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Assessing data completeness in a four-state newborn screening long-term follow-up pilot project

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Abstract

Assessing data completeness in a four-state newborn screening long-term follow-up pilot project

By Rebecca P. Rutledge

CDC's National Center on Birth Defects and Developmental Disabilities funded a pilot project to develop and implement population-based surveillance of confirmed newborn screening conditions using existing data collection systems in 4 U.S. states. Long-term follow-up outcomes were collected on each child through their third birthday. The purpose of this thesis is to examine the data completeness of the long-term follow-up data collected through the pilot project. Over three years of follow-up, 261 metabolic cases were identified in 1,343,696 live births. The primary outcome of this analysis is the percentage of completeness for each variable (number of observations with data for that variable/total number of observations). The denominator decreases from year 1 to year 3 to exclude those that died or moved out of the catchment area during the previous year. Data completeness was compared across the three types of data collection systems used in four states: 2 active birth defects surveillance systems, 1 passive system with case confirmation, and 1 newborn screening system. A fairly consistent level of completeness was observed across the five types of variables (demographic, diagnosis, service utilization, development, co-morbidities). Of the variables that focused on long-term follow-up outcomes for these children, the service utilization and co-morbidity variables were of the highest quality. The developmental variables showed the most variation in data completeness. The two active systems and the passive with case confirmation system contributed the data with the highest completeness. The NBS system contributed the most number of cases to the cohort and was still able to contribute high quality data.

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BACKGROUND/LITERATURE REVIEW

History of Newborn Screening in the United States

Newborn Screening (NBS) Programs in the United States began in 1963 when Dr. Robert Guthrie published a paper describing a novel method for detecting phenylketonuria (PKU) in a large population of newborns (1). The new screening method used bacterial inhibition techniques on a very small amount of blood collected on filter paper (2). Before Guthrie's development, PKU was often diagnosed after mental retardation had already set in (1). In the 1950s, the Children's Bureau tried a different screening method for PKU – evaluating the efficacy of the ferric chloride test on wet diapers (2). Guthrie's method was an improvement over the previous method because it was much simpler, inexpensive, and more sensitive (2). Early detection is crucial in caring for children with PKU. Implementing a phenylalanine-restricted diet early in life can help tremendously, even avoiding mental retardation completely (1). These developments in screening for and treating PKU represented a great success story of NBS programs in the United States (1,3), and paved the way for our current population-based system of screening newborns for various genetic and metabolic conditions.

Currently, NBS is a state-based public health program "aimed at the early identification of infants who are affected by certain genetic/metabolic/infectious conditions" (4). Over the last few decades, research and new technologies in genetic and metabolic conditions furthered the knowledge base and allowed for multiple conditions to be screened for using one blood sample (5). In 2000, all states screened newborns for PKU and congenital hypothyroidism, and some states screened for additional inherited disorders (2). This important preventive public health program identifies selected

conditions “that would otherwise become catastrophic health problems” (2), and attempts to ensure that children receive timely medical care before becoming greatly affected. The conditions that are tested in NBS programs are unique in that they “could be managed effectively with intervention early in life” (2).

Because NBS is a state-based program, there was great heterogeneity across the United States in how these programs were designed and what information they collect. Heterogeneity across states could be due to “level of state resources available (personnel, equipment, and service capacity); programs’ interpretations of available evidence concerning given conditions (incidence, treatability, and impact); availability or expense of new screening methods; and public advocacy by families, health care professionals, and state legislators” (5). In 2006, in order to move the United States toward national newborn screening standards, the American College of Medical Genetics was commissioned by HRSA to, among other responsibilities, create a recommended uniform screening panel (RUSP) (5). Through this process, 29 core conditions were considered appropriate because they “have a screening test, efficacious treatment, and adequate knowledge of natural history” (5).

By the end of 2009, every state NBS program screened for (at least) the 29 recommended conditions (6, 7). In addition, by 2009, every state had implemented screening using tandem mass spectrometry (7). Additional conditions can be nominated to the RUSP. In 2010 and 2011, critical congenital heart disease and severe combined immunodeficiency were added to the RUSP. Currently, there are 31 core conditions on the RUSP including metabolic, endocrine, hemoglobin, and other disorders (8).

Components of a Newborn Screening Program

In order to be a successful public health prevention program that consistently makes diagnoses and provides timely care to newborns, the NBS program needs to address other aspects of care beyond giving a positive screen test result (9). According to the 2000 *Pediatrics* article that laid out newborn screening system guidelines from the Council of Regional Networks for Genetic Services (CORN), there are 5 significant parts of a newborn screening program (2). They include:

i. "Screening: testing of newborns.

ii. Follow-up: rapid location, follow-up, and referral of the screen-positive infant.

iii. Diagnosis: Evaluation of the infant with a positive screening test to make a definitive diagnosis or exclude the disorder.

iv. Management: Rapid planning and implementation of long-term therapy.

v. Evaluation: Validation of testing procedures, assessment of the efficiency of follow-up and intervention, and assessment of the benefit to the patient, family, and society."(2)

An additional sixth part of newborn screening programs has been thought of as education (for prospective parents, beginning at prenatal visits) (10). "The sixth, education, permeates the system and provides the mechanism for enhancing all other system components" (11). Additionally, the follow-up component of an NBS program can be split up into short-term and long-term follow-up (to be discussed in further detail later). Generally, "short-term follow-up begins when the laboratory obtains an initial

result that is screen positive and ends with a definitive diagnosis… Long-term follow-up begins with treatment and continues throughout life" (2).

Medical Home

Children born with a metabolic or genetic condition often "require an extensive range of different services" and could need these services over the course of their entire life (2). The medical home is a concept developed to alleviate some of the challenges faced by patients and their families in the medical system. "Families have had to navigate a maze of organizations, providers, and geographic and financial barriers" in order to get appropriate care (2). Pass, et al. presented the medical home as a place where "all providers and parents share responsibility for ensuring that a child has access to the medical and non-medical services needed to help him or her achieve maximum potential" (2). Put another way, "the medical home is defined as care that is accessible, continuous, comprehensive, family-centered, coordinated, compassionate, and culturally effective" (9). "Most often the medical home is provided by primary care physicians; however, in a limited number of cases, specialty clinics can provide a full range of services (including primary care) and be considered the medical home for a child with complex health care needs" (9). The medical home is an integral part of ensuring that children are actually receiving adequate care for their conditions and are not lost to follow-up. A 2003 survey regarding the medical home found that twelve states (24%) indicated there was a procedure in place for identifying the infant's medical home before the child's birth (9). By 2006, 69% of states (n = 38) ensured that patients had access to a medical home over their lifespan (18).

Importance of Tandem Mass Spectrometry

Scientific and technological advances in recent decades have changed how NBS programs operate and their capabilities (12). One of the most important advances regarding testing capacity comes with the adoption of tandem mass spectrometry (MS/MS) used by states to increase the number of screened conditions (13, 14). When this technology first became a reality for states to incorporate into their screening systems, there were challenges and differences in adopting this technology (15). In 2004, a 10-question survey was sent out to 106 individuals identified as key newborn screening contacts in each state to identify challenges (if any) in implementing this new technology. A majority of states that did not yet have MS/MS technology cited funding limitations as the main hindrance (15). Other challenges included acquiring support within the organization, and a legislative mandate was required (15). By the end of 2009, every state reported they used MS/MS technology in their screening programs (7). Besides being able to screen for more conditions, the use of tandem mass spectrometry has been shown to provide better outcomes in children who screen positive for a condition - better outcomes, in this case, refer to fewer deaths and fewer clinically significant disabilities (16).

