MICHIGAN NEWBORN SCREENING PROGRAM

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Michigan Newborn Screening Program

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EXECUTIVE SUMMARY

This report provides an overview of Michigan's Newborn Screening Program (NBS), target outcomes and quality assurance information, as well as updates on supporting legislation and research guidelines (provided in appendices). The NBS program includes three components: screening, follow-up, and medical management; the primary focus of this report is on follow-up.

Since the program began in 1965, when the state began screening infants for phenylketonuria, more than 40 additional disorders have been added to the screening panel and millions of infants have been screened. In 2006, 126,020 infants were screened, 125,600 were Michigan residents; of those, 0.15% were diagnosed as having a disease.

Developments occurring in 2006:

- On February 23, 2006, SB 794 was passed and amended Public Act 368 of 1978 by adding sections 5430 and 5432. In summary, this bill created a ten-member Newborn Screening Quality Assurance Advisory Committee to be appointed by the department.

- The fee for newborn screening cards will be increased to $85.52, as recommended by the Quality Assurance Advisory Committee, as of October 1, 2007.

- A pilot second tier congenital adrenal hyperplasia (CAH) test was added to the NBS program in August, 2006. The addition of this test resulted in a 90% reduction in false positive screening results for CAH. However, medical decisions are not based on these results at this point.

- Newsletters will be disseminated twice a year and will detail a particular condition in each edition.

- Cystic Fibrosis will be added to the NBS panel of disorders as of October 1, 2007.

TABLE OF CONTENTS

Acronym[1]	Name
ACMG	American College of Medical Genetics
ASA	Argininosuccinic Aciduria
CAH	Congenital Adrenal Hyperplasia
CH	Congenital Hypothyroidism
CHM	Children's Hospital of Michigan
CHMMC	Children's Hospital of Michigan Metabolic Clinic
EBC	Electronic Birth Certificate
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
MSUD	Maple Syrup Urine Disease
NBS	Newborn Screening Program
NICU	Neonatal Intensive Care Unit
PCP	Primary Care Physician
PEAC	Pediatric Endocrinology Advisory Committee
PKU	Phenlyketonuria
PPV	Positive Predictive Value
QA	Quality Assurance
QAAC	Quality Assurance Advisory Committee
SC	Sickle Cell
SCDAA	Sickle Cell Disease Association of America
TMS	Tandem Mass Spectrometry
TSH	Thyroid Stimulating Hormone
U of M	University of Michigan

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

I: INTRODUCTION

WHAT IS NEWBORN SCREENING?

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 included 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 for signs of treatable disorders.

NBS began in the 1960s when Dr. Robert Gutherie developed the bacterial inhibition assay to diagnose phenlyketonuria (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. Gutherie'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 (See Appendix A: NBS legislation) 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, mandated a fee to fund the program, and added comprehensive programs for follow-up, medical management, and quality assurance. Congenital adrenal hyperplasia (CAH) was added to the screening panel in 1993.

The introduction of tandem mass spectrometry (TMS) in 2003 enabled the state laboratory to efficiently screen for a large number of disorders detectable from a single blood spot. The first was 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 TMS disorders recommended by the American College of Medical Genetics (ACMG) and the March of Dimes. Screening for Cystic Fibrosis is scheduled to begin October 1, 2007, thus meeting another recommendation of the ACMG. Table 1 provides the complete list of disorders currently screened for in Michigan. 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. Information about the legislation supporting Michigan's NBS Program can be found in Appendix A.

Table 1: Disorders Included in the Newborn Screening Panel, Michigan, 2006

Phenylketonuria (PKU)	Isovaleric acidemia (IVA)
Benign hyperphenylalaninemia (H-PHE)	2-Methyl butyryl-CoA dehydrogenase deficiency (2MBG)
Biopterin cofactor biosynthesis (BIOPT (BS))	3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
Defects of biopterin cofactor regeneration (BIOPT(Reg))	3-OH 3-CH3 glutaric aciduria (HMG)
Maple syrup disease (MSUD)	3-Methylglutaconic aciduria (3MGA)
Homocystinuria (HCY)	Beta-ketothiolase deficiency (BKT)
Hypermethioninemia (MET)	Glutaric acidemia type I (GA I)
Citrullinemia (CIT)	Propionic acidemia (PA)
Citrullinemia Type II (CIT II)	Methylmalonic acidemia (mutase deficiency) (MUT)
Argininosuccinic acidemia (ASA)	Methylmalonic acidemia (Cbl A,B) MA
Tyrosinemia Type I (TYR I)	Methylmalonic acidemia (Cbl C,D) MA
Argininemia (ARG)	Multiple carboxylase deficiency (MCD)
Carnitine:acylcarnitine translocase deficiency (CACT)	2-Methyl 3 hydroxy butyric aciduria (2M3HBA)
Carnitine palmitoyltransferase II deficiency (CPT II)	Malonic acidemia (MAL)
Carnitine uptake defect (CUD)	Isobutyryl-CoA dehydrogenase deficiency (IBG)
Carnitine palmitoyltransferase IA deficiency (liver) (CPT 1A)	Congenital adrenal hyperplasia (CAH)
Short-chain acyl-CoA dehydrogenase deficiency (SCAD)	Congenital hypothyroidism (CH)
Glutaric acidemia type II (GA II)	Galactosemia (GALT)
Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)	Biotinidase deficiency (BIOT)
Long-chain L-3-OH acyl-CoA dehydrogenase deficiency (LCHAD)	Sickle cell anemia (Hb SS)
Trifunctional protein deficiency (LCHAD/TFP)	Hb S/C Disease (Hb S/C)
Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	Hb S/Beta-thalassemia (Hb S/Beta-Th)
Medium-chain ketoacyl-CoA thiolase deficiency (MCKAT)	

Figure 1: Overview of the Michigan Newborn Screening Program

HOSPITALS

Michigan currently has 94 hospitals with newborn nurseries. Each hospital has a designated hospital 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 mailed or 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 late and unsatisfactory specimens and improperly completed specimen cards with the state average for these indicators. In addition, hospitals receive site visits by the NBS follow-up nurse to evaluate the screening process and make recommendations for improving the process.

MIDWIVES AND HOME BIRTH ATTENDANTS

There are 58 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 occur in populations with a high incidence of several of the NBS disorders such as the Amish and Mennonite populations served by midwives.

MICHIGAN DEPARTMENT OF COMMUNITY HEALTH

The MDCH NBS program includes the NBS laboratory, the follow-up program and three medical management centers. The follow-up program is responsible for the coordination of the medical management centers. Each component is described in the following subsections.

-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. Francis 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 lab actively participates in HRSA region 4 initiatives for the standardization of tandem mass spectrometry for screening for metabolic diseases along with the standardixation of screening activities for CAH and CH. Testing is available during weekdays with additional laboratory reporting available on Saturdays. More than 700 specimens can be analyzed each day for 48 disorders.

-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. The follow-up starts with referring these infants to one of three 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 14 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.

-NEWBORN SCREENING MEDICAL MANAGEMENT CENTERS

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

-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.

-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.

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 Charles Whitten, M.D. A clinical services component is at Children's Hospital of Michigan, 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.

This section describes the methods used to calculate: a) total number of newborns in the population to be screened (statewide and regionally), 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 at MDCH to calculate the total number of live births eligible to be screened both statewide and regionally. Regions as defined by the former Michigan Perinatal Health Care Systems are presented in Appendix B. County population estimates for the year 2005[2] were used to calculate regional population estimates because county population estimates for 2006 have yet to be released in a final format. The total number is not expected to change significantly from 2005 to 2006. Regional population estimates are used as denominators for the regional prevalence of NBS cases depicted in section 3.

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

We used the MDCH laboratory information system (Perkin Elmer Life Sciences, Inc.) to identify positive cases and case-related information. 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. Further information about case definitions and confirmation processes can be found in the NBS program manual at www.michigan.gov/newbornscreening. 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.

SCREENING PERFORMANCE INDICATORS

Table 2 provides a description of each screening performance indicator 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 screening for metabolic disorders by TMS and hemoglobinopathies by high performance liquid chromatography (HPLC) is very 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.

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[2] Obtained from http://www.mdch.state.mi.us/pha/osr/chi/pop/frame.html

Table 2: 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 and the percentage of those positive screens among infants in the NICU
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 has been confirmed
Detection Rate*	The number of confirmed cases of a 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 false positive screens divided by the total number of infants screened expressed as a percentage (%)
PPV	Positive Predictive Value: the number of confirmed cases divided by the number of total positive screens expressed as a percentage (%)

includes only in-state residents in the denominator

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, c) the quality of the specimens received and d) time from birth to treatment of each disorder.

III: SCREENING RESULTS

DEMOGRAPHICS OF INFANTS SCREENED

This section describes the population of infants screened during 2006 in terms of geographic location, race, sex, birth weight, gestational age, and birthplace (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 predominately found in African Americans, thus the number of cases and regional prevalence will fluctuate with the birthrate and location of African Americans.

The Michigan NBS program screened 99.6% (126,020) of the 126,509 live births occurring in Michigan in 2006. There were 415 live births (0.3% of 126,020 live births screened in Michigan) to out-of-state residents. Tables 3 and 4 report the demographics of in-state and out-of-state residents screened in 2006 respectively. As indicated in Table 3, the majority of in-state infants screened were white, born in hospital nurseries at term (>37 weeks gestational age), and were of normal birth weight (>2500g). Overall, 10.8% of infants screened were in the NICU, 1.4% weighed less than 1500g at birth, and 0.6% were born prior to 28 weeks gestational age. Infants transferred to the NICU, born premature (<37 weeks gestational age), and of low birth weight (<2500g) were over-represented among African Americans.

