Throughout the rest of the 1960's, more states began mandatory screening newborns for PKU. By 1975, 43 states had laws for mandatory NBS for PKU. Currently, every state screens newborns for PKU.

HISTORY OF NEWBORN SCREENING FOR PKU IN MICHIGAN

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 in Michigan. Since October 2004, Children's Hospital of Michigan Metabolic Clinic has been the primary referral site for all infants who have a positive screen for a metabolic disorder, including PKU. The clinic is responsible for the diagnosis and medical management of all referred infants.

PKU SCREENING PROGRAM EVALUATION STUDIES

Women with PKU must closely follow the low-phenylalanine diet to maintain appropriate levels of blood phenylalanine both before and during pregnancy. If a woman had high blood phenylalanine levels during pregnancy, the risk of spontaneous abortion, mental retardation, microcephaly, and/ or congenital heart disease in the child is increased. Since all infants born in Michigan since 1965 have been screened for PKU, many females with PKU are now of reproductive age.

We were interested in exploring maternal PKU in Michigan, specifically focusing on the number of women with PKU who deliver live births and their birth outcomes. Following the cohort of patients with PKU diagnosed through NBS in Michigan is challenging. However, we can utilize statewide databases to evaluate the prevalence of PKU and the birth outcomes of women with PKU.

NBS CHMMC DATABASE

The NBS Follow-up Program maintains a database of initial screening results and additional information received from the Children's Hospital of Michigan Metabolic Clinic (CHMMC) on patients referred for follow-up. The CHMMC is responsible for the diagnosis and medical management of all newborns with any of the 42 metabolic disorders detected by NBS, including PKU. The clinic also provides biochemical and molecular genetic diagnostic laboratory services. The CHMMC sends information about confirmatory results and health outcomes of patients with PKU to the NBS Follow-up Program for program evaluation. We used this database to provide detailed information on the 2009 birth cohort of cases.

Since screening for PKU began in 1965, 613 confirmed cases have been identified in Michigan. In 2009, 15 newborns were diagnosed with PKU; the detection rate was 1:7,686 newborns screened (Table 18). Of patients with PKU in the 2009 birth cohort, 40% had classic PKU, 20% had mild PKU, and the remaining 40% had benign hyperphenylalaninemia. Only patients with classic or mild PKU are diet-treated.

Table 18. Phenylketonuria Screening, Michigan, 2009

PKU Subtype	Confirmed (N)	Detection Rate
Classic	6	1:19,215
Mild	3	1:38,431
Hyperphenylalaninemia	6	1:19,215
Total	*15*	*1:7,686*

The CHMMC also sends data on pregnancy outcomes for women with PKU who live in Michigan at the time of pregnancy or who request medical management from CHMMC and live out of state. Recording of phenylalanine blood levels is incomplete, so we are not able to assess diet-compliance before and during pregnancy. We used pregnancy information on women with PKU who were born from 1965-1992.

In total, 428 cases of PKU were diagnosed from 1965-1992. Information was found on 55 women who had 94 pregnancies (Table 19). Approximately one-third of the pregnancies occurred in women with classic PKU (37%), one-third in women with mild PKU (30%), and one-third in women with hyperphenylalaninemia (33%).

Table 19. Pregnancies for women with PKU born 1965-1992, by PKU Type, Michigan

	Classic PKU		Mild PKU		Hyperphe		Total
	N	%	N	%	N	%	
Women	25	45.5	13	23.6	17	30.9	55
Pregnancies	35	37.2	28	29.8	31	33.0	94

Nearly one-third (N=30, 31.9%) of pregnancies ended in abortion (13 therapeutic and 17 spontaneous), and 64 (68.1%) ended in live birth. Of the 64 live births, no information was found for 20 infants (31.3%) (Table 20). As PKU subtype severity increased, the percentage of normal live births decreased; 56% of newborns to mothers with hyperphenylalaninemia were normal compared to 24% of newborns to mothers with classic PKU.