Short-Term and Long-Term Follow-Up

"The primary function of the follow-up component is to locate infants with screening results that are screen positive and to facilitate the entry of these infants into the diagnostic and management components of the NBS system in a timely fashion" (2). The job of an NBS program is not finished after the screening is complete. Locating the infants who have an abnormal screen is imperative to ensuring that families are aware of

the potential issue and know how to locate specialists and providers for further testing and therapies. Historically, "traditional emphasis has been placed on short-term follow-up (STFU)" (17) (which ends at the time of diagnosis (2)). Long-term follow-up (LTFU) takes over after diagnosis and ensures that individuals are receiving appropriate care (4). Other activities included in LTFU include program evaluation and quality assurance (4,11). LTFU also "provides an opportunity to better define the outcomes of these rare, usually poorly defined conditions, and evaluate the value of established and new treatments" (21). "Unfortunately, the long-term follow-up activities within public health programs lack coordination and have been of low priority for funding compared with activities related to screening and diagnosis" (20). With the increase in technology, including MS/MS screening techniques, there have been advances in the screening component of NBS. With the increase in identifying infants with potential disorders, there needs to be a subsequent increase in the ability to provide care and therapies to these infants. "If individuals with confirmed diagnoses cannot receive timely, accessible, appropriate care for their conditions, then identifying them is of less value" (18).

Long-Term Follow-Up – 2006

Recently, attention has been put towards the potential role of NBS programs in performing and strengthening their LTFU activities (17, 18). Because of the variety of activities that constitute LTFU, and because NBS is a state-based program, a 2005 survey by Hoff et al., aimed to obtain more detailed information on LTFU practices and perceptions among state NBS programs (18). The survey had a 91% response rate among laboratory and follow-up screening program coordinators listed in the National Newborn

Screening and Genetics Resource Center. "Two thirds of responding programs thought that LTFU at the state level consisted of ensuring that patients have access to a medical home during their lifespans and ensuring that support services, such as transportation and information are available to patients" (18). At this point in time, 24 of 48 states answered that they conducted LTFU services. The results of this survey brought up some issues in regards to conducting LTFU in NBS programs – including the need for greater capacity for staff to spend time on this topic and financial resources to sustain LTFU activities. Another issue brought up by this study was the importance of standardization of LTFU program elements among programs. An important finding from two Hoff surveys conducted in 2005 and 2006 is that "half of U.S. NBS programs do not currently engage in any type of LTFU activity past the confirmatory diagnosis phase" (17). This brings up the issue of oversight and responsibility as to who (state, national level) should begin the standardization process.

Regional Collaboratives

In response to the rapidly expanding newborn screening services, lack of oversight in LTFU activities across NBS state programs, and the geographic maldistribution of genetic specialists – HRSA launched an initiative to establish Regional Genetic and Newborn Screening Service Collaboratives across the United States (19). "Each Regional Collaborative was expected to: (1) enhance newborn and child screening and related follow-up services for heritable disorders, including an expansion of LTFU activities; (2) augment workforce capacity through such activities as training and education; (3) enhance subspecialty linkage by strengthening linkages between medical

homes and tertiary care centers; (4) enhance genetic counseling services; and (5) strengthen communication and education to families and health practitioners" (19). A regional sharing of experiences and physicians can increase the quality of care available to children (especially those in rural areas) (19). In 2006, the regional collaboratives had strengthened partnerships among states, initiated projects within the regional groups, and worked to expand technologies in their area (19, 21).

Long-Term Follow-Up – 2008

In 2008, a statement released by the US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDGDNC), described the key features of LTFU after diagnosis (20). This statement in 2008 expanded the concept of LTFU from "data management to systematic and comprehensive care of affected individuals" (20). The components stressed by ACHDGDNC included the coordination of care through a medical home, evidence-based treatment, continuous quality improvement and new knowledge discovery (20).

Interviews with NBS follow-up coordinators from 38 state NBS programs found that "approximately 45% of state programs (17/38) reported conducting no activities past the point of confirming diagnoses for children identified through NBS as potentially having a particular disorder" (22). Insight from the interviews revealed "approximately half of the 38 state programs believed that LTFU was not something within the scope of their role" (22). "Twenty-four of the 38 state NBS programs also believed that LTFU was something oriented more toward the direct patient care activities performed by specialists, and less the population –based approaches and activities that might occur at a

governmental agency level" (22). This report speaks to the need for development of national standards or a governmental role of oversight in ensuring that LTFU activities are defined and completed to improve outcomes of those diagnosed with a disorder screened for by these programs.

Long-Term Follow-Up – 2010

In 2010, a number of state NBS programs began publishing their work on LTFU and how to incorporate into their NBS activities (26, 27, 28, 29). An overall consensus from these articles reflects the move towards a core set of data elements that can be used to collect LTFU data, and collaboration between states to gain insight into rare conditions. An important benefit of quality LTFU data on newborn screening conditions is the increasing knowledge of the natural history of these rare conditions. "A much more troubling problem… is our lack of definitive information about the natural history of several disorders that are encountered in screening with relative frequency but which previously were only rarely reported" (23). A collection of data on outcomes of these newborns should "not merely [be] a repository of information. It is also a provider of information and should offer clinical decision support by providing condition-specific information to the provider…" (24). A concerted effort towards collecting national-level data on health outcomes will help to answer questions about best treatment practices of the rare newborn screening conditions (25, 29).

California's Experience with Follow-Up

California's Genetic Disease Screening Program (GDSP) implemented a Web-based screening information system (SIS) in July 2005 (26). "Eight state-contracted laboratories electronically send all prenatal and NBS test results to the SIS and positive test results are followed up through a network of clinical care coordinators (CCCs) who ensure that all at-risk women and newborns are referred to 1 of the 104 prenatal and 60 newborn specialty follow-up centers throughout the state" (26). Metabolic centers are paid in return for the collection and entry of follow-up data into the information system. The STFU system has "New Cases", "Pending Cases" and "Resolved Cases" depending on how much information is present in the system about their confirmed diagnosis and clinical visits. Once a child is diagnosed with a disorder, and that information is put into the SIS, the child is automatically entered into the LTFU system. The LTFU system relies on an annual survey that is electronically sent to the designated follow-up contact for each child up to age 5. Specific data elements include services provided by the metabolic center, date of last visit/interaction with the patient, total number of patient visits to the metabolic center, symptoms, etc. (26). This system is unique in that it covers such a wide geographic region and is made simpler by automating electronic messages from provider to NBS program and back.

New England's Experience with LTFU

Essential to the New England NBS Program is the centralized NBS program, which includes laboratory, follow-up and other data (27). Using Massachusetts' centralized state-based comprehensive NBS program as a model – this was implemented in five of the six New England states. A qualified diagnostic center sends a notice to the

NBS program that an infant meets the case definition for a certain NBS condition. The staff members revise the infant status in the database from "screen positive" to "case" and at this point, the infant enters the LTFU module (27). The LTFU section includes laboratory and clinical data, in addition to the name of the diagnostic center. Overall, 9% of cases have been lost to follow-up (27), but the system represents a sustainable method for collecting outcome data from providers.

Other efforts in LTFU

National efforts, including regional collaborative efforts, research partners (Eunice Kennedy Shriver National Institute of Child Health and Human Development), and the Centers for Disease Control and Prevention (CDC) have put emphasis towards establishing "LTFU after NBS as an essential surveillance activity" (28). "All three federal partners see the confluence of improved NBS and subsequent management, surveillance, quality assurance, and advancing research as a common means for understanding this action" (28).

One recent effort to improve LTFU was a project put together by the HRSA Region 4 Genetics Collaborative Priority 2 Workgroup (29). This project focused on improving laboratory performance and data collection for long-term NBS follow-up. The workgroup began defining both short-term and long-term follow-up common data sets including critical demographic and diagnostic-related elements that would collect information about the "general status of the child, the frequency and type of medical encounters, laboratory and other clinical monitoring parameters, ongoing dietary and medication management, developmental outcomes, and coordination of care" (29). This

data system was put into use in 2009 to collect information on medium chain acyl-CoA dehydrogenase deficiency (MCADD), and fatty acid oxidation disorder (FAOD) from various centers across the region (29).

CDC's Pilot Project

Another recent effort was initiated by CDC's National Center on Birth Defects and Developmental Disabilities to "offer funding to develop and implement a collaborative pilot project with population-based surveillance and tracking of confirmed newborn screening conditions using already established newborn screening or birth defects surveillance programs" (28). The project focused on enhancing the collection and quality of population-based data for children with a confirmed metabolic NBS disorder using birth defects surveillance and NBS programs that were already in place (30). "The purpose of the project is to demonstrate the feasibility of expanding existing population-based, public health data collection programs (birth defects surveillance or NBS) to conduct LTFU of children with 1 of the 19 metabolic disorders through to the age of 3 years" (30).