GEOGRAPHIC DISTRIBUTION OF CASES IDENTIFIED BY NEWBORN SCREENING

Figures 2-4 depict the regional prevalence (regions are defined in Appendix B) of cases having disorders included in the NBS panel through 2006. Maps depict the density of cases by region; darker shades indicate a greater number of cases. Tables present, by region, the prevalence estimates for each group of disorders per 100,000 residents, and the number and frequency of cases.

HEMOGLOBIN DISORDERS

Figure 2 provides the regional prevalence of hemoglobinopathies (Hb SS, Hb SC, Hb S/beta thal). As indicated in the table, most of the hemoglobinopathies (75%) are diagnosed in Metropolitan Detroit (regions 1-3) with region 1 having the greatest prevalence (27.7 cases per 100,000 residents). This is why the hemoglobinopathy medical management program and the major sickle cell clinic in Michigan are located in Detroit. Other clinics that see 50 or more sickle cell patients are located in Grand Rapids, Kalamazoo, East Lansing, Ann Arbor and Flint/Saginaw.

ENDOCRINE DISORDERS

Figure 3 provides the regional prevalence of endocrine disorders (CH and CAH) through 2006. While the overall prevalence of the endocrine and hemoglobin disorders is similar, 13.2 and 12.7 per 100,000 residents respectively, the prevalence of endocrine disorders does not vary as much from region to region compared to the hemoglobinopathies. The Metropolitan Detroit area (Regions 1-3), which includes the Pediatric Endocrine Follow-up Program at the University of Michigan, accounts for approximately 50% of all cases. The endocrine follow-up program coordinates re-testing, diagnosis and medical management for all newborns with positive screens for CH or CAH through a network of pediatric endocrinologists in Metropolitan Detroit, Ann Arbor, Lansing, Kalamazoo, Grand Rapids and Saginaw/Flint.

Table 3: Demographics of Infants Screened, Michigan, 2006, Excluding Out-of-State Residents, N=125,600

Race/ Ethnicity *Missing data: n=11,905*	Row Total	Nursery Type						Birth weight (grams) *Missing data: n=1,559*						Gestational Age (weeks) *Missing data: n=4,494*					
		Hosp. Nursery^		Midwife		NICU		<1500		1500- 2500		>2500		< 28		28-37		>37	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Black	21,598	17,986	83.2	4	.02	3,626	16.8	622	2.9	2,359	10.9	18,339	84.9	268	1.2	4,578	21.2	15,654	72.5
White	81,139	73,213	90.2	255	0.3	7,671	9.5	797	1.0	4,666	5.8	74,730	92.1	308	0.4	13,755	17.0	64,841	79.9
Hispanic*	8,378	7,639	91.2	9	0.1	730	8.7	82	1.0	453	5.4	7,748	92.5	34	0.4	1,331	15.9	6,777	80.9
American Indian	589	543	92.2	0	0	46	7.8	5	0.9	22	3.7	553	93.9	2	0.3	91	15.5	479	81.3
Asian/Pac. Islander	2,291	2,108	92.0	1	.04	182	7.9	23	1.0	146	6.4	2,097	91.5	3	0.1	370	16.2	1,840	80.3
Middle Eastern	3,658	3,313	90.6	0	0	345	9.4	51	1.4	242	6.6	3,340	91.3	25	0.7	551	15.1	2,976	81.4
Multi-Racial	4,420	3,996	90.4	10	0.2	414	9.4	53	1.2	309	7.0	4,014	90.8	25	0.6	788	17.8	3,473	78.6
Column Total:	*113,695*	101,141	*89.0*	270	*0.24*	12,284	*10.8*	1,551	*1.4*	7,744	*6.8*	103,073	*90.7*	631	*0.6*	20,133	*17.7*	89,263	*78.5*

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.*

*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 4: Demographics of Infants Screened, Michigan, 2006, Out-of-State Residents, N=415

Race/ Ethnicity *Missing data: n=38*	Row Total	Nursery Type						Birth weight (grams) *Missing data: n=4*						Gestational Age (weeks) *Missing data: n=19*					
		Hosp. Nursery^		Midwife		NICU		<1500		1500- 2500		>2500		< 28		28-37		>37	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Black	38	25	65.8	-	-	13	34.2	1	2.6	7	18.4	30	79.0	-		14	36.8	22	57.9
White	312	260	83.3	-	-	52	16.7	10	3.2	15	4.8	283	90.7	5	1.6	64	20.5	229	73.4
Hispanic**	14	10	71.4	4	28.6			-	-	1	7.1	13	92.9	-	-	5	35.7	7	50.0
American Indian	1	1	100	-	-	-	-	-	-	-	-	1	100	-	-	1	100	-	-
Asian/Pac. Islander	6	4	66.7	-	-	2	33.3	-	-	2	33.3	4	66.7	-	-	2	33.3	3	50.0
Middle Eastern	12	11	91.7	-	-	1	8.3	1	8.3	1	8.3	10	83.3	-	-	5	25.0	9	75.0
Multi-Racial	8	8	100	-	-	-	-	-	-	1	12.5	7	87.5	-	-	2	25.0	6	75.0
Column Total:	*377*	*309*	*82.0*	*-*	*-*	*68.1*	*18.0*	*12*	*3.2*	*26*	*6.9*	*335*	*88.9*	*5*	*1.3*	*86*	*22.8*	*269*	*71.4*

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.

*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.

Region	Regional Population 2005 (N)	Regional Prevalence Per 100,000 (N)	Cases	
			N*	%
[1] Detroit	2,999,096	27.7	831	64.62
[2] Oakland	1,214,361	6.7	81	6.3
[3] Ann Arbor	942,961	6.3	59	4.59
[4] Kalamazoo	1,002,722	7.7	77	5.99
[5] Grand Rapids	1,341,815	4.8	64	4.98
[6] Lansing	570,605	6.1	35	2.72
[7] Flint	537,244	15.3	82	6.38
[8] Saginaw	755,879	7.5	57	4.43
[9] North Lower Peninsula	441,492	0.0	0	0
[10] Upper Peninsula	314,685	0.0	0	0
Total	10,120,860	12.7	1286	100
*45 cases missing address information, 2 moved out-of-state				
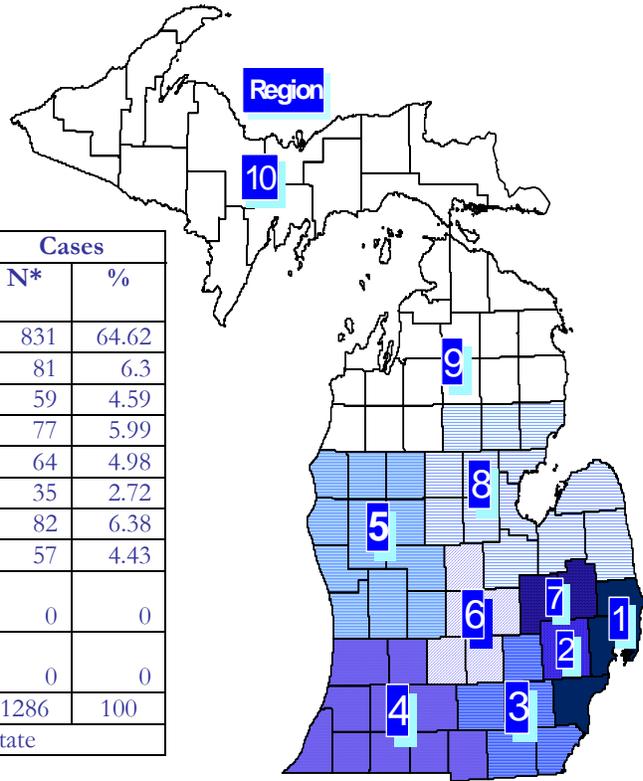
Figure 2: Number and Regional Prevalence of Hemoglobinopathy Cases Identified by Newborn Screening, Michigan, 1987-2006

Region	Regional Population 2005 (N)	Regional Prevalence Per 100,000 (N)	Cases	
			N*	%
[1] Detroit	2,999,096	14.3	428	29.5
[2] Oakland	1,214,361	13.3	161	11.1
[3] Ann Arbor	942,961	11.5	108	7.4
[4] Kalamazoo	1,002,722	12.2	122	8.4
[5] Grand Rapids	1,341,815	16.0	215	14.8
[6] Lansing	570,605	11.7	67	4.6
[7] Flint	537,244	14.9	80	5.5
[8] Saginaw	755,879	11.9	90	6.2
[9] North Lower Peninsula	441,492	8.8	39	2.7
[10] Upper Peninsula	314,685	7.0	22	1.5
Total	10,120,860	13.2	1,332	100
*165 cases missing address information				

