MICHIGAN DEPARTMENT OF COMMUNITY HEALTH

MICHIGAN NEWBORN SCREENING PROGRAM

ANNUAL REPORT
2007

Michigan Department of Community Health
MDCH
Jennifer M. Granholm, Governor
Janet Olszewski, Director

Public Health
FOR MICHIGAN
FOR YOU

Michigan Newborn Screening Program

ANNUAL REPORT- 2007

Acknowledgements

State of Michigan
Governor **Jennifer M. Granholm**

Michigan Department of Community Health
Director **Janet Olszewski**

Public Health Administration
Chief Administrative Officer **Jean C. Chabut**

Bureau of Epidemiology
Corinne Miller, Ph.D., DDS

Bureau of Laboratories
Frances Pouch Downes, DrPH

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Authors

Steven J. Korzeniewski, M.A., M.Sc.
Newborn Screening Epidemiologist, Division of Genomics, Perinatal Health and Chronic Disease Epidemiology, Bureau of Epidemiology

William, I. Young, Ph.D.
Manager, Newborn Screening Follow-up Program, Division of Genomics, Perinatal Health and Chronic Disease Epidemiology, Bureau of Epidemiology

Karen Andruszewski, M.S.
Data Coordinator Newborn Screening Follow-up Program, Division of Genomics, Perinatal Health and Chronic Disease Epidemiology, Bureau of Epidemiology

Harry C. Hawkins, B.S.
Manager, Newborn Screening Laboratory, Chemistry and Toxicology Division, Bureau of Laboratories

EXECUTIVE SUMMARY

The Newborn Screening (NBS) annual report provides an overview of the Michigan Program, target outcomes, screening performance metrics, and quality assurance information. This report differs from the one released in 2006 in several ways. First, this is an abridged report in that it does not include appendices which have not changed since 2006 including the NBS research guidelines, supportive legislation, or website description.* Second, this report includes a chapter providing in-depth information on a single NBS condition, congenital hypothyroidism (Chapter IV). In this chapter an overview of congenital hypothyroidism (CH) screening, past and present, is provided, information on definition, diagnosis, and treatment are provided, and updates on ongoing CH related NBS program evaluation research are provided. Subsequent NBS annual reports will each include a chapter detailing a different disorder each year. Third, regional prevalence estimates are not provided (numerically or graphically) because these estimates will not have changed significantly from 2006 to 2007.

Since the program began in 1965 with the screening for phenylketonuria, 48 additional disorders have been added to the screening panel and millions of infants have been screened with approximately 4,000 being diagnosed with diseases included in the NBS panel.

In 2007, of 123,477 infants screened, 123,181 were Michigan residents; 0.16% (200 of 123,181 resident newborns screened) of them were diagnosed as having a disease. More than half of the 127 cases having treatment information reported were treated within two weeks of life.

Developments occurring in 2007:

- A NICU screening protocol was implemented to address the reliability/validity of testing among premature/low birth weight infants; the protocol advocates re-testing infants born weighing less than 1800g at two and four weeks of life.
    - The NICU/LBW screening protocol increased the congenital hypothyroidism (CH) detection rate more than three fold among infants weighing less than 1800g at birth; 14 cases of CH would not have been detected if only the initial screen were utilized.
- As of October 1st, 2007, the fee for the NBS card was increased to $85.61 as recommended by the Quality Assurance Advisory Committee.
- Early hearing detection was officially added to the NBS panel in 2007.
- Screening for Cystic Fibrosis began October 1st, 2007.
    - Seven cases were detected out of 132 positive screens in 2007.

* Both the 2006 & 2007 NBS Annual Reports are available at www.michigan.gov/newbornscreening

- A courier service was implemented in 2007 to transport dried blood spot samples from hospitals to the NBS laboratory in order to reduce time to diagnosis and accordingly time to treatment for conditions included in the NBS panel.
    - At the end of 2007 38% of the birthing hospitals sent 58% of the NBS samples by courier;.
    - As of July, 2008, 90% of hospitals are sending 93% of the specimens via courier. Thus, we expect significant improvements in time from birth to lab receipt of specimens in 2008.

- The NBS Follow-up Program began matching live birth records provided by the Division of Vital Records and Health Statistics to NBS records in order to identify potentially unscreened infants.
    - Thus far, more than 99% of live birth records have been matched to NBS records.

- The NBS Follow-up Program implemented a Three Year Follow-up Protocol to confirm the diagnosis of permanent congenital hypothyroidism among borderline cases (those having pre-treatment serum thyroid stimulating hormone levels in the lowest 15th percentile) after age three years.
    - Thus far, half of the cases followed up are thought not to have permanent congenital hypothyroidism, although tracking is ongoing.

- A pilot second tier congenital adrenal hyperplasia (CAH) screen added to the NBS program in August, 2006 was continued through 2007.
    - Compared to the traditional method, addition of the 2nd tier screen results in a ~95% reduction in false positive screening results for CAH.
    - Among non-NICU births the positive predictive value (number of true cases of disease out of the total number of positive screens) increased by more than 7 fold and the decrease in the false positive rate (number of false screens out of the total number of screens) was equally impressive for the second tier screen.
    - A modified tier-based screening algorithm is currently under consideration.
    - *Medical decisions are not based on these results at this point; follow-up of newborns continues to be based on results of the initial screening method.*

- NBS analyses were presented at the National Maternal and Child Health Epidemiology conference and the Preconception Health and Care: Second National Summit.

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ACRONYM KEY

Acronym†	Name
ACMG	American College of Medical Genetics
ASA	Argininosuccinic Aciduria
CAH	Congenital Adrenal Hyperplasia
CF	Cystic Fibrosis
CH	Congenital Hypothyroidism
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
M/SCHAD	Medium/short-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency
MCIR	Michigan Care Improvement Registry
MDCH	Michigan Department of Community Health
MS/MS	Tandem Mass Spectrometry
MSUD	Maple Syrup Urine Disease
NBS	Newborn Screening Program
NICU	Neonatal Intensive Care Unit
PCP	Primary Care Physician
PEAC	Pediatric Endocrinology Advisory Committee
PKU	Phenylketonuria
PPV	Positive Predictive Value
QA	Quality Assurance
QAAC	Quality Assurance Advisory Committee
SC	Sickle Cell
SCDAA	Sickle Cell Disease Association of America
TSH	Thyroid Stimulating Hormone
U of M	University of Michigan

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

I: INTRODUCTION

The Newborn Screening (NBS) Annual Report provides an overview of Michigan's Program (NBS), target outcomes, screening performance metrics related to conditions included in the NBS panel, and quality assurance information. This report differs from the one released in 2006 in several ways. First, this is an abridged report in that it does not include appendices which have not changed since 2006 including the NBS research guidelines, supportive legislation, or website description.‡ Second, this report includes a chapter providing in-depth information on a single NBS condition, congenital hypothyroidism (Chapter IV). This chapter includes an overview of CH screening, information on definition, diagnosis, and treatment, and updates on ongoing CH related NBS program evaluation research. Subsequent NBS annual reports will each include a chapter detailing a different disorder each year. Third, regional prevalence estimates are not provided (numerically or graphically) because these estimates will not have changed significantly from 2006 to 2007. 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,
- detail quality assurance information,
- provide a detailed account of CH screening in Michigan, past present and future, 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 for signs of treatable disorders.