Four states participated in this project: California, New York, Iowa, and Utah. Three approaches were used among the four states to take advantage of the strengths of each existing state program. Iowa and Utah used an active case-finding methodology to collect LTFU data (30). New York combined many data sources including the NBS program, Congenital Malformations Registry, vital records, hospital discharge files, and data from the Early Intervention Program through data linkage using identifiers such as last name, sex, and date of birth, residential address, medical record number, and birth

weight (31). California used its existing state-wide NBS reporting program to collect LTFU data (26, 30).

An important aspect of this project was collaboration between states and federal health agencies to develop a data dictionary to better collect LTFU data in a relatively uniform manner. Lastly, “this pilot project not only improved the state-level data but also provided pooled data that permitted a better understanding of rare disorders that might otherwise require many years for a single state to gather enough cases to better understand the long-term outcomes of these children” (30).

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MANUSCRIPT

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ABSTRACT

CDC's National Center on Birth Defects and Developmental Disabilities funded a pilot project to develop and implement population-based surveillance of confirmed newborn screening conditions using existing data collection systems in 4 U.S. states. Long-term follow-up outcomes were collected on each child through their third birthday. The purpose of this thesis is to examine the data completeness of the long-term follow-up data collected through the pilot project. Over three years of follow-up, 261 metabolic cases were identified in 1,343,696 live births. The primary outcome of this analysis is the percentage of completeness for each variable (number of observations with data for that variable/total number of observations). The denominator decreases from year 1 to year 3 to exclude those that died or moved out of the catchment area during the previous year. Data completeness was compared across the three types of data collection systems used in four states: 2 active birth defects surveillance systems, 1 passive system with case confirmation, and 1 newborn screening system. A fairly consistent level of completeness was observed across the five types of variables (demographic, diagnosis, service utilization, development, co-morbidities). Of the variables that focused on long-term follow-up outcomes for these children, the service utilization and co-morbidity variables were of the highest quality. The developmental variables showed the most variation in data completeness. The two active systems and the passive with case confirmation system contributed the data with the highest completeness. The NBS system contributed the most number of cases to the cohort and was still able to contribute high quality data.

INTRODUCTION

Currently, newborn screening (NBS) is a state-based public health program "aimed at the early identification of infants who are affected by certain genetic/metabolic/infectious conditions" (1). Developments in screening for and treating phenylketonuria (PKU) in the 1960s represent a great success story of NBS programs in the United States (2,3), and paved the way for our current population-based system of screening newborns for various genetic and metabolic conditions. This important preventive public health program identifies selected conditions "that would otherwise become catastrophic health problems" (4), and attempts to ensure that children receive timely medical care before becoming greatly affected. Over the last few decades, research and new technologies in genetic and metabolic conditions furthered the knowledge base and allowed for multiple conditions to be screened for using one blood sample (5). In the year 2000, all states screened newborns for PKU and congenital hypothyroidism, and some states screened for additional inherited disorders (4).

In 2006, in order to move the United States toward national NBS standards, the American College of Medical Genetics was commissioned by HRSA to, among other responsibilities, create a recommended uniform screening panel (RUSP) (5). Through this process, 29 core conditions were considered appropriate because they "have a screening test, efficacious treatment, and adequate knowledge of natural history" (5). By the end of 2009, every state NBS program screened for (at least) the 29 recommended conditions (6, 7).

There are essentially 6 components of a successful NBS program: education, screening, follow-up, diagnosis, management, and evaluation (4, 8). The follow-up

component of NBS programs can be split into two parts: short- and long-term follow-up (LTFU). Generally, "short-term follow-up begins when the laboratory obtains an initial result that is screen positive and ends with a definitive diagnosis… Long-term follow-up begins with treatment and continues throughout life" (4). Other activities included in LTFU include program evaluation and quality assurance (1,9). LTFU also "provides an opportunity to better define the outcomes of these rare, usually poorly defined conditions, and evaluate the value of established and new treatments" (10).

"Unfortunately, the long-term follow-up activities within public health programs lack coordination and have been of low priority for funding compared with activities related to screening and diagnosis" (11). With the increase in technology, including MS/MS screening techniques, there have been advances in the screening component of NBS. With the increase in identifying infants with potential disorders, there needs to be a subsequent increase in the ability to provide care and therapies to these infants. "If individuals with confirmed diagnoses cannot receive timely, accessible, appropriate care for their conditions, then identifying them is of less value" (12). Recently, attention has been put towards the potential role of NBS programs in performing and strengthening their LTFU activities (12, 13).

In 2008, a statement put out by the US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDGDNC), described the key features of LTFU after diagnosis (11). The components stressed by ACHDGDNC included the coordination of care through a medical home, evidence-based treatment, continuous quality improvement and new knowledge discovery (11). An important effort initiated by CDC's National Center on

Birth Defects and Developmental Disabilities was to "offer funding to develop and implement a collaborative pilot project with population-based surveillance and tracking of confirmed newborn screening conditions using already established newborn screening or birth defects surveillance programs" (14). "The purpose of the project is to demonstrate the feasibility of expanding existing population-based, public health data collection programs (birth defects surveillance or NBS) to conduct LTFU of children with 1 of the 19 metabolic disorders through to the age of 3 years" (15).

An important aspect of any surveillance system is to not merely collect information and store it somewhere - the system needs to inform decisions for the future and add knowledge to the subject matter. A collection of data on outcomes of these newborns should "not merely [be] a repository of information. It is also a provider of information and should offer clinical decision support by providing condition-specific information to the provider…" (16). "The purpose of evaluating public health surveillance systems is to ensure that problems of public health importance are being monitored efficiently and effectively" (17). CDC's Updated Guidelines for Evaluating Public Health Surveillance described 9 system attributes of surveillance systems: simplicity, flexibility, data quality, acceptability, sensitivity, predictive value positive, representativeness, timeliness, and stability (18). This report will focus on evaluating the data quality aspect of the pilot project's ability to collect LTFU data using existing NBS and birth defect surveillance systems in 4 different states. The MMWR article indicated a way to evaluate data quality is to "examine the percentage of "unknown" or "blank" responses to items…" (18). The purpose of this report is to examine data completeness in the pilot project recently completed by CDC and four states to collect LTFU data.

METHODS

Study Population

Four states –California (CA), Iowa (IA), New York (NY), and Utah (UT) – participated in a CDC-funded LTFU pilot project to expand birth defect surveillance or newborn screening (NBS) programs to collect LTFU data on 19 metabolic disorders. Details on birth cohorts and methods are presented in Hinton et al., 2013. Over three years of follow-up (1,343,696 live births), 261 metabolic cases were identified. Each state varied in their approach to collecting LTFU data. IA and UT expanded their active birth defect surveillance systems to collect LTFU data. CA relied on their state-wide NBS surveillance reporting program. NY combined active and passive data collection methods using a variety of data sources and record linkage. States were encouraged to expand ongoing surveillance programs and strengthen data linkages among administrative and clinical program databases.

Data Collection

Standardized data elements were created during the first year of the pilot project by key staff at CDC in the Birth Defects Division, principal investigators and data managers at the state level. Variables were based upon the National Birth Defects Prevention Network (NBDPN) minimal dataset, American College of Medical Genetics' ACTion Sheets, as well as existing data dictionaries used by participating states' surveillance programs. The data variables fell into 5 categories (demographic, diagnosis, service utilization, co-morbidities, and developmental). The variables included data available on birth certificates, hospital discharge data, metabolic clinic records, infant's

medical record, mother's medical record, autopsy report, death certificate, etc. For a complete listing of the data variables collected, see Appendix 1.

Demographic Variables

Demographic variables included information on the mother (mother's education, marital status, race/ethnicity, cigarette smoking status, diabetes status), the infant (gestational age, birth weight, sex), and additional insurance information.

Diagnosis Variables

The diagnosis category included variables that indicated which specific tests were used to make a clinical diagnosis for one of the 19 metabolic conditions in the NBS panel. This section of variables also indicated which metabolic condition was diagnosed, the timing of diagnosis and initial interventions, as well as an administrative follow-up variable. The follow-up variable was collected at the end of each year of data collection for each child. The child could be classified as 'active', 'lost to follow-up', 'moved out of state', 'refused follow-up', 'treatment not necessary', 'patient died', or 'unknown'.