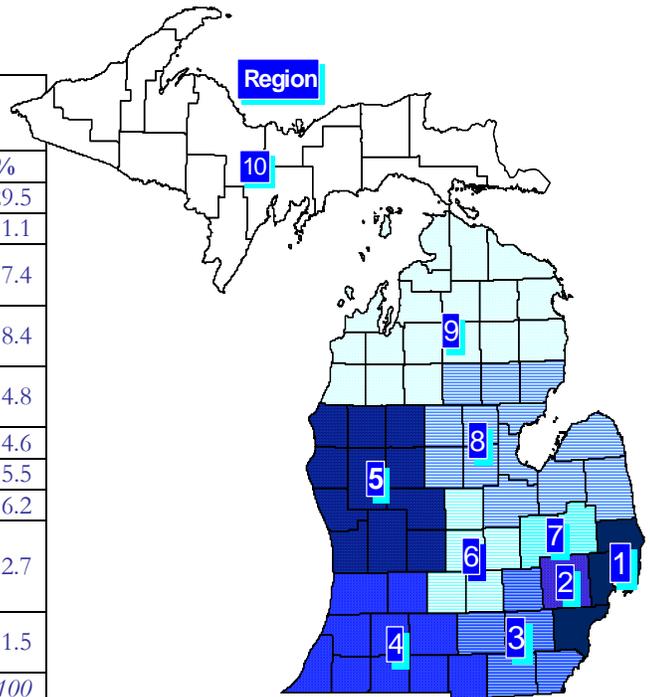**Figure 3: Number and Regional Prevalence of Endocrine Disorder Cases Identified by Newborn Screening, Michigan, 1987-2006**

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METABOLIC DISORDERS

Figure 4 depicts the regional prevalence of metabolic disorders including the disorders detected by TMS (amino acid, organic acid, and fatty acid oxidation disorders), galactosemia and biotinidase deficiency. The prevalence of these disorders is greatest in the Grand Rapids and Lansing regions, 12.3 and 10.5 per 100,000 residents respectively and lowest in the Flint region, 5.2 per 100,000 residents. The Metropolitan Detroit area (Regions 1-3) accounts for 52% of metabolic cases. The Children's Hospital of Michigan's Metabolic Clinic, located in Detroit is responsible for diagnosis and management of the metabolic disorders. A second NBS metabolic clinic in Grand Rapids, affiliated with Spectrum Hospital and staffed by physicians from CHMMC and Michigan State University, provides coverage for patients in central and western Michigan and the northern lower and upper peninsulas.

Region	Regional Population 2005 (N)	Regional Prevalence Per 100,000 (N)	Cases	
			N*	%
[1] Detroit	2,999,096	7.5	224	26.7
[2] Oakland	1,214,361	7.1	86	10.3
[3] Ann Arbor	942,961	8.2	77	9.2
[4] Kalamazoo	1,002,722	7.7	77	9.2
[5] Grand Rapids	1,341,815	12.3	165	19.7
[6] Lansing	570,605	10.5	60	7.2
[7] Flint	537,244	5.2	28	3.3
[8] Saginaw	755,879	8.9	67	8.0
[9] North Lower Peninsula	441,492	7.7	34	4.1
[10] Upper Peninsula	314,685	6.4	20	2.4
Total	10,120,860	8.3	838	100.0
*65 cases were missing address information				

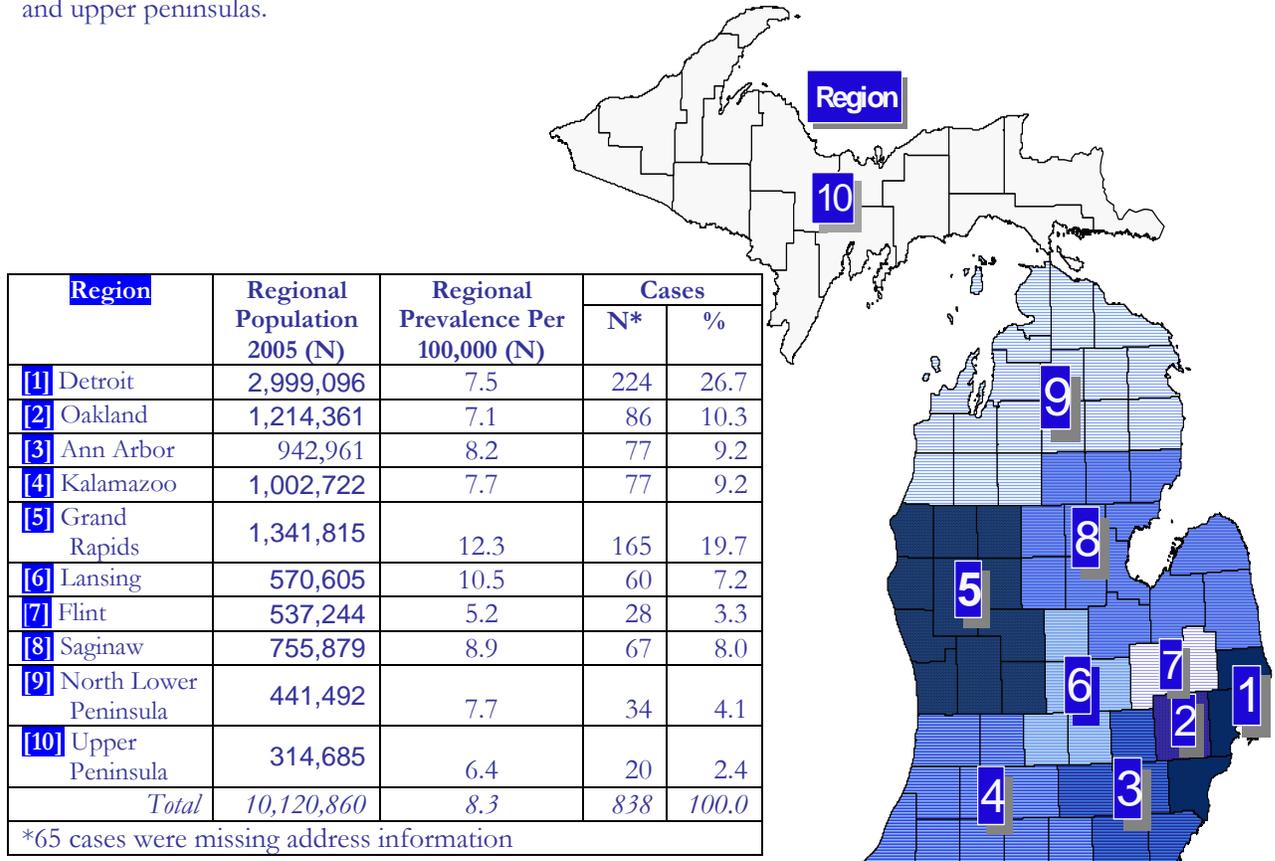**Figure 4: Number and Regional Prevalence of Metabolic Disorder Cases Identified by Newborn Screening, Michigan, 1965-2006**

Outcome information is provided for the 48 disorders screened for in 2006 in the following sub-sections. The total number of cases detected both in and through 2006 is presented along with screening performance metric targets and screening performance metrics. The disorders are organized into three categories: metabolic, endocrine and hemoglobin, corresponding to the three medical management programs responsible for diagnosis and medical treatment.

CUMULATIVE DETECTION RATE

Table 5 reports the cumulative detection rate of disorders identified via NBS by classification both in and through 2006. The metabolic disorders detected by TMS are grouped by category (amino acid, organic acid and fatty acid oxidation disorders). Two metabolic disorders, galactosemia and biotinidase deficiency, not detectable by TMS (they are detectable by enzyme assay screening) 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 treating 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 2006, while galactosemia disorders were the least prevalent.

Table 5: Disorders Identified via Newborn Screening, Michigan Residents, 1965-2006

Type of Disorder Classification (Year Screening Began)	Cases in 2006 (N)	Cases Through 2006 (N)	Cumulative Detection Rate*
Galactosemia (1985)	11	116	1: 24,850
Biotinidase Deficiencies (1987)	20	148	1: 16,928
Amino Acid Disorders (1965)	16	590	1: 9,901
Organic Acid Disorders (2005)	8	10	1: 12,752
Fatty Acid Oxidation Disorders (2003)	11	39	1: 9,951
Congenital Hypothyroidism (1987)	59	1,394	1: 1,870
Congenital Adrenal Hyperplasias (1993)	3	103	1: 16,819
Hemoglobinopathies (1987)	63	1,336	1: 1,951

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. Galactosemia includes both classical cases and Duarte varients (DG) since 2004. Biotinidase Deficiency includes both partial and profound biotinidase deficiency.

Congenital hypothyroidism accounted for 31.7% of all disorders detected in 2006 and 37.4% of all cases detected cumulatively. Hemoglobinopathies account for 31.2% of all cases detected in 2006 and 35.7% of all cases detected cumulatively. Disorders detected by TMS (amino acid, organic acid and fatty acid oxidation disorders) accounted for 24% of cases in 2006 and 17% cumulatively. Galactosemia, including Duarte compound heterozygotes, accounted for 6% of all disorders detected in 2006 and 3% cumulatively. Biotinidase deficiency, including partial biotinidase deficiency, accounted for 11% of all cases detected in 2006 and 4% of all cases detected cumulatively. CAH accounted for 1.6% all of cases in 2006 and 2.8% of all cases detected cumulatively.

In summary, CH and hemoglobin disorders account for about two-thirds of all cases detected annually. Although TMS disorders currently account for about one-quarter of cases detected annually, it is expected that this proportion will increase as this technology is expanded to detect additional disorders. Also, it is now possible, but not yet practical, to detect all of the current disorders except CH by TMS. This suggests that over time TMS screening will become even more dominant as the primary platform for newborn screening. The current cumulative prevalence of TMS detected disorders is 1:607.

SCREENING PERFORMANCE METRIC TARGETS

Screening performance metric targets are presented in Table 6. 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 classical 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.