Table 20. Live Births Outcomes among Women with PKU born 1965-1992, by PKU Type, Michigan

Birth Outcome	Classic PKU		Mild PKU		Hyperphe		Total	
	N	%	N	%	N	%	N	%
Normal	5	23.8	9	50.0	14	56.0	28	43.8
Microcephaly	8	38.1	4	22.2	2	8.0	14	21.9
No info. found	8	38.1	5	27.8	7	28.0	20	31.3
PKU-affected	0	0.0	0	0.0	2	8.0	2	3.1
Total	21	100.0	18	100.0	25	100.0	64	100.0

The findings from this study have been presented at the Second National Summit on Preconception Health and Health Care, the 23rd Annual Healthy Mothers, Healthy Babies Conference, and the Michigan State Medical Society (MSMS) Perinatal Conference.

MICHIGAN INPATIENT DATABASE

The Michigan Inpatient Database (MIDB) is a database of hospital information collected by the Michigan Health & Hospital Association (MHA). Each hospital in the state reports data to the MHA, and the MHA de-identifies the reported data. The Michigan Department of Community Health purchases the MIDB from the MHA. The Division for Vital Records and Health Statistics at the Michigan Department of Community Health routinely links the MIDB with live births records to create a linked file of hospital discharge records for mothers with deliveries. We used the 1999-2008 MIDB to determine the number of hospitalizations among those with PKU and the demographic characteristics of those hospitalized. We also used the 1999-2008 linked maternal discharge dataset to investigate birth outcomes among women with PKU.

A total of 183 hospitalizations occurred from 1999-2008 where PKU (ICD-9 code 270.1) was listed as a diagnosis. Approximately one-quarter of the hospitalizations occurred among children less than 10 years of age (Table 21). The majority of the 183 hospitalizations occurred among whites (88.5%), and 7% of the records were missing race information. Females comprised 58% of the hospitalizations. This skewed distribution towards females is most likely influenced by deliveries since this was the most common principal diagnosis. The second most common principal diagnosis was pneumonia (5.5% of hospitalizations), though 120 unique diagnoses were listed as the principal diagnosis for these 183 hospitalizations. The mean length of stay was 9.6 days, with a median of 4.0 days, a mode of 2.0 days, and a range of 1 to 125 days.

Table 21. Age Distribution of Hospitalized Patients with Phenylketonuria Listed as a Diagnosis, MIDB, 1999-2008

Age (in years)	N	%
<10	47	25.7
10-19	14	7.7
20-29	19	10.4
30-39	11	6.0
40-49	25	13.7
50-59	29	15.8
60-69	21	11.5
≥70	17	9.3

Using the 1999-2008 linked file of maternal discharge records and live births, 15 women who delivered a live birth had PKU listed as a diagnosis. This linked file will be used to assess pregnancy outcomes among women with PKU who are not seen at CHMMC. It will also be used with the information from CHMMC for a validation study.

The Michigan NBS Follow-up Program utilized NBS data, data from the CHMMC, and other databases to assess the prevalence of PKU, to determine the number of hospitalizations and demographic characteristics of those hospitalized with PKU, and to evaluate birth outcomes to women with PKU. We plan to compare the linked file with the file maintained by the CHMMC and the NBS Follow-up Program to determine the completeness of reporting maternal PKU on hospital records.

Due to the potentially increased prevalence of microcephaly among offspring of women with mild and classic PKU compared to women with hyperphenylalaninemia, we are challenged to include pre-conception and inter-conception health assessment with NBS long-term follow-up strategies and standards of care. Further collaboration and partnership with other public health programs focused on these kind of health issues are underway. Also, we need to continue to educate patients and providers of different specialties who see both children and adults about the life-time challenges and needs of patients with disorders diagnosed through NBS.

V: QUALITY ASSURANCE INFORMATION

This section includes QA information about NBS specimen characteristics, turn-around time from birth to specimen collection, from birth to laboratory receipt of specimens, and time to treatment initiation.