NBS began in the 1960s when Dr. Robert Gutherie 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. 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

‡ Both the 2006 & 2007 NBS Annual Reports are available at www.michigan.gov/newbornscreening

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 (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 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. 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, 2007

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 (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/short-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency (M/SCHAD)	Dienoyl-CoA reductase deficiency (DERED)
Variant Hemoglobinopathies	Cystic Fibrosis (CF)
Medium-chain ketoacyl-CoA thiolase deficiency (MCKAT)	Hearing*

**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.*

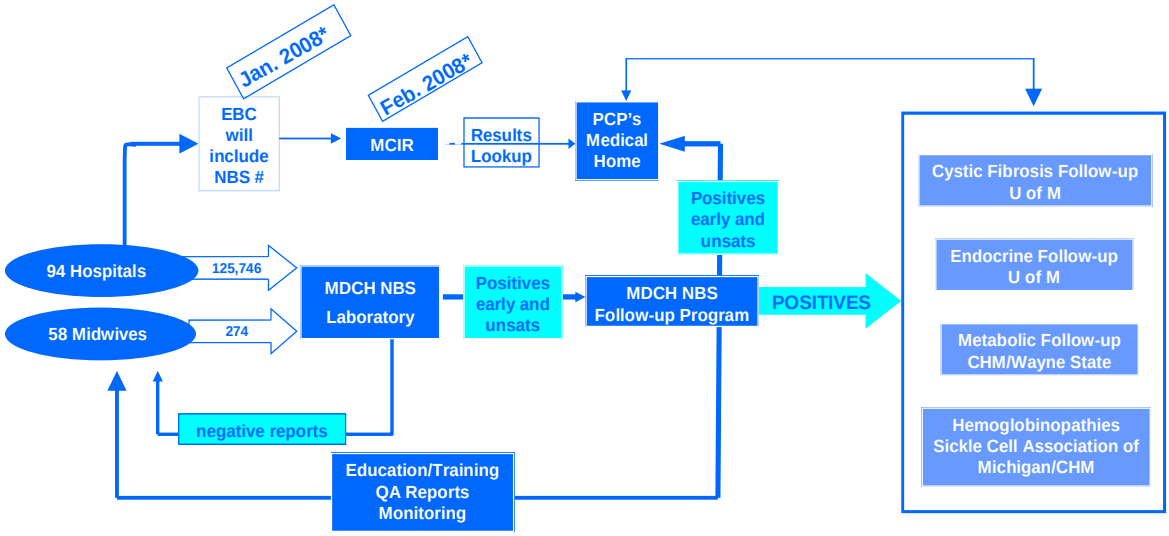

Figure 1: Overview of the Michigan Newborn Screening Program

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 coordinator 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 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 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. Frances 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 standardization 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 49 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. Follow-up starts with referring these 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 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 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 Program, the Sickle Cell Disease Association of America, Michigan Chapter, and the Cystic Fibrosis Program at the University of Michigan.

-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 43 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.

-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 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.

- 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 of 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 Dr. Samya Nasr. 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 at MDCH to calculate the total number of live births eligible to be screened statewide. The number of live births among Michigan residents in 2007 (n=124,211) is a preliminary estimate. For cystic fibrosis cumulative detection rate calculation we multiplied the average number of births per month (124,181/12) by three to obtain a denominator representative of births from October, when CF screening began, through the end of December.

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 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. 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 2 provides a description of screening performance metrics included in subsequent tables. These indicators are commonly used to assess the performance of screening tests and allow for comparisons both over time and with other screening programs. Ideal screening tests have a high positive predictive value (perfect=100%) and a low false positive rate (perfect=0%); a perfect screening test correctly identifies all cases of a disorder with no false positives. No NBS test is perfect but screening for metabolic disorders by MS/MS 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.

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.

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 that has been confirmed among Michigan resident infants screened
False +	A positive screen among Michigan resident infants screened 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 (%)
Se^	Sensitivity: the number of true positive screens divided by the number of true positive and false negative screens. [True Positives/ (True Positives + False Negatives)]
Sp^	Specificity: the number of true negative screens divided by the total number of true negative and false positive screens. [True Negatives/(False Positives + True Negatives)]

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

^***Note**: Sensitivity and specificity can only be calculated if false negative screens are known; thus, sensitivity and specificity are reported for CAH only for comparison of first and second tier screening because false negatives were able to be investigated in other than a passive manner while evaluating the efficacy of second tier screening.*

III: SCREENING RESULTS

DEMOGRAPHICS OF INFANTS SCREENED

This section describes the population of infants screened during 2007 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% (n=123,514) of the live births occurring in Michigan in 2007; the proportion of live births screened is based on the estimated live births occurring in Michigan in 2007. 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 2007. (Table 3: Internal data) Unmatched records have either: a) been identified as having been screened, or b) signed a parental refusal of NBS letter. To date, less than five infants are known to have been missed by newborn screening and have been contacted for obtaining a screen.

Table 3: Newborn Screening & Live Births Records Linkage Results, Michigan, 2007

Birth Year	Total	Matched		Un-Matched Excluding Expired Infants	
	N	N	%	N	%
2007	123,981	122,515	98.8	1,083	0.9

There were 333 live births (0.27% of live births screened in Michigan) to out-of-state residents. Tables 4 and 5 report the demographics of in-state and out-of-state residents screened in 2007 respectively. This report details screening results of in-state residents only. As indicated in Table 4, 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, 11% of infants screened were in the NICU, 9% weighed less than 2,500g at birth, and 11% were born preterm (<37 weeks gestational age). African Americans were over-represented among NICU, preterm, and low birth weight (<2,500g) births.

Table 4: Demographics of Infants Screened, Michigan, 2007, Excluding Out-of-State Residents, N=123,181

Race/ Ethnicity *Missing data: n=11,325*	**Row Total**		**Nursery Type**						**Low Birth Weight** *(missing data: n=12,610)*		**Gestational Age** *(missing data: n=14,484)*	
			Hosp. Nursery^		**Midwife**		**NICU**		**<2500 grams**		**< 37 weeks**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
White	79,709	71.26	72,255	90.6	279	0.4	7,175	9.0	5,380	6.7	7,402	9.3
Black	21,430	19.16	17,850	83.3	2	0.0	3,578	16.7	2,864	13.4	2,959	13.8
American Indian	574	0.51	521	90.8	0	0.0	53	9.2	40	7.0	46	8.0
Asian/Pac Islander	2,432	2.17	2,251	92.6	1	0.0	180	7.4	186	7.6	179	7.4
Middle Eastern	3,359	3	3,058	91.0	0	0.0	301	9.0	259	7.7	278	8.3
Multi-Racial	4,352	3.89	3,897	89.5	7	0.2	448	10.3	395	9.1	445	10.2
Hispanic*	8,319	6.75	7,695	92.5	7	0.1	617	7.4	525	6.3	631	7.6
Column Total:	*111,856*		*99,832*	*89.3*	*296*	*0.3*	*11,735*	*10.5*	*9,649*	*8.6*	*11,940*	*10.7*

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.*

**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 5: Demographics of Infants Screened, Michigan, 2007, Out-of-State Residents, N=331

Race/ Ethnicity *Missing data: n=333*	**Row Total**		**Nursery Type (missing data n=33)**				**Low Birth Weight (missing data n=103)**		**Gestational Age (missing data n=109)**	
			Hosp. Nursery^		**NICU**		**<2500 grams**		**<37 weeks**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
White	233	77.67	193	82.8	40	17.2	20	8.6	33	14.2
Black	32	10.67	26	81.3	6	18.8	5	15.6	5	15.6
American Indian	1	0.33	1	100	0	-	0	-	0	-
Asian/Pac. Islander	10	3.33	10	100	0	-	0	-	2	80.0
Middle Eastern	12	4	10	83.3	2	16.7	1	8.3	1	8.3
Multi-Racial	12	4	10	83.3	2	16.7	3	25.0	3	25.0
Hispanic*	16	-	14	87.5	2	12.5	1	6.3	1	6.3
Column Total:	*300*	*100*	*250*	*83.3*	*50*	*16.7*	*29*	*9.7*	*44*	*14.7*

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.*

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^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 2007 in the following sub-sections, excluding hearing screening results. The total number of cases detected both in and through 2007 is presented along with screening performance metric targets and screening performance metrics. The disorders are organized into four categories: metabolic, endocrine, cystic fibrosis and hemoglobin, corresponding to the four medical management programs responsible for diagnosis and medical treatment.

CUMULATIVE DETECTION RATE

Table 6 reports the cumulative detection rate of disorders identified via NBS by classification both in and through 2007. 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, not detectable by MS/MS (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 2007, while galactosemia disorders were the least prevalent.; however, considering the MS/MS disorders separately, several have yet to be detected. Of note is that 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 46% of all disorders detected in 2007 and 38% of all cases detected cumulatively. Hemoglobinopathies account for 28% of all cases detected in 2007 and 35% of all cases detected cumulatively. Disorders detected by MS/MS (amino acid, organic acid and fatty acid oxidation disorders) accounted for 15% of cases in 2007 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 detection rate. The MS/MS detection rate does not include formiminoglutamic acid disorder (FIGLU) cases because the disorder is not included in the NBS panel and is not treated. Galactosemia, including Duarte compound heterozygotes, accounted for 4% of all disorders detected in 2007 and 3% cumulatively. Biotinidase deficiency, including partial biotinidase deficiency, accounted for 6% of all cases detected in 2007 and 4% of all cases detected cumulatively. CAH accounted for 1% all of cases in 2007 and 3% of all cases detected cumulatively. CF accounted for nearly 4% of cases detected in 2007.

