MICHIGAN DEPARTMENT OF
COMMUNITY HEALTH

MICHIGAN NEWBORN SCREENING PROGRAM

ANNUAL REPORT
2008

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- 2008

Acknowledgements

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EXECUTIVE SUMMARY

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

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 4,165 being diagnosed with diseases included in the NBS panel.

In 2008, of 119,661 infants screened, 119,327 were Michigan residents; 226 (0.2%) were diagnosed as having a disease.

Developments occurring in 2008:

- The Michigan NBS Program received funding from the Region 4 Genetics Collaborative to develop evaluation studies of pilot testing of endocrine screening with the ultimate goal of improving screening for congenital hypothyroidism and congenital adrenal hyperplasia.
- A laboratory scientist from the NBS Program was appointed to the expert committee of the Clinical Laboratory Standards Institute for the standardization of laboratory practices for NBS with tandem mass spectrometry
- The laboratory increased operations from five days a week to six beginning on June 21, 2008.
    - Twelve confirmed cases have been identified and referred to follow-up on Saturdays.
- In 2007, the NBS Follow-up Program implemented a Three Year Follow-up Protocol to confirm the diagnosis of permanent congenital hypothyroidism among borderline cases after age three years. In 2008, the study population was expanded to include all cases in the lowest 25th percentile of pre-treatment serum thyroid stimulating hormone levels.
- The NBS Follow-up Program initiated an educational effort to encourage all hospitals to send specimens to the NBS laboratory by a MDCH designated courier rather than the US mail and to include the NBS kit number on the electronic birth certificate.
- The NBS Parent and Family Network Initiative formally launched in September of 2008 with a kick-off event at a local science center for children and families affected by disorders included in the NBS panel.
- The NBS Follow-up Program began holding regional NBS Hospital Coordinator Trainings.
    - One meeting was held in 2008 and four more have been scheduled in 2009.

- NBS analyses were presented at the National Maternal and Child Health Epidemiology conference, the Cystic Fibrosis Annual Meeting, and the Michigan Healthy Mothers/Healthy Babies Conference.

- The presentation "Variation Among Immunoreactive Trypsinogen Concentrations, Michigan Newborn Screening, 10/2007-4/2008" won the award for the best abstract at the National Maternal and Child Health Epidemiology Conference.

- A manuscript entitled "Methodological Innovations in Data Gathering: Newborn Screening Linkage with Live Births Records, Michigan, 1/2007-3/2008" was accepted for publication in the Maternal and Child Health Journal.

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ACRONYM KEY

Acronym[1]	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
NICU	Neonatal Intensive Care Unit
PCP	Primary Care Physician
PEAC	Pediatric Endocrine Advisory Council
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

[1] 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 NBS Program, target outcomes, screening performance metrics related to conditions included in the NBS panel, and quality assurance information. This report differs from the previously released reports in several ways. First, this is an abridged report in that it does not include appendices which have not changed since 2006 including the NBS research guidelines, supportive legislation, or website description.[2] Second, this report includes a chapter providing in-depth information on a single NBS condition, cystic fibrosis (Chapter IV). This chapter includes an overview of CF screening, information on definition, history, and diagnosis, and updates on ongoing CF-related NBS program evaluation research. Third, this report contains two new appendices. Appendix A details the advisory committees for the NBS Program, and Appendix B describes the development of the NBS Parent and Family Network. 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 cystic fibrosis screening in Michigan
- provide an update on follow-up activities, and
- detail future directions for NBS in Michigan

WHAT IS NEWBORN SCREENING?

NBS is a process of early identification of health conditions followed by their subsequent timely treatment before the onset of disease processes thereby minimizing the risk of long-term sequelae. Depending on the condition, potential outcomes of disorders in the NBS panel include, but are not limited to, brain/neurological damage, mental retardation, damage to the liver, eyes, spleen, stroke, or death if not detected early. To prevent such outcomes from occurring, NBS programs test blood spots collected from infants during the first few days of life and then further monitors for signs of treatable disorders.

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

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

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. Table 2 provides a list of disorders that are screened for in Michigan but have never been diagnosed. Screening for all of the disorders listed in Table 2, except for Citrullinemia Type II, began in 2005, so nearly 500,000 infants have been screened for the disorders through 2008 and no cases have been detected. Screening for Citrullinemia Type II began in 2004, meaning approximately 625,000 infants have been screened and no cases have been detected. Detailed information about the disorders in the screening panel, confirmation of diagnoses, and follow-up of positive tests including algorithms can be found in the NBS Procedure Manual available at: www.michigan.gov/newbornscreening.

Table 1: Disorders Included in the Newborn Screening Panel, Michigan, 2008

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

Note: The following disorders are reported together on the same letter: CIT/ASA, HCY/MET, CACT/CPT II, LCHAD/TFP, 2MBG/IVA, PA/MMA, HMG/3MGA, SCAD/IBG

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

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

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

**Screening for CIT II began in 2004 (625,000 screens) and for all other disorders in the table in 2005 (500,000 screens).*

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

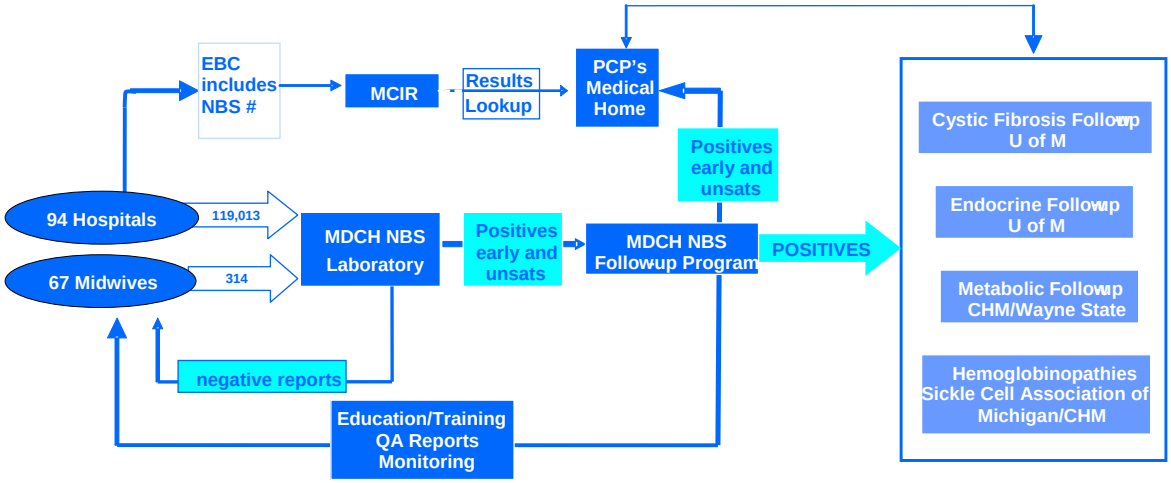

Figure 1: Overview of the Michigan Newborn Screening Program

HOSPITALS

Michigan currently has 94 hospitals with newborn nurseries. Each hospital has a designated NBS coordinator who helps facilitate the screening process by assuring that a) a NBS specimen is properly obtained from all newborns between 24 and 36 hours of age, b) appropriate documentation occurs, and c) all specimens are sent by courier to the NBS laboratory immediately after drying and no later than 24 hours after obtaining the specimens. Each hospital receives a quarterly quality assurance report comparing the number of 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 67 midwives registered with the NBS program. Midwives also receive quarterly quality assurance reports and are provided individual assistance in meeting quality assurance standards. Although the number of midwife deliveries is small, they often occur in the Amish and Mennonite populations which have a higher incidence of several of the NBS disorders screened.

MICHIGAN DEPARTMENT OF COMMUNITY HEALTH

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

A. NEWBORN SCREENING LABORATORY

Newborn Screening is performed within the Division of Chemistry and Toxicology in the Bureau of Laboratories. The laboratory is accredited by CLIA and is directed by Dr. Frances Pouch Downes. The laboratory establishes a newborn reference range for each disorder that maximizes detection rates while minimizing the rate of false positives and false negatives. The 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 performed Monday through Saturday. More than 700 specimens can be analyzed each day for 49 disorders.

B. NEWBORN SCREENING FOLLOW-UP PROGRAM

The NBS Follow-up Program, located in the Division of Genomics, Perinatal Health and Chronic Disease Epidemiology within the Bureau of Epidemiology, oversees short-term and long-term follow-up of infants identified through the screening program. Follow-up starts with referring 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 fourteen days of life for all other disorders. Education and training, as well as quality assurance measures are also responsibilities of the NBS follow-up program. These activities are primarily targeted toward hospital staff involved in the NBS process. The follow-up program maintains short and long-term follow-up databases for program monitoring and evaluation.

C. NEWBORN SCREENING MEDICAL MANAGEMENT CENTERS

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

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

The Endocrine Follow-up Program in the Department of Pediatrics, University of Michigan, maintains a centralized communication, referral and treatment assessment office that provides follow-up to ensure appropriate diagnostic evaluation and treatment of all infants with positive CH or CAH screening results. The overall program is directed by Ram Menon, M.D. Ming Chen M.D., Ph.D. is the director of the Center of Excellence for the Diagnosis and Management of CAH.

The Pediatric Endocrinology Advisory Council (PEAC) provides advice to the Michigan NBS Program on screening, diagnosis and medical management of newborns with suspected endocrine disorders.

2. CHILDREN'S HOSPITAL OF MICHIGAN METABOLIC CLINIC

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

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

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

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

The NBS and Coordinating Program for Cystic Fibrosis is housed within the department of pediatrics 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 2008 (n=120,194) is a preliminary estimate.