Piero Rinaldo, M.D., Ph.D., et al. (2006) recently reported screening performance targets for TMS disorders based on a worldwide database in *Mental Retardation and Developmental Disability Reviews.*[3] Performance metrics (detection rate, false positive rate (FPR) and positive predictive value (PPV)) provide NBS programs with a method of assessing screening performance over time and in meeting established or consensus performance targets. Performance targets for TMS screening, based on data reported by Rinaldo et al., are included in Table 6.

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 electrophoresis. There are some disease cases that are re-classified (SS to S/beta thal) or occasionally to sickle cell trait on confirmatory testing but this does not significantly change the FPR and PPV for hemoglobinopathies of close to 0% and 100% respectively.

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[3] 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.

Table 6: Screening Performance Metric Targets

Disorder Category	Disorder	Performance Metric	Performance Target
Galactosemia Classical (G/G)		Detection Rate	1: 47,000
		FPR	< 0.5%
		PPV	> 5%
Biotinidase Deficiency (profound)		Detection Rate	1:109,300 - 1:211,20
		FPR	<0.5%
		PPV	>5 %
TMS 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 7 reports screening performance metrics for all disorders for 2006. Performance metrics for individual TMS disorders are provided in the following section in Tables 10, 11, and 12. Overall, 50% of positive screens are from newborns in the NICU compared to 11% of births in the NICU. NICU positive screens ranged from 92.3% for CAH to 24.5% for amino acid disorders. The incidence of NBS disorders in the NICU is 1:368 compared to an incidence of 1:718 in non-NICU births.

GALACTOSEMIA AND BIOTINIDASE DEFICIENCY

The galactosemia detection rate (including Duarte D/G variants) was 1:11,418 in 2006. The FPR and PPV were .01% and 47.8% respectively. The biotinidase deficiency (including partial biotinidase deficiency) detection rate was 1:6280; the FPR and PPV were 0.34% and 4.4% respectively. The purpose of galactosemia screening is to detect classical galactosemia. One case of classical galactosemia was detected for a detection rate of 1:125,600. The cumulative detection rate for classical galactosemia of 1:43,025 is consistent with the 1:47,000 incidence estimate reported by the National Newborn Screening and Genetics Center.[4] The FPR of 0.02% is significantly better than the target of 0.5% and PPV of 4.3% approaches the PPV target of 5%.

The detection rate for profound biotinidase deficiency was 1:41,867 for 2006 which exceeds the detection rate reported by Wolf and Heard (1990) in *Pediatrics* of 1:137,401 live births (95% CI-1:109,300 to 1:211,200)[5]; however, Michigan's profound biotinidase deficiency cumulative detection rate of 1:124,142 is within the expected range. The biotinidase deficiency FPR of 0.36% is within the

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[4] National Newborn Screening and Genetics Research Center. National Newborn Screening Report: 1999. Austin, TX: National Newborn Screening and Genetics Research Center; 2002.
[5] Wolf, B., and Heard, G.S. (1990) Pediatrics, 85(4): 512-517.

target range; however, the PPV of 0.7 is well below the target of 5%. Biotinidase deficiency screening, as indicated by FPR and PPV, ranks second to last in overall performance. Only CAH screening has lower performance metrics.

Table 7: Screening Results and Performance Metrics, Michigan, 2006

Disorder Type	Total N**	Total + N (% NICU)	Strong + N	Confirmed + N	Positive Detection Rate	FPR %	PPV %
Galactosemia Classic (GG)		23 (26.1)	3	1	1 : 125,600	0.02	4.3
Duarte (DG)				10	1 : 12,560	0.01	43.5
Total				11	1 : 11,418	0.01	47.8
Biotinidase Deficiency							
Profound		454 (28.9)	5	3	1: 41,867	0.36	0.7
Partial				17	1 : 7,388	0.35	3.7
Total				20	1 : 6,280	0.35	4.4
Congenital Hypothyroidism (CH)	125,600	695 (28.2)	156	59	1 : 2,128	0.50	8.5
Congenital Adrenal Hyperplasias (CAH) Salt wasting		714 (92.3)	267	3	1 : 41,866	-	-
Non-Salt wasting				-	-		-
Total				*3*	*1 : 41,866*	*0.56*	*0.42*
Hemoglobinopathies		-	-	63	1 : 1,994	-	-
Amino Acid*		52 (25.0)	26	16	1 : 7,850	0.03	30.8
Organic Acid*		134 (32.8)	33	8	1 : 15,700	0.1	6.0
Fatty Acid Oxidation*		75 (27.7)	39	11	1 : 11,418	0.05	14.7
TMS Disorders Total		261	98	35	1 : 3,589	0.18	13.4

Note: *In the above table galactosemia includes both classical cases and Duarte variant cases. Biotinidase includes both partial and profound biotinidase deficiencies.*
*Detected by TMS
**Total number of Michigan resident infants screened

ENDOCRINE DISORDERS CH AND CAH

The detection rate for CH of 1: 2,128 is slightly less than the target range of 1:1,500 to 1:2,000. The CH screening FPR of 0.5% exceeded the target range of 0.3% to 0.4%; the PPV of 8.5% approaches the target of 10% to 15%. 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. Michigan is currently in the process of estimating the incidence of permanent CH among diagnosed newborns by re-evaluating the CH diagnosis at three years of age.

The detection rate for CAH of 1:41,866 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. The cumulative CAH detection rate of 1:16,819 is within the target range; however the PPV of 0.42% is well below the already low PPV target of one to two percent and the FPR of 0.56% exceeds the target FPR of 0.5%. Three cases of salt-wasting CAH were detected among 714 positive screens. 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 TMS for newborns with an initial positive 17-OHP. Preliminary data, presented in Table 8, indicate that second tier testing reduces the percent of false positives by 89.7% without increasing false negatives.

Table 8: Congenital Adrenal Hyperplasia Screening Results Pre- and Post- Second Tier Testing Implementation, Michigan, 2006

Result	Pre-2nd Tier Testing	Post-2nd Tier Testing
	Jan 01, 2006-July 27, 2006	July 28, 2006-Dec 31, 2006
Total +	463	9
True +	2	1
False +	459	8

HEMOGLOBINOPATHIES

Hemoglobinopathy screening outcome information is reported in Table 9. 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.

Table 9: Hemoglobinopathy Screening Performance Indicators, Michigan, 2006

Disorder	Newborns (N)	Confirmed + (N)		Positive Detection Rate	
		Total	Among Blacks	Total*	Among Blacks*
Sickle Cell Anemia		34	32	1: 3,694	1:675
SC Disease	125,600	23	20	1: 5,461	1:1,079
Sickle β thalassemia		6	6	1:20,933	1:3,600
Total		*63*	*58*	*1 : 1,994*	*1:372*

Out of the number of Michigan resident infants screened, total N=125,600, among Blacks N=21,596

As depicted in Table 9, hemoglobinopathies are quite common among African Americans who account for 91% of the total number of confirmed cases in 2006. While the overall incidence is

approximately one case per 2,000 infants screened, the incidence in African American infants is one in 372 screened in Michigan.

The overall FPR for TMS of 0.18% is below the target of 0.3%. The PPV of 13.4% and detection rate of 1:3,589 for TMS approach but do not meet the target metrics suggested by Rinaldo, et al. (2006). A recent evaluation of Michigan's screening cutoffs, particularly for the organic acid disorders has increased screening performance. Preliminary data indicate that Michigan's TMS performance metrics should meet or exceed performance targets for 2007.

SCREENING PERFORMANCE METRICS – INDIVIDUAL TMS DISORDERS

AMINO ACID DISORDERS

Sixteen amino acid disorders (Table 10) were detected by TMS. PKU is the most frequent condition, found in one of every 8,373 newborns screened. As indicated in the table, PKU screening had the highest PPV (75%); only the test for the fatty acid oxidation disorder LCHAD had a greater PPV among all screened disorders (100%). The FPR for PKU screening of .004% reflects the very high sensitivity of TMS screening for this disorder. In addition to PKU, one case of arginosuccinic academia (ASA) was detected.

ORGANIC ACID DISORDERS

Eight organic acid disorders (Table 11) were detected by TMS. The FPR for each of these disorders is below .05%. The PPV exceeds 5% for IVA (5.9%), GAI (28.6%) and IBG (7.1%).

FATTY ACID OXIDATION DISORDERS

Eleven fatty acid oxidation disorders (Table 12) were detected (nine MCAD, one LCHAD and one VLCAD). All FPRs were less than .02% and the PPVs were all greater than 25% with MCAD at 90% and LCHAD at 100%.