In summary, CH and hemoglobin disorders account for about two-thirds of all cases detected annually. Although MS/MS disorders currently account for about one-seventh 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 MS/MS. This suggests that over time MS/MS screening will become even more dominant as the primary platform for newborn screening. The current cumulative prevalence of MS/MS detected disorders is 1:4,105.

Table 6: Disorders Identified via Newborn Screening, Michigan Residents, 1965-2007

Type of Disorder Classification (Year Screening Began)	Cases in 2007 (N)	Cases Through 2007 (N)	Cumulative Detection Rate*
Galactosemia (1985)	8	124	1:25277
Biotinidase Deficiencies (1987)	12	160	1:17,867
Amino Acid Disorders (1965)	10	600	1:10,155
Organic Acid Disorders (2005)	3	13	1:29,174
Fatty Acid Oxidation Disorders (2003)	16	55	1:11,633
Congenital Hypothyroidism (1987)	88	1,482	1:1,929
Congenital Adrenal Hyperplasias (1993)	3	106	1:18,718
Hemoglobinopathies (1987)	53	1,389	1:2,058
Cystic Fibrosis (began, October 2007)	7	7	1:4,436
Total	200	3,936	-

**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 was calculated by multiplying the average number of births per month by four. Galactosemia includes both classical cases and Duarte varients (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 7. 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.

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.*§ 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

§ 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.

performance targets. Performance targets for MS/MS screening, based on data reported by Rinaldo et al., are included in Table 7.

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.

Table 7: 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 - 1:211,200
		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 8 reports screening performance metrics for all disorders for 2007. Performance metrics for individual MS/MS disorders are provided in the following section in Tables 11, 12, and 13. Overall, 64% of positive screens are from newborns in the NICU compared to 11% of births in the NICU. NICU positive screens ranged from 95% for CAH to 11% for organic acid disorders. The incidence of NBS disorders in the NICU is approximately 1:300 compared to an incidence of 1:1,100 in non-NICU births.

GALACTOSEMIA, BIOTINIDASE DEFICIENCY, & CYSTIC FIBROSIS

The galactosemia detection rate (including Duarte D/G variants) was 1:15,398 in 2007. The FPR and PPV were .01% and 42% respectively. However, considering that the purpose of galactosemia

screening is to detect classical galactosemia only, we report a detection rate of 1:61,591 for the two cases identified. The biotinidase deficiency (including partial biotinidase deficiency) detection rate was 1: 10,265; the FPR and PPV were 0.15% and 6% respectively. The FPR and PPV of both galactosemia and biotinidase deficiency significantly exceed the targets of less than 0.5% and greater than 5% for FPR and PPV respectively. One case of profound biotinidase deficiency was detected in 2007 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)**. Seven cases of cystic fibrosis (CF) were detected from October through the end of December 2007 (detection rate- 1:4,436); the associated FPR and PPV were 0.4% and 5.3% respectively.

ENDOCRINE DISORDERS CH AND CAH

The detection rate for CH of 1:1,400 is slightly greater 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 12.6% meets 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. Chapter IV provides more detailed information about CH screening in Michigan.

While the detection rate for CAH of 1:41,060 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 is that the cumulative CAH detection rate of 1:18,744 is within the target range; however the PPV of 0.38% is well below the already low PPV target of one to two percent and the FPR of 0.63% exceeds the target FPR of 0.5%. Two cases of salt-wasting CAH were detected among 781 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 MS/MS for newborns with an initial positive 17-OHP. Preliminary data, presented in Table 9, indicate that second tier testing reduces the percent of false positives by 95% without increasing false negatives. As indicated in Table 9, the improvement in performance metrics particularly among non-NICU births is quite impressive; the PPV increased by more than 7 fold and the decrease in FPR was equally impressive. However, second tier screening for CAH is still being evaluated and is conducted in tandem with our traditional CAH screening algorithm; thus, medical decisions are not made based solely on second tier screening results for CAH at this time. A modified CAH screening algorithm is currently being considered.

** Wolf, B., and Heard, G.S. (1990) Pediatrics, 85(4): 512-517.

Table 8: Screening Results and Performance Metrics, Michigan, 2007

Disorder Type	Total N	Total + N (% NICU)	Confirmed + N	Positive Detection Rate	FPR %	PPV %
Galactosemia	123,181	19 (11.8)			0.01%	42.11%
Classic (GG)			2	1:61,591		
Duarte (DG)			6	1:20,530		
Total			8	1:15,398		
Biotinidase Deficiency		191 (39.7)			0.15%	6.28%
Profound			1	1:123,181		
Partial			11	1:11,198		
Total			12	1:10,265		
Cystic Fibrosis (8 pending as of 6/18/08)		132 (27.9)	7	1:4,436	0.40%	5.30%
Congenital Hypothyroidism (CH)		697 (34.4)	88	1:1,400	0.49%	12.63%
Congenital Adrenal Hyperplasias (CAH)		781 (94.9)			0.63%	0.38%
Salt wasting			2	1:61,591		
Non-Salt wasting			1	1:123,181		
Total			*3*	*1:41,060*		
Hemoglobinopathies		75 (26.1)	53	1:2,324	0.061%	70.667%
Amino Acid*		43 (21.1)	10	1:12,318	0.02%	23.26%
Organic Acid*		96 (11.2)	3	1:41,060	0.08%	3.13%
Fatty Acid Oxidation*		74 (20.6)	16	1:7,699	0.05%	21.9%
MS/MS Disorders Total		213 (16.5)	29	1:4,248	0.15%	13.15%

***Note**: In the above table galactosemia includes both classical cases and Duarte variant cases. Biotinidase includes both partial and profound biotinidase deficiencies.*

**Detected by MS/MS (maternal cases detected are not included in the table; the associated narrative includes performance metrics including maternal cases of CUD and 3MCC for comparison with other programs)*

Table 9: Congenital Adrenal Hyperplasia Screening Results Pre- and Post- Second Tier Testing Implementation, Michigan, 2007-2008

Inclusion Criteria	Tier	(N)	Confirmed (N)	Detection Rate	FPR (%)	PPV (%)	Se (%)	Sp (%)
All Births Screened	1	177,143	5	1:35,429	0.56	1.00	100	99.44
	2		5	1:35,429	0.03	8.00	100	99.97
NICU Only	1	19,131	3	1:6,377	4.80	<0.01	100	95.20
	2		3	1:6,377	0.25	6.00	100	99.80
Non-NICU Only	1	158,012	2	1:79,006	0.03	4.00	100	99.97
	2		2	1:79,006	< 0.01	29.00	100	100.

HEMOGLOBINOPATHIES

Hemoglobinopathy screening outcome information is reported in Table 10. 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 indicated in Table 10, the overall detection rate for hemoglobinopathies in 2007 was 1:2,324; however, the detection rate is known to be approximately six-fold greater among African Americans.

Table 10: Hemoglobinopathy Screening Performance Indicators, Michigan, 2007

Disorder	Newborns (N)	Confirmed + (N)	Positive Detection Rate
		Total	Total*
Sickle Cell Anemia	123,181	27	1:4,562
SC Disease		20	1:6,159
Sickle β thalassemia		6	1:20,530
Total		*53*	*1:2,324*

MS/MS DISORDERS

While the overall FPR for MS/MS of 0.15% is within the target of less than or equal 0.3%, the detection rate of 1:4,248 and PPV of 13.15% are below but close to the target metrics of 1:3,000 and 20% respectively. This leads to what others have noted (Rinaldo et al. 2006, Frazier 2006)[1], 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.

SCREENING PERFORMANCE METRICS – INDIVIDUAL MS/MS DISORDERS

AMINO ACID DISORDERS

Nine amino acid disorders (Table 11) were detected by MS/MS. PKU is the most frequent condition, found in one of every 12,318 newborns screened. One case of hyperphenylalaninemia had a normal (slightly below the abnormal cut-off) repeat screening result, although the laboratory noted the level of phenylalanine to medical management and recommended follow-up which lead to the diagnosis of the case. We include this as a detected case. One case of tyrosinemia was also detected clinically after having a normal newborn screen. As indicated in the table, PKU screening had the highest PPV (74%). The FPR for PKU screening of .0.003% reflects the very high sensitivity of MS/MS screening for this disorder. No other cases of amino acid disorders were confirmed in 2007.

ORGANIC ACID DISORDERS

Three organic acid disorders (Table 12) were detected by MS/MS. The FPR for each of the detected disorders was at or below .05%; however, several conditions screened positive were not confirmed resulting in a 100% FPR. Among individual conditions, the PPV was greatest for 3MCC (12%). In April, 2007, the laboratory cut-offs for PA/MMA were changed from elevated C3 or C3/C2 to elevated C3 and C3/C2 and C3/C16 which led to a halving of the number of positive screens without a known increase in false negative screens.

