

**Attachment 8**  
**Additional Details about Study Background and Methodology**

## **Descriptive Epidemiology of Missed or Delayed Diagnoses For Conditions Detected by Newborn Screening**

### **Newborn Screening Process**

Newborn screening in the United States began in 1963 following the introduction of the Guthrie test for PKU. There are now screening programs in all 50 states, although not all states operate their own screening laboratories. Each state currently has dried blood spots screened by a designated laboratory for PKU and congenital hypothyroidism. Most states also screen for other disorders, including galactosemia, CAH and MSUD. Most states also screen infants for hemoglobinopathies such as SCD. Each state maintains responsibility for screening, determines which tests are to be required, outlines the protocols for screening and coordinates follow-up and treatment individually.

The screening process begins with collection of blood onto filter paper from a newborn, usually before discharge from the hospital. The specimens are then sent to the laboratory for testing. Specimens with abnormal results are reported to the physician and to a follow-up coordinator who is responsible for locating patients who do not come back for retesting. Patients affected with any of the diseases included in the screening panels require prompt diagnosis and treatment to prevent injury or death. Screening is a multi-step process and at each of these steps, the potential exists for an event to occur that would allow a delayed diagnosis or a missed case.

### **Missed Cases**

A “missed case” is defined as a case of a screened metabolic disorder identified outside of the newborn screening system (i.e. clinically) or identified through newborn screening but with a delay in diagnosis.

Delay in diagnosis is defined as either the occurrence of serious clinical symptoms or death that could have been prevented through earlier diagnosis or a case where no injury was documented but diagnosis and treatment did not commence in a timely manner (within one month of birth).

There are many potential scenarios for a missed case:

1. A clerical error occurred either at the hospital or at the testing laboratory resulting in incorrect identification of the newborn or incorrect result recording/transmission.
2. An adequate blood spot was never collected.
3. Collection was untimely (e.g. baby was in intensive care) and results were reported too slowly.
4. Blood was collected incorrectly (i.e. inadequate or unsatisfactory specimen required repeat).

5. Transport to the testing laboratory was untimely and analysis was delayed.
6. Analysis by the testing laboratory was untimely (e.g. holiday scheduling delayed testing)
7. Blood specimen was lost in transit, so no screening test was performed.
8. “False negative” laboratory screening test result for any of a number of potential reasons, including, but not limited to, normal biological variations, early specimen collection, technical problems in analysis, etc.
9. A correct (positive) screening result was incorrectly interpreted or transmitted somewhere in the follow-up protocol.
10. The infant screened positive, but was not diagnosed or had a delayed diagnosis because of a failure to identify the physician or family or because the physician or family did not seek evaluation in a timely manner.

“Missing” a case does not necessarily imply fault with the screening system. For example, a missed case can occur as a result of a biological variant that a screening program cannot be reasonably expected to detect. A “miss” might also result from a disastrous disruption of part of the system (such as with the September 11 issues).

For purposes of this study, the cases of interest include children born in the United States, Puerto Rico or the US Virgin Islands with a clinical diagnosis of classic phenylketonuria, primary congenital hypothyroidism, galactosemia (any type if law is not restrictive), maple syrup urine disease, homocystinuria, biotinidase deficiency, classic congenital adrenal hyperplasia (saltwasting or simple virilizing) or sickle cell disease if the state where they were born screened for these disorders at the time of the child’s birth.

A previous study sought to ascertain missed cases of two disorders, phenylketonuria and congenital hypothyroidism, occurring in the United States through the end of 1983 (Holtzman et al. 1986). The cases included were identified by a telephone survey of state public health laboratory directors of neonatal screening programs. Forty-three missed cases of PKU and 33 missed cases of congenital hypothyroidism were reported. The reasons for these misses were categorized and included missed opportunities at each step in the screening process.

In another descriptive epidemiologic study conducted in a referral hospital in Chicago, during 1989-1991, three children with 21-hydroxylase deficiency CAH and seven with hemoglobinopathies had abnormal screening results but delayed clinical diagnosis due to a failure of the follow-up procedures (Listernick et al. 1992).