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 3 provides a description of screening performance metrics included in subsequent tables. These indicators are commonly used to assess the performance of screening tests and allow for comparisons both over time and with other screening programs. Ideal screening tests have a high positive predictive value (perfect=100%) and a low false positive rate (perfect=0%); a perfect screening test correctly identifies all cases of a disorder with no false positives. No NBS test is perfect but 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. Cases are defined as newborns identified with disorders via NBS. Maternal disorders identified by NBS are not included in the performance metrics.

QUALITY ASSURANCE INDICATORS

Quality assurance (QA) data were obtained from NBS cards and information recorded by the state NBS laboratory and medical management centers. QA indicators include: a) time from birth to specimen collection, b) time from specimen collection to specimen arrival at the State NBS Laboratory, c) the quality of the specimens received and d) time from birth to treatment of each disorder.

Table 3: Screening Performance Indicator Descriptions

Indicator	Description
Newborns N	The total number of live births *among in-state residents*
Total + (% NICU)	Total number of positive screens (positive = screening value exceeds cutoff) among in-state residents 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 2008 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% of the live births occurring in Michigan in 2008; the proportion of live births screened is based on the estimated live births occurring in Michigan in 2008. 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 2008 (Table 4). Unmatched records have either: a) been identified as having been screened, or b) signed a parental refusal of NBS letter. In 2008, 43 infants are known to have been missed by newborn screening and hospitals have been contacted to obtain a screen. Of the 43 infants, 19 have been screened to date. One of the infants identified as a missed screen through linkages and later screened was found to be a carrier of the sickle cell trait.

Table 4: Newborn Screening & Live Births Records Linkage Results, Michigan, 2008

Birth Year	Total	Matched		Un-Matched Excluding Expired Infants	
	N	N	%	N	%
2008	120,194	118,553	98.6	1,150	1.0

There were 334 live births (0.28% of live births screened in Michigan) to out-of-state residents. Tables 5 and 6 report the demographics of in-state and out-of-state residents screened in 2008, respectively. This report details screening results of in-state residents only. As indicated in Table 5, 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 (≥2500 g). Overall, 10% of infants screened were in the NICU, 8% weighed less than 2,500 g at birth, and 10% were born preterm (<37 weeks gestational age). African Americans were over-represented among NICU, preterm, and low birth weight (<2,500 g) births.

Table 5: Demographics of Infants Screened, Michigan, 2008, Excluding Out-of-State Residents, N=119,327

Race/ Ethnicity *Missing data: n=11,592*	Row Total		Nursery Type						Low Birth Weight *(missing data: n=12,895)*		Gestational Age *(missing data: n=14,343)*	
			Hosp. Nursery^		Midwife		NICU		<2500 grams		< 37 weeks	
	N	%	N	%	N	%	N	%	N	%	N	%
White	76,007	70.55	69,508	91.4	289	0.4	6,210	8.2	5,017	6.7	7,066	9.4
Black	21,464	19.92	18,304	85.3	5	0.0	3,155	14.7	2,837	13.4	2,914	13.7
American Indian	544	0.50	505	92.8	0	-	39	7.2	35	6.5	39	7.2
Asian/Pac Islander	2,491	2.31	2,312	92.8	4	0.2	175	7.0	183	7.4	184	7.5
Middle Eastern	2,693	2.50	2,477	92.0	0	-	216	8.0	187	7.0	213	8.0
Multi-Racial	4,536	4.21	4,112	90.7	10	0.2	414	9.1	369	8.2	429	9.5
Hispanic*	8,079	9.50	7,509	92.9	9	0.2	561	6.9	475	6.0	617	7.7
Column Total:	*107,735*	*100*	*97,218*	*90.2*	*308*	*0.3*	*10,209*	*9.5*	*8,628*	*8.1*	*10,845*	*10.2*

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 6: Demographics of Infants Screened, Michigan, 2008, Out-of-State Residents, N=334

Race/ Ethnicity *Missing data: n=32*	**Row Total**		**Nursery Type**						**Low Birth Weight** *(missing data: n=38)*		**Gestational Age** *(missing data: n=49)*	
			Hosp. Nursery^		**Midwife**		**NICU**		**<2500 grams**		**<37 weeks**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
White	245	81.13	194	79.2	2	0.8	49	20.0	23	9.6	34	14.7
Black	26	8.61	16	61.5	0	-	10	38.5	6	23.1	9	34.6
American Indian	1	0.33	0	-	0	-	1	100	1	100	1	100
Asian/Pac Islander	11	3.64	9	81.8	0	-	2	18.2	1	10.0	1	10.0
Middle Eastern	6	1.99	5	83.3	0	-	1	16.7	1	16.7	1	20.0
Multi-Racial	13	4.30	10	76.9	0	-	3	23.1	1	7.7	2	16.7
Hispanic*	12	3.97	11	91.7	0	-	1	8.3	0	-	0	-
Column Total:	*302*	*100*	*234*	*77.5*	*2*	*0.7*	*66*	*21.9*	*33*	*10.9*	*48*	*15.9*

Note: *percentages expressed in the above table are row percentages across the columns aside from the final row of the table in which column totals and column percentages are expressed. The number 'missing data' for low birth weight and gestational age are indicative of the total number missing race and/or birth weight, gestational age.*
**Although 'Hispanic' is an ethnic category and not a racial category, most respondents failed to indicate their race when indicating they were of Hispanic ethnicity; thus, we present 'Hispanic' as its own category and not by racial categories. However, the 'Hispanic' row does not contribute to the column totals listed in the bottom row of the above table.*
^Hospital nursery defined as not midwife or NICU.

SCREENING OUTCOME INFORMATION

In the following sub-sections, outcome information is provided for the 49 disorders screened for in 2008. The total number of cases detected both in and through 2008 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 management.

CUMULATIVE DETECTION RATE

Table 7 reports the cumulative detection rate of disorders identified via NBS by classification both in and through 2008. The metabolic disorders detected by MS/MS are grouped by category (amino acid, organic acid and fatty acid oxidation disorders). Two metabolic disorders, galactosemia and biotinidase deficiency, detectable by enzyme assay screening and not by MS/MS, are listed separately. The galactosemia cumulative detection rate includes both Duarte compound heterozygotes (D/G) and classic galactosemia (G/G); however, only D/G cases that have been detected since 2004, the year that CHMMC began short-term treatment of this disorder, are included in the cumulative detection rate. Similarly, the biotinidase deficiency cumulative detection rate includes both partial and profound biotinidase deficiency. Treatment of partial biotinidase deficiency did not begin until 2000.

As indicated in the table, CH and the hemoglobinopathies were the most prevalent both in and through 2008, while CAH was 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 31% of all disorders detected in 2008 and 37% of all cases detected cumulatively. Hemoglobinopathies accounted for 20% of all cases detected in 2008 and 35% of all cases detected cumulatively. CF accounted for 17% of cases detected in 2008 and 1% of cases detected cumulatively. Disorders detected by MS/MS (amino acid, organic acid and fatty acid oxidation disorders) accounted for 20% of cases in 2008 and 17% cumulatively. However, PKU, the first disorder screened in 1965 in Michigan, is now screened by MS/MS, meaning the overall proportion of cases detected by MS/MS is an over-estimate because it includes cases detected by other means prior to 2003 when MS/MS screening was initiated. The cumulative detection rate for fatty acid oxidation disorders is an underestimate because MCAD screening began in 2003, while other conditions were not screened until 2005. This means that births included in the denominator from 2003-2005 were not eligible for being diagnosed with disorders other than MCAD leading to an artificially low cumulative detection rate. The MS/MS detection rate does not include eight cases of formiminoglutamic acid disorder (FIGLU) detected because the disorder is not included in the NBS panel and is not treatable. Galactosemia, including Duarte compound heterozygotes, accounted for 6% of all disorders detected in 2008 and 3% cumulatively. Biotinidase deficiency, including partial biotinidase deficiency, accounted for 4% of all cases detected in 2008 and 4% of all cases detected cumulatively. CAH accounted for 1% all of cases in 2008 and 3% of all cases detected cumulatively.

In summary, CH, CF, and hemoglobin disorders account for about two-thirds of all cases detected annually. Although MS/MS disorders currently account for about one-fifth 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.

Table 7: Disorders Identified in Newborns via Newborn Screening, Michigan Newborn Residents, 1965-2008

Type of Disorder Classification (Year Screening Began)	Cases in 2008 (N)	Cases Through 2008 (N)	Cumulative Detection Rate*
Galactosemia (1985)	13	137	1:23,749
Biotinidase Deficiencies (1987)	8	168	1:17,726
Amino Acid Disorders (1965)	17	620	1:10,020
Organic Acid Disorders (2005)	12	25	1:19,944
Fatty Acid Oxidation Disorders (2003)	17	73	1:10,399
Congenital Hypothyroidism (1987)	70	1,552	1:1,919
Congenital Adrenal Hyperplasia (1993)	3	109	1:19,298
Hemoglobinopathies (1987)	47	1,436	1:2,074
Cystic Fibrosis (October 2007)	39	46	1:3,269
Total	226	4,166	-

**Note: Denominators, the number of live births eligible to have been screened, are calculated from the year screening began onward; thus, if screening commenced other than at the start of the year the denominator will be slightly larger than the true denominator. The CF detection rate denominator for 2007 was calculated by multiplying the average number of births per month by four. Galactosemia includes both classical cases and Duarte variants (DG) since 2004. Biotinidase Deficiency includes both partial and profound biotinidase deficiency. While MCAD, a fatty acid oxidation disorder, began being screened for in 2003 other disorders were not added to the NBS panel until later; thus, the cumulative detection rate artificially low.*

SCREENING PERFORMANCE METRIC TARGETS

Screening performance metric targets are presented in Table 8. 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.* [1] Performance metrics (detection rate, false positive rate (FPR) and positive predictive value (PPV)) provide NBS programs with a method of assessing screening performance over time and in meeting established or consensus

performance targets. Performance targets for MS/MS screening, based on data reported by Rinaldo et al., are included in Table 8.