FATTY ACID OXIDATION DISORDERS

Sixteen fatty acid oxidation disorders (Table 13) were detected (eight MCAD, six SCAD, and two VLCAD); three FIGLU cases were detected, although FIGLU is not officially included in the NBS panel. Among detected disorders, all FPRs were less than .02% and the PPVs were all greater than 25% with MCAD at 67%.

Table 11: Amino Acid Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2007

Disorder	Newborns N	Total + N (% NICU)	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Phenylketonuria Classic (PKU)	123,181	14	3	1:40,060	0.003	71.4
Mild			2	1:61,590		
Benign Hypephenyla-laninemia (H-PHE)			5	1:24,636		
Biopterin Cofactor Defects (BIOPT)			0	-		
Total			10	1:12,318		
Maple Syrup Urine Disease (MSUD)		1	0	-	0.001	0
Homocystinuria (HCY)		2	0	-	0.002	0
Arginemia (ARG)		1	0	-	0.001	0
Citrullinemia/ASA (CIT/ASA)		5	0	-	0.004	0
Tyrosinemia (TYR I)*		20	0	-	0.016	0

**One case was detected clinically after having a normal newborn screen.*

Table 12: Organic Acid Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2007

Disorder	Newborns N	Total + N (%NICU)	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Isovaleric Acidemia (IVA)/2MBG	123,181	9	0	-	0.007	0%
3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC))		16	2	1:61,591	0.011	12.50
Glutaric Acidemia Type I (GA I)		3	0	-	0.002	0%
Proprionic Acidemia(PA) / Methylmalonic Acidemia (Mutase Deficiency) MA/ Methylmalonic Acidemia (MA-Cbl C, D)		68	1	1:123,181	0.054	1.471
Multiple carboxylase deficiency (MCD)		1	0	-	0.001	0%
Isobutyryl-CoA Dehydrogenase Deficiency (IBG)^		16	0	-	0.013	0%

^ ***Note**: IBG testing uses the same analyte as SCAD, a fatty acid oxidation disorder. While no cases of IBG were confirmed, six cases of SCAD were detected in 2007as indicated in Table 12. Because IBG and SCAD are classified differently their performance metrics are presented in separate tables unlike other disorders utilizing the same analyte for screening (i.e., IVA/2MBG). To avoid confusion, we did not calculate FPR/PPV for IBG screening because the test did detect cases (six SCAD), but none were IBG; instead, we report performance metrics for SCAD in table 13.*

Table 13: Fatty Acid Oxidation Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2007

Disorder	Newborns N	Total + N (%NICU)	Confirmed + (N)	Positive Detection Rate*	FPR (%)	PPV (%)
Carnitine Uptake Defect- (CUD)	123,181	32	0		0.026	0%
Carnitine/Acylcarnitine Translocase Deficiency- (CACT)/Carnitine Palmitoyltransferase II Deficiency-(CPT II)		7	0	-	0.006	0
Short-Chain Acyl-CoA Dehydrogenase deficiency- (SCAD)/		16	6	1:20,530	0.006	56.3
Formiminoglutamic acid disorder (FIGLU)			3	1:40,060		
Total			9	1:13,683		
Glutaric Acidemia Type II- (GA II)		1	0	-	0.001	0
Medium-Chain Acyl-CoA Dehydrogenase Deficiency- (MCAD)		12	8	1:15,398	0.003	66.67
Long-Chain L-30H Acyl-CoA Dehydrogenase Deficiency- (LCHAD)/ Tryfunctional Protein Disease- (TFP)		1	0	-	0.001	0
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency-(VLCAD)		3	2	1:61,591	0.001	66.67
Medium/short-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency (M/SCHAD)		3	0		0.002	0
Medium-Chain Ketoacyl-CoA Thiolase Deficiency- (MCKAT)		1	0	-	0.001	0

SCRENING 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 14 because their performance metrics have been previously reported. Disorders not detected in 2007 are also not reported in Table 14 as there would be no change in screening performance (FPR and PPV would be 100% and 0% respectively for both total positives and strong positives).

Performance metrics among strong positive 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 14, the FPRs and PPVs among strong positives are significantly improved relative to the overall screening performance metrics among all positives.

Table 14: Screening Performance Metrics (FPR and PPV) among Strong Positive Screens

Disorder Type	Among All +		Among Strong +	
	FPR	PPV	FPR	PPV
	%	%	%	%
Galactosemia	0.01	15.79	0.002	60.00
Biotinidase Deficiency	0.15	6.28	0.002	25.00
Cystic Fibrosis	0.10	5.30	0.10	5.30
Congenital Hypothyroidism (CH)	0.49	12.63	0.10	34.43
Congenital Adrenal Hyperplasias (CAH)	0.63	0.38	0.24	1.02
Phenylketonuria (PKU)*	0.003	71.4	0.0	100
3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC))	0.011	12.50	0.002	40.00
Proprionic Acidemia(PA) / Methylmalonic Acidemia (Mutase Deficiency) MA/ Methylmalonic Acidemia (MA-Cbl C, D)*	0.054	1.471	0.007	10.00

*MS/MS disorders

The FPR for galactosemia screening is reduced eight fold while the PPV is increased nearly four fold among strong positives. The reduction in the FPR for biotinidase deficiency is more drastic representing a nearly 60 fold decrease while the PPV increased nearly four fold. The FPR and PPV for cystic fibrosis did not change because all positives in 2007 were strong positive screens.

The FPR for CH is reduced by five fold for strong positives and the PPV increased by nearly three fold. The FPR and PPV for CAH are decreased and increased respectively by nearly three fold among strong positives. Among MS/MS disorders, all strong positive screens for PKU, an amino acid disorder, were true positives; thus, the PPV was 100% and accordingly the FPR was 0%. Increases in the PPV and decreases in the FPR among 3MCC and PA were also significant improvements relative to total positive screening results.

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

IV: CONGENITAL HYPOTHYROIDISM SCREENING IN MICHIGAN

This section provides a detailed account of CH screening in Michigan including: 1) an overview of CH and the Michigan CH screening algorithm, 2) a modified algorithm for detection of CH in low birth weight/premature newborns; a group at high risk for CH, and 3) the design and preliminary results of a study to determine if newborns diagnosed with CH have either a permanent or transient form of the disorder and 4) future direction of newborn screening for CH in Michigan.

OVERVIEW OF MICHIGAN NEWBORN SCREENING FOR CH

CH is an endocrine disorder usually characterized by a malfunction of the thyroid gland that leads to increased concentration of thyroid stimulating hormone (TSH) and decreased concentration of thyroxin (T_4), a hormone that is involved in both controlling the rate of metabolic processes in the body and influencing physical development. CH may be caused by dysgenesis, an abnormality in thyroid gland development, or dyshormongenesis, defects in synthesis of thyroxine. In rare cases (1/25,000 – 1/100,000)[2] CH is caused by defects in hypothalamus or pituitary (central or secondary/tertiary hypothyroidism).

Figure 1 depicts the hypothalamic-pituitary-thyroid axis that controls thyroid function. As shown in figure 1, T_4 is stimulated by secretion of TSH by the pituitary. When the level of T_4 is low (negative feedback) the hypothalamus secretes additional thyrotropin releasing hormone (TRH) which in turn stimulates the release of TSH thereby stimulating the thyroid gland to increase secretion of T_4. When the thyroid does not respond to TSH stimulation (primary CH), due to dysgenesis or dyshormonogenesis, the result is low T_4 and high TSH.

Newborn screening for primary CH is based on detection of low T_4, high TSH, or both. Hypothalamus and pituitary defects result in secondary and tertiary CH, respectively. As a group, these forms of CH are referred to as central CH and are characterized by the inability of the glands to initiate a TRH/TSH response to low T_4. As there is little or no TSH stimulation in central CH, these disorders can only be detected by screening programs that include an evaluation of low T_4

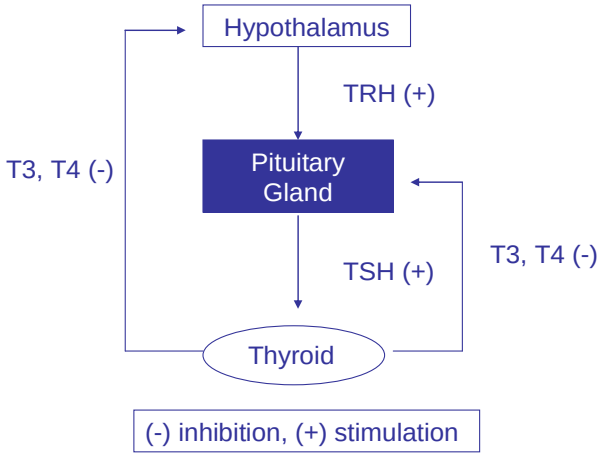

Figure 2: Hypothalamic *Pituitary Axis*

NBS for CH began in 1974 in Quebec, Canada, and Pittsburgh, Pennsylvania.[3,4,5] In Michigan, CH was added to the NBS panel in 1977. From 1977 to 1998 Michigan used a primary T_4, secondary TSH screening method. DBS T_4 concentrations were obtained on all newborns and those in the bottom 10th percentile were then evaluated for elevated TSH.