### **Justification for study**

Approximately four million babies are born each year in the United States. Each of these children currently undergoes screening for between three and twenty-one disorders. In the absence of a federal newborn screening program, separate programs have been developed by each state. Although all programs share the same basic structure, i.e. specimen collection, testing and follow-up, there are many differences in procedure between them. Each state decides which disorders to include in their screens, the procedures for sample collection and sample quality, the protocols for testing, the methods of record keeping and the procedures for follow up and notification.

Many states are also considering the use of tandem mass spectrometry (MS/MS) to analyze samples, thus potentially raising the number of disorders that can be screened to 30 or more. As programs become increasingly more complex, there are more opportunities for potential system failures that would allow children born with serious metabolic, endocrinologic, or hematologic disease to pass through the system undetected or untreated in a timely manner. It is important, therefore, to study and categorize cases of missed cases from newborn screening to determine their cause. Analysis of these data should highlight the areas of potential improvement of the screening system and may suggest ways to change the procedures that currently exist and possible ways to add new ones that will protect children from the consequences of these treatable conditions.

The previous study by Holtzman et al. (1986) was conducted as a telephone survey of 49 of the 50 newborn screening laboratory directors. The participants were asked for information regarding missed cases of PKU and congenital hypothyroidism, specifically; the stage in the screening process when the miss occurred, the size of the screening program, type of screening program (state, regional or private laboratory), length of time screening program had operated, age and health of infant when the initial specimen was collected, the results of initial and repeat testing, current health status and legal status of each case.

Our proposed study will extend the previous study by Holtzman et al to include missed cases in the United States occurring from 1984 to 2004. We will also expand the number of diseases examined to include not only phenylketonuria and congenital hypothyroidism, but also galactosemia, maple syrup urine disease, homocystinuria, biotinidase deficiency, congenital adrenal hyperplasia, and sickle cell disease. These diseases are conditions screened for by newborn screening programs in fifteen or more states. We also plan to search for missed cases using sources not used in the previous study such as follow up coordinators, metabolic clinics, legal records and parent advocacy groups.

It is our hope that the comprehensive study we plan to undertake will reveal opportunities for improvement by sharing information among states. These results may suggest ways in which policies and procedures may be changed to reduce the chance that an error can result in a missed case.

### **Intended/potential use of study findings**

We intend to publish the results of this study in a medical journal. We expect that our main audience will be pediatricians, metabolic specialists, genetic counselors, and follow up coordinators, public health laboratory directors and staff, state public health staff and federal public health staff. The data generated from this study should provide guidance to those directly involved in the screening process such as physicians, laboratory staff and follow up coordinators and also to those involved in quality control and procedure such as laboratory directors and public health staff. It should highlight the vulnerable points in the current system and suggest ways in which these problems could be avoided in the future by changes in procedures and policies. We hope that our data will better document how, where and why misses occur so states can continue to develop aggressive safeguards to prevent these devastating events from occurring in the future.

### **Study design**

We plan to solicit information about missed cases by distributing a data collection form that requests information related to a missed case of any of the diseases listed above in that occurred between 1984 and 2004. We will ask that they provide us only with information pertaining to the state, the child's birth month/year, disorder, the circumstances surrounding the miss and the medical and legal outcomes, including any decisions of the court. We will request that the information be provided to us without any personal identifiers such as names or addresses. After collecting the data, we will organize it based on disease, reason for miss and outcomes. Duplicate reports of the same case will be identified by comparing the state, the birth month/year, the disorder and the details of each case.

Since detailed records about missed cases are not routinely kept, we will collect this information from people involved in newborn screening such as screening laboratory staff, follow up coordinators, metabolic clinics and parent advocacy groups. A letter describing our study and our definitions of missed cases as well as a data collection form and a prepaid return envelope will be distributed directly to newborn screening laboratory directors, follow up coordinators and metabolic clinics in each state. This letter (see attachments 1a and 1b) will function as informed consent. Return of the letter by the participant will imply their consent. A simplified language version of the letter and data collection form will be given to parent advocacy groups (attachment 2), including The Coalition for PKU and Allied Disorders and Save Babies Through Screening, to distribute to their membership on their website and in their newsletter. This version of the letter also contains informed consent language. Return of this survey to the CDC by the participant will imply their consent. All surveys will be returned to the CDC by regular mail. We will also search published legal records to gather information about cases that have been litigated. Information about a few missed cases can also be derived from the medical literature.