Table 10: Amino Acid Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2006

Disorder	Newborns N*	Total + N (% NICU)	Strong + (N)	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Phenylketonuria Classic (PKU)	125,600	20 (5.0)	15	3	1: 41,866	0.01	15.0
Mild				6	1: 20,933	0.01	30.0
Benign Hypephenyla-laninemia (H-PHE)				6	1: 20,933	0.01	30.0
Biopterin Cofactor Defects (BIOPT)				-	-	0.02	-
Total				15	1: 8,373	0.004	75.0
Maple Syrup Urine Disease (MSUD)		4 (25.0)	1	0	0	0.003	0
Homocystinuria (HCY)		5 (0.0)	4	0	0	0.004	0
Arginemia (ARG)		3 (100)	1	0	0	0.002	0
Citrullinemia/ASA ** (CIT/ASA)		7 (14.3)	4	1	1 : 125,600	0.005	14.3
Tyrosinemia (TYR I)		13 (61.5)	1	0	0	0.01	0

Total number of Michigan resident infants screened
**Confirmed case was ASA
^Borderline + = (Total+ - Strong+)

Table 11: Organic Acid Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2006

Disorder	Newborns N*	Total + N (%NICU)	Strong + (N)	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Isovaleric Acidemia (IVA)	125,600	17 (58.8)	2	1	1 : 125,600	0.01	5.9
3-Methylcrotonyl-CoA Carboxylase Deficiency		37 (16.2)	6	1	1 : 125,600	0.029	2.7
Glutaric Acidemia Type I (GA I)		7 (28.6)	7	2	1 : 62,893	0.004	28.6
Proprionic Acidemia/MMA (PA)		58 (34.4)	8	0	-	0.046	0
Methylmalonic Acidemia (Mutase Deficiency) MA		58 (34.4)	8	2	1 : 62,893	0.045	3.4
Methylmalonic Acidemia (MA-Cbl C, D)		58 (34.4)	8	1	1 : 125,600	0.045	1.7
Isobutyryl-CoA Dehydrogenase Deficiency (IBG)		15 (0.0)	10	1	1 : 125,600	0.01	7.1
2-Methylbutyryl-CoA Dehydrogenase Deficiency (2MBG)		17 (58.8)	2	0	-	0.01	0

*Total number of Michigan resident infants screened

^Borderline + = (Total+ - Strong+)

Note: *2MBG and IVA screening utilizes the same analyte; similarly, PA, methylmalonic acidemia and mutase deficiency utilize the same analyte.*

Table 12: Fatty Acid Oxidation Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2006

Disorder	Newborns N*	Total + N (%NICU)	Strong + (N)	Confirmed + (N)	Positive Detection Rate*	FPR (%)	PPV (%)
Carnitine/Acylcarnitine Translocase Deficiency- (CACT)		3 (0.0)	0	0	-	0.002	0
Carnitine Uptake Defect- (CUP)		19 (31.6)	1	0	-	0.02	0
Carnitine Palmitoyltransferase I Deficiency- (CPT 1A)		6 (33.3)	2	0	-	0.01	0
Carnitine Palmitoyltransferase II Deficiency-(CPT II)		3 (33.3)	0	0	-	0.002	0
Short-Chain Acyl-CoA Dehydrogenase deficiency- (SCAD)	125,600	15 (40.0)	10	0	-	0.01	0
Glutaric Acidemia Type II- (GA II)		1 (100.0)	1	0	-	0.001	0
Medium-Chain Acyl-CoA Dehydrogenase Deficiency- (MCAD)		10 (10.0)	10	9	1 : 13,955	0.001	90.0
Long-Chain L-30H Acyl-CoA Dehydrogenase Deficiency- (LCHAD)		1 (100.0)	1	1	1 : 125,600	0	100
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency- (VLCAD)		4 (0.0)	3	1	1 : 125,600	0.002	25.0
Medium-Chain Ketoacyl-CoA Thiolase Deficiency- (MCKAT)		3 (0.0)	3	0	-	0.002	0
Tryfunctional Protein Disease- (TFP)		10 (0.0)	8	0	-	0.008	0

Total number of Michigan resident infants screened

IV: QUALITY ASSURANCE INFORMATION

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

SPECIMEN CHARACTERISTICS

Table 13 reports specimen characteristics by nursery type. Although only 11% of infants were in the NICU, 52% of positive specimens (strong and borderline positives) were received from the NICU. Isolated elevations of one or more amino acids and/or acyl-carnitines were also more prevalent among specimens from the NICU; these elevations commonly associated with infants receiving TPN. While the overall number of unsatisfactory specimens was greatest among hospital nurseries, the proportion of unsatisfactory specimens was greatest among NICU samples (three percent). Early and transfused specimens were also more common among infants from the NICU. Late specimens, those collected after six days of life, were more common among midwife deliveries. The NBS follow-up program tracks all strong and borderline positive, isolated elevation, unsatisfactory, early, and transfused specimens; a total of 6,562 specimens were followed up in 2006. Strong positive results (n=509) are immediately referred to medical management centers for evaluation.

Table 13: Specimen Characteristics by Nursery Type, Michigan, 2006

Indicator	Type of Birth		
	Regular Nursery N(%)	NICU N(%)	Midwife N(%)
Strong + Specimens	174 (0.002)	335 (2.5)	0 (0.0)
Borderline + Specimens	913 (0.008)	673 (5.1)	4 (0.01)
Isolated elevations of amino acids and acyl carnitines	22 (0.0002)	515 (3.9)	0 (0.0)
TPN Specimens	93 (0.08)	2,168 (16.3)	0 (0.0)
Unsatisfactory Specimens	1,312 (1.2)	397 (3.0)	8 (2.9)
Late (>6 days) Specimens	174 (0.2)	103 (0. 8)	17 (6.2)
Early (<1 day) Specimens	874 (0.8)	1,125 (8.5)	0 (0.0)
Transfused Specimens	13 (0.02)	197 (1.5)	0 (0.0)
Specimens Missing Demographics *	12,260 (10.9)	1,068 (8.0)	19 (6.9)
Total Births Screened	112,478 (89.1)	13,268 (10.6)	274 (0.22)

Defined as missing demographics needed for laboratory determination of normal or abnormal results: race, specimen collection time, or birth weight

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 (MSUD, CAH, Galactosemia and disorders detected by TMS) is no later than the seventh 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 first important for hospitals and midwives to collect and mail specimens within the recommended guidelines.

TIME TO SPECIMEN COLLECTION AND MAILING

Table 14 reports the time from birth to collection and mailing of NBS specimens by nursery type. Michigan recommends that specimens should be obtained between 24 to 36 hours after birth and mailed within 24 hours of specimen collection; however, the time from birth until specimen collection and mailing varies considerably by nursery type. While 88% of specimens collected in hospital nurseries are collected within 24 to 36 hours of birth, only 30% of midwife/non-hospital birth specimens are collected in the recommended time frame.

Table 14: Time From Birth to Collection & Laboratory Receipt of Specimens by Nursery Type, Michigan, 2006

Action	Nursery Type	Time	N (%)	Mean Time
Time from birth to specimen collection	Hospital Nursery	0-23 hrs	271 (0.2)	30.2 hrs
		24-36 hrs	98,547 (88.1)	
		36-47 hrs	11,179 (10.0)	
		48-73 hrs	1,398 (1.3)	
		>72 hrs	409 (0.4)	
	NICU	0-23 hrs	280 (2.3)	35.2 hrs
		24-36 hrs	9,337 (75.2)	
		36-47 hrs	2000 (16.1)	
		48-73 hrs	543 (4.4)	
		>72 hrs	254 (2.1)	
	Midwife/ Non-Hospital	0-23 hrs	0 (0.0)	68.0 hrs
		24-36 hrs	84 (30.7)	
		36-47 hrs	55 (20.1)	
		48-73 hrs	52 (19.0)	
		>72 hrs	83 (30.3)	
Time from specimen collection to receipt in lab	Hospital Nursery	**1-3 days**	78,549 (70.0)	2.8 days
		4-5 days	29,033 (25.9)	
		6-7days	3,887 (3.5)	
		>7 days	755 (0.7)	
	NICU	**1-3 days**	8,539 (64.5)	3.0 days
		4-5 days	3,900 (29.4)	
		6-7days	663 (5.0)	
		>7 days	139 (1.1)	
	Midwife/ Non-Hospital	**1-3 days**	197 (72.7)	3.0 days
		4-5 days	58 (21.4)	
		6-7days	9 (3.3)	
		>7 days	7 (2.6)	

Note: *These data are presented as proportions of the total number of screens, 126,020, regardless of residence. 195 subjects were missing specimen dates.*

Thirty percent of specimens from midwife/non-hospital births are collected after three days of life compared to 0.4% and two percent of specimens collected in hospital nurseries and the NICU respectively. The average time of specimen collection for midwife/non-hospital births (68 hours) is nearly twice that of average collection times for hospital nursery and NICU births (30 and 35 hours, respectively).

A critical time for initiating early treatment is the time from birth to receipt of specimens by the 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. As indicated in Table 15, currently only 41.5% of hospital nursery specimens, 37.2% of NICU specimens, and 23% of midwife specimens are received by the laboratory by the third day of life. Two program changes are being implemented to decrease time between birth and laboratory receipt of specimens: 1) a courier system for delivering specimens directly to the state laboratory within 24 hours of specimen collection, and 2) increase laboratory operation from five to six days a week. These changes are scheduled for October 2007.

Table 15: Time from Birth to Receipt of Specimen by NBS Laboratory by Nursery Type, Michigan, 2006

Action	Nursery Type	Time	N	%	Mean Time (days)
Time from Birth to Laboratory Receipt of Specimen	Hospital Nursery	**1-3 days**	46,626	41.5	4.1
		4-5 days	46,548	44.1	
		6-7days	14,145	12.6	
		>7 days	2,159	1.9	
	NICU	**1-3 days**	4,939	37.2	4.5
		4-5 days	5,643	42.5	
		6-7days	2,132	16.1	
		>7 days	554	4.2	
	Midwife	**1-3 days**	63	23.0	5.8
		4-5 days	95	34.7	
		6-7days	64	23.4	
		>7 days	52	19.0	

Table 16 reports the time to treatment for disorders other than hemoglobinopathies; hemoglobinopathy treatment (penicillin prophylaxis) is provided later (by four months of life) than for other disorders and is reported in a separate table. As indicated in Table 16, time to treatment ranged from two days to 170 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 hyperphenylalanemia is included in the table but is not diet treated.