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 these changes do not significantly change the FPR and PPV for hemoglobinopathies of close to 0% and 100%, respectively.

Table 8: 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 9 reports screening performance metrics for all disorders for 2008. Performance metrics for individual MS/MS disorders are provided in the following section in Tables 12, 13, and 14. Although 10% of infants born in Michigan in 2008 were admitted to a NICU, over half (51%) of the positive screens came from infants in a NICU. NICU positive screens ranged from 93% for CAH to 18% for galactosemia.

GALACTOSEMIA, BIOTINIDASE DEFICIENCY, & CYSTIC FIBROSIS

The galactosemia detection rate (including Duarte D/G variants) was 1:9,179 in 2008. The FPR and PPV were 0.01% and 46% respectively. However, considering that the purpose of galactosemia

screening is to detect classical galactosemia only, we report a detection rate of 1:29,832 for the four cases identified. One infant had a negative screen for galactosemia but was later confirmed with Duarte galactosemia. Since this case was not detected through a positive initial screen, the case was excluded from the calculations of screening performance metrics. The biotinidase deficiency (including partial biotinidase deficiency) detection rate was 1:14,916; the FPR and PPV were 0.11% and 6% respectively. The FPR and PPV of both galactosemia and biotinidase deficiency meet, and significantly exceed, performance targets of FPR <0.5% and PPV >5%. Thirty-nine cases of cystic fibrosis (CF) were detected in 2008 (detection rate-1:3,060); the associated FPR and PPV were 0.4% and 8.4% respectively.

ENDOCRINE DISORDERS CH AND CAH

The detection rate for CH of 1:1,705 is in the target range of 1:1,500 to 1:2,000. The CH screening FPR of 0.41% is slightly higher than the target range of 0.3% to 0.4%; the PPV of 12.5% 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 of the 2007 Annual Report provides more detailed information about CH screening in Michigan.

While the detection rate for CAH of 1:39,776 is lower than the target range of 1:15,000 to 1:20,000, this is not unusual for a rare disorder in any single year. Of note, the cumulative CAH detection rate of 1:19,298 is within the target range; however, the PPV of 0.41% is well below the already low PPV target of one to two percent and the FPR of 0.61% is higher than the target FPR of 0.5%. One case of salt-wasting CAH and two cases of non-salt-wasting CAH were detected among 728 positive screens in 2008.

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 10, indicate that second tier testing reduces the percent of false positives by 95% without increasing false negatives. As indicated in Table 10, 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.

Table 9: Screening Results and Performance Metrics, Michigan, 2008

Disorder Type	Total N	Total + N (% NICU)	Confirmed + N	Positive Detection Rate	FPR %	PPV %
Galactosemia	119,327	28 (17.9)			0.01	46.43
Classic (GG)			4	1:29,832		
Duarte (DG)			9	1:13,259		
Total			13	1:9,179		
Biotinidase Deficiency		138 (32.6)			0.11	5.80
Profound			1	1:119,327		
Partial			7	1:17,047		
Total			8	1:14,916		
Cystic Fibrosis		463 (27.2)	39	1:3,060	0.36	8.42
Congenital Hypothyroidism (CH)		559 (34.0)	70	1:1,705	0.41	12.52
Congenital Adrenal Hyperplasias (CAH)		728 (92.6)			0.61	0.41
Salt wasting			1	1:119,327		
Non-Salt wasting			2	1:59,664		
Total			*3*	*1:39,776*		
Hemoglobinopathies		71 (16.9)	47	1:2,539	0.02	66.20
Amino Acid*		56 (23.2)	17	1:7,019	0.03	30.36
Organic Acid*		58 (24.1)	12	1:9,944	0.04	20.69
Fatty Acid Oxidation*		58 (20.7)	17	1:7,019	0.03	29.31
*MS/MS Disorders Total***		156 (25.0)	46	1:2,594	0.09	29.49

***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)*

***SCAD and IBG are screened using the same analyte. Thus, the 16 infants with elevated levels of that analyte are included in the both the organic acid and fatty acid oxidation total positive screens, but counted only once for the MS/MS Disorders total.*

Table 10: 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 11. Hemoglobinopathy screening differs from screening for the other disorders. The purpose of hemoglobinopathy screening is to identify the presence or absence of abnormal hemoglobins and not to quantify selected analytes as with other screening tests. There is no screening reference range and the results of screening are essentially considered a confirmatory diagnosis. Confirmatory testing is primarily for differentiating sickling genotypes.

As depicted in Table 11, hemoglobinopathies are quite common among African Americans, who account for 87% of the cases in 2008. While the overall incidence is approximately one case per 2,539 screened, the incidence in African American infants is one in 524 screened in Michigan.

Table 11: Hemoglobinopathy Screening Performance Indicators, Michigan, 2008

Disorder	Newborns (N)	Confirmed + (N)		Positive Detection Rate	
		Total	Among Blacks	Total*	Among Blacks*
Sickle Cell Anemia	119,327	31	27	1:3,849	1:795
SC Disease		11	9	1:10,848	1:2,385
Sickle β thalassemia		5	5	1:23,865	1:4,293
Total		*47*	*41*	*1:2,539*	*1:524*

**Out of the number of Michigan resident infants screened, total N=119,327, among Blacks N=21,465*

MS/MS DISORDERS

The overall FPR for MS/MS of 0.09% is within the target of less than or equal to 0.3%. The detection rate of 1:2,594 and PPV of 29.49% both exceed the target metrics of 1:3,000 and 20%, respectively. In 2007, the MS/MS disorders did not meet the target metrics. Maternal cases were not included in the calculation. The improvement is largely driven by a change in PPV for organic acid disorders from 3.1% in 2007 to 20.7% in 2008. This increase in PPV is likely due to changes in disease profiles and refinements in laboratory cut-offs in order to identify all true cases, while minimizing the number of false positives. Others have noted until there is uniformity of testing, aggregate performance metrics are less informative than those of specific conditions explaining our presentation of disorder specific performance metrics in subsequent tables.[1]

SCREENING PERFORMANCE METRICS – INDIVIDUAL MS/MS DISORDERS

AMINO ACID DISORDERS

Seventeen amino acid disorders (Table 12) were detected by MS/MS. PKU is the most frequent condition, found in one of every 9,179 newborns screened. As indicated in the table, PKU screening had the second highest PPV (68%), after hypermethioninemia (PPV-100%). The FPR for PKU screening of 0.005% reflects the very high sensitivity of MS/MS screening for this disorder. One case of hypermethioninemia and three cases of citrullinemia/ASA were confirmed in 2008.

ORGANIC ACID DISORDERS

Twelve organic acid disorders (Table 13) were detected by MS/MS. The FPR for each of the detected disorders was at or below 0.05%. Among individual conditions, the PPV was greatest for glutaric acidemia Type 1 (60%) and isovaleric acidemia (50%). Both glutaric academia Type 1 and isovaleric academia had 0% PPV in 2007, indicating a marked improvement in the screening algorithm in 2008. Of note, three of the infants who screened positive, but were not diagnosed with 3MCC, had mothers with 3MCC.

FATTY ACID OXIDATION DISORDERS

Seventeen fatty acid oxidation disorders (Table 14) were detected (one CUD, ten SCAD, five MCAD, and one VLCAD). Among detected disorders, all FPRs were less than 0.02% except for CUD (FPR-0.022%). However, four of the infants who screened positive, but were not diagnosed with CUD, had mothers with CUD.

Table 12: Amino Acid Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2008

Disorder	Newborns N	Total + N	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Phenylketonuria Classic (PKU)	119,327	19	3	1:39,776	0.005	68.4
Mild			2	1:59,664		
Benign Hyperphenyl-alaninemia (H-PHE)			8	1:14,916		
Biopterin Cofactor Defects (BIOPT)			0	-		
Total			*13*	*1:9,179*		
Hypermethioninemia (MET)		1	1	1:119,327	0.000	100
Argininemia (ARG)		8	0	-	0.007	0
Citrullinemia/ASA (CIT/ASA)		8	3	1:39,776	0.004	37.5
Tyrosinemia (TYR I)		20	0	-	0.017	0

Table 13: Organic Acid Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2008

Disorder	Newborns N	Total + N	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Isovaleric Acidemia (IVA)/2MBG	119,327	2	1	1:119,327	0.001	50.0
3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC))		7	2	1:59,664	0.004	28.6
Glutaric Acidemia Type I (GA I)		5	3	1:39,776	0.002	60.0
Propionic Acidemia (PA) / Methylmalonic Acidemia (Mutase Deficiency) (MA)/ Methylmalonic Acidemia (MA-Cbl C, D)		25	4	1:29,832	0.018	16.0
3-OH 3-Methyl Glutaric Aciduria (HMG)		3	0	-	0.003	0
Isobutyryl-CoA dehydrogenase deficiency (IBG)		16	2	1:59,664	0.012	12.5

Table 14: Fatty Acid Oxidation Disorders Detected by Tandem Mass Spectrometry, Screening Performance Indicators, Michigan, 2008

Disorder	Newborns N	Total + N	Confirmed + (N)	Positive Detection Rate	FPR (%)	PPV (%)
Carnitine Uptake Defect- (CUD)	119,327	27	1	1:119,327	0.022	3.7
Short-Chain Acyl-CoA Dehydrogenase deficiency- (SCAD)		16	10	1:11,933	0.005	62.5
Carnitine Palmitoyltransferase I Deficiency (CPT I)		2	0	-	0.002	0
Carnitine/Acylcarnitine Translocase Deficiency- (CACT)/Carnitine Palmitoyltransferase II Deficiency-(CPT II)		4	0	-	0.003	0
Glutaric Acidemia Type II- (GA II)		1	0	-	0.001	0
Medium-Chain Acyl-CoA Dehydrogenase Deficiency- (MCAD)		5	5	1:23,865	0.000	100
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency-(VLCAD)		2	1	1:119,327	0.001	50.0
Medium-Chain Ketoacyl-CoA Thiolase Deficiency- (MCKAT)		1	0	-	0.001	0

SCREENING PERFORMANCE METRICS AMONG STRONG POSITIVE SCREENS

This section provides screening performance metrics (FPR and PPV) among strong positive screens relative to those among total positive screens (strong plus borderline positive). Disorders lacking a borderline positive category are not reported in Table 15 because their performance metrics have been previously reported. Disorders not detected in 2008 are also not reported in Table 15, 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 15, the FPRs and PPVs among strong positives are significantly improved relative to the overall screening performance metrics among all positives. Maternal cases found through NBS are not included in Table 15.