SPECIMEN CHARACTERISTICS

Table 22 reports specimen characteristics by nursery type. Although 10.7% of infants were in the NICU, 66% and 47% of strong and borderline positives were received from the NICU, respectively. Isolated elevations of one or more amino acids and/ or acyl-carnitines were also significantly more prevalent among specimens from the NICU; these elevations are commonly associated with infants receiving TPN, of low birth weight, born preterm, and having been transfused. While the overall number of unsatisfactory specimens was greatest among hospital nurseries, the proportion of unsatisfactory specimens was greatest among midwife samples (5.5%). Early and transfused specimens were also more common among infants from the NICU. Late specimens, those collected after six days of life, were most common among midwife deliveries. The NBS Follow-up Program tracks all strong and borderline positive, isolated elevation, unsatisfactory, early, and transfused specimens; approximately 5,500 specimens were followed up in 2009. Strong positive results (n=515) are immediately referred to medical management centers for evaluation.

Table 22: Specimen Characteristics by Nursery Type, Michigan, 2009

Indicator	Type of Birth					
	Regular Nursery		NICU		Midwife	
	N	%	N	%	N	%
Strong Positive Specimens	175	0.17	340	2.76	0	-
Borderline Positive Specimens	576	0.56	515	4.18	0	-
All Positive Specimens*	1,118	1.09	924	7.50	0	-
Isolated elevations of amino acids and acyl-carnitines	4	0.004	547	4.44	0	-
Unsatisfactory Specimens	983	0.96	239	1.94	17	5.48
Late (>6 days) Specimens	98	0.10	72	0.58	18	5.81
Early (<1 day) Specimens	457	0.45	941	7.64	1	032
Transfused Specimens	7	0.01	135	1.23	0	-
Specimens Missing Demographics **	11,740	11.44	959	7.78	19	6.13
Total Births Screened	102,659	89.0	12,323	10.7	310	0.3

**Includes all strong and borderline specimens plus specimens positive for cystic fibrosis or hemoglobinopathies*
***Defined as missing race, specimen collection time, or birth weight*
Note: *Percentages expressed in the above table are column percentage.*

SCREENING TURN-AROUND TIME

Turn-around time in newborn screening 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 (PKU, MSUD, CAH, galactosemia and disorders detected by MS/ MS) is no later than the 7th day of

life; the target for other disorders is to initiate treatment by the 14th day of life when possible. To achieve this objective, it is important for hospitals and midwives to collect and mail specimens within the recommended guidelines.

TIME FROM BIRTH TO SPECIMEN COLLECTION

Table 23 reports the time from birth to NBS specimen collection by nursery type. The NBS Program recommends that specimens be obtained 24 to 36 hours after birth and mailed within 24 hours of specimen collection. As seen in Table 23, the time from birth until specimen collection varies considerably between hospital and non-hospital deliveries.

Over 95% of specimens from hospital nurseries are collected within 24 to 36 hours of birth; only 36% of midwife/ non-hospital birth specimens are collected in the recommended time frame. While less than 1% of initial specimens collected in hospital nurseries and NICUs are collected after 3 days of life, over 20% of specimens from midwife/ non-hospital births are collected after 3 days of life. The median time of specimen collection for midwife/ non-hospital births (42 hours) is twice that of the median collection times for hospital nursery and NICU births (each at 26 hours of life).

Table 23: Time from Birth to Specimen Collection by Nursery Type, Michigan, 2009

Action	Nursery Type	Time	N	(%)	Mean Time	Median Time
Time from birth to specimen collection (Hours)	Hospital Nursery	< 24 hrs	457	0.45	28.4	26.0
		24-36 hrs	97,758	95.30		
		36-48 hrs	3,553	3.46		
		48-72 hrs	594	0.58		
		>72 hrs	221	0.22		
	NICU	< 24 hrs	941	7.64	29.8	26.0
		24-36 hrs	10,153	82.45		
		36-48 hrs	895	7.27		
		48-72 hrs	204	1.66		
		>72 hrs	121	0.98		
	Midwife/ Non-Hospital	< 24 hrs	1	0.32	74.4	42.0
		24-36 hrs	111	35.81		
		36-48 hrs	62	20.00		
		48-72 hrs	72	23.23		
		>72 hrs	64	20.65		