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GALACTOSEMIA AND BIOTINIDASE DEFICIENCY

The single case of confirmed classic galactosemia was treated within four days. There were three cases of profound biotinidase deficiency; one was treated within 14 days of life and a second case was treated at 15 days of life. The third case was an initial borderline positive screen that was diagnosed at 170 days due to delays in NBS re-testing and confirmatory serum testing.

TMS DISORDERS

There were 34 newborns with disorders detected by TMS (six newborns with hyperphenylalanemia did not require treatment). Of those requiring treatment, 26% were treated by the 7th day of life, 37% by the 14th day of life, and 37% at greater than 14 days of life. Most, but not all, of the delay in treatment for this group of disorders is due to delays in specimen collection and mailing. If the mean time from birth to receipt of the specimens at the state laboratory was reduced by two to three days, as is expected with implementation of courier delivery and extended weekend work hours this should also reduce the mean turnaround time to treatment by two to three days.

ENDOCRINE DISORDERS CAH AND CH

The salt-wasting form of CAH is life-threatening in the first few weeks of life. The three CAH cases detected were salt-wasting; one was treated by the seventh day of life and two were treated by the 14th day of life. The target for CH is treatment by 14 days of age for newborns with initial TSH values greater than 50. There were 44 diagnosed cases with initial TSH >50; 36 (82%) were treated by 14 days of age. For the 15 diagnosed cases with initial TSH <= 50 only two (13%) were treated by 14 days of age.

HEMOGLOBINOPATHIES

Table 17 reports the time to treatment among hemoglobinopathies. The target is to initiate penicillin prophylaxis by three months of life. Of the 44 cases treated, 86% were treated with penicillin prior to four months, 9% were treated at four months of age, and 4% were treated beyond four months of age.

Table 16: Time to Treatment of Amino Acid Disorders, Organic Acid, Fatty Acid Oxidation, and Endocrine Disorders, Michigan, 2006

Disorder		Total (N)	Treatment Time (days from birth) N			Treatment Time Range (days)
			1-7	8-14	>14	
Galactosemia (GG)		1	1	-	-	4
Biotinidase Deficiency Partial		17	-	1	16	14-31
Profound		3	0	1	2	11-170
Amino Acid Disorders	Phenylketonuria Classic	3	1	2	-	5-10
	Mild	6	3	2	1	5-20
	Benign Hypephenylalaninemia	6	-	-	-	-
	Arginosuccinic Acidemia (ASA)	1	-	1	-	11
	Total	*16*	*4*	*5*	*1*	*5-20*
Organic Acid Disorders	Isovaleric Acidemia	1	1			7
	3-Methylcrotonyl-CoA Carboxylase Deficiency	1	-	-	1	22
	Glutaric Acidemia Type I*	2	-	-	1	15
	Methylmalonic Acidemia (Cbl C, D)	1	1	-	-	6
	Methylmalonic Acidemia (Mutase Deficiency)^	2	-	1	-	8
	Total	*7*	*2*	*1*	*2*	*6-22*
Fatty Acid Oxidation Disorders	Medium-Chain Acyl-CoA Dehydrogenase Deficiency	10	-	4	6	8-33
	Long-Chain L-30H Acyl-CoA Dehydrogenase Deficiency	1	-	-	1	22
	Very Long-Chain Acyl-CoA Dehydrogenase Deficiency	1	1	-	-	7
	Total	*12*	*1*	*4*	*7*	*7-33*
Endocrine Disorders	Congenital Hypothyroidism TSH > 50	44	10	26	8	5-65
	TSH ≤ 50	15	-	2	13	10-76
	Congenital Adrenal Hyperplasias					
	Salt-Wasting	3	1	2	-	2-10
	Non Salt-Wasting		-	-	-	-

*1 case moved out of state and is followed up there; thus, we do not have a treatment start date.
^1 case missing treatment start date

Table 17: Time to Penicillin Initiation for Hemoglobinopathies, Michigan, 2006

Disorder	Penicillin Prophylaxis Initiation Time			
	≤ 4 months	4 months	5 months	6 months
Sickle Cell Disorders	38	4	1	1

V: CONCLUSIONS & RECENT DEVELOPMENTS

NBS is a critical public health program protecting the lives of our State's newest residents. In 2006, the NBS follow-up program tracked 6,562 strong and borderline positive, isolated elevation, unsatisfactory, early, and transfused specimens; 509 strong positive results were immediately referred to medical management centers for evaluation. A total of 187 newborns were identified with a disorder by NBS in 2006 and treatment was initiated, where necessary, to prevent long-term morbidity and mortality. Since NBS began in Michigan in 1965, 3,731 newborns have been diagnosed and treated through newborn screening.

TMS screening for 42 disorders has revolutionized newborn screening. The overall detection rate (1:3,589), PPV (13.4%), and FPR (0.18%), are significant, cost-effective improvements over the screening metrics obtained using other screening methodologies that screen for one disorder at a time. Many of the TMS disorders require rapid diagnosis and treatment increasing the need to reduce turnaround time to treatment. The target for Michigan is to treat all TMS disorders by the seventh day of life. This has not yet been achieved but plans for a courier system for delivering specimens to the state laboratory within 24 hours of collection and expanding the laboratory and follow-up work schedule from five to six days should help in meeting this target.

Introduction of TMS 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 for from seven in 2003 to 48 in 2006. The addition of CF screening in October of 2007 will increase the screening panel to 49. Michigan also screens newborns for hearing loss on a voluntary basis. Hearing screening will also be included in the mandatory screening panel in 2007 and will complete the ACMG/HRSA/March of Dimes recommended screening panel for state newborn screening programs.

Expansion of newborn screening was facilitated by legislation creating the NBS Quality Assurance Advisory Committee. On February 23, 2006, SB 794 was passed and amended Public Act 368 of 1978 by adding sections 5430 and 5432. The Bill created the QAC, a ten-member committee of physicians and scientists with expertise in clinical genetics/metabolism and the newborn screening process and two family members of children with disorders included in the NBS panel. The responsibilities of the committee include: 1) recommendations for additions of new screening tests or deletion of screening tests that have not proved to be cost effective, and 2) establishing a fee to cover the cost of the NBS screening program. The Committee meets annually and forwards recommendations to the DCH. On approval by the DCH the recommendations are then forwarded to the legislature and become law in 90 days if there is no opposition. Prior to formation of the Committee it would take one to two years to complete the process of adding a single new disorder to the screening panel. Further improvement of the long-term follow-up data collected at each of the three medical management centers is in the planning process. Also, to accommodate researchers interested in using available NBS data, the follow-up program has developed guidelines to facilitate such endeavors. (see appendix C: NBS Research Guidelines).

Finally, to offer continued education/information about NBS we will disseminate newsletters twice per year beginning in 2007; each edition will also include expanded information about a particular condition. For further information about the NBS program please visit our website, www.michigan.gov/newbornscreening. (See Appendix B: Information Available on NBS Website).

APPENDIX A: NEWBORN SCREENING LEGISLATION

The newborn screening program is legislatively mandated through Public Health Code Act 368 of 1978 with additional amendments from 1986 through 2003. The specific enabling legislation is written as follows:

333.5431 Testing newborn infant for certain conditions; reporting positive test results to parents, guardian, or person in loco parentis; compliance; fee; "Detroit consumer price index" defined; violation as misdemeanor; hardship waiver; conduct of department regarding blood specimens; pamphlet; additional blood specimen for future identification.

Sec. 5431.

(1) A health professional in charge of the care of a newborn infant or, if none, the health professional in charge at the birth of an infant shall administer or cause to be administered to the infant a test for each of the following:
    (a) Phenylketonuria.
    (b) Galactosemia.
    (c) Hypothyroidism.
    (d) Maple syrup urine disease.
    (e) Biotinidase deficiency.
    (f) Sickle cell anemia.
    (g) Congenital adrenal hyperplasia.
    (h) Medium-chain acyl-CoA dehydrogenase deficiency.
    (i) Other treatable but otherwise disabling conditions as designated by the department.

(2) The informed consent requirements of sections 17020 and 17520 do not apply to the tests required under subsection (1). The tests required under subsection (1) shall be administered and reported within a time and under conditions prescribed by the department. The department may require that the tests be performed by the department.

(3) If the results of a test administered under subsection (1) are positive, the results shall be reported to the infant's parents, guardian, or person *in loco parentis*. A person is in compliance with this subsection if the person makes a good faith effort to report the positive test results to the infant's parents, guardian, or person *in loco parentis*.

(4) Subject to the annual adjustment required under this subsection and subject to subsection (6), if the department performs one or more of the tests required under subsection (1), the department may charge a fee for the tests of not more than $53.71. The department shall adjust the amount prescribed by this subsection annually by an amount determined by the state treasurer to reflect the cumulative annual percentage change in the Detroit consumer price index. As used in this subsection, "Detroit consumer price index" means the most comprehensive index of consumer prices available for the Detroit area from the bureau of labor statistics of the United States department of labor.

(5) A person who violates this section or a rule promulgated under this part is guilty of a misdemeanor.

(6) The department shall provide for a hardship waiver of the fee authorized under subsection (4) under circumstances found appropriate by the department.