Table 15: Screening Performance Metrics (FPR and PPV) among Strong Positive Screens, 2008

Disorder Type	Among All +		Among Strong +	
	FPR	PPV	FPR	PPV
	%	%	%	%
Galactosemia	0.01	46.43	0.002	77.78
Biotinidase Deficiency	0.11	5.80	0.003	25.00
Congenital Hypothyroidism (CH)	0.41	12.52	0.057	41.88
Congenital Adrenal Hyperplasia (CAH)	0.61	0.41	0.247	1.01
Phenylketonuria (PKU)*	0.005	68.42	0.0	100
3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)*	0.004	28.57	0.003	40.00
Propionic Acidemia (PA) / Methylmalonic Acidemia (Mutase Deficiency) MA/ Methylmalonic Acidemia (MA-Cbl C, D)*	0.02	16.00	0.004	44.44
Carnitine Update Defect (CUD)*	0.022	3.70	0.005	14.29

*MS/MS disorders

The FPR for galactosemia screening is reduced five fold while the PPV is increased nearly two fold among strong positives. The reduction in the FPR for biotinidase deficiency is more drastic representing a nearly 37 fold decrease while the PPV increased over four fold.

The FPR for CH is reduced by seven fold for strong positives and the PPV increased by over three fold. The FPR and PPV for CAH are decreased and increased respectively by nearly 2.5 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 for 3MCC, PA, and CUD 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: CYSTIC FIBROSIS SCREENING IN MICHIGAN

This section provides a detailed account of CF screening in Michigan including: 1) an overview of CF, 2) early history of CF diagnoses, 3) the history of NBS for CF worldwide and in the United States, 4) the history of NBS for CF in Michigan and the Michigan CF screening algorithm, 5) CF performance metrics and detection rates in Michigan, 6) CF screening program evaluation studies and 7) future direction of newborn screening for CF in Michigan.

OVERVIEW OF CF

Cystic fibrosis (CF) is an autosomal recessive disease affecting the exocrine system, affecting about 1 in 3500 newborns in the United States.[2] Over 1500 mutations have been identified in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene on chromosome #7. A list of the *CFTR* mutations is being updated continuously and is maintained within the Cystic Fibrosis Genetic Analysis Consortium (CFGAC) database (www.genet.sickkids.on.ca/cftr). Abnormal CFTR function results in a failure of salt to be reabsorbed in various exocrine secretions leading to a high salt content in sweat. Normal functioning of CFTR protein in critical organs such as the lungs and pancreas is also disrupted causing chronic pulmonary infection and in many cases malabsorption due to pancreatic exocrine insufficiency.[3]

CF can occur in all individuals, but the prevalence of CF and the presence of particular mutations in the *CFTR* gene differ among populations. For example, F508del, the most common CF mutation, accounting for about two-thirds of all CFTR alleles in patients with CF, has decreasing prevalence from Northwest to Southeast Europe. In discrete populations, certain mutations can reach a higher frequency due to founder effect but less than 20 mutations have a worldwide frequency above 0.1% and none are as prevalent as F508del.[4] This mutation variation makes population screening difficult due to the wide range of ancestral backgrounds represented in the United States. Newborn screening programs must be cognizant of this when selecting mutation panels for use in screening that will be reflective of their ethnic/racial populations.

CF is most common among non-Hispanic whites with a prevalence of 1:2,500-1:3,500 births; least common among non-Hispanic blacks with a prevalence of 1:15,000-1:20,000 births; and Hispanics have a prevalence of 1:4,000-1:10,000 births.[2,5,6]

EARLY HISTORY OF CF DIAGNOSES

In 1938, the disease 'cystic fibrosis of the pancreas' was described in detail for the first time.[7] During a heat wave in New York City, di Sant'Agnese noted that the heat seemed to affect people with CF more profoundly than the general population, leading him to postulate that patients with CF may have "disturbance[s] of multiple glandular structures."[8] To investigate his hypothesis, di Sant'Agnese measured the electrolyte composition of sweat from patients with CF and patients in the hospital who did not have CF and found that patients with CF had higher concentrations of chloride, sodium, and potassium in their sweat compared to the other patients.

A diagnostic breakthrough occurred in 1959 when Gibson and Cooke created a quantitative pilocarpine iontophoresis test to measure sweat electrolytes.[9] This test is still the main diagnostic test for CF and is reliable for roughly 98% of patients with CF.[10]

The discovery of the *CFTR* gene in 1989 offers significant support in obtaining a diagnosis of CF, but care must be used in interpreting the results of *CFTR* mutation analysis. Modifier genes, clinical significance of complex alleles and rare mutations used for genotype/phenotype correlation in individual patients can all create significant issues for a clinician trying to incorporate molecular test results into the diagnostic process.[4] For example, individuals with the D1152H mutation and a CF-causing mutation, *i.e. F508del*, have been reported with a wide clinical variability with some having CBAVD (congenital bilateral absence of the vas deferens) alone to CF with significant lung disease.

The ability of two different intron 8 variants to act as modifiers of the R117H mutation is another example of the complexities involved in molecular analysis of the *CFTR* gene for clinical interpretation. The polythymidine tract of intron 8 can vary in length commonly consisting of 5(5T), 7(7T) or 9(9T) thymidines. Just upstream of this tract lies a sequence of TG repeats varying in length from 9 to 13 (very rarely 15) repeats.[11] Low numbers of thymidines and high numbers of TG repeats cause decreased CFTR functioning. The R117H mutation in *cis* (found on the same parental CF gene) with a polythymidine tract consisting of a low number of thymidines, *i.e. T5*, and a high number of TG repeats, *i.e. T12 or T13*, will usually result in more severe clinical presentation.[4]

Newborn screening programs utilizing DNA mutation analysis in their screening methodology must be aware of the complexities and usefulness of their analyses. The American College of Medical Genetics recommends a screening panel that consists of a core 23 mutation panel. The Newborn Screening Laboratory in MI utilizes the Inplex™ Panel of 42 mutations that offers a slightly higher detection rate for our various racial/ethnic groups. All infants with positive screens are referred for genetic counseling at the time of confirmatory sweat testing so that any complexities presented by DNA testing may be further explored and explained.

HISTORY OF NEWBORN SCREENING FOR CF

Universal newborn screening for CF was made possible in 1979 with the development of a test that could measure immunoreactive trypsinogen (IRT) in dried blood spots, since IRT levels are higher among infants with CF.[12] Australia became the first country to universally screen newborns for CF in July 1981.[13]

In 1982, Colorado became the first state in the United States to screen newborns for CF.[6] A grant from the Bureau of Maternal and Child Health funded the program, and CF became part of Colorado's standard screening panel in 1987. Wisconsin and Wyoming were the next states to begin screening newborns for CF starting in 1985 and 1994, respectively.[14]

Wisconsin conducted a randomized, controlled trial of CF NBS from 1985 to 1998 to determine whether the benefits from early detection and treatment for infants with CF would outweigh any risks associated with NBS.[15,16] In 1985, infants were randomized to either a "screening diagnosis group" or a "symptom diagnosis group." For both groups, the dried blood spot IRT concentration was determined. After that point, the algorithm for the two groups diverged.

If a child in the "screening diagnosis group" had elevated IRT concentration, the results were sent to both the primary physician and parents within 6 weeks of life. Before 1991, infants with IRT concentrations greater than the 99.8th percentile underwent confirmatory sweat tests. After 1991, a combination of IRT concentration and DNA mutation analysis was used to decrease the number of false-positives.[17] Infants diagnosed with CF were entered in a longitudinal study with an evaluation and treatment protocol to standardize care.[18]

In contrast, the IRT results from infants in the "symptom diagnosis group" were not reported to either health-care providers or parents. The results were stored and released upon the child being diagnosed with CF, the child reaching four years of age, or parental request. If infants in this group were diagnosed with CF, they were also invited to participate in the longitudinal study with standardized care.

This large-scale trial found that early detection of CF through NBS resulted in significant improvements in nutrition status and growth.[18,19] Length/height, weight, and head circumference were all significantly higher at diagnosis in infants detected through screening compared to those detected clinically. Also, infants detected earlier had significantly greater growth despite the standardization of care between the two groups. Lastly, infants detected with CF through NBS were less likely to be below the 10th percentile for weight and height throughout childhood.