TIME FROM SPECIMEN COLLECTION TO LABORATORY RECEIPT

The time from specimen collection to laboratory receipt (Table 24) is also an important quality assurance indicator in that it measures how quickly specimens are shipped from birthing centers/midwives to the state NBS laboratory. While specimen collection can be delayed for various reasons, some medically necessary, the time from specimen collection to laboratory receipt should not be influenced by such delays. The target time from specimen collection to laboratory receipt is fewer than two days.

Approximately 58-59% of specimens from hospitals, NICUs, and mid-wives were transmitted to the NBS laboratory within 2 days of collection. The proportion of specimens received more than 6

days after collection is 6.5 times greater among midwife/ non-hospital births compared to NICU births and approximately 9 times greater relative to hospital births.

Table 24: Time from Specimen Collection to Laboratory Receipt by Nursery Type, Michigan, 2009

Action	Nursery Type	Time	N	(%)	Mean Time	Median Time
Time from specimen collection to receipt in lab (Days)	Hospital Nursery	**<2 days**	60,827	59.33	1.96	1.63
		2-3 days	36,043	35.16		
		4-5 days	5,126	5.00		
		≥ 6 days	525	0.51		
	NICU	**<2 days**	7,134	58.04	2.02	1.75
		2-3 days	4,395	35.75		
		4-5 days	677	5.51		
		≥ 6 days	86	0.70		
	Midwife/ Non-Hospital	**<2 days**	179	57.74	2.21	1.53
		2-3 days	105	33.87		
		4-5 days	12	3.87		
		≥ 6 days	14	4.52		

TIME FROM BIRTH TO SPECIMEN RECEIPT BY NEWBORN SCREENING LABORATORY

The laboratory should receive specimens no later than 72 hours of life to meet the target of treatment by the seventh day of life. Table 26 reports the time from birth to NBS Laboratory receipt of specimens.

As indicated in Table 25, currently slightly more than half of hospital nursery/NICU specimens (55.4% and 52.3%, respectively) and less than 30% of midwife/non-hospital birth specimens are received by the NBS laboratory within three days of life.

Two program changes were implemented in 2008 to decrease time between birth and laboratory receipt of specimens: 1) increased laboratory operation from five to six days a week (started June 21st, 2008), and 2) funded a courier system for delivering specimens directly to the state laboratory within 24 hours of specimen collection.

Table 25: Time from Birth to Receipt of Specimen by NBS Laboratory by Nursery Type, Michigan, 2009

Action	Nursery Type	Time	N	%	Mean Time (days)	Median Time (days)
Time from Birth to Laboratory Receipt of Specimen	Hospital Nursery	**<3 days**	56,907	55.43	3.16	2.78
		4-5 days	38,967	37.96		
		6-7 days	6,013	5.86		
		≥7 days	771	0.75		
	NICU	**<3 days**	6,440	52.26	3.31	2.92
		4-5 days	4,870	39.52		
		6-7 days	804	6.52		
		≥7 days	208	1.69		
	Midwife	**<3 days**	89	28.71	5.31	3.91
		4-5 days	139	44.84		
		6-7 days	46	14.84		
		≥7 days	36	11.61		

TIME TO TREATMENT

Table 26 reports the time to treatment for disorders other than hemoglobinopathies; hemoglobinopathy treatment (penicillin prophylaxis) is provided later than for other disorders and is reported in a separate table. As indicated in Table 25, time to treatment ranged from 3 to 78 days after birth among all disorders. There are limiting factors in the screening and diagnostic process for some disorders like partial biotinidase deficiency and CH that affect the opportunity to meet treatment targets. These disorders often require one or more retests before being referred for confirmatory diagnosis. Benign hyperphenylalaninemia is included in the table but is not diet treated. The 2 cases of persistent isolated hypercitrullinemia are included in the table, but they are not treated, so they have no treatment start date.