After the data are collected we will identify cases reported more than once by matching information about state, disorder, birth month/year and the details of the case. If clarification of data is necessary we will not attempt to contact the participants. We will contact the state laboratory and request additional information. The data will be

organized based on disease, reason for miss and outcome as described in the planned tables/figures described below. Data relating to participant or the state and birth month/year of the child will not be included in any published report or presented in any form.

We have included the information regarding informed consent in the cover letter to the data collection form. We request a waiver of documentation under 45 CFR 46.117(c)(1). We feel that if a signature was required it would create a link between the participant and the data. This connection may result in legal liability should there be a breach of confidentiality. We also hope to reduce the anxiety of the participants by making the data collection anonymous. We indicate that by returning the data consent form, the participant is implying consent. We also request a waiver of informed consent for the cases we will be investigating under 45 CFR 46.116 (d). The research involves no more than minimal risk for these cases because the disease has been identified and the data will be collected anonymously and there will be no health risk to them. This waiver will not affect the rights and welfare of these cases. The research could not practicably be carried out without this waiver of informed consent because it would require identifying the cases as well as finding and asking permission of the parents. The study results will be published in a peer reviewed scientific journal.

## **Objectives**

1. To collect examples of missed cases of phenylketonuria, congenital hypothyroidism, galactosemia, maple syrup urine disease, homocystinuria, biotinidase deficiency, congenital adrenal hyperplasia and sickle cell diseases that have occurred in the United States from 1984 to 2004 in states that screened for the conditions at the time the infant was born.
2. To identify and categorize the causes of missed cases of each disease that occurred in the United States from 1984 to 2004.
3. To categorize the medical and legal outcomes of these missed cases.
4. To compare these results to those of the previous study to determine whether the causes of missed cases have changed in the last 18 years and to identify new causes.
5. To document changes in policies and practices instituted as a result of investigations into missed cases within institutions and compile these into lists of steps that can be taken to improve the newborn screening system throughout the United States.
6. Look for best practices in timely identification of missed cases and their causes

## **Hypotheses or questions**

1. What are the causes of missed cases in the newborn screening process?
2. What are the consequences of a missed case for the patient and society?
3. What can be done to prevent missed cases in the future?

## **General approach**

Our approach to this study will be descriptive. We will collect data on past events and categorize it

## **Procedures/Methods**

### **Design**

#### **How study design or surveillance system addresses the hypotheses and meets objectives**

Our primary objective is to obtain as exhaustive a listing of missed cases as possible through ascertainment of multiple sources of information. To avoid duplication of reported cases, a central database will be maintained with information on state, birth month/year, diagnosis, cause of miss, and outcome. Cases will be recorded even if definitive information about causes of a “miss” is not known. More than one cause may be attributed, and there may be differences of opinion among those involved. The outcomes of missed cases must be compared with outcomes that occur among treated cases in order to ensure that only adverse outcomes due to missed cases are recorded. This will require consultation with experts. Program managers will be consulted on the third hypothesis to identify changes in policies and procedures that were put in place in specific states in response to missed cases. An attempt will be made to identify “best practices” that could be shared to minimize the risk of missed cases elsewhere.

#### **Audience and stakeholder participation**

We expect that our main audience will consist of pediatricians, metabolic specialists, genetic counselors, and follow up coordinators, public health laboratory directors and staff, state public health staff and federal public health staff. The data for this study will be collected from public health labs and follow up coordinators, metabolic clinics as well as parent advocacy groups. Each group may express views and concerns during the information collection process. Families of patients will not be contacted and will not be involved in any aspect of the study.

#### **Study time line**

We hope to begin collecting data early in 2006. We anticipate it will take approximately 6 months to complete the data acquisition and another 6 months to analyze the data and prepare a paper for publication.

## **Study Population**

### **Description and source of study population and catchment area**

The cases used in this study will be those that occurred in one of the 50 United States, District of Columbia, US Virgin Islands, or Puerto Rico. We will not make any geographical or population based inferences.

**Case definitions** Clinical diagnoses of classic phenylketonuria, congenital hypothyroidism, classic galactosemia, maple syrup urine disease, homocystinuria, biotinidase deficiency, classic congenital adrenal hyperplasia, or sickle cell disease will be used. If a doubt exists about the diagnosis of a case, we will consult with metabolic experts to determine whether, in their opinion, the case has been properly diagnosed, based on available information.