Detecting infants with CF through screening as opposed to clinical symptoms is cost-effective. A study in Wisconsin found that the estimated cost of newborn screening and diagnosis was $4.58 per newborn, whereas the estimated cost for each child diagnosed clinically was $4.97 per newborn infant.[20] The results from Wisconsin support using NBS as a cost-effective measure to identify infants with CF in order to decrease the average age at identification and treatment initiation and thereby, improve health outcomes of infants with CF.

HISTORY OF NEWBORN SCREENING FOR CF IN MICHIGAN

In 2005, the American College of Medical Genetics released an executive summary, supporting the addition of CF to the recommended core panel disorders in NBS.[21] With the guidance of the CF NBS Advisory Council, the Michigan NBS program began screening for CF in October 2007. Michigan adopted the IRT/DNA screening protocol for CF after consultation with several other state NBS programs (Figure 2). The protocol initially measures IRT concentrations from newborn dried blood spots to identify infants at increased risk of CF. Further analysis, using a panel of 42 CF mutations, is completed for infants beyond the 96th percentile of IRT. Infants with more than one mutation undergo sweat testing to determine CF status. If an infant does not have a DNA mutation in the panel, sweat testing is recommended for infants having IRT concentrations greater than the 99.8th percentile. Beginning in February 2009, infants with no DNA mutation and IRT concentrations greater than the 99.8th percentile are no longer considered positive screens. These infants are not referred for sweat testing unless signs of CF develop or if a family history of CF is present.

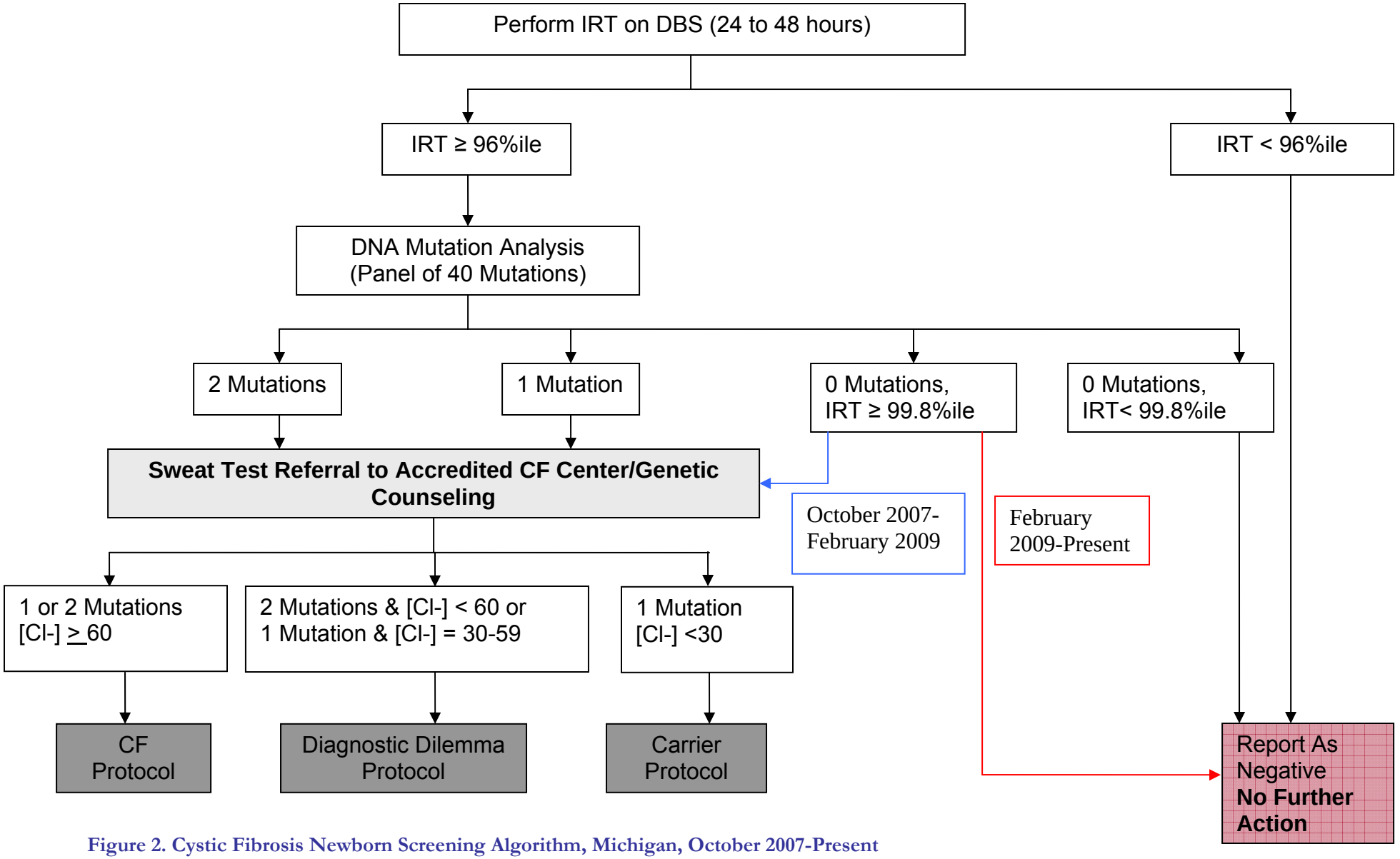

Figure 2. Cystic Fibrosis Newborn Screening Algorithm, Michigan, October 2007-Present

Sweat testing is performed at one of five CF Foundation-accredited clinics in Michigan. The five CF centers in Michigan employ two different methods of sweat testing. Three of the centers use pilocarpine iontophoresis to stimulate sweat production and collect the sweat on gauze pads. The other two centers use the Wescor Macroduct® Sweat Stimulation and Sweat Collection system. A study assessing the two methods found no difference between the results obtained from the Macroduct system and pilocarpine iontophoresis.[22]

CF PERFORMANCE METRICS AND DETECTION RATES IN MICHIGAN

Of the 463 infants who screened positive for CF in 2008, 27% were in the NICU (Table 16). The false positive rate for CF is 0.36%, and the positive predictive value is 8.42%. In 2008, 39 infants were diagnosed with CF (Table 17), resulting in 46 cases of CF detected since screening began. The cumulative detection rate is 1:3,269 and the 2008 detection rate is 1:3,060. The detection rate in Michigan is slightly higher than the overall birth prevalence in the United States of 1:3:500-3,700.[2] However, Michigan has a large population of non-Hispanic whites, the racial group with the highest birth prevalence of CF at 1:2,500-1:3,500. The variation in racial distribution may potentially explain the higher prevalence of CF in Michigan compared to the United States as a whole.[5]

Table 16: Screening Results and Performance Metrics of Cystic Fibrosis, Michigan, 2008

Disorder Type	Total N	Total + N (% NICU)	Confirmed + N	Positive Detection Rate	FPR %	PPV %
Cystic Fibrosis	119,327	463 (27.2)	39	1:3,060	0.36	8.42

Table 17: Number of Cases of Cystic Fibrosis Identified via Newborn Screening, Michigan Residents, 2007-2008

Type of Disorder Classification (Year Screening Began)	Cases in 2008 (N)	Cases Through 2008 (N)	Cumulative Detection Rate*
Cystic Fibrosis (October 2007)	39	46	1:3,269

**Note: The CF detection rate denominator for 2007 was calculated by multiplying the average number of births per month by four.*

Table 18 presents the regional prevalence of CF cases identified by NBS per 10,000,000 people. Region 5 (Grand Rapids area) had the highest prevalence of CF at 77.2 cases/10,000,000 people, while Region 1 (Detroit area) had the lowest regional prevalence at 13.4 cases/10,000,000 people. No cases of CF have been detected in the Upper Peninsula since CF screening began. Since CF prevalence varies by race/ethnicity, the population percent White is also included for each region. Region 9 (North Lower Peninsula) has the highest percentage of White inhabitants at 97.1% and Region 1 (Detroit area) has the lowest percentage at 66.7%. A scatter plot of regional prevalence of CF and regional population percent White is shown in Figure 3. As regional population percent White increases, the regional prevalence of CF also appears to increase.

Table 18. Number and Regional Prevalence of Cystic Fibrosis Cases Identified by Newborn Screening, Michigan, October 2007-2008

Region Label	Region Name	Regional Population (N)*	Population Percent White	Regional Prevalence Per 10,000,000	Cases	
					N	%
1	Detroit	3,720,549	66.7	13.4	5	11.1
2	Oakland	1,517,819	81.4	32.9	5	11.1
3	Ann Arbor	1,187,044	88.7	33.7	4	8.9
4	Kalamazoo	1,250,026	89.9	32.0	4	8.9
5	Grand Rapids	1,682,971	90.0	77.2	13	28.9
6	Lansing	711,329	88.6	42.2	3	6.7
7	Flint	669,659	81.1	44.8	3	6.7
8	Saginaw	938,335	91.7	42.6	4	8.9
9	North Lower Peninsula	551,631	97.1	72.5	4	8.9
10	Upper Peninsula	390,191	92.4	0.0	0	0.0
Total	*Michigan*	*12,619,554*	*82.0*	35.7	*45*	*100*

Note: Counties in each region defined in Appendix C
*Estimated using 2006 data plus one-quarter of 2006 data

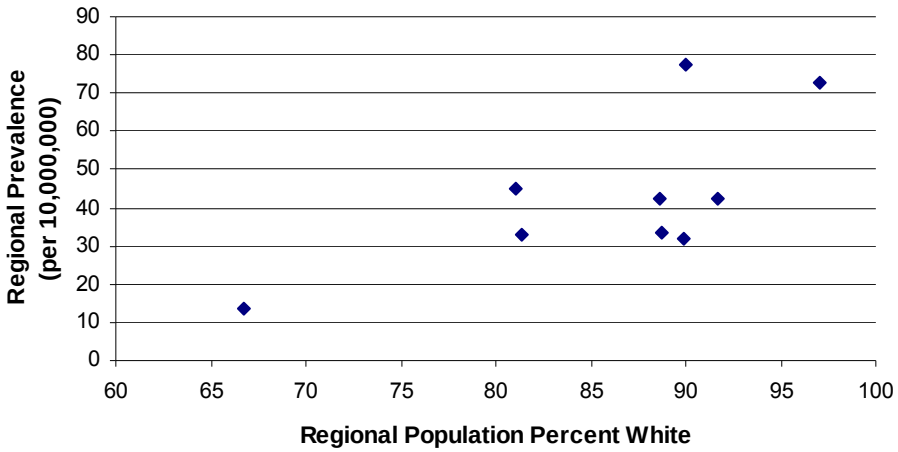

Figure 3. Regional Prevalence of Cystic Fibrosis Cases Identified by Newborn Screening by Regional Population Percent White, Michigan, October 2007-2008.