Service Utilization Variables

The service utilization variables were collected for each year of data follow-up. This section focuses on if certain providers were seen by the child during the previous year (three years of data collected), and how many times during the previous year. This section captured data on physician consults, ER visits, hospitalizations, ICU stays, metabolic clinics, medical geneticists, dieticians, nurse practitioners, social workers, genetic counselors, and other paramedical services.

Development Variables

The development section of variables included information on date of last office visit of the year, weight and OFC at last visit, if the child experienced developmental delay (and the level of delay), if child made developmental progress during the year, and various developmental tests that the child went through (including BSID-III, BINS, Batelle Developmental Inventory).

Co-morbidity Variables

The co-morbidities section of variables included potential co-morbidities that the child might face during their first three years of life. They included morbidities in a variety of systems (general, neurologic, malformations, pancreas, liver, heart/muscle, blood/immunology, skin, metabolic, kidney).

Analysis

Emory IRB agreed with the CDC determination that "this doesn't constitute human subjects research but is public health practice that does not require IRB review" on April 25, 2013 (Appendix 2). The primary outcome of this analysis is the percentage of completeness for each variable (number of observations with data for that variable/total number of observations). The first step in analysis was to ensure that 'missing' values for variables were consistently coded across all 4 states. All missing data was coded as a SAS missing to ensure that percent complete of each variable could be calculated. Each variable was analyzed to explore the completeness by surveillance approach: 2 states used an active birth defect surveillance system, 1 state used their NBS reporting program, and 1 state used a passive record linkage system with case confirmation. Each variable was analyzed for the three years of data collection.

Because there are multiple years of data, the denominator decreases slightly from the beginning to the end of the data collection period to subtract those that died or moved out of the catchment area during the previous year. This study uses the same exclusion criteria as Hinton, et al 2013. The denominator for year 1 included all 261 births divided by approach (active = 72, NBS = 132, passive with case confirmation = 57) The denominator for year 2 excluded those that died or moved out of the catchment area in year 1 to total (active = 69, NBS = 127, passive with case confirmation = 52). The denominator for year 3 excluded those that died or moved out of the catchment area in year 2 (active = 65, NBS = 120, passive with case confirmation = 44). All analyses were performed in SAS 9.3.

RESULTS

A significant amount of LTFU data was able to be collected on the 261 confirmed metabolic cases from the four states that participated in the CDC pilot project using existing data collection systems.

Demographics

Table 1 displays the percentage complete for all the demographic variables ascertained. Because the two active systems were almost identical in their percent completeness of variables, they have been averaged together to represent what the active systems can collect. Many of the variables were 100% complete across all three types of surveillance systems used to collect data. Variables that had more variation in completeness include the primary, secondary, and tertiary insurance at birth, as well as, smoking status of the mother. The NBS system did not collect the insurance information, and one of the active systems was able to collect 100% of this data. Completeness of the

smoking status variable averaged to be 88% complete across all four states. Maternal diabetes status was not collected by the NBS program or the passive with case confirmation program, and was only 2-3% complete for the active systems. Overall, the demographic variables were collected by the multitude of surveillance systems in place in the four states.

Diagnosis

Table 2 shows the percentage complete for every diagnosis variable. The various tests used to make a diagnosis were collected very well in the NBS and active systems. The passive with case confirmation system was not able to effectively collect this type of data (although every child in the dataset had their specific condition collected). All three types of systems were able to collect date of diagnosis, and date of intervention. In the future, one could use this dataset to analyze how time until diagnosis or time until intervention affects long-term outcomes in these children.

Service Utilization

Figure 1 portrays the percent complete for all of the potential services utilized during the first year of data collection across the three types of surveillance systems used by the four states. The variables in Figure 1 are a yes/no type of answer – was there a physician consult in year 1? The active and passive with case confirmation systems have almost 100% data completeness for the first year of these services. The NBS system has a more variation in data completeness ranging from 0% for nurse practitioner and other provider, to 11% complete for ICU stay, and to 98% complete for medical geneticist.

In order to observe any trends that occur from the first to the last year of data collection, Figure 2 portrays the data completeness for the metabolic clinic variable across three years. The active and passive with case confirmation systems are above 95%

complete for all three years of data collected. The NBS system has a slightly downward trend in variable completeness from year 1 to year 3, but is still above 75% complete by year 3. Figure 3 shows the data completeness for the metabolic geneticist variable across the three years for the different surveillance systems. In this case, the passive with case confirmation system was able to collect this variable completely in all 3 years. The active systems were also very close to completely collecting this variable (98%). The NBS system is fairly consistent, higher than 90% complete for all three years. This is a high quality variable that was able to be collected across a range of systems that currently exist in these four states.

Figures 4-6 show the percent complete for the hospitalization variables, including if there was a hospitalization in the previous year (Figure 4), the number of hospitalizations in the previous year (Figure 5), and the length of stay in the hospital (Figure 6) by type of surveillance system. These variables show a similar pattern to the other service utilization variables. The passive with case confirmation system has 100% completeness for all three years – and the active system is close to 100% complete (94% in year 2). The NBS system's completeness decreases from 91% in year 1 to 77% in year 3.

Development

Figure 7 shows the percent complete for the developmental delay variable by type of surveillance system. The active systems decreased their data completeness from 100% in year 1 to 85% in year 3. The passive with case confirmation system was fairly consistent in collecting this data (averaging 57% complete).

Co-morbidities

Figure 8 shows the percent complete for the metabolic co-morbidities including metabolic acidosis, metabolic alkalosis, hypoglycemia, hyperammonemia, and electrolyte abnormalities. All of these specific metabolic co-morbidity variables showed the same pattern and are averaged together for Figure 8. These variables were easier to collect compared to the developmental variables. The active and passive with case confirmation systems were able to collect 90-100% of this data and the NBS system slightly lower, but still above 75% complete by year 3.

DISCUSSION

A fairly consistent level of completeness was observed across the five types of variables collected in the data dictionary (including demographic, diagnosis, service utilization, co-morbidities, and developmental variables). Of the variables that focused on long-term follow-up outcomes for these children, the service utilization and co-morbidity variables were the most complete (80% and 94%, respectively), while developmental variables were less complete (61%).

Given the different approaches to collecting the data, we observed some variability. One reason for the variation in data completeness for services utilized could be that the NBS system collects their data through the contractual agreement between the metabolic clinics and the Genetic Disease Screening Program. This would account for the high quality data the NBS system shows for metabolic clinic /geneticist usage, and the poorer data completeness for nurse visits and other practitioners. From Figures 4-6, it is clear that when the data collection system can collect information on if there was a hospitalization, the system can also collect information on the number per year, and how long the stay was.

The developmental variables proved to be the most difficult to collect and resulted in the most amount of missing data across all three types of surveillance systems. This is a case in which the NBS system was better able to collect a variable compared with the passive with case confirmation system. The developmental delay variable was created by the active BD surveillance systems but was still one of the hardest variables to collect. One reason for this could be that the developmental tests are not used until a later age for the children (19) or parents are denying the use of these tests in their children (observed in the notes section of the dataset). If the developmental tests are not being used until a later age in these children, data would need to be collected until age 5 to ascertain this type of development outcomes.

There are not many current publications that examine data completeness of NBS LTFU data collected from a variety of state data collection systems. This project is similar to a paper published in 2010 that examined the LTFU outcomes and data quality of a centralized NBS system, the New England NBS Program (20). This paper provides information about the type of specialists seen by the children with confirmed NBS conditions. Further analysis of the current dataset should be conducted to compare subspecialist use across various geographic regions.

Strengths and Limitations

There are many strengths to this project. This report proves that it is feasible for states to use their existing population-based data systems to expand and enhance their data collection to include long-term follow-up data for children with confirmed metabolic NBS conditions. This data collection project was adaptable for different types of surveillance systems. Some states were able to augment and change their procedures along the way to increase the types of variables they were able to collect. One example of

this is in year 2, NY added data abstractors to their record linkage system to increase the type of variables they could collect. Also, CA saw the benefit of collecting certain variables included in this data dictionary and added those to their NBS reporting system as a result of being involved in this pilot project. Because the purpose of this pilot project was to enhance existing data collection systems, and not create new ones, this project was relatively low cost. Lastly, having pooled data across multiple states could potentially allow for better understanding of the long-term outcomes of these children. It would take considerably longer for an individual state to accumulate enough of these rare condition cases to get this type of information on outcomes and co-morbidities.