(7) The department shall do all of the following in regard to the blood specimens taken for purposes of conducting the tests required under subsection (1):
    (a) By April 1, 2000, develop a schedule for the retention and disposal of the blood specimens used for the tests after the tests are completed. The schedule shall meet at least all of the following requirements:
        (i) Be consistent with nationally recognized standards for laboratory accreditation and federal law.
        (ii) Require that the disposal be conducted in compliance with section 13811.
        (iii) Require that the disposal be conducted in the presence of a witness. For purposes of this subparagraph, the witness may be an individual involved in the disposal or any other individual.
        (iv) Require that a written record of the disposal be made and kept, and that the witness required under subparagraph (iii) signs the record.
    (b) Allow the blood specimens to be used for medical research during the retention period established under subdivision (a), as long as the medical research is conducted in a manner that preserves the confidentiality of the test subjects and is consistent to protect human subjects from research risks under subpart A of part 46 of subchapter A of title 45 of the code of federal regulations.

(8) The department shall rewrite its pamphlet explaining the requirements of this section when the supply of pamphlets in existence on March 15, 2000 is exhausted. When the department rewrites the explanatory pamphlet, it shall include at least all of the following information in the pamphlet:
    (a) The nature and purpose of the testing program required under this section, including, but not limited to, a brief description of each condition or disorder listed in subsection (1).
    (b) The purpose and value of the infant's parent, guardian, or person *in loco parentis* retaining a blood specimen obtained under subsection (9) in a safe place.
    (c) The department's schedule for retaining and disposing of blood specimens developed under subsection (7)(a).
    (d) That the blood specimens taken for purposes of conducting the tests required under subsection (1) may be used for medical research pursuant to subsection (7)(b).

(9) In addition to the requirements of subsection (1), the health professional described in subsection (1) or the hospital or other facility in which the birth of an infant takes place, or both, may offer to draw an additional blood specimen from the infant. If such an offer is made, it shall be made to the infant's parent, guardian, or person *in loco parentis* at the time the blood specimens are drawn for purposes of subsection (1). If the infant's parent, guardian, or person *in loco parentis* accepts the offer of an additional blood specimen, the blood specimen shall be preserved in a manner that does not require special storage conditions or techniques, including, but not limited to, lamination. The health professional or hospital or other facility employee making the offer shall explain to the parent, guardian, or person *in loco parentis* at the time the offer is made that the additional blood specimen can be used for future identification purposes and should be kept in a safe place. The health professional or hospital or other facility making the offer may charge a fee that is not more than the actual cost of obtaining and preserving the additional blood specimen.

APPENDIX B: REGIONAL DEFINITIONS

Region	Counties	Region	Counties
Detroit (1)	Wayne	Saginaw (8)	Ogemaw
	Macomb		Iosco
	St. Clair		Arenac
Oakland (2)	Oakland		Gladwin
Ann Arbor (3)	Washtenaw		Bay
	Livingston		Tuscola
	Jackson		Huron
	Lenawee		Sanilac
	Monroe	North Low Peninsula (9)	Grand Traverse
Kalamazoo (4)	Kalamazoo		Leelanau
	Van Buren		Benzie
	Allegan		Manistee
	Barry		Wexford
	Calhoun		Missaukee
	Hillsdale		Kalkaska
	Branch		Crawford
	St. Joseph		Oscoda
	Cass		Alcona
	Berrien		Alpena
Grand Rapids (5)	Kent		Montmorency
	Ottawa		Otsego
	Muskegon		Antrim
	Oceana		Charlevoix
	Mason		Emmet
	Lake		Cheboygan
	Newaygo		Presque Isle
	Osceola	Upper Peninsula (10)	Marquette
	Mecosta		Alger
	Montcalm		Luce
	Ionia		Chippewa
Lansing (6)	Ingham		Mackinac
	Eaton		Schoolcraft
	Clinton		Delta
	Shiawassee		Menominee
	Gratiot		Dickinson
Flint (7)	Genesee		Iron
	Lapeer		Gogebic
Saginaw (8)	Saginaw		Ontonagon
	Midland		Houghton
	Isabella		Keweenaw
	Clare		Baraga
	Roscommon		
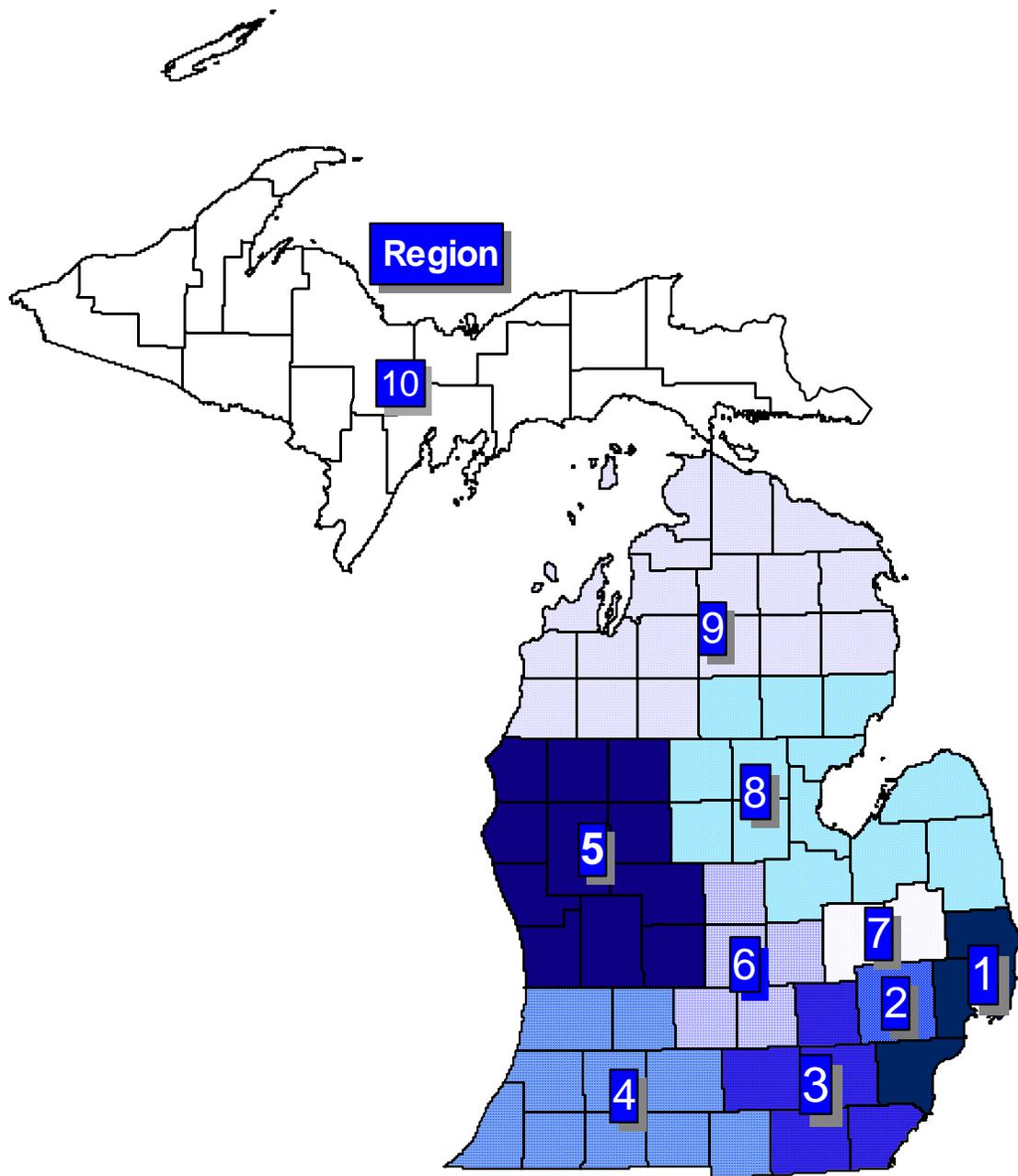
Figure 5: Regions Defined by Michigan Perinatal Health Systems

APPENDIX C: NEWBORN SCREENING FOLLOW-UP PROGRAM GUIDELINES FOR CONDUCTING RESEARCH/DATA ANALYSES

OVERVIEW OF THE NEWBORN SCREENING (NBS) FOLLOW-UP PROGRAM

The NBS follow-up program is housed within the Division of Genomics, Perinatal Health and Chronic Disease Epidemiology, Bureau of Epidemiology at the Michigan Department of Community Health. It oversees short-term and long-term follow-up of infants identified through the screening program. The program ensures that infants identified through the newborn screening program enter into a seamless system of care including consultation with specialists, and routine care within a medical home.

Collection of data for long-term tracking of infants identified through newborn screening is imperative. As a result, clinical databases have been developed by the NBS follow-up program at the Endocrine, Metabolic, Sickle Cell and Cystic Fibrosis Centers (see below).