A “missed case” is defined as a case of a screened metabolic disorder identified outside of the newborn screening system (i.e. clinically) or identified through newborn screening but with a delay in diagnosis. It includes cases where:

1. Blood spot was never collected, collection was delayed, or the blood was collected incorrectly;
2. Blood specimen was not received by screening lab, so screening test was not performed;
3. False negative laboratory screening test result for any of a number of potential reasons, including normal biological variants, early collection of specimen, improper cut-off value, as well as mishandling of specimens;
4. Screened positive but infant was not diagnosed or had a delayed diagnosis because of a failure to locate the patient, failure to identify the physician, failure of the physician or family to seek diagnostic evaluation in a timely manner, failure of laboratory to perform confirmation test, failure of laboratory to perform the correct test or provide appropriate test results.

### **Case inclusion criteria**

Persons born in the United States, Puerto Rico, or the US Virgin Islands afflicted with a clinical diagnosis of classic phenylketonuria, congenital hypothyroidism, classic galactosemia, maple syrup urine disease, homocystinuria, biotinidase deficiency, classic congenital adrenal hyperplasia, or sickle cell disease are eligible for inclusion if their condition was screened for in their state of birth at the time they were born.

### **Case exclusion criteria**

Patients who were diagnosed in a timely manner by the standard protocol of the newborn screening program in the state where they were born will be excluded, as will those whose conditions were not part of the state’s routine screening panel when they were born.



### **Participant inclusion criteria**

Study participants will be newborn screening laboratory staff, follow-up coordinators, employees of metabolic clinics and members of parent advocacy groups with potential knowledge of missed cases.

### **Estimated number of participants**

We estimate that the number of participants will be about 250. This will include laboratory directors, follow up coordinators, metabolic clinics and parent advocacy groups in each of the fifty states, Washington DC, Puerto Rico, or the US Virgin Islands.

### **Variables/interventions**

#### **Variables**

The variables we will address in this study are:

1. Disorder – which disorder does the patient have
2. Reason for miss – which steps in the screening process led to a missed or delayed diagnosis

We plan to evaluate the circumstances for each missed or delayed diagnosis and assign each case to one or more categories. We anticipate that the main categories will be: specimen collection, specimen transport, laboratory procedures, health provider practices, follow-up and biologic variants. These categories can be further subdivided to classify each miss (see below). We also plan to categorize the cases based on the legal outcomes. We predict these categories will be: active, pending, settled out of court, no legal action, and unknown.

#### **Reason(s) for Missed or Delayed Diagnosis:**

##### **Specimen collection**

- No specimen collected
- Transfer to another hospital, no specimen collected
- Delayed first specimen because of home delivery
- Delayed first specimen because NICU infant
- No satisfactory specimen collected (initial specimen invalid)

##### **Specimen Transport**

- Specimen not shipped in a timely manner
- Specimen delayed in transport
- Specimen lost in transport

##### **Laboratory procedures**

- Delay in running analysis
- Measurement error - Chemistry
- Measurement error - Instrument

- Misinterpretation of result
- Improper cutoff used
- Mishandling of specimen
- Wrong specimen assayed
- Abnormal value not recorded
- Misread identification number
- Clerical error
- Lack of notification of physician

#### **Follow up**

- No follow-up
- Second specimen requested but not received
- Follow-up coordinator unable to locate physician of record
- Follow-up coordinator unable to locate family of patient

#### **Health provider practices**

- Physician of record fails to notify patient or other physician of result
- Physician does not ensure that patient is retested in timely manner
- Provider does not prescribe treatment
- Parent refuses retesting or treatment

#### **Biological variants**

- Sample collected too early
- Late onset variant not detectable in first few days
- Form of disorder not detectable through assay used by screening laboratory

#### **Study instruments, including questionnaires, laboratory instruments, and analytic tests**

To obtain data for our study we will distribute a letter explaining the reasons for our study and measures, such as secured file cabinets and electronic records, that we will use to protect the information. We will also explain our positions and expertise, the purpose of our study and its intended use. The letter will include a brief data collection sheet requesting information (without personal identifiers) on missed cases. There will be three forms of this letter. One will be distributed by regular mail to state newborn screening laboratory directors and follow up coordinators. This form will, in addition to the content described above, also contain information about informed consent (Attachment 1a) As requested by the OMB, this version of the survey will have a separate coversheet that has the preprinted name of the state to which it was sent, and asks the recipient to check one of the two following choices: “We are not aware of any cases of delayed diagnosis (missed cases) between the years 1984 and 2004”. or “We have \_\_\_\_ (#) of cases of delayed diagnosis (missed cases) to report”. The form asks the recipient to “return this page even if you have no cases to report”. Collection of this information will allow us to contact non-responding state newborn screening and follow-up programs to increase the response rate. Attachment 1b is for metabolic clinics. It is

the same as Attachment 1a except that it does not have the separate coversheet described above.