There are a few limitations to this study. Follow-up stops at age 3 and this limits the understanding of some of the outcomes for these children. This is especially true in the case of the developmental variables. It would be beneficial to collect data until age 5 to have more information about types of developmental delay or progress these children face throughout their first few years of life. There is also limited clinical information in some instances because of the source of data used. For example, the NBS system wasn't able to capture information about nurse practitioner visits, or ICU stays because they get most of their data through the metabolic clinic annual reports. Lastly, it is unclear if some of the outcomes are due to the metabolic condition or are due to any number of other reasons. This was attempted to be ascertained, but proved difficult. An example of this is if a child had been hospitalized, it is unclear if they were hospitalized because they fell off their bike and broke their arm, or if it was a result of their metabolic condition.

This thesis provided a comprehensive review of over 500 variables collected across three years. This analysis will provide a tool to other states looking to collect this

type of LTFU information. This analysis will also be a guide in decision-making and help to elucidate categories of data that states might have trouble collecting and should provide more resources to collecting.

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TABLES

Table 1. Percentage complete of demographic variables collected in the long-term follow-up pilot project by four states: 1 NBS program, 2 active systems (averaged together), and 1 passive with case confirmation.

Variable	NBS	Active	Passive w/ CC%
State	100	100	100
Infant Sex	100	100	100
Year of Birth	100	100	100
Month of Birth	100	100	100
Day of Birth	100	100	100
Gestational Age, clinical	97	100	95
Birth weight (grams)	100	100	100
Mother's Race/Ethnicity	100	100	95
Mother's Age (years)	98	100	100
Gravidity	98	100	98
Plurality	98	100	100
Mother's Education	96	100	100
Marital Status	NC	100	NC
Primary Insurance at Birth	96	79	100
Secondary Insurance at Birth	NC	53	5
Tertiary Insurance at Birth	NC	53	NC
Was child insured at last visit of 1st year?	NC	100	84
Was child insured at last visit of 2nd year?	NC	95	54
Was child insured at last visit of 3rd year?	7	92	73
If yes, what type of insurance? 1st year	NC	100	100
If yes, what type of insurance? 2nd year	NC	100	100
If yes, what type of insurance? 3rd year	100	96	100
Rural/Urban Continuum	100	100	100
Cigarette Smoking Status	67	97	91
Maternal Diabetes	98	78	100
Maternal Diabetes Status	NC	3	NC
Maternal HELLP	NC	57	NC
Maternal Pre-eclampsia	98	97	NC

*NC = not collected by program

%CC = case confirmation

Table 2. Percentage complete of diagnosis variables collected in the long-term follow-up pilot project by four states: 1 NBS program, 2 active systems (averaged together), and 1 passive with case confirmation.

Variable	NBS	Active	Passive with CC*
NBS Condition/Disorder	100	100	100
Enzyme Activity Diagnostic Test for NBS condition	100	100	9
Fibroblasts Diagnostic Test for NBS condition	100	100	2
Blood Diagnostic Test for NBS condition	100	100	11
Tissue (not otherwise specified NOS) Diagnostic Test for NBS condition	0	100	0
Carnitine Panel Diagnostic Test for NBS condition	100	100	26
Orotic Acid Levels Diagnostic Test for NBS condition	0	100	0
Plasma Acylcarnitine Diagnostic Test for NBS condition	100	100	42
Plasma MMA Diagnostic Test for NBS condition	100	100	2
Plasma Organic Acids Diagnostic Test for NBS condition	100	100	2
Urine Acylglycines Diagnostic Test for NBS condition	100	99	14
Urine Organic Acids Diagnostic Test for NBS condition	100	100	46
Urine MMA Diagnostic Test for NBS condition	100	100	0
Plasma Amino Acids Diagnostic Test for NBS condition	100	100	39
DNA Diagnostic Test for NBS condition	100	100	21
Year of Definitive Diagnosis	100	100	100
Month of Definitive Diagnosis	100	97	100
Day of Definitive Diagnosis	100	95	100
Year Initial Intervention	100	95	93
Month Initial Intervention	100	100	93
Day Initial Intervention	100	100	93
Follow-up Status Year 1	93	100	100
Follow-up Status Year 2	93	100	100
Follow-up Status Year 3	95	100	98
Year of Death	100	100	100
Month of Death	100	100	100
Day of Death	100	100	100
Cause of Death	100	100	100
Cause of Death related to NBS disorder?	0	100	100

* CC = case confirmation

FIGURES

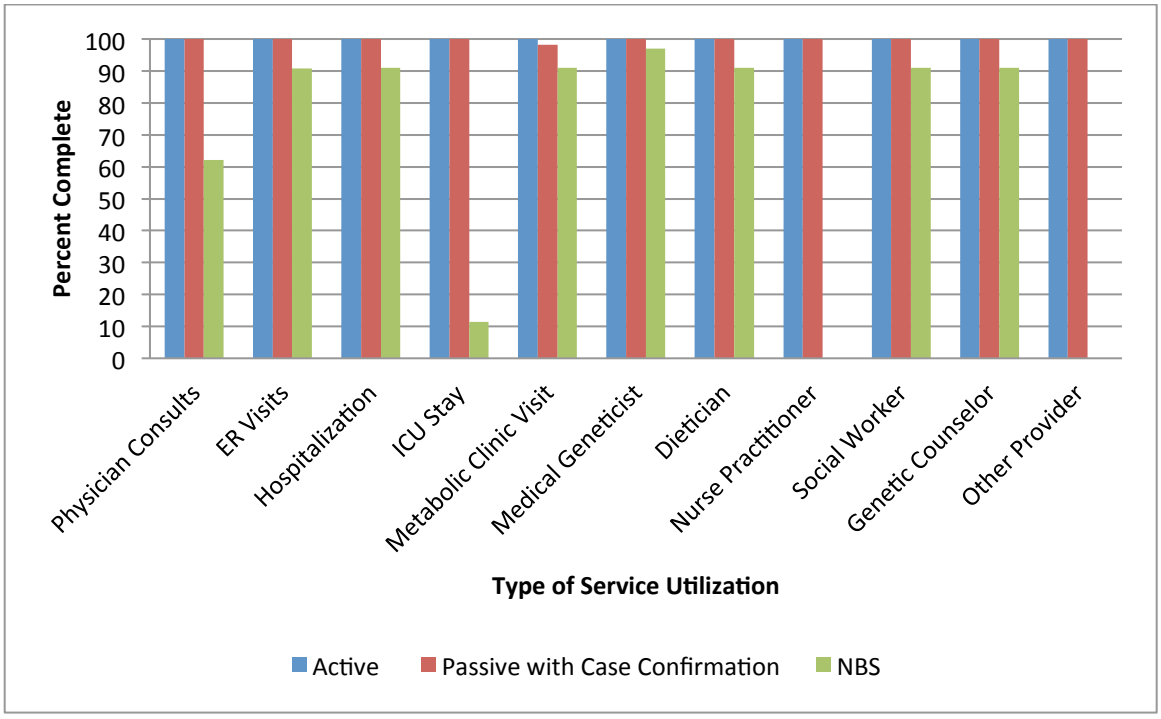


Figure 1. Percent complete for service utilization variables collected in year 1 by type of surveillance system used.