To facilitate the planning and implementation of analyses, ensure scientific quality and appropriate use of the data collected in these databases, and to avoid duplication of efforts, any researcher intending to analyze NBS follow-up data must prepare a research proposal for review and approval by the respective Center, the NBS program and the appropriate IRB(s). Proposals should be sent to the appropriate clinic leader, depending on the research topic. The clinic leaders of the coordinating centers are as follows:

Endocrine: Ram Menon MD, Professor of Pediatrics, Professor of Molecular and Integrative Physiology, Director, Ped Endocrinology, University of Michigan Med Sch, D1205 MPB Box 0718, Ann Arbor, MI 48109-0718
Metabolic: Jerry Feldman, MD, PhD, FACMG, Professor, Molecular Medicine and Genetics, Pediatrics and Pathology, Director, Clinical Genetics Services, Wayne State University School of Medicine
Sickle Cell: Charles F. Whitten, MD, Board Chairperson, Sickle Cell Disease Association of America, Michigan Chapter, Inc.
Cystic Fibrosis: Samya Z. Nasr, MD, Associate Professor of Pediatrics, Director, Cystic Fibrosis Center, University of Michigan Health System

After clinic leader review, the decision and comments shall be sent to the NBS follow-up program for review and approval. Upon the mandatory approvals from the clinic and NBS follow-up program as well as the corresponding IRBs, a data file will be created by the NBS follow-up program and sent to researchers. Details concerning research proposal content and the review process follow.

Research proposals should include the following information: a title; background; methods; projected results; proposed discussion; resources needed; project time frame; and references. In brief, each proposal section should include the following information:

Title page   Include a working study title; a list of study researchers, their institutional affiliations and contact information.

Background   Summarize the literature, cite strengths and limitations of earlier research, and state the purpose for the proposed study. Provide a rationale why NBS data are useful for the proposed project.

Methods   Mention which years of NBS data you will need for your analysis, a list of the specific variables needed and the statistical methods you will use to conduct your analysis. Describe whether your analysis relies on any implicit assumptions.

Results   Although the analysis will not have been initiated, we recommend that researchers provide some sample table shells, figures or anticipated results for NBS staff review.

Discussion   While the results are not known, we suggest that researchers discuss the potential strengths and limitations of their project and how the findings from the proposed project may enhance the literature and public health practice. Identify potential benefits to MDCH and how the knowledge can contribute to state-level public health practice.

Resources needed   Indicate whether technical assistance will be needed from NBS follow-up staff. If assistance is needed, describe the technical assistance needed.

Time frame   List a starting date and anticipated milestones for the project.

References   Provide a listing of references cited in the research proposal.

SUBMISSION STEPS

1. Present the research proposals to the lead of the Metabolic or Sickle Cell clinics, PEAC or CF, depending on the topic, for the initial review and approval. The respective clinic leaders will review and send decisions and comments to the NBS follow-up program manager (currently, William Young, PhD, Michigan Department of Community Health, Division of Genomics, Perinatal Health and Chronic Disease Epidemiology, P.O. Box 30195, Lansing, MI 48909; YoungW@michigan.gov) for NBS follow-up team input.

2. The NBS follow-up team will respond to the primary researcher within two weeks. This response will include a summary of comments received from the NBS team (clinic leads, advisory committees, PEAC and CFAC, as well as the follow-up program staff) and notification of an approval to conduct the analysis.

3. Separate IRB approval from the clinics/universities as well as MDCH is needed to ensure the appropriate use of data. Access to data will not be granted otherwise.

4. Upon receipt of approvals, all researchers who are listed on the proposal will complete a Data Sharing agreement and return the form to the NBS follow-up program manager. The Data Sharing Agreement must receive the final approval from the Director of the Division of Genomics, Perinatal Health and Chronic Disease Epidemiology.

5. Approval to analyze NBS data applies only to the topic described in the research proposal. If a researcher desires to conduct additional analyses, a separate research proposal is required.

6. In order to enroll any of the NBS positive cases in the research study, the attached consent form must be signed by either the guardian (parent) or the patient, depending on the age of the study population. A hard copy will be kept at the clinic and the electronic consent will be recorded in the clinical database.

   For those not seen at a clinic, the Michigan Department of Community Health is responsible to seek the consent by sending out a letter. A fee will be charged depending on the program policy at that time. The Department requires written permission from participants in the NBS program before allowing access to their information for research. The consent form is not a substitute for the IRB(s) approval(s) required for any research/analysis.

7. Authors communicate in writing with the NBS follow-up program regarding the year(s), and variables they need for their project, so the analysis data set can be created.

8. MDCH NBS follow-up will create the file with de-identified information for the primary researcher on a CD-ROM or a diskette(s). A letter describing the contents of the CD-ROM or diskette will accompany the data.

9. Any additional or other use of data will be considered a breach of the research contract and sanctioned accordingly, unless agreed to in writing by both parties beforehand.

10. Data provided under the data agreement are not to be copied or reproduced for distribution by others.

11. Upon completion of the analysis described in the research proposals, researchers are to confirm in writing in writing that their copy of the data has been destroyed and/or return the data to MDCH.

PUBLICATION OR PRESENTATION

Two weeks prior to submitting an abstract for presentation or a manuscript for publication, researchers are required to share copies of their work with the NBS team (clinic leads, PEAC and CFAC, MDCH NBS follow-up). If the intent is to submit a manuscript to a peer-reviewed journal, four weeks prior notification is encouraged.

AGREEMENT FOR SHARING DATA

This contract specifies the conditions for release of all unpublished NBS data, research, and reports for legitimate public health or related research. The intent of this contract is to foster such research and to prevent misrepresentation of the data.

    I.   Requests for data must be made in writing

    II.   The principal investigator and relevant collaborators shall provide their curriculum vita.

    III.   The requestor who receives the data must also sign and agree to the following consent:

I, _____, as principal investigator on this proposed analysis agree to the following requirements for the use of Newborn Screening (NBS) follow-up data and assure compliance with the requirements.

1.   I will not use nor permit others to use these data except for statistical analysis and reporting.

2.   I will not use nor permit others to use these data to conduct analyses other than those described in the proposal, titled
_____, which accompanies this statement.

3.   I will not release nor permit others to release the data set or any part of it to any person others than those listed as collaborators in the attached proposal.

4.   I will not attempt nor permit others to attempt to use the data set to learn the identity of any participant. If the identity of a respondent should be inadvertently discovered, I will make no use of this knowledge, nor will I permit others to use the knowledge. I will inform the MDCH-NBS follow-up staff of the discovery, so they can prevent future discoveries. I pledge that neither I nor other members of my team will inform anyone else of this knowledge.

5.   All oral or written presentations of the results of the analyses will include an acknowledgment of the data sources and those who provided assistance including the MDCH NBS Follow-up staff.

6.   When the proposed analyses are completed, all copies of these data will be destroyed or returned to the NBS follow-up program data analyst responsible for the clinical database management. Written confirmation that the data has been destroyed is requested.

8.   I understand that the sharing of this data does not imply, in whole or in part, that the proposed topic has not been investigated before, or will not be investigated now or in the future, by other investigators interested in this topic.

The person signing this document is responsible for compliance with the conditions of this agreement and agrees to these conditions by his or her signature below.

Name (print): _____

Title: _____

Organization: _____

Address: _____

Phone: (___)-_____

Date: _____

Signature: _____

CONSENT FORM

The goal of the Michigan Department of Community Health Newborn Screening program is early identification of children at increased risk for selected metabolic or genetic diseases so that medical treatment can be promptly initiated to avert metabolic crises and prevent irreversible neurological and developmental sequelae. Your child has been diagnosed through this NBS.

Please carefully read each sentence below and think about your choice. Circle and initial the answer that is right for you. If you have any questions please ask your doctor or nurse.

My child's (my personal) data collected at the clinic may be used in research to learn more about the disorders diagnosed through the newborn screening.

Yes   No   Initials & Date

I may be contacted in the future and asked to participate in different research studies.

Yes   No   Initials & Date

Your consent to participate in any research is voluntary and therefore your decision will have no impact on the care you and your child will receive. By signing this form you ARE NOT GIVING permission to disclose your identity or the identity of your child.

You have the right to withdraw this permission at any time for any reason but it is your responsibility to inform the Michigan Department of Community Health Newborn Screening follow-up program if you decide to do so.

I have read and understand the above questions prior to signing.

Signature _____   Date _____

Name (please print) _____

Clinic doctor/nurse
Signature _____   Date _____

Name (please print) _____

Further information about the NBS program displayed on our website,
www.michigan.gov/newbornscreening, includes:

- **NBS Program Manual**

- **Disorder fact sheets**

- **Newborn Screening: What Prenatal Caregivers Need to Know**, a self-paced, online educational module provided by the Region 4 Genetics Collaborative free of charge to all health care professionals and providers involved in the care of new and expectant mothers (Free CEUs available)

- **Newborn Screening Educational Online Tutorial** for nurses

- **NBS Annual Report 2004**

- **NBS Updates**

- **Information for Parents and Families**
  - A First Step to Your Baby's Health (brochure containing information on the NBS program, a brief description of 11 of the disorders screened, and contact information)
  - Parent Consultant contacts
  - PKU Resource Website link
  - Children's Special Health Care Services contact information
  - Early Hearing Detection and Intervention Program contact information
  - Early on contact information

- **Information for Professionals**
  - NBS program brochures available in Spanish and Arabic, ordering information provided
  - Genomics Resource Order Form
  - Instructions for completing the NBS card
  - Weight Conversion Charts
  - Military Time Charts
  - Automatic Fax Reporting of NBS Results
  - Newborn Screening Disorders Table
  - Supplemental Newborn Screening Information
  - The Congenital Hypothyroidism screening program
  - Interpretation of the Newborn Hemoglobin Screening Process
  - Newborn Screening Online Tutorial Flyer
  - NBS Specimen Collection Presentation
  - NBS Program Presentation

LISTING OF TABLES & FIGURES

TABLES

FIGURES