From 1998 to 2003 Michigan used a dual T_4/TSH screening method that provided a T_4 and TSH determination for all newborns. The purpose of the change in screening method was to improve the

detection rate for primary CH (TSH >sensitivity and specificity than T_4 for primary CH) and retain the ability to detect central hypothyroidism by evaluating low T_4.

In 2003 primary TSH screening only (no secondary T_4 screen) was implemented and the dual T_4/TSH assay was discontinued due to an unacceptable false positive rate of 3-5% and the detection of few cases of central CH. In addition, it was determined by reviewing all T_4 and TSH values on cases diagnosed by the dual assay that cases of primary CH were significantly more likely to be missed by a primary T_4 vs. primary TSH screening algorithm. The current screening method is based on age adjusted cut-offs selected to maximize the detection rate of primary CH and minimize the false positive rate. Strong positives (those with high TSH concentrations) are immediately referred for diagnostic evaluation. Borderline positives (those with moderately elevated TSH) are retested either by use of another DBS or serum testing. Retest positives, strong or borderline, are also referred for diagnostic evaluation.

Since 1977, 1,482 cases of CH have been identified by NBS (Table 6). On average, one case of CH is detected in Michigan for every 1,900 infants screened. As mentioned previously, CH is the most common disease detected by NBS in Michigan accounting for 38 % of all disease cases detected since 1965. Michigan's detection rate is higher than the rates reported in the literature of one case detected for every 3,000-4,000 births; however Michigan's detection rate is consistent with other states that use primary TSH screening.

CH is more common among Hispanics and less common among Blacks than Whites. There are more females diagnosed than males (expected ratio 2:1) and the incidence is much higher among twins than single births. Newborns with Down Syndrome are at high risk for CH. Infants born prematurely (< 37 weeks gestational age) are also at increased risk of CH; however, initial screening results among premature infants may be unreliable. To address the reliability of screening results among premature/LBW infants for all conditions included in the NBS panel, Michigan implemented an NICU/LBW screening protocol for infants weighing less than 1800g at birth March 1st, 2007.

CH SCREENING AMONG PREMATURE/LOW BIRTH WEIGHT INFANTS

Neonatal immaturity, illness, and need for therapeutic interventions among premature/LBW infants can interfere with the NBS process. CH screening is particularly sensitive to such interference due to the impact of the maturity of the neonatal endocrine system on the negative feedback loop responsible for an increase in TSH (the hormone detected by screening) in response to low T_4 concentrations. Specifically, premature infants with CH may not exhibit increased TSH concentrations at the time of NBS because of a delayed rise in TSH leading to false negative screens.

Michigan's NICU/LBW screening protocol involves re-testing all infants born weighing less than 1800g at two and four weeks of life, or prior to discharge. Figure 4 details the NICU/LBW screening algorithm. . Detailed information about the NICU/LBW screening protocol can be found on the MDCH NBS website (www.michigan.gov/newbornscreening) including a fact sheet and practitioners manual.

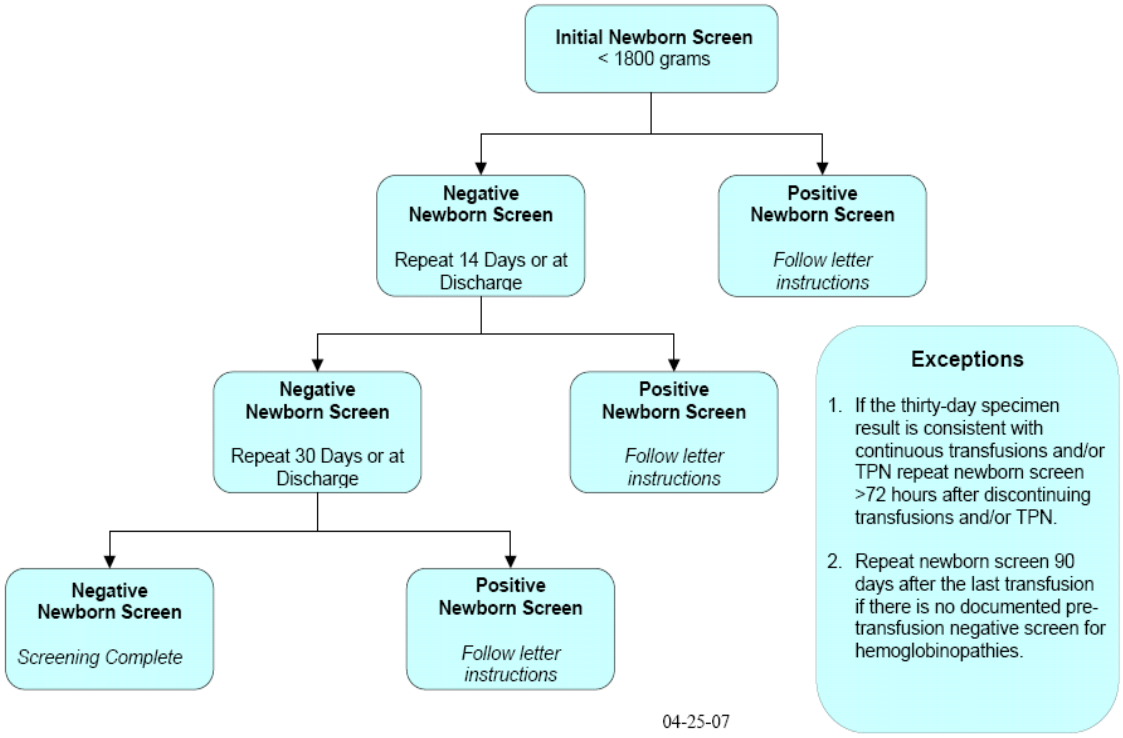

Figure 3: NICU/LBW Screening Protocol Algorithm

To investigate the impact of the NICU protocol on CH detection, detection rates were calculated stratified by birth weight using Michigan newborn screening system data and CH case data maintained by the Michigan NBS Follow-up Program from 2005-2007. Birth weight was stratified in both a traditional manner (<750g, 750-1,499g, 1500g-2,499g, >2,500g) and according to the Michigan NBS NICU/LBW screening protocol (<1800g, 1800g-2,499g, >2,500g). CH detection rates are reported in Table 14. As indicated in table 14, the CH detection rate increased from 1:698 to 1:211 from 2006 to 2007 among infants born weighing less than 1800g. Analysis of CH detection among traditional birth weight strata revealed that the majority of cases detected by the NICU/LBW protocol weighed less than 1500g at birth.

Table 15: CH Cases by Birth Weight & Birth Year, Michigan, 2005-2007

Birth Year	Birth Weight								
	< 1800g			1800-2499g			≥ 2500g		
	Cases	Screened	Rate	Cases	Screened	Rate	Cases	Screened	Rate
2005	5	2587	1:517	9	6873	1:764	58	108052	1:1863
2006	4	2793	1:698	5	7300	1:1460	50	114136	1:2283
2007	14	2961	1:211	5	7050	1:1410	68	111893	1:1645

The detection rate among normal birth weight infants also increased in 2007 relative to previous years; however, the detection rate among infants born weighing 1800g-2,499g remained relatively stable. While the NICU/LBW screening protocol increased the CH detection rate more than three fold among infants weighing less than 1800g at birth, it is possible that CH cases in the 1800 –2,499 have been missed due to the <1800g NICU protocol inclusion cut-off. Some NICU's that previously re-screened all newborns stopped this practice in response to the new <1800 NICU protocol. The protocol is being re-evaluated to determine

the impact on the NBS laboratory and follow-up system if birth weight/gestational age criteria are expanded to include more NICU newborns in the protocol. .

The impact in terms of increased numbers of newborns requiring 2nd and 3rd screens based on 2007 data is shown in Table 15. As indicated in the table, increasing the NICU/LBW birth weight inclusion criteria to less than 2200g would increase the number of newborns included in the protocol by approximately 2,500 if all LBW infants were added to the NICU/LBW protocol then approximately 7,000 infants would become eligible.