Note: Regional prevalence and percent white in the region estimated using 2006 data.

CF SCREENING PROGRAM EVALUATION STUDIES

During the first year of CF screening in MI, members of the MI NBS Program and the NBS CF Advisory Committee reported concern about the number of infants with high IRT concentrations and negative DNA tests in the neonatal intensive care unit (NICU). This observation was consistent with previous reports of elevated IRT concentrations in blacks and in premature/low birth weight infants.[23-25] A cross-sectional study was designed to analyze associations between IRT concentrations and demographic and perinatal characteristics among resident infants screened in Michigan to better understand the rate of negative DNA tests among infants with high IRT concentrations.

IRT concentrations were measured from the newborn dried blood spots collected from resident births occurring in MI during the first year of CF screening (October 1, 2007 through September 30, 2008). Infant demographic and perinatal data were obtained from the NBS card. Medical management data maintained by the MI NBS Follow-up Program were used to differentiate diagnosed CF cases from infants with high IRT concentrations and negative DNA tests.

A total of 118,775 resident infants were screened in MI during the study period. Of those, 37 (1:3,198) were diagnosed with CF. IRT mean concentrations and percentiles vary significantly by race, birth weight, gestational age, fetal growth, and to a lesser degree by sex (Table 19). The greatest variation in mean IRT concentration was observed among racial categories; black infants had an adjusted mean IRT concentration of 36 ng/ml and Asian/Pacific Islander infants had a mean concentration of 25 ng/ml compared to an average concentration of 28 ng/ml in white infants and infants of other races.

Variation in IRT concentrations resulted in the overrepresentation of certain groups (particularly black infants) referred for confirmatory testing, particularly referrals for sweat-testing based on very high ($\geq$99.8th percentile) concentrations alone. After reviewing the results of the first year of screening and learning of the experiences of other states, the Michigan CF NBS program decided to recommend that clinicians monitor infants with very high IRT ($\geq$99.8%) and no identified CF mutations for clinical symptoms of CF instead of referring them for sweat testing. This change became effective in February 2009.

Table 19: Demographic and Perinatal Characteristics, Immunoreactive Trypsinogen Concentration Crude and Adjusted Least Squares Means, MI NBS, 10/2007-10/2008

Variables and Categories		N	%	Crude		Adjusted*	
				LS Mean	P-Value	LS Mean	P-value
Race	White	75563	70.65	26.0	<.0001	27.9	<.0001
	Black	21144	19.77	34.0		35.8	
	American Indian	541	0.51	26.6		28.6	
	Asian/Pacific Islander	2540	2.37	22.9		24.8	
	Arab Descent	2710	2.53	27.1		28.9	
	Multi-Racial	4461	4.17	27.8		29.7	
Gestational Age	< 32 wks	1780	1.55	34.3	<.0001	33.1	0.0002
	32-36	9991	8.7	28.8		28.2	
	>=37 wks	103074	89.75	27.3		27.2	
Birth Weight	<1500 g	1609	1.38	35.0	<.0001	33.7	<.0001
	1500g-2499g	7823	6.7	29.6		28.5	
	2500g-3999g	96432	82.64	27.5		27.2	
	>4000g	10825	9.28	25.7		26.3	
Sex	Female	57506	48.91	28.0	<.0001	29.7	<.0001
	Male	60073	51.09	27.0		28.9	
Total		118775	100		-	-	

*Adjusted for other covariates listed in this table. To avoid multicolinearity, birth weight and gestational age were assessed independently in adjusted models; both remained significantly associated with IRT when added to the same model adjusted for other factors.

Note: Missing data are as follows: Race: n=11,361, Gestational Age: n=1,631, Birth Weight: n=3,475

During the first year of screening for CF, the NBS CF Advisory Committee also noticed increased rates of 'quantity not sufficient' (QNS) results from confirmatory sweat testing for CF among infants in the NICU. When infants fail to produce a sufficient quantity of sweat chloride to test for CF, disease confirmation is delayed and sweat-testing is later repeated. In this study, we evaluated potential predictors of QNS results.

We conducted a retrospective cohort study of predictors of insufficient chloride production during NBS confirmatory testing for CF. Information from the NBS cards including birth weight, gestational age, race, sex, NICU admission, and multiple birth status and diagnostic confirmation data including test clinic, diagnostic results, presence of meconium ileus and age at test were used for this study. Birth weight and gestational age were assessed as dichotomous variables. Low birth weight was defined as <2500 grams, and preterm birth was defined as <37 weeks. Two measures of age at time of sweat test were used. The first measure was age after delivery at time of sweat test. The second measure, age in weeks, was calculated by adding gestational age at delivery to week of life at time of sweat test. We used age in weeks to account for the potential impact of prematurity on QNS results.

Overall, 119,327 resident infants born in 2008 had a newborn screen, and 315 infants were sweat tested. Of the 315 infants sweat tested, 63 (20%) had QNS results. The mean age at time of sweat test was 26.4 days and the median was 20 days (range 4-159 days). Bivariate analyses revealed that preterm birth, low birth weight, NICU admission, CF center, and black race were significantly associated with QNS sweat testing results (Table 20). Of note, all infants born at <32 weeks gestational age (N=3) who underwent a sweat test had QNS results.

Multivariate analyses included all variables significantly associated with QNS results in the bivariate analysis as covariates. The results indicated that infants born <37 weeks gestation were significantly more likely to have QNS sweat-test results (OR=3.4 95% CI 1.1, 10.2) relative to term infants (Table 21). The other factors assessed including birth weight, race, CF center and NICU admission were no longer significantly associated with QNS results.

Age after delivery at time of test was not associated with QNS results. However, age at time of test in weeks (weeks of gestation plus age at time of test) was significantly associated with QNS results. Infants aged <40 weeks at time of test were 3 times more likely to have QNS (95% CI 1.3, 6.7) and low birth weight infants were 5 times more likely to have QNS results (95% CI 1.6, 14.9) (Table 3). Nearly 20% of infants were aged 40 weeks or less at time of sweat test after accounting for gestational age; of those, 24 (41.4%) had QNS results.

This study indicates that age at time of test, accounting for gestational age, is the driving predictor of QNS rates. It may be appropriate for clinicians to wait until infants screening positive for CF reach 40 weeks of age, adjusted for gestational age, prior to sweat-testing to reduce the QNS rate and associated repeat sweat-tests. However, further research is necessary to evaluate the potential impact of delays in treatment derivative of implementation of this recommendation.

Table 20: Demographic Characteristics of Infants with Sweat Tests and Predictors of Quantity Not Sufficient (QNS) Sweat Tests, Michigan, 2008

Demographics		Infants with Sweat Tests		Infants with QNS		Unadjusted	
		N	**Percent**	**N**	**Percent**	OR	95% CI
Age at Test	<14 days	82	26.0%	23	36.5%	1.6	(0.8, 3.4)
	14-29 days	150	47.6%	24	38.1%	0.8	(0.4, 1.6)
	30+days	83	26.3%	16	25.4%	1.0	
Birth Weight[a]	<2500 g	29	9.4%	18	29.0%	**8.8**	**(3.9, 19.9)**
	≥2500 g	281	90.6%	44	71.0%	1.0	
Gestational Age[b]	<37 wks	29	9.7%	16	28.6%	**7.0**	**(3.1, 15.8)**
	≥37 wks	269	90.3%	40	71.4%	1.0	
Race[c]	White	222	75.0%	38	62.3%	1.0	
	Black	56	18.9%	16	26.2%	**1.9**	**(1.0, 3.8)**
	Other	18	6.1%	7	11.5%	**3.1**	**(1.1, 8.5)**
Sex[d]	Female	159	50.8%	35	55.6%	1.3	(0.7, 2.2)
	Male	154	49.2%	28	44.4%	1.0	
NICU[e]	Yes	45	15.6%	21	36.2%	**4.7**	**(2.4, 9.3)**
	No	244	84.4%	37	63.8%	1.0	
Meconium Ileus	Yes	8	2.5%	3	4.8%	2.5	(0.6, 10.6)
	No	307	97.5%	60	95.2%	1.0	
Multiple Birth[f]	Multiple	8	2.6%	3	4.9%	2.5	(0.6, 10.9)
	Singleton	303	97.4%	58	95.1%	1.0	

