2018 Blood Spot Newborn Screening Program Follow Up Activities, Data and Education Report

The Iowa Newborn Screening Program (INSP) is administered by the Iowa Department of Health (IDPH) in collaboration with the University of Iowa State Hygienic Laboratory (SHL) to provide testing and the Stead Department of Pediatrics at the University of Iowa Stead Family Children's Hospital to provide follow up services.

Iowa Newborn Screening Dried Blood Spot Program Report
Follow Up Activities, Data and Education

The following report describes the purpose, processes and activities of the short term and long term follow up program component of the Iowa Newborn Screening Program. There is an appendix listing terms and definitions that readers may wish to refer to while reviewing this document. Program staff members are willing to answer any questions the reader might have. Contact information is provided at the end of the report.

Of note, this report is written and submitted in 2019 so that we have complete data for calendar year 2018.

Why Do Blood Spot Newborn Screening?

Blood spot newborn screening is done to identify babies that are at increased risk of having one of the disorders that we screen for. These disorders can be time critical – meaning that the baby has just a few hours to a day or two before an untoward outcome occurs. If screening and follow up doesn't occur in a timely manner, the baby could pass way or have permanent disabilities. The same outcomes could occur if the baby isn't screened at all. It's also important to know that babies can look and act perfectly healthy but still have one of these disorders; which highlights another reason why screening is so important. It is estimated that at least 12,000 babies are positively impacted by newborn screening efforts in the United States each year. Newborn blood spot screening saves babies lives – it's as simple as that.

An Overview of the Laboratory and Clinical Process of Newborn Screening in Iowa

Local Hospital - At 24-48 hours of age, a few drops of blood are taken from a baby's heel to perform the newborn screening test. These drops are placed on a card that contains information about the baby, the mother, and the blood sample. This is called the dried blood spot card.

Courier - The card is picked up at the local hospital by a courier service and is driven to our newborn screening laboratory in Ankeny. Cards from throughout the state arrive in the laboratory around 9:00 pm each night (seven days a week).

Newborn Screening Laboratory - Once the card arrives in the lab, quality checks are performed and the data from the card is entered into a database by data entry staff. Laboratory staff start the testing process soon after the card arrives at the lab. A laboratory staff member calls and emails the short term follow up staff with any abnormal endocrine or metabolic results so that immediate (and sometimes life-saving) action can occur. These results, along with testing results of other screened disorders, are entered into a database.

Short Term Follow Up/Medical Consultant – Short term follow up staff are informed of abnormal testing results. This is called a "presumptive positive" or "borderline" result. Presumptive positive means that the screening test for the disorder is abnormal and requires further action. It does not mean that the baby has that disorder. That is why the short term follow up component of the newborn screening program is crucial. Follow up staff help local care providers through the process of determining if a screening result is real (ie a "true positive") or a "false positive" (baby is not affected with a disorder/disease). Follow up staff inform the local hospital (if baby is still an inpatient) or local provider (if baby has gone home) of the abnormal results. Recommendations are provided to the primary care provider (PCP) verbally and then followed by a fax and/or email with the same information as per protocol. Education regarding the disorder that screened positive is also provided. A medical consultant (a MD who specializes in one of the disorders that we screen for) will also review abnormal results and assist staff and local providers when necessary. Sometimes it is recommended to repeat the newborn screen and/or to get additional specialized testing called confirmatory testing. The follow up staff review the tests recommended with local providers (and sometimes local laboratories too) and keep in touch with the PCP to make sure that these tests are obtained. Once the tests are obtained, follow up staff remain in communication with the local hospital or provider to obtain the results of further testing. Once these results are in, follow up staff review the results with the medical consultant to see if further action is necessary. Sometimes no further action is necessary and the case is closed as a "false positive". If the specialized testing is reviewed and does not appear to be normal, then a referral is made to a specialist so the baby can be further evaluated.

Long Term Follow Up – Referrals are made to specialized physicians and allied health care providers when a newborn screen is abnormal and/or a disorder is confirmed. Sometimes, the long term follow up staff recommend additional testing or decide to start treatment. For instance, if a baby is "presumptive positive" for PKU, a referral is made to a metabolic genetics center. Confirmatory testing is performed if not yet completed or the results of the confirmatory tests are reviewed. If it is determined that the baby has PKU, the parents are educated about the disorder and how to care for the child. This includes information not only about the disorder, but extensive education on how to manage the special diet required to treat this condition is given by the metabolic dietitian. The baby diagnosed with PKU will need to follow this special diet and will need to been seen by metabolic specialists for their lifetime.