While the current NICU protocol uses only birth weight as an inclusion criterion, there has been interest in evaluating gestational age (GA) as a potential inclusion criterion because GA is thought to be a better indicator of maturity than birth weight. Because it is maturity that influences infants' ability to mount a TSH response and not birth weight both GA and birth weight were evaluated as inclusion criteria (again, based on 2007 data).

Table 16: Number of NICU Protocol Eligible Infants by Incremental Increase in Birth Weight Inclusion Criteria

Birth Weight	Frequency	%	Cumulative Frequency	Cumulative %	Number of Eligible Infants Added
< 1800g	2,794	2.31	2,794	2.31	-
1800-1999g	1,019	0.84	3,813	3.15	1,019
2000-2199g	1,554	1.28	5,367	4.43	2,573
2200-2499g	4,422	3.65	9,789	8.08	6,995
>=2500g	111,291	91.92	121,080	100	-

Inclusion of moderately pre-term and below (gestational age <32 weeks) infants in the protocol as it currently exists (inclusion: <1800g) would add approximately 215 infants annually. The number added by including GA as a criterion reduces as the birth weight inclusion cut-off increases; specifically, if the birth weight cut off were increased to 2200g and all moderately pre-term infants and below were included in the NICU protocol regardless of birth weight then approximately 77 infants would be added.

In conclusion, the NICU protocol seems to lead to improved detection of CH among infants weighing less than 1800g at birth. Had the screening decision (positive/negative) been made by the initial result, rather than on screens conducted at 2 and 4 weeks of life, 14 CH cases detected by the LBW protocol would not have been considered positive screens. We are continuing to assess the impact of altering the NICU protocol inclusion criteria in various ways. It is anticipated that criteria for inclusion in the NICU protocol may be expanded to include additional newborns in 2009.

CH CLASSIFICATION

Interestingly, while Michigan's newborns have been screened for CH since 1977, a distinct case definition does not exist. The CH diagnosis is based primarily on the evaluation of serum levels of the hormones free T_4 (FT_4) and TSH over time. In only a minority of cases is the diagnosis supported by additional thyroid imaging and function studies. For this reason, the diagnosis of permanent CH cannot be established at the time of treatment. The expectation is that a sub-set of newborns diagnosed with CH should be re-evaluated

for permanent CH at 3-years of age. In an attempt to identify sub-sets of newborns needing re-evaluation at 3-years of age, CH cases identified from 9/2003-9/2007 were grouped by the following pre-treatment serum TSH/FT_4 based categories :strata:

- (FT4 < .9, TSH >=40)
- (FT4 >=.9, TSH >=40)
- (FT4 < .9, TSH < 40)
- (FT4 >=.9, TSH <40)

Table 17 reports the characteristics of CH cases stratified by these categories. Cases populating the first two rows of the table are assumed to have a high probability of permanent CH due to significant elevations of pre-treatment serum TSH concentrations. Cases having borderline pre-treatment serum TSH elevations populate the bottom two rows of Table 16 and are assumed to have a lower probability of permanent CH. Of note, is that cases having pre-treatment FT_4 concentrations less than .9 and serum TSH concentrations below 40 are the only group having a mean GA prior to term (< 37 weeks) and mean birth weight below normal (< 2,500g). This sub-set is likely to increase proportionately as the NICU protocol inclusion criteria are expanded.

Table 17: CH Cases Classified by Pre-Treatment Serum TSH/FT4 Values, Michigan, 9/2003-9/2007

Classification	N	%	Mean GA	Mean BW	White (%)	Male (%)	NICU (%)
FT_4< .9, TSH >=40	103	44.78%	37.9	3156	79.1	39.2	19.6
FT_4>=.9, TSH >=40	48	20.87%	38	3254	61.5	33.3	18.2
FT_4< .9, TSH < 40	9	3.91%	34.1	2461	50	66.7	55.6
FT_4>=.9, TSH <40	70	30.43%	38.5	3001	53.1	58	25.8

As indicated in Table 17, CH cases having borderline elevations of pre-treatment serum TSH (<40) are more likely to be racial minorities, NICU births, and are born sooner and of lower birth weight. Interestingly, the expected 2:1 female to male sex ratio characteristic of CH is reversed among borderline cases as indicated in the proportion of males among cases populating the bottom two rows of Table 15. These differences among cases stratified by pre-treatment serum TSH/ FT_4 concentrations likely reflect differences in etiology with over representation of cases of ectopic thyroid and thyroid agenesis in the high TSH categories and cases of dyshormonogenesis and non-permanent CH overrepresented in the low TSH categories. To determine the incidence of permanent CH in the low TSH categories, these newborns are now being systematically followed up at 3-years of age.

CH DIAGNOSTIC RE-EVALUATION AFTER AGE THREE YEARS

The standard of care for CH management is to verify the initial diagnosis among potentially transient cases by challenging the thyroid via cessation/reduction of thyroxin replacement medication at age three years and evaluating subsequent TSH levels. If TSH levels increase following treatment reduction/cessation, then treatment is resumed and the CH diagnosis is confirmed. If TSH levels remain stable following treatment

cessation, the diagnosis is not confirmed and treatment is not resumed. This 'thyroid challenge' is the basis of differentiating permanent from transient hypothyroidism. Newborn screening programs typically follow newborns through diagnosis and initiation of treatment (short-term follow-up). This presents a problem for CH since the diagnosis is often delayed for 3 or more years following the initiation of treatment. For this reason, it was decided to extend the short-term follow-up period for CH until the determination of permanent CH has been made at 3 or more years of age. It is believed that Michigan is the first state newborn screening program in the United States to incorporate routine 3-year follow-up as part of CH screening. The following describes the process and initial outcomes of implementing the program:

The first step was to define the group that required a 3-year re-evaluation. . Several approaches were considered. First, we discussed possible criteria for defining the group requiring 3-year follow-up with the Pediatric Endocrine Advisory Committee (PEAC). One suggestion was to follow-up only those that had an initial newborn screening TSH<50. This was rejected because the decision to treat is not based on the initial newborn screen. A second suggestion was to derive a threshold serum TSH range based on the overlap of TSH values for treated cases and untreated cases (false positives). Only newborns diagnosed within the threshold range would require a 3-year follow-up. This approach was also not practical as essentially all diagnosed newborns exceeded the threshold cut-off range. Finally, it was decided to use a percentile based approach to define the 3-year follow-up group. Specifically, newborns in the bottom 15th percentile of pre-treatment serum TSH values would be included in the 3-year follow-up group. Depending on the results of follow-up for this group the percentile would be expanded by increments until a pretreatment serum TSH percentile cut-off is reached that separates most cases of permanent CH from cases of transient CH. Newborns above the cut-off percentile would be assumed to have permanent CH.

Next, a survey document was created and mailed to endocrinologists treating these children to determine: if the children were currently being treated or treatment had been discontinued and if treatment was discontinued what was the reason. Also if the child had not been treated and was still on treatment, the endocrinologist was asked whether or not diagnostic re-evaluation is planned. The survey was developed in stages, was informed by the PEAC, and pilot tested on several endocrinologists prior to being disseminated.†† If the endocrinologist was no longer seeing the child, NBS follow-up staff tracked the child using the Michigan Care Improvement Registry (MICR) and the child's current physician was contacted by phone to determine the status of CH treatment.

Data collection for the 3-year follow-up study began January, 2008; preliminary results are provided in Table 18. To date, we have attempted to survey 16 endocrinologists; one patient was lost to follow-up, five patients are currently undergoing diagnostic re-evaluation. Five children had undergone a thyroid challenge, five had stopped treatment of their own (family's) accord, and one child did not undergo a challenge because the TSH/medication dosage increased over time.

Interestingly, for five of six children reported to not have permanent CH, treatment was discontinued without informing the endocrinologist or the primary care provider. This contrasts with the five children re-evaluated by an endocrinologist after 3 years where only one was considered to have had transient CH. Low medication dosage was the most common reason cited by endocrinologists for conducting a thyroid challenge. The follow-up procedure most often cited thus far was to re-evaluate thyroid function 6 weeks after initiating the challenge.