[a]Missing data on 5 infants
[b]Missing data on 17 infants
[c]Missing data on 19 infants
[d]Missing data on 2 infants
[e]Missing data on 24 infants
[f]Missing data on 4 infants

Table 21: Adjusted Associations between Demographic and Perinatal Characteristics, Gestational Age, and QNS Sweat Test Results, Michigan, 2008

Demographics		Adjusted[a] OR	
Birth Weight	<2500 g	2.9	(0.8, 10.4)
	≥2500 g	1.0	
Gestational Age	<37 weeks	**3.4**	**(1.1, 10.2)**
	≥37 wks	1.0	
Race	White	1.0	
	Black	2.2	(0.8, 5.5)
	Other	2.2	(0.6, 8.0)
NICU	Yes	2.2	(0.8, 6.4)
	No	1.0	

[a]Adjusted for all other variables in the table and CF clinic

Table 22: Adjusted Associations between Demographic and Perinatal Characteristics, Age in Weeks, and QNS Sweat Test Results, Michigan, 2008

Demographics		Adjusted[a] OR	
Birth Weight	<2500 g	**5.0**	**(1.6, 14.9)**
	≥2500 g	1.0	
Age[b]	<40 weeks	**3.0**	**(1.3, 6.7)**
	≥40 wks	1.0	
Race	White	1.0	
	Black	2.2	(0.9, 5.4)
	Other	2.4	(0.7, 8.4)
NICU	Yes	1.8	(0.7, 4.8)
	No	1.0	

[a]Adjusted for all other variables in the table and CF clinic

[b]Defined by adding gestational age and age at time of test

CONCLUSION

Michigan is in a unique position to evaluate CF algorithms and confirmatory results due to the state coordinated NBS Follow-up Program that includes a medical management program and clinical database for the disorder. Specifically, the database includes initial screening, diagnostic and follow-up data on all newborns treated for CF. All CF cases are treated at one of five centers and follow-up and medical management data are maintained in a central database. Michigan's ability to track virtually all CF cases identified by NBS provides a unique opportunity to evaluate CF medical management and outcomes.

The MDCH NBS program will continue to evaluate and refine the program to evaluate CF intervention outcomes.

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 23 reports specimen characteristics by nursery type. Although only 9.2% of infants were in the NICU, 67% and 54% 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 midwife samples (5%). Early and transfused specimens were also more common among infants from the NICU. Late specimens, those collected after six days of life, were most common among midwife deliveries. The NBS follow-up program tracks all strong and borderline positive, isolated elevation, unsatisfactory, early, and transfused specimens; approximately 5,000 specimens were followed up in 2008. Strong positive results (n=509) are immediately referred to medical management centers for evaluation.

Table 23: Specimen Characteristics by Nursery Type, Michigan, 2008

Indicator	Type of Birth					
	Regular Nursery		NICU		Midwife	
	N	%	N	%	N	%
Strong + Specimens	165	0.15	343	3.13	1	0.32
Borderline + Specimens	491	0.45	606	5.53	3	0.96
All + Specimens*	1,052	0.97	1,087	9.92	4	1.27
Isolated elevations of amino acids and acyl-carnitines	7	0.01	453	4.14	0	-
Unsatisfactory Specimens	964	0.89	378	3.45	16	5.10
Late (>6 days) Specimens	114	0.11	37	0.34	33	10.51
Early (<1 day) Specimens	1,080	1.00	829	7.57	4	1.27
Transfused Specimens	24	0.02	555	5.06	0	-
Specimens Missing Demographics **	12,058	11.16	848	7.74	24	7.64
Total Births Screened	108,060	90.5	10,953	9.2	314	0.3

**Includes all strong and borderline specimens plus specimens positive for cystic fibrosis or hemoglobinopathies*
***Defined missing demographics as missing 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 24 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 are collected within 24 to 36 hours of birth; only 31% 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, over thirty percent of specimens from midwife/non-hospital births are collected after three days of life. The median time of specimen collection for midwife/non-hospital births (50 hours) is nearly twice that of the median collection times for hospital nursery and NICU births (each at 26 hours of life).

Table 24: Time from Birth to Specimen Collection by Nursery Type, Michigan, 2008

Action	Nursery Type	Time	N	(%)	Mean Time	Median Time
Time from birth to specimen collection (Hours)	Hospital Nursery	< 24 hrs	633	0.59	28.0	26.0
		24-36 hrs	102,174	94.58		
		36-48 hrs	4,215	3.90		
		48-72 hrs	745	0.69		
		>72 hrs	265	0.25		
	NICU	< 24 hrs	617	5.64	29.1	26.0
		24-36 hrs	9,081	82.95		
		36-48 hrs	926	8.46		
		48-72 hrs	227	2.07		
		>72 hrs	96	0.88		
	Midwife/ Non-Hospital	< 24 hrs	0	-	85.7	50.0
		24-36 hrs	97	30.89		
		36-48 hrs	49	15.61		
		48-72 hrs	60	19.11		
		>72 hrs	108	34.39		

TIME FROM SPECIMEN COLLECTION TO LABORATORY RECEIPT

The time from specimen collection to laboratory receipt (Table 25) 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 74% of specimens from hospitals and NICUs and 62% of specimens from midwives were transmitted to the NBS laboratory within three days of collection. The proportion of specimens mailed after one week from collection is nearly 1.3 times greater among midwife/non-hospital births relative to NICU births and over 4 times greater relative to hospital births.

Table 25: Time from Specimen Collection to Laboratory Receipt by Nursery Type, Michigan, 2008

Action	Nursery Type	Time	N	(%)	Mean Time	Median Time
Time from specimen collection to receipt in lab (Days)	Hospital Nursery	**1-3 days**	80,592	74.63	2.24	1.96
		4-5 days	23,406	21.67		
		6-7days	3,427	3.17		
		>7 days	569	0.53		
	NICU	**1-3 days**	8,077	73.80	2.35	2.00
		4-5 days	2,266	20.70		
		6-7days	418	3.82		
		>7 days	184	1.68		
	Midwife/ Non-Hospital	**1-3 days**	195	62.10	2.75	2.46
		4-5 days	101	32.17		
		6-7days	11	3.50		
		>7 days	7	2.23		

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

As indicated in Table 26, currently slightly less than half of hospital nursery/NICU specimens (47.0% and 43.7%, respectively) and less than 15% of midwife/non-hospital birth specimens are received by the NBS laboratory within three days of life.

Two program changes have been 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.

Table 26: Time from Birth to Receipt of Specimen by NBS Laboratory by Nursery Type, Michigan, 2008

Action	Nursery Type	Time	N	%	Mean Time (days)	Median Time (days)
Time from Birth to Laboratory Receipt of Specimen	Hospital Nursery	**1-3 days**	50,732	46.95	3.4	3.1
		4-5 days	44,817	41.47		
		6-7days	10,710	9.91		
		>7 days	1,799	1.66		
	NICU	**1-3 days**	4,785	43.69	3.6	3.2
		4-5 days	4,606	42.05		
		6-7days	1,134	10.35		
		>7 days	428	3.91		
	Midwife	**1-3 days**	44	14.01	6.3	4.9
		4-5 days	117	37.26		
		6-7days	81	25.80		
		>7 days	72	22.93		

TIME TO TREATMENT

Table 27 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 27, time to treatment ranged from 1 day to 68 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

All four cases of confirmed classic galactosemia were treated within seven days, and seven cases of Duarte galactosemia were treated within fourteen days of life. The single case of profound biotinidase deficiency was treated within seven days of life. One case of partial biotinidase deficiency was treated by the second week of life; the remaining eight cases (DG & partial biotinidase deficiency) were treated beyond the second week of life.

MS/MS DISORDERS

There were 47 newborns with disorders detected by MS/MS (seven newborns with hyperphenylalanemia did not require treatment). Four of the five cases of PKU were treated within the first week of life. One case of PKU was treated on the ninth day of life. The majority of fatty acid oxidation and organic acid disorders were treated within the first 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, 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. One of the three CAH cases detected was salt-wasting; all cases of CAH were treated by the fourteenth day of life, and

the salt-wasting CAH case was treated by the seventh day. 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 (74%) were treated by 14th day of life.

Table 27: Time to Treatment of Amino Acid Disorders, Organic Acid, Fatty Acid Oxidation, and Endocrine Disorders, Michigan, 2008

Disorder		Total	Treatment Time (days from birth) N			Treatment Time Range (days)
		(N)	1-7	8-14	>14	
Galactosemia	Classic (GG)	4	4			1-5
	Duarte (DG)	9	3	4	2	5-26
Biotinidase Deficiency	Partial	7		1	6	12-36
	Profound	1	1			4
Amino Acid Disorders	Citrullinemia/ASA (CIT/ASA)*	3	1	1		3-8
	Phenylketonuria Classic	3	2	1		5-9
	Mild	2	2			2-6
	Benign Hyperphenylalaninemia	8				N/A
	Hypermethioninemia (MET)	1				N/A
	Total	*17*	*5*	*2*		*2-9*
Organic Acid Disorders	Glutaric Acidemia Type I	3	1	1	1	5-15
	Isovaleric Acidemia (IVA)/2MBG	1			1	27
	3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)	2	1		1	5-17
	Propionic Acidemia (PA)	4	3	1		4-8
	Isobutyryl-CoA dehydrogenase deficiency (IBG)	2	2			4-5
	Total	*12*	*7*	*2*	*3*	*4-27*
Fatty Acid Oxidation Disorders	Carnitine Uptake Defect (CUD)	1			1	17
	Short-Chain Acyl-CoA Dehydrogenase deficiency- (SCAD)	10	7	2	1	4-16
	Medium-Chain Acyl-CoA Dehydrogenase Deficiency- (MCAD)	5	4	1		5-8
	Very Long-Chain Acyl-CoA Dehydrogenase Deficiency-(VLCAD)	1	1			5
	Total	*17*	*12*	*3*	*2*	*4-17*
Endocrine Disorders	Congenital Hypothyroidism TSH > 50**	49	13	22	12	1-48
	TSH $\leq$ 50	21			21	19-68
	Congenital Adrenal Hyperplasias Salt-Wasting	1	1			7
	Non Salt-Wasting	2		2		10-14

*1 case missing treatment start date

**2 cases missing treatment start date

HEMOGLOBINOPATHIES

Table 28 reports the time to treatment among hemoglobinopathies. The target is to initiate penicillin prophylaxis within the first three months of life. Of the 39 cases having a penicillin start date reported, 85% were treated with penicillin prior to four months, approximately 3% were treated during the first four months of life, and 12% were treated beyond four months of age.