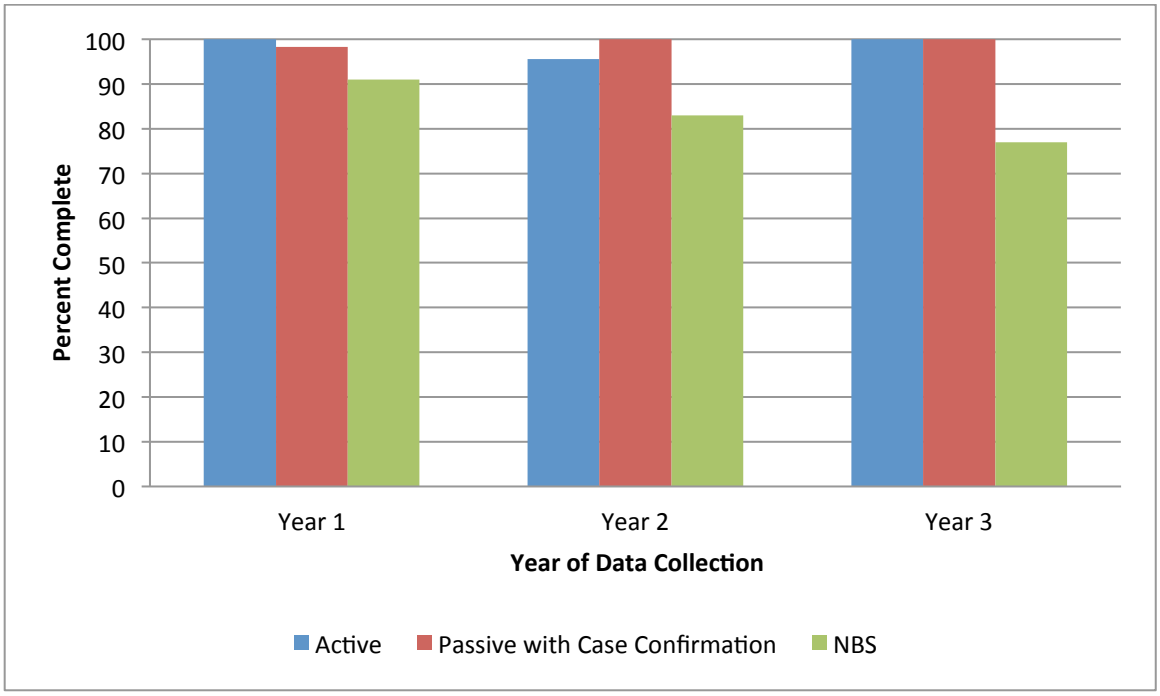


Figure 2. Percent complete for the metabolic clinic variable collected across three years by type of surveillance system.

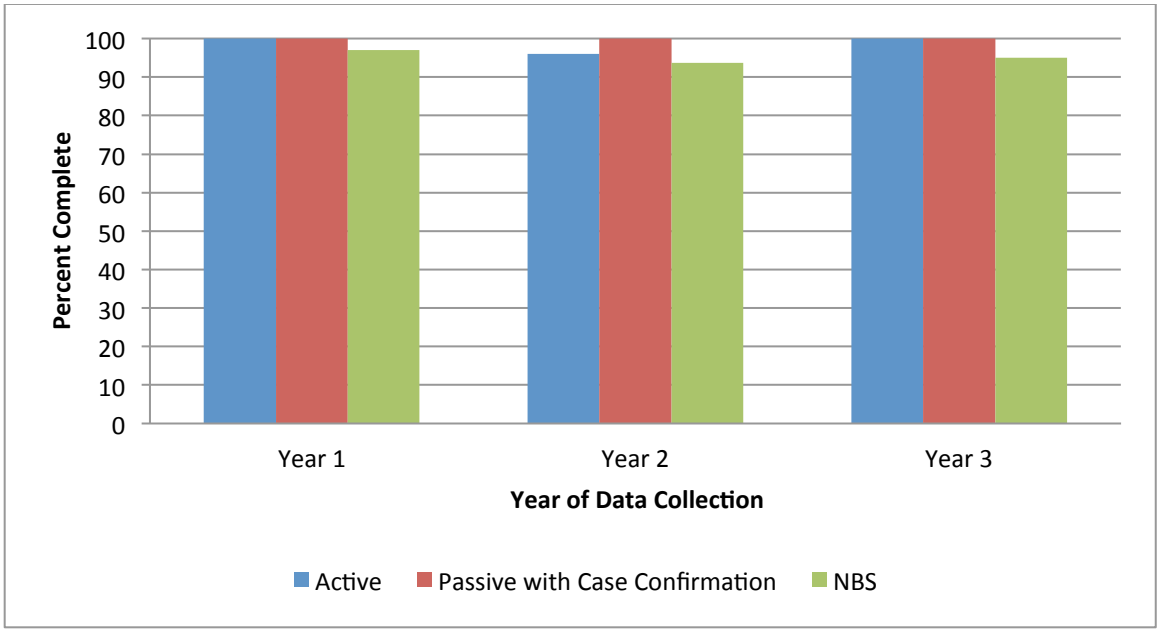


Figure 3. Percent complete for the metabolic geneticist variable collected across three years by type of surveillance system.

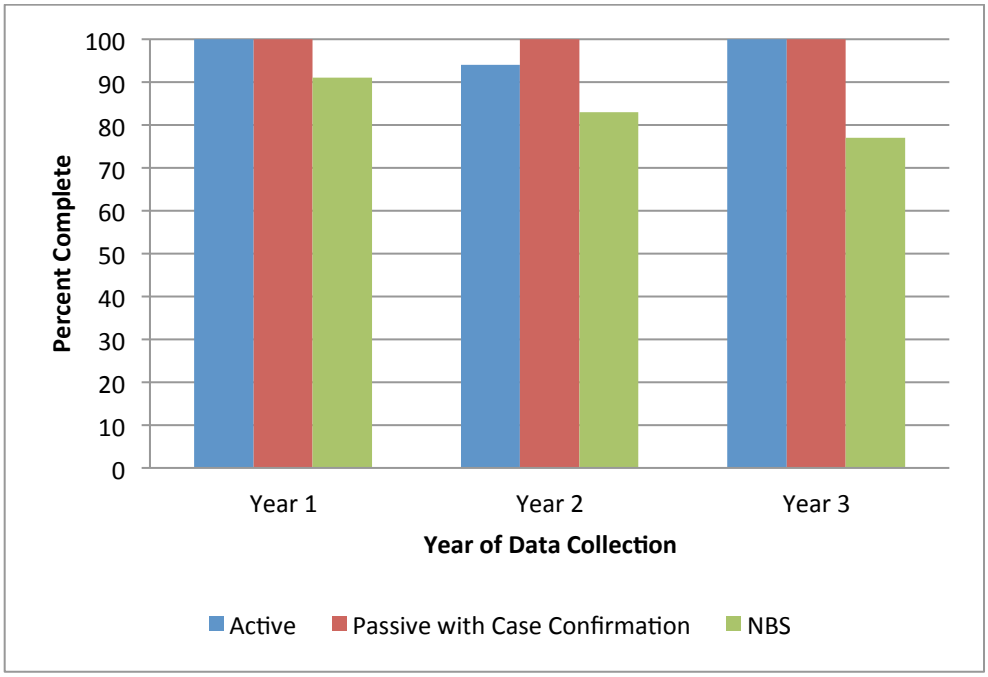


Figure 4. Percent complete for the hospitalization variable collected across three years by type of surveillance system.

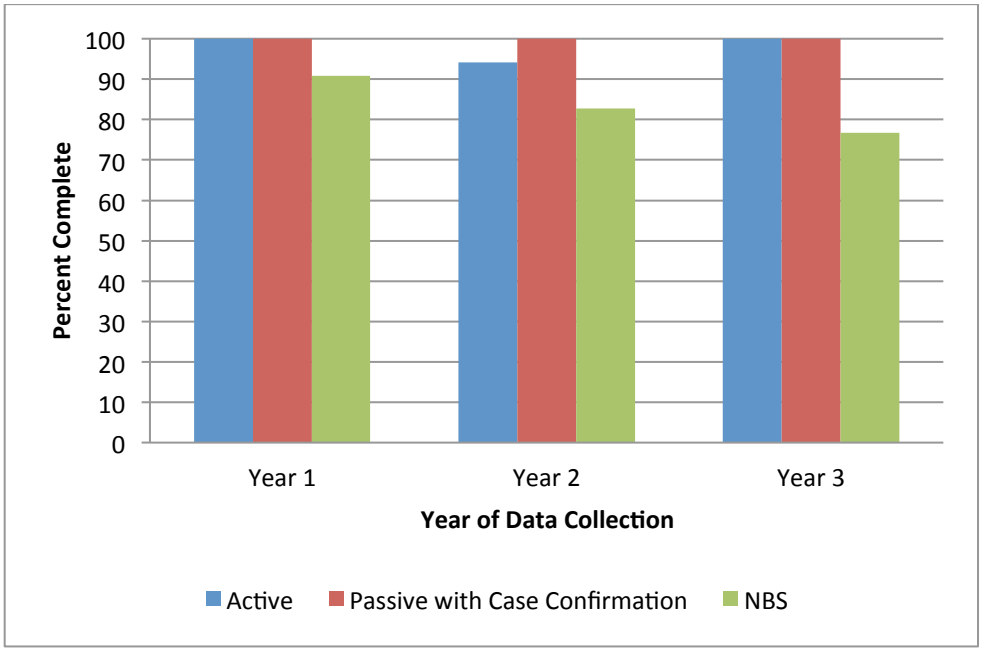


Figure 5. Percent complete for the number of hospitalizations variable collected across three years by type of surveillance system.