Return of the data collection form included with these letters will imply consent. If we do not get a response from the first mailing to the state newborn screening and follow-up programs, we will send another copy to the non-responders. A follow up phone call will be made to those who still do not respond to the second mailing (see attachment 3). Phone calls may be needed to clarify some responses, however, we will not attempt to contact the participant, instead we will just confirm details with the state lab.

We will also provide another form of this letter with informed consent (Attachment 2) to selected parent advocacy groups: The Coalition for PKU and Allied Disorders and Saving Babies through Screening. This letter is at the eighth grade reading level. We will ask these organizations to electronically distribute the letter and data collection form on their websites and newsletters to their members. Parents with information about missed cases are instructed to fill out the data collection form and return it to the CDC by regular mail.

### **Data Handling and Analysis**

#### **Data analysis plan, including statistical methodology and planned tables and figures**

We plan to analyze data using descriptive statistics.

Planned tables and figures:

Y-axis	X-axis
Table 1: Category of miss	Disease, Total # misses (all diseases), % total misses
Table 2: Category of miss and further subdivisions	Number of cases
Table 3: Category of legal status	Disease, Total #, % total misses

### **Data collection**

#### **Information management and analysis software**

Microsoft Excel will be used to manage data.

#### **Data entry, editing and management, include handling of data collection forms, different versions of data, and data storage and disposition**

The data collected will be responses to our written query. We will enter the data into a password protected excel file based on the disease, category of miss and medical/legal status. Electronic data will be stored in a protected folder on a physically secured

Windows 2000 file server running under Microsoft Active Directory System. The data will be stored in a locked file cabinet or protected electronic file organized by the state in which the case occurred. We will restrict access to this file to study staff and it will be password protected. We will protect the confidentiality of the patients by requesting that our informants only provide us with the details and the month/year and state of the case but not patients' names. In order to remove the link between the informant and the data, we will destroy the envelope used to return the data collection form. Upon completion of the study, Harry Hannon will store the records in a locked file cabinet and the computer data in a secure electronic file.

### **Quality control/assurance**

#### **Bias in data collection, measurement and analysis**

Our participants may bias the reporting of the information, in that missed cases leading to more severe outcomes cases that are litigated are more likely to be reported. Laboratory directors may be unaware of cases that occurred before they arrived or may be reluctant to relate information for reasons related to personal liability. Additionally, most states do not have a means to identify potentially missed cases and may be unaware of them.

#### **Intermediate reviews and analyses**

The authors of this study will meet periodically to discuss the data and evaluate them prior to assessing the final results.

#### **Limitations of study**

We will not be able to document all missed cases that have occurred during the study period. Therefore, findings such as average number of missed cases per year will be underestimates. We will report the causes of missed cases that were reported to us, which may differ from missed cases that were not reported. We expect that the findings will highlight the extent to which newborn screening programs succeed in identifying nearly all infants born with serious disorders that are currently tested for. The findings may also call attention to the need for continuous quality improvement to ensure that all preventable missed cases are prevented.

We are also aware that by providing us with information relating to missed cases, the laboratory directors and other participants place themselves at risk for liability. To alleviate this risk, we applied for an Assurance of Confidentiality from the CDC. The Confidentiality Review Group, however, did not grant an Assurance to this study.

#### **Notifying participants of study findings**

The informants will not be offered preliminary findings or individual data. We will provide aggregated results in scientific presentations and in a published paper. The cases and their families will not be contacted.

**Disseminating results to public**

The results of this study will be published in a medical journal such as Pediatrics. This widely read journal should be accessible to the physicians and public health workers to whom we expect this information will be relevant. The work will also be presented at scientific meetings related to newborn screening and can be discussed with public health laboratories during routine quality control assessments.