GALACTOSEMIA AND BIOTINIDASE DEFICIENCY

The one case of confirmed classic galactosemia with treatment start date information was treated within seven days, and nineteen cases of Duarte galactosemia were treated within fifteen days of life. The three cases of profound biotinidase deficiency were treated within seven days of life. One case of partial biotinidase deficiency was treated by the first week of life; the remaining eleven cases of partial biotinidase deficiency were treated beyond the first week of life.

MS/MS DISORDERS

Thirty-eight newborns were confirmed with disorders detected by MS/ MS (six newborns with hyperphenylalaninemia did not require treatment). Five of the six cases of classic PKU were treated within the first week of life. The remaining case of classic PKU was treated on the eighth day of life. One case of homocystinuria was treated on the seventh day of life, and one case of methylmalonic acidemia was treated on the eighth day of life. Of the sixteen infants with fatty acid oxidation disorders and a treatment start date, fourteen (87.5%) were treated within the first week of life.

ENDOCRINE DISORDERS CAH AND CH

The salt-wasting form of CAH is life-threatening in the first few weeks of life. One of the two CAH cases detected was salt-wasting; both cases of CAH were treated by the eighth day of life, and

the salt-wasting CAH case was treated by the fifth day. The target for CH is treatment by fourteen days of life for newborns with initial TSH values greater than 50. Of the CH cases with a reported medication start date and an initial TSH >50, 30 (75%) were treated by the 14th day of life.

Table 26: Time to Treatment of Amino Acid Disorders, Organic Acid, Fatty Acid Oxidation, and Endocrine Disorders, Michigan, 2009

Disorder		Total	Treatment Time (days from birth) N			Treatment Time Range (days)
		(N)	1-7	8-14	>14	
Galactosemia	Classic (GG)	1	1			3
	Duarte (DG)	21	8	11	2	4-45
Biotinidase Deficiency	Partial	12	1	2	9	5-42
	Profound	3	3			6-7
Amino Acid Disorders	Citrullinemia/ASA (CIT/ASA)	2				
	Phenylketonuria Classic	6	5	1		6-8
	Mild	3		2	1	8-43*
	Benign Hyperphenylalaninemia	6				N/A
	Homocystinuria (HCY)/ Hypermethioninemia (MET)[1]	2	1			7
	Total	*18*	*6*	*3*	*1*	*6-43*
Organic Acid Disorders	Methylmalonic Acidemia (MMA)[2]	2		1		8
	Total	*2*		*1*		*8*
Fatty Acid Oxidation Disorders	Carnitine Uptake Defect (CUD)	1			1	18
	Short-Chain Acyl-CoA Dehydrogenase deficiency (SCAD)	5	4		1	3-17
	Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)[3]	9	8			4-6
	Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)	2	2			4-5
	Total	*17*	*14*		*2*	*4-18*
Endocrine Disorders	Congenital Hypothyroidism TSH > 50	40	11	19	10	5-55
	TSH ≤ 50	27		2	25	9-78
	Congenital Adrenal Hyperplasias Salt-Wasting	1	1			5
	Non Salt-Wasting	1		1		8

[1]1 case missing treatment start date
[2]1 case missing treatment start date
[3]1 case missing treatment start date
*PKU mild case who started treatment at 43 days was originally classified as benign hyperphenylalaninemia, a disorder that does not require diet-treatment.

HEMOGLOBINOPATHIES

Table 29 reports the time to treatment among hemoglobinopathies. The target is to initiate penicillin prophylaxis within by four months of life. Of the 44 cases having a penicillin start date reported, 86% were treated with penicillin within the first four months, 7% began treatment between four and five months of life, 2% began treatment between five and six months, and 5% began treatment beyond six months of age.