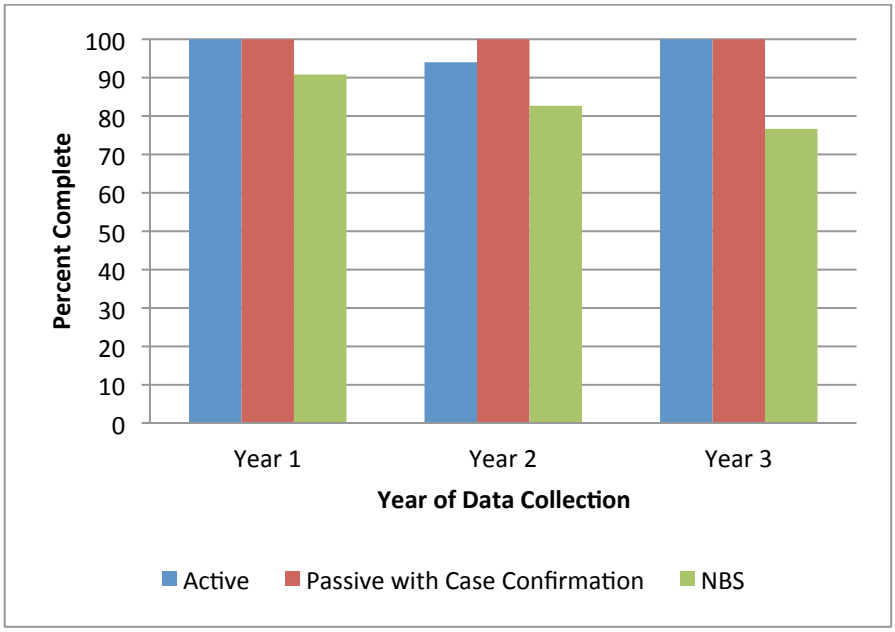


Figure 6. Percent complete of the Length of stay – hospitalization variable collected across three years by type of surveillance system.

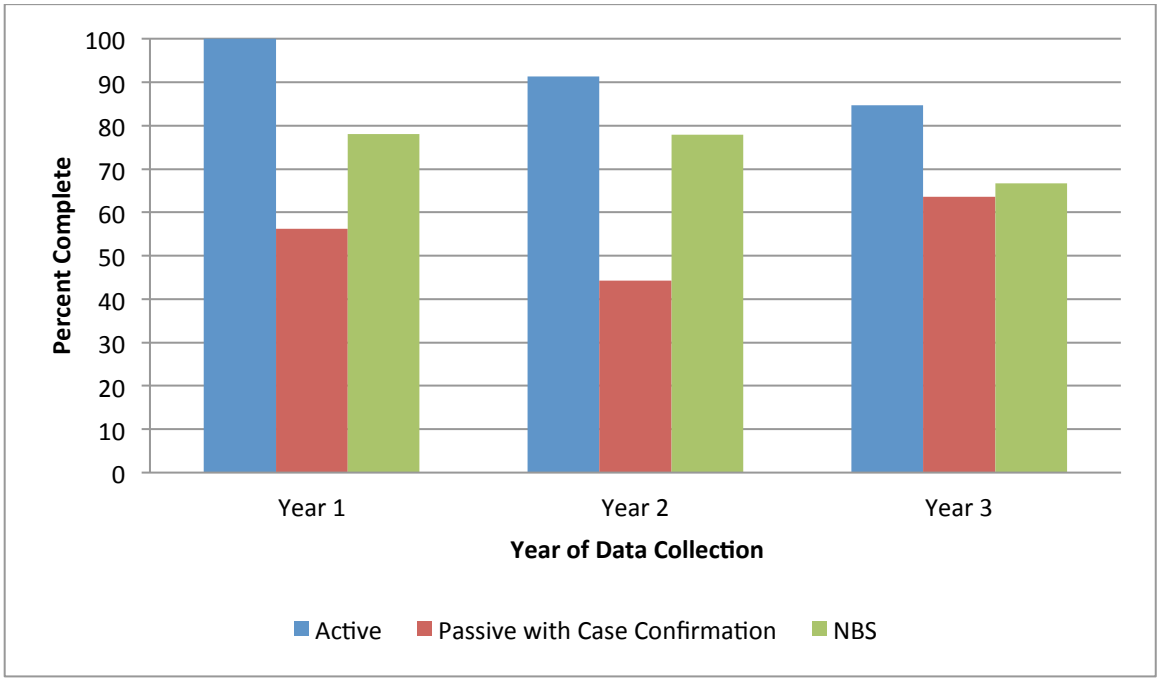


Figure 7. Percent complete for the developmental delay variable collected across three years by type of surveillance system.

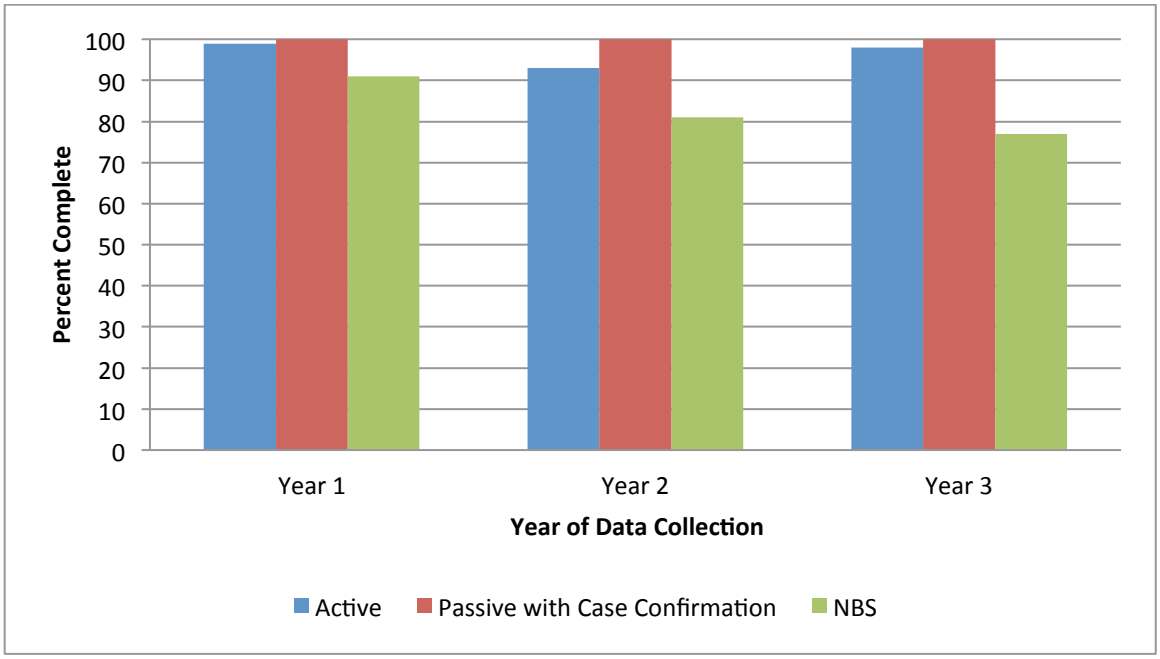


Figure 8. Percent complete for the metabolic co-morbidity variables across three years by type of system.