†† survey is available by request, email: KorzeniewskiS@Michigan.gov

Table 18: Preliminary CH Three Year Follow-up Study Results

Re-Evaluated (Yes/No)	Permanent CH (Yes/No)	Sex	Race	NICU	DBS TSH	SERUM		Initial Medication Dose	Medication dose at survey
						TSH	FT4		
LTFU		M	Asian/Pac. Islander	No	43	14.6	1.38	37.5 mcg	
In Progress *	Pending	M	Black	Yes	45	9.76	1.07	0.125 mcg	Not on Tx
Yes*	No	M	Black	No	47	13.98	1.3	25 mcg	Not on Tx
Yes*	No	F	White (Hispanic)	No	135	13.49	1.7	25 mcg	Not on Tx
Yes*	No	F	Black	No	40	14.02	1.7	25 mcg	Not on Tx
Yes*	No	M	Black	Yes	16	14.56	1.35	12.5 mcg	Not on Tx
Yes	Yes	F	White	No	33	8.65	.	50 mcg	37.5 mcg
In Progress	Pending	M	White	No	10	5.91	0.95	25 mcg	
In Progress	Pending	M	Black	No	45	13.4	.	25 mcg	25 mcg
Yes	Yes	F	Middle Eastern	No	51	9.3	1.2	25 mcg	50 mcg
Yes	Yes	F	White	Yes	51	8.92	1.3	25 mcg Qd	25 mcg
Yes	Yes	M		No	53	9.33	0.97	37.5 mcg	75 mcg
Yes	No	F	Black	No	36	8.62	1.27	25 mcg QD	Not on Tx
In Progress	Pending	M	Black	Yes	35	10.21	0.81	25 mcg	25 mcg
No	Yes	M	Black	Yes	14	5.55	.	25 mcg QD	50 mcg
In Progress	Pending	M	Multi-Racial	Yes	66	11.7	1.3	25 mcg QD	Not on Tx

***= patient stopped treatment, not evaluated by an endocrinologist**

Preliminary findings of the CH Three Year Follow-up Study have several potential implications. The finding that 5/16 patients followed-up to date have taken themselves off treatment indicates that NBS CH follow-up protocols should include tracking at least until age three years to confirm that appropriate treatment has been provided and utilized. The American Academy of Pediatrics (AAP) recommends monitoring CH at 2-4 weeks after initial treatment begins, every 1-2 months in the first 6 months of life, and every 3-4 months thereafter until age 3; the AAP recommendation also advocates monitoring once or twice per year from age three until the end of growth. Standardized tracking of CH patient interaction with medical management would make NBS Follow-up staff aware of cases lost to follow-up soon enough to intervene and assure continuation of treatment when necessary.

The finding that all patients who stopped treatment without the knowledge of the endocrinologist are reported not to have permanent CH while four of five evaluated by an endocrinologist are reported to have permanent CH may have implications for the method of diagnostic re-evaluation. Specifically, the method of re-evaluation and the point at which treatment should be re-instated should be clarified and standardized to ensure that treatment is not resumed prematurely. One of the AAP guidelines recommend confirming the permanence of CH and resuming treatment when serum TSH concentrations rise to 20 uM/L after challenging the thyroid by reducing medication dosages.[6] This study is ongoing but it is already apparent that the inclusion cut-off should be increased from the 15th to the 25th percentile.

CONCLUSION

The diagnosis of CH is complicated by the inability to differentiate permanent from transient forms of CH in the newborn period. While the disorder has been screened for since 1977 in Michigan, there is still no consensus on the appropriate screening algorithm as evidenced by updates in the screening method as recently as 2003 and research currently under way to advocate improvement in diagnostic and follow-up protocols. This is also true of CH screening programs in other states.

In the United States few NBS programs follow-up CH cases longitudinally. Michigan is in a unique position to evaluate CH management and long-term outcomes due to the state coordinated NBS Follow-up Program that includes a medical management program and clinical database for the endocrine disorders. Specifically, the database includes initial screening, diagnostic and follow-up data on all newborns treated for CH. The majority of CH cases are treated at the University of Michigan (U of M) Medical Center, which is the NBS Follow-Up Endocrine Coordinating Center. Data on CH cases treated outside of the U of M system are also reported to the central database. Michigan's ability to track virtually all CH cases identified by NBS provides a unique opportunity to evaluate CH medical management and outcome in the United States.

The MDCH, NBS program will continue to evaluate and refine the program in hopes of improving outcomes for CH and the other disorders included in the NBS panel. Current CH related plans include continuing the Three Year Follow-up Study, evaluating NICU/LBW screening protocol inclusion criteria, assessing co-morbidities, and evaluating implications of fixed vs. daily percentile cut-off in response to significant variations in mean TSH observed, over time, using the autodefia test kits.

V: 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 19 reports specimen characteristics by nursery type. Although only 10.5% of infants were in the NICU, 60% and 50% 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, premature birth, and having been transfused. While the overall number of unsatisfactory specimens was greatest among hospital nurseries, the proportion of unsatisfactory specimens was greatest among NICU samples (7%). 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 5,000 specimens were followed up in 2007. Strong positive results (n=695) are immediately referred to medical management centers for evaluation.

Table 19: Specimen Characteristics by Nursery Type, Michigan, 2007

Indicator	Type of Birth					
	Regular Nursery		NICU		Midwife	
	N	%	N	%	N	%
Strong + Specimens	275	0.25%	418	3.32%	2	0.68%
Borderline + Specimens	664	0.60%	676	5.37%	2	0.68%
Isolated elevations of amino acids and acyl carnitines	3	0.003%	423	3.36%	0	
TPN Specimens	52	0.05	2416	20.3	67	23.4
Unsatisfactory Specimens	1215	1.11	391	3.11	20	6.87
Late (>6 days) Specimens	144	0.12	109	0.86	31	10.73
Early (<1 day) Specimens	820	0.74	906	7.19	2	0.69
Transfused Specimens	15	0.02	196	1.74	1	0.37
Specimens Missing Demographics *	11691	10.6	1,015	8.06	18	6.16
Total Births Screened	110,274	89.5	12,616	10.2	291	0.24

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

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 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 FROM BIRTH TO SPECIMEN COLLECTION

Table 20 reports the time from birth to NBS specimen collection and mailing of 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.

Nearly 95% of specimens collected in hospital nurseries/NICUs are collected within 24 to 36 hours of birth; only 30% of midwife/non-hospital birth specimens are collected in the recommended time frame. While less than one percent of initial specimens collected in hospital nurseries and the NICU are collected after three days of life, nearly thirty percent 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 (47 hours) is nearly twice that of the median collection times for hospital nursery and NICU births (each at 26 hours of life).

Table 20: Time From Birth to Specimen Collection by Nursery Type, Michigan, 2007

Action	Nursery Type	Time	N	(%)	Mean Time	Median Time
Time from birth to specimen collection (Hours)	Hospital Nursery	< 24 hrs	720	0.65	28.7	26
		24-36 hrs	103,805	94.33		
		36-48 hrs	4,459	4.05		
		48-72 hrs	753	0.68		
		>72 hrs	304	0.28		
	NICU	< 24 hrs	870	6.9	32.6	26
		24-36 hrs	10,020	79.73		
		36-48 hrs	1,187	9.4		
		48-72 hrs	309	2.46		
		>72 hrs	182	1.45		
	Midwife/ Non-Hospital	< 24 hrs	2	0.69	105.3	47
		24-36 hrs	85	29.5		
		36-48 hrs	58	20.14		
		48-72 hrs	63	21.88		
		>72 hrs	80	27.78		

TIME FROM SPECIMEN COLLECTION TO LABORATORY RECEIPT

The time from specimen collection to laboratory receipt (Table 21) is also an important quality assurance indicator in that it measures how quickly specimens are shipped from birthing centers/midwifes 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 one to three days.

Approximately 70% of specimens were transmitted to the NBS laboratory within three days of collection regardless of birth place. However, the proportion of specimens mailed after one week from collection is nearly three times greater among midwife/non-hospital births relative to hospital/NICU births.

Table 21: Time From Specimen Collection to Laboratory Receipt by Nursery Type, Michigan, 2007

Action	Nursery Type	Time	N	(%)	Mean Time	Median Time
Time from specimen collection to receipt in lab (Days)	Hospital Nursery	**1-3 days**	81,797	74.65	2.7	2
		4-5 days	23,639	21.5		
		6-7days	3,277	2.99		
		>7 days	868	0.79		
	NICU	**1-3 days**	8,948	71.5	2.9	3
		4-5 days	2,763	22.08		
		6-7days	585	4.67		
		>7 days	219	1.75		
	Midwife/ Non-Hospital	**1-3 days**	200	69.69	3.2	3
		4-5 days	63	21.95		
		6-7days	14	4.88		
		>7 days	10	3.48		

TIME FROM BIRTH TO SPECIMEN RECEIPT BY NEWBORN SCREENING LABORATORY

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. Table 22 reports the time from birth to NBS laboratory receipt of specimens.