Table 28: Time to Penicillin Initiation for Hemoglobinopathies, Michigan, 2008

Disorder	Penicillin Prophylaxis Initiation Time			
	< 4 months	4 months	5 months	≥ 6 months
Sickle Cell Disorders*	33 (84.6%)	1 (2.6%)	3 (7.7%)	2 (5.1%)

*8 cases missing penicillin initiation date

VI: CONCLUSIONS & RECENT DEVELOPMENTS

NBS is a critical public health program protecting the lives of our State's newest residents. In 2008, the NBS laboratory screened 119,661 infants and the NBS follow-up program tracked approximately 5,000 strong and borderline positive, isolated elevation, unsatisfactory, early, and transfused specimens; strong positive results were immediately referred to medical management centers for evaluation. A total of 226 newborns were identified with a disorder by NBS in 2008. Treatment was initiated, where necessary, within 2 weeks of life for approximately half of the cases having reported information. Since NBS began in Michigan in 1965, over 4,150 newborns have been diagnosed and treated.

Introduction of MS/MS technology in 2003 to screen for MCAD screening initiated a rapid expansion of newborn screening over the next three years increasing the number of disorders screened from seven in 2003 to 48 in 2006. The addition of CF and hearing screening in October of 2007 increased the screening panel to 50, completing the ACMG/HRSA/March of Dimes recommended screening panel for state newborn screening programs. Other developments occurring in 2008 include:

- The Michigan NBS Program received funding from the Region 4 Genetics Collaborative to help provide pilot testing of endocrine screening evaluation studies to improve newborn screening for congenital hypothyroidism and congenital adrenal hyperplasia.

- A laboratory scientist from the NBS Program was appointed to the expert committee of the Clinical Laboratory Standards Institute for the standardization of laboratory practices for NBS with tandem mass spectrometry

- The laboratory increased operations from five days a week to six beginning on June 21, 2008.

    - Eighteen true cases have been identified and referred to follow up earlier due to Saturday testing.

- In 2007, the NBS Follow-up Program implemented a Three Year Follow-up Protocol to confirm the diagnosis of permanent congenital hypothyroidism among borderline cases after age three years. In 2008, the study population was expanded to include all cases in the lowest 25th percentile of pre-treatment serum thyroid stimulating hormone levels.

- The NBS Follow-up Program initiated an educational effort to encourage all hospitals to send specimens to the NBS laboratory by an MDCH designated courier rather than the US mail and to include the NBS kit number on the electronic birth certificate.

- The NBS Parent and Family Network Initiative formally launched in September of 2008 with a kick-off event at a local science center for children and families affected by disorders included in the NBS panel.

- The NBS Follow-up Program began holding regional NBS Coordinator Trainings.
    - One meeting was held in 2008 and four more have been scheduled in 2009.
- NBS analyses were presented at the National Maternal and Child Health Epidemiology conference, the Cystic Fibrosis Annual Meeting, and the Michigan Healthy Mothers/Healthy Babies Conference.
- The presentation "Variation Among Immunoreactive Trypsinogen Concentrations, Michigan Newborn Screening, 10/2007-4/2008" won the award for the best abstract at the National Maternal and Child Health Epidemiology Conference.
- A manuscript entitled "Methodological Innovations in Data Gathering: Newborn Screening Linkage with Live Births Records, Michigan, 1/2007-3/2008" was accepted for publication in the Maternal and Child Health Journal.

Future plans include examining home monitoring phenylalanine levels for PKU patients, continuing to provide outreach and education for NBS coordinators through regional trainings, and initiating outreach to midwives and birthing educators about NBS. 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.

APPENDIX A: NBS ADVISORY COMMITTEES

The Newborn Screening Program has six advisory committees. These committees are: Newborn Screening Quality Assurance Advisory Committee; Newborn Screening Advisory Committee; Pediatric Endocrine Advisory Council; Cystic Fibrosis Newborn Screening Advisory Council; Hemoglobinopathy Quality Improvement Committee; and Metabolic Disorders Quality Improvement Committee.

Newborn Screening Quality Assurance Advisory Committee (NBSQAAC)

The NBSQAAC was legislatively mandated in 2006 by Senate Bill 794. It meets annually to review newborn screening tests and protocols. The mission of the NBSQAAC is to advise the Michigan Department of Community Health (MDCH) regarding recommended changes or additions to the NBS panel. The goals are to review the existing panel of newborn screening tests, submit a written report to the MDCH about the appropriateness of the existing panel of required newborn screening tests, recommend adding disorders to the panel or removing disorders that no longer satisfy criteria for inclusion in the newborn screening panel and conduct a financial review of the NBS program to establish the amount of the NBS fee. The ten members of the committee are appointed by the MDCH and represent various health agencies. Since its inception, the committee has increased the screening panel to 50 disorders.

Newborn Screening Advisory Committee (NBSAC)

The NBSAC was established in 1981 and was originally called the Genetic Disease Advisory Committee. The mission of the NBSAC is to advise the MDCH regarding public health policies in providing comprehensive newborn screening services. The goals are to review current newborn screening practices, consider the addition of new disorders to be recommended to the NBSQAAC for inclusion in the screening panel, solicit community input with regard to newborn screening, evaluate newborn screening program infrastructure, policies, and outcomes, and make recommendations to the MDCH regarding best practices in newborn screening. This group meets quarterly.

Pediatric Endocrine Advisory Council (PEAC)

The Michigan Pediatric Endocrine Advisory Council (PEAC) was founded in September of 1987. The purpose of the PEAC is to review proposed procedures, results and policies for screening newborns for congenital hypothyroidism and congenital adrenal hyperplasia. Recommendations are made to the MDCH Newborn Screening Program. PEAC meets 3 times per year and has six voting members.

Cystic Fibrosis Newborn Screening (CF NBS) Advisory Council

Oversight for the Cystic Fibrosis Newborn Screening Program is provided by the CF NBS Advisory Council comprised of all five Michigan CF Foundation accredited CF Care Center Directors. To ensure a successful initiation of CF newborn screening, the council met on regular intervals prior to the start of screening in 2007 and continues to meet quarterly to develop/update protocols for CF screening and follow-up.

Hemoglobinopathy Quality Improvement Committee (HemQIC)

The HemQIC was founded in April 2009 by the Michigan NBS Follow-up Program and meets 4 times per year. The purpose of the HemQIC is to review current MDCH systems for provision of diagnosis, follow-up and treatment services for newborns/children with hemoglobinopathies detected by newborn screening. This group reviews: diagnostic protocols; medical management protocols; short (through confirmation and referral to a specialist) and long-term follow-up protocols; database management; and efficiency and cost effectiveness of the current service delivery system.

Metabolic Disorders Quality Improvement Committee (MetdQIC)

The MetdQIC was founded in April 2009 by the Michigan NBS Follow-up Program and meets 4 times per year. The purpose of the MetdQIC is to review services (laboratory and clinical) and proposed strategies and policies related to inborn errors of metabolism that may be detected in Michigan newborns. Recommendations shall be made to the Michigan Department of Community Health and to other individuals or groups with responsibility for review of newborn screening follow-up procedures/data collection such as the NBSAC.

APPENDIX B: DEVELOPMENT OF PARENT AND FAMILY NETWORK

Children with certain rare disorders benefit immensely from the early detection and treatment afforded them through newborn screening, but optimal outcomes for these children are only achieved through the continued follow-up and management of their disorder. The NBS Follow-up Program's commitment to ensuring continued care for these children throughout their lifespan is facilitated in part through its Newborn Screening Parent and Family Network Initiative. The Initiative formally launched in September of 2008 with a kick-off event at a local science center for children and families affected by disorders included in the NBS panel. The event was attended by over one hundred family members and staff working in all aspects of newborn screening diagnostic, treatment and follow-up care. The NBS Follow-up Program continues to place value and importance in the longitudinal and holistic care of newborns identified through newborn screening. During 2008/2009 the mission for the NBS Parent and Family initiative was established and objectives for 2009/2010 were set. They include:

Mission: *to establish a forum for networking and information sharing for families of children with conditions detected by newborn screening.*

Objective #1: Ensure newly diagnosed families are connected to medical management as well as financial and support resources

- Welcome Packet developed by NBS Follow-up Program in conjunction with medical management clinics.

Objective #2: Investigate the need for a forum for family networking and information sharing

- MDCH Listserv/Social Networking Page proposed if a need is identified by families. Work is underway to investigate and determine the underlying need.

Objective #3: Provide event for families to network & share information as well as receive education

- The second NBS Parent and Family Recognition Day is planned for May, 2010. A broader scope for the day is envisioned with multiple educational breakout session for families and children.

APPENDIX C: REGIONAL DEFINITIONS

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

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