APPENDICIES

Appendix 1:

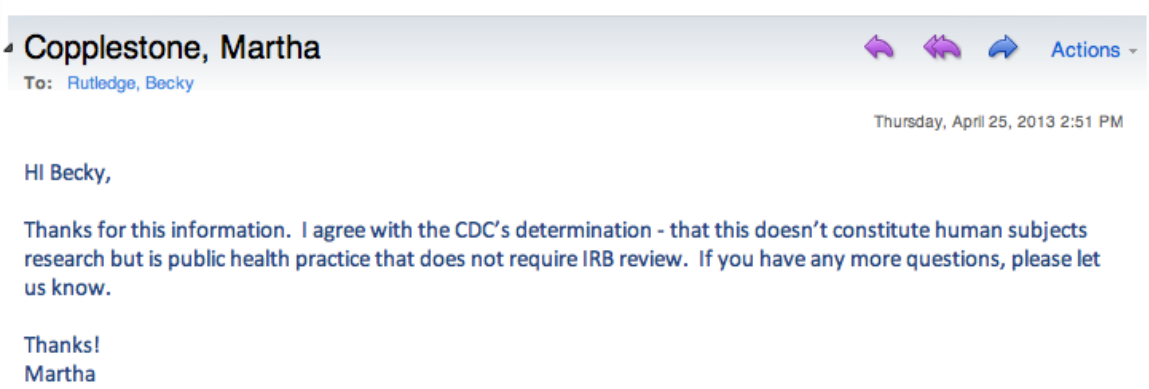
Variable Description	
DEMOGRAPHICS	
Random ID #	Marital Status
State	Primary Insurance at Birth
Infant Sex	Secondary Insurance at Birth
Year of Birth	Tertiary Insurance at Birth
Month of Birth	Was child insured at last visit of the year?
Day of birth	If yes, what type of insurance was it?
Gestational Age, clinical	County Mother resides in at time of birth
Birth weight (grams)	Rural/Urban Continuum
Mother's Race/Ethnicity	Cigarettes Smoked
Mother's Age in Years	Maternal Diabetes
Gravidity	Maternal Diabetes Status
Plurality	Maternal HELLP
Mother's Education	Maternal Pre-eclampsia
DIAGNOSIS	
NBS Condition/Disorder	Diagnostic Test Other
Enzyme Activity Diagnostic Test for NBS condition	Genotypes
Fibroblasts Diagnostic Test for NBS condition	Diagnostic comments
Blood Diagnostic Test for NBS condition	Year of Definitive Diagnosis
Tissue (not otherwise specified NOS) Diagnostic Test for NBS condition	Month of Definitive Diagnosis
Carnitine Panel Diagnostic Test for NBS condition	Day of Definitive Diagnosis
Orotic Acid Levels Diagnostic Test for NBS condition	Year Initial Intervention
Plasma Acylcarnitine Diagnostic Test for NBS condition	Month Initial Intervention
Plasma MMA Diagnostic Test for NBS condition	Day Initial Intervention
Plasma Organic Acids Diagnostic Test for NBS condition	Follow-up Status Year 1,2,3
Urine Acylglycines Diagnostic Test for NBS condition	Year of Death
Urine Organic Acids Diagnostic Test for NBS condition	Month of Death
Urine MMA Diagnostic Test for NBS condition	Day of Death
Plasma Amino Acids Diagnostic Test for NBS condition	Cause of Death

DNA Diagnostic Test for NBS condition	Cause of death related to disorder?
SERVICE UTILIZATION (Year 1,2,3)	
Was there a physician consult during previous year?	Was a Nurse Practitioner seen during the previous year?
How many physician consults	Was a Social Worker seen during the previous year?
ER visit during previous year?	Was a Genetic Counselor seen during the previous year?
ER visit number	Did the child receive other paramedical services?
Hospitalization during previous year?	Did the child see another provider during the previous year?
Hospitalization number	Types of other services, if known
Hospital Length of Stay Yr 1 (Days)	Treatment Yr 1 Medications
Did client have ICU Stay in Yr 1	Treatment Yr 1 Medical Foods/Formulas
ICU Number	Treatment Yr 1 Vitamins and Co-Factors
ICU Length of stay Yr 1 (days)	Treatment Yr 1 Enzymes
Did child visit a metabolic clinic visit during previous year?	Treatment Yr 1 G-Tube
How many visits to a metabolic clinic?	Treatment Yr 1 Port-a-Cath
Was a Medical Geneticist (Metabolic Subspecialty) seen during the previous year?	Treatment Yr 1 Transplant Kidney
Medical Geneticist (other than a Metabolic specialist) visited during the previous year?	Treatment Yr 1 Transplant Liver
Was a Dietician seen during the previous year?	Treatment Yr 1/Other
COMORBIDITIES (Year 1,2,3)	
General	Reviewer comments
Failure to thrive	**Hemat/Immun.**
Reviewer comments	Anemia
Short stature	Reviewer comments
Reviewer comments	Thrombocytosis
Small for gestational age	Reviewer Comments
Reviewer comments	Thrombocytopenia
Large for gestational age	Reviewer comments
Reviewer comments	Neutropenia
Microcephaly	Reviewer comments
Reviewer comments	Sepsis
Macrocephaly	Reviewer comments
Reviewer comments	Pancytopenia

Death	Reviewer comments
Neurologic	**Skin**
Seizures	Dermatologic findings
Reviewer comments	Reviewer comments
Lethargy	**Metabolic**
Reviewer comments	Metabolic acidosis
Coma	Reviewer comments
Reviewer comments	Metabolic alkalosis
Abnormal brain findings	Reviewer comments
Reviewer comments	Hypoglycemia
Dystonia	Reviewer comments
Reviewer comments	Hyperammonemia
Spasticity/hypertonia	Reviewer comments
Reviewer comments	Electrolyte abnormalities
Hypotonia	Reviewer comments
Reviewer comments	**Metabolic Decompensation Episode**
Other neurologic	Reviewer comments
Neurologic Reviewer Comments	**Kidney**
Malformations	Chronic renal disease
Congenital malformations	Reviewer comments
Malformation Reviewer Comments	Other renal disease
Pancreas	Reviewer comments
Pancreatitis	Dialysis
Reviewer comments	Reviewer comments
Liver	**Eye**
Liver failure	Eye pathology
Reviewer comments	Reviewer comments
Liver cancer	**Other**
Reviewer comments	Other (specify)
Hepatomegaly	Other text field
Reviewer comments	**California Variables**
Elevated liver enzymes	Morbidity Yr 1 Poor Feeding
Reviewer comments	Morbidity Yr 1 Poor weight gain
Other liver	Morbidity Yr 1 vomiting
Reviewer comments	Morbidity Yr 1 Diarrhea
Heart/muscle	Morbidity Yr 1 Lethargy
Cardiomyopathy	Morbidity Yr 1 Dehydration
Reviewer comments	Morbidity Yr 1 Respiratory Disorders
Myopathy	Morbidity Yr 1 Fever
DEVELOPMENT (Year 1,2,3)	
Year of last office visit	Child lost skills during year
Date of last office visit	reviewer comment on skills lost

Month of last office visit	Developmental tests used in past year General Physician Assessment
OFC at last visit of year	Developmental tests used in past year Parent Evaluation
weight at last visit of year	Developmental tests used in past year Ages and Stages
length at last visit of year	Developmental tests used in past year BSID-III
Has child experienced Developmental delay over the year?	Developmental tests used in past year Denver II
Level of Delay	Developmental tests used in past year BINS
Reviewer comment on types of delay	Developmental tests used in past year Batelle Developmental Inventory
Child made developmental progress during the year	Developmental tests used in past year Other
reviewer comment on skills gained	Other Developmental tests used in past year

Appendix 2:



Copplestone, Martha

To: Rutledge, Becky

Actions

Thursday, April 25, 2013 2:51 PM

HI Becky,

Thanks for this information. I agree with the CDC's determination - that this doesn't constitute human subjects research but is public health practice that does not require IRB review. If you have any more questions, please let us know.

Thanks!
Martha