Table 22: Time from Birth to Receipt of Specimen by NBS Laboratory by Nursery Type, Michigan, 2007

Action	Nursery Type	Time	N	%	Mean Time (days)	Median Time (days)
Time from Birth to Laboratory Receipt of Specimen	Hospital Nursery	**1-3 days**	52,755	47.85	3.8	4
		4-5 days	44,461	40.3		
		6-7days	10,970	9.95		
		>7 days	2,061	1.87		
	NICU	**1-3 days**	5,628	44.68	4.2	4
		4-5 days	4,943	39.24		
		6-7days	1,480	11.75		
		>7 days	546	4.33		
	Midwife	**1-3 days**	55	18.84	7.7	5
		4-5 days	112	38.36		
		6-7days	64	21.92		
		>7 days	61	20.89		

As indicated in Table 22, currently slightly less than half of hospital nursery/NICU specimens (47.8% and 44.7% respectively) and less than 20% of midwife/non-hospital birth specimens are received by the NBS laboratory within three days of life.

Two program changes are being implemented to decrease time between birth and laboratory receipt of specimens: 1) increase laboratory operation from five to six days a week (started June, 21st, 2008), and 2) a courier system for delivering specimens directly to the state laboratory within 24 hours of specimen collection. At the end of 2007 38% of the birthing hospitals sent 58% of the NBS samples by courier; however, as of July, 2008, 90% of hospitals are sending 93% of the specimens via courier. Thus, we expect significant improvements in time from birth to lab receipt of specimens in 2008.

TIME TO TREATMENT

Table 23 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 23, time to treatment ranged from 5 days to 182 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.

GALACTOSEMIA AND BIOTINIDASE DEFICIENCY

Both cases of confirmed classic galactosemia were treated within 10 days. The single case of profound biotinidase deficiency was treated within seven days of life. Two cases of partial biotinidase deficiency were treated by the second week of life; the remaining 13 cases (DG & partial biotinidase deficiency) were treated beyond the second week of life.

MS/MS DISORDERS

There were 28 newborns with disorders detected by MS/MS (four newborns with hyperphenylalanemia did not require treatment). Each case of PKU was treated within the first week of life. The majority (75%) of fatty acid oxidation disorders were treated within the first week of life. All of the organic acid disorders were treated beyond the second week of life. 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 thereby improving the proportion of MS/MS disorders 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. Two of the three CAH cases detected were salt-wasting; all cases of CAH (salt-wasting and non-salt-wasting) were treated by the seventh day of life. The target for CH is treatment by 14 days of age for newborns with initial TSH values greater than 50. Of the CH cases with a reported medication start date and an initial TSH >50, 35 (73%) were treated by 14th day of life; of the remainder, three (11%) were treated by 14 days of age.

Table 23: Time to Treatment of Amino Acid Disorders, Organic Acid, Fatty Acid Oxidation, and Endocrine Disorders, Michigan, 2007

Disorder		Total	Treatment Time (days from birth) N			Treatment Time Range (days)
		(N)	1-7	8-14	>14	
Galactosemia	Classic (GG)	2	1	1		6-10
	Duarte (DG)	5	1		4	6-17
Biotinidase Deficiency	Partial	11	1	1	9	11-80
	Profound	1	1			5
Amino Acid Disorders	Phenylketonuria Classic	3	3			6-7
	Mild	2	2			5
	Benign Hypephenylalaninemia	4				N/A
	Total	*9*	*5*			*5-7*
Organic Acid Disorders	3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)	2			2	9-18
	Proprionic Acidemia (PA)	1			1	20
	Total	*3*			*3*	*9-20*
Fatty Acid Oxidation Disorders	Short-Chain Acyl-CoA Dehydrogenase deficiency- (SCAD)	6	3	2	1	3-15
	Medium-Chain Acyl-CoA Dehydrogenase Deficiency- (MCAD)	8	7	1		4-11
	Very Long-Chain Acyl-CoA Dehydrogenase Deficiency-(VLCAD)	2	2			4-7
	Total	*16*	*12*	*3*	*1*	
Endocrine Disorders	Congenital Hypothyroidism** TSH > 50	48	14	21	13	8-182
	TSH ≤ 50	28	0	3	25	5-73
	Congenital Adrenal Hyperplasias Salt-Wasting	2	2			1-2
	Non Salt-Wasting	1	1	-	-	3

*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
**10 cases missing either initial TSH value or treatment start date

HEMOGLOBINOPATHIES

Table 24 reports the time to treatment among hemoglobinopathies. The target is to initiate penicillin prophylaxis by three months of life. Of the 48 cases having a penicillin start date reported, 75% were treated with penicillin prior to four months, approximately 15% were treated at four months of age, and almost 11% were treated beyond four months of age.

Table 24: Time to Penicillin Initiation for Hemoglobinopathies, Michigan, 2007

Disorder	Penicillin Prophylaxis Initiation Time			
	< 4 months	4 months	5 months	≥ 6 months
Sickle Cell Disorders	36 (75.0%)	7 (14.6%)	2 (4.2%)	3 (6.3%)

VI: CONCLUSIONS & RECENT DEVELOPMENTS

NBS is a critical public health program protecting the lives of our State's newest residents. In 2007, the NBS follow-up program tracked approximately 5,000 strong and borderline positive, isolated elevation, unsatisfactory, early, and transfused specimens; 275 strong positive results were immediately referred to medical management centers for evaluation. A total of 200 newborns were identified with a disorder by NBS in 2007 and treatment was initiated, where necessary, to prevent long-term morbidity and mortality within 2 weeks of life for more than half of the cases having reported information. Since NBS began in Michigan in 1965, nearly 4,000 newborns have been diagnosed and treated through newborn screening.

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. Other developments occurring in 2007 include:

- The NBS program implemented a NICU/Low Birth Weight screening protocol for infants weighing less than 1800g at birth.
    - In 2007, the detection of congenital hypothyroidism increased nearly three fold among infants screened via the NICU/Low Birth Weight protocol.
    - The NBS program is currently considering altering inclusion criteria to expand eligibility for this protocol.

- Screening for Cystic Fibrosis began October 1st, 2007.
    - Seven cases were detected out of 132 positive screens in 2007.

- A courier service was implemented in 2007 to transport dried blood spot samples from hospitals to the NBS laboratory in order to reduce time to diagnosis and accordingly time to treatment for conditions included in the NBS panel.
    - At the end of 2007 38% of the birthing hospitals sent 58% of the NBS samples by courier.
    - As of July, 2008, 90% of hospitals are sending 93% of the specimens via courier. Thus, we expect significant improvements in time from birth to lab receipt of specimens in 2008.

- The NBS Follow-up Program began matching live birth records provided by the Division of Vital Records and Health Statistics to NBS records in order to identify potentially unscreened infants.
    - Thus far, more than 99% of live birth records have been matched to NBS records.
    - Unmatched records have either: a) been identified as having been screened or signed a parental refusal of NBS letter via further follow-up, b) been sent a request to have their child screened or return a parental refusal of NBS letter, or c) been screened.

- The NBS Follow-up Program implemented a Three Year Follow-up Protocol to confirm the diagnosis of permanent congenital hypothyroidism among borderline cases (those having pre-treatment serum thyroid stimulating hormone levels in the bottom 15th percentile) after age three years.

    - Thus far, half of the cases are no longer and treatment and are thought not to have permanent congenital hypothyroidism, although tracking is ongoing.

- A pilot second tier congenital adrenal hyperplasia (CAH) test added to the NBS program in August, 2006, continued through 2007.

    - The addition of this test has could result in a ~95% reduction in false positive screening results for CAH.
    - Among non-NICU births the positive predictive value (number of true cases of disease out of the total number of positive screens) increased by more than 7 fold and the decrease in the false positive rate (number of false screens out of the total number of screens) was equally impressive for the second tier screen.
    - A modified tier-based screening algorithm is currently under consideration.
    - *However, medical decisions are not based on these results at this point.*

- NBS analyses were presented at the Centers for Disease Control and Prevention's Maternal and Child Health Epidemiology conference and the Preconception Health and Care: Second National Summit.

- As of October 1st, 2007, the fee for the NBS card was increased to $85.61 as recommended by the Quality Assurance Advisory Committee.

Future plans include revision of inclusion criteria for the NICU/Low Birth Weight screening protocol, expansion of our three year follow-up study of borderline CH cases, and evaluating a modified second tier screening algorithm for CAH. 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.

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