Table 29: Time to Penicillin Initiation for Hemoglobinopathies, Michigan, 2009

Disorder	Penicillin Prophylaxis Initiation Time			
	< 120 days	120-149 days	150-179 days	≥ 180 days
Sickle Cell Disorders*	38 (86.4%)	3 (6.8%)	1 (2.3%)	2 (4.5%)

*13 cases missing penicillin initiation date

VI: CONCLUSIONS

NBS is a critical public health program protecting the lives of our State's newest residents. In 2009, the NBS Laboratory screened 115,619 infants, and the NBS Follow-up Program tracked approximately 5,500 strong and borderline positive, isolated elevation, unsatisfactory, early, and transfused specimens; strong positive results were immediately referred to medical management centers for evaluation. A total of 234 newborns were identified with a disorder by NBS in 2009. Treatment was initiated, where necessary, within 2 weeks of life for 64% of the cases having reported information. Since NBS began in Michigan in 1965, 4,411 newborns have been diagnosed and treated.

Introduction of MS/ MS technology in 2003 to screen for MCAD screening initiated a rapid expansion of newborn screening over the next three years increasing the number of disorders screened from seven in 2003 to 48 in 2006. The addition of CF and hearing screening in October of 2007 increased the screening panel to 50, completing the ACMG/ HRSA/ March of Dimes recommended screening panel for state newborn screening programs.

Future plans include using administrative databases to learn more about the prevalence, healthcare utilization, morbidity, and mortality of NBS disorders across the lifespan. In conclusion, we are continuing to both expand and refine the NBS program in order to better protect the health of infants born in Michigan.

REFERENCES

1. Rinaldo, P., Zafari, S., Tortorelli, S., and Matern, D. (2006) Making The Case for Objective Performance Metrics In Newborn Screening by Tandem Mass Spectrometry. Mental Retardation and Developmental Disabilities Research Reviews. 12: 255-261.
2. PAH: Phenylalanine hydroxylase locus knowledgebase. http://www.pahdb.mcgill.ca/ (Accessed 16 June 2010).
3. Hanley WB. Adult Phenylketonuria. Am J Med 2004;117:590-5.
4. Hardelid P, Cortina-Borja M, Munro A, et al. The Birth Prevalence of PKU in Populations of European, South Asian and Sub-Saharan African Ancestry Living in South East England. Annals of Human Genetics 2008;76:65-71.
5. Scriver CR, Kaufman S. Hyperphenylalaninemia: Phenylalanine Hydroxylase Deficiency. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kenzler K, Vogelstein B, editors. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. New York: McGraw-Hill; 2001. p. 1667-724.
6. Følling I. The Discovery of Phenylketonuria. Acta Pediatr Suppl 1994;407:4-10.
7. Følling A. Über ausscheidung von phenylbrenztraubensäure in den harn als stoffwechselanomalie in verbindung mit imbezillität. Hoppe-Seylers Z Physiol Chem 1934;227:169-76.
8. Jervis G. Phenylpyruvic oligophrenia: Introductory study of 50 cases of mental deficiency associated with excretion of phenylpyruvic acid. Archives of Neurology and Psychiatory. 1937;38:944.
9. Bicket H, Gerrard J, Hickmans EM. Influence of phenylalanine intake in phenylketonuria. Lancet 1953;2:812.
10. Lee PJ, Ridou H, Walter JH, Cockburn F. Maternal phenylketonuria: Report from the United Kingdom Registry 1978-97. Arch Dis Child 2005;90:143-6.
11. Lenke RR, Levy HL. Maternal phenylketonuria and hyperphenylalaninemia: An international survey of the outcome of untreated and treated pregnancies. N Engl J Med 1980;303:1208-18.
12. Levy HL, Gharami M. Maternal phenylketonuria; A metabolic teratogen. Teratology 1976;53:176-84.
13. Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. Pediatrics 1963;32:338-43.
14. Guthrie R, Whitney S. Phenylketonuria detections in the newborn infant as a routine hospital procedure: A trial of a phenylalanine screening method in 400,000 infants. Children's Bureau Publication 419. Washington (DC): US Department of Health, Education, and Welfare; 1964.