Disorders Screened for in Iowa

AMINO ACIDEMIAS AND UREA CYCLE DISORDERS

- (ASA) Argininosuccinic aciduria*
- (CIT) Citrullinemia, type 1 or ASA Synthetase Deficiency*
- (HCY) Homocystinuria (cystathionine beta synthetase)*
- (MSUD) Maple Syrup Urine Disease*
- (PKU) Classic Phenylketonuria*
- (TYR-1) Tyrosinemia, type I*
- (ARG) Argininemia**
- (BIOPT-BS) Defects of biopterin cofactor biosynthesis**
- (CIT-II) Citrullinemia, type II**
- (BIOPT-REG) Defects of biopterin cofactor regeneration**
- (H-PHE) Benign hyperphenylalaninemia**
- (MET) Hypermethioninemia**
- (TYR II) Tyrosinemia, type II**
- (TYR III) Tyrosinemia, type III**

ORGANIC ACIDEMIAS

- (GA-1) Glutaric acidemia type I*
- (HMG) 3-Hydroxy 3-methylglutaric aciduria *
- (IVA) Isovaleric acidemia*
- (3-MCC) 3-Methylcrotonyl-CoA carboxylase*
- (Cbl-A,B) Methylmalonic acidemia (cobalamin disorders, vitamin B12 disorders)*
- (βKT) βeta-Ketothiolase*
- (MUT) Methylmalonic Acidemia (methylmalonyl-CoA mutase)*
- (PROP) Propionic acidemia*
- (MCD) Holocarboxylase synthase*
- (2M3HBA) 2-Methyl-3-hydroxybutyric aciduria**
- (2MBG) 2-Methylbutyrylglycinuria**
- (3MGA) 3-Methylglutaconic aciduria**
- (Cbl-C, D) Methylmalonic acidemia with homocystinuria**
- (MAL) Malonic acidemia**

FATTY ACID OXIDATION DISORDERS

- (CUD) Carnitine uptake defect (Carnitine transport defect)*
- (LCHAD) Long-chain L-3 hydroxyacyl-CoA dehydrogenase*
- (MCAD) Medium chain acyl-CoA dehydrogenase*
- (TFP) Trifunctional protein deficiency*
- (VLCAD) Very long-chain acyl-CoA dehydrogenase*
- (CACT) Carnitine acylcarnitine translocase**
- (CPT-Ia) Carnitine palmitoyltransferase type I**
- (CPT-II) Carnitine palmitoyltransferase type II**
- (GA2) Glutaric acidemia type II**
- (MCAT) Medium-chain ketoacyl-CoA thiolase**
- (M/SCHAD) Medium/Short chain L-3-hydroxyacyl-CoA dehydrogenase**

ENDOCRINE

- (CAH) Congenital adrenal hyperplasia *
- (CH) Primary Congenital hypothyroidism *

HEMOGLOBINOPATHIES

- (Hb SS) S,S Disease (Sickle Cell Anemia)*
- (Hb S/C) S,C Disease*
- (HB S/βTh) S, βeta-thalassemia*
- (Var Hb) Variant hemoglobinopathies **

OTHER

- (BIOT) Biotinidase deficiency *
- (CF) Cystic Fibrosis *
- (GALT) Classic Galactosemia *
- (GALE) Galactoepimerase deficiency **
- (HEAR) Hearing loss*

* Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) Recommended Uniform Screening Panel - Core Panel

** SACHDNC Recommended Uniform Screening Panel - Secondary Targets - Screening for the Core Panel of disorders may show information about secondary conditions (by-products of mandatory screening)

Disorders on the SACHDNC recommended panel that we do not screen for:

(DE-RED) 2,4 Dienoyl-CoA reductase deficiency**;(GALK) Galactokinase deficiency**; (SCAD) Short-chain acyl-CoA dehydrogenase**; (IBG) Isobutyrylglycinuria**, Pompe, Mucopolysaccharidoses I (MPS 1), Adrenoleukodystrophy (ALD), and Spinal Muscular Atrophy (SMA).

Screens Submitted (Calendar 2018)

There were 39,879 newborn screening cards submitted to the newborn screening laboratory for testing (37,394 initial screens and 2,485 repeat screens).

Borderline and Presumptive Positive Cases for CY 2018

Disorder	Borderline/ Indeterminate	Presumptive Positive
Biotinidase	N/A	2
Cystic Fibrosis	53	4
Endocrine Disorders		
Congenital Adrenal Hyperplasia	345	22

Congenital Hypothyroidism	708	28
Galactosemia	0	0
Hemoglobinopathies	N/A	16
Metabolic Disorders	N/A	471
Severe Combined Immunodeficiency		
Indeterminate due to Prematurity	74	
Indeterminate Other	77	
Presumptive Positive		18
TOTAL	1026	651

Confirmed Cases for Calendar 2018

Confirmed cases are counted in the year that they were confirmed, not necessarily the year the baby was born.

Primary Conditions

Newborn screening is designed to find disorders that are designated as primary disorders on the Recommended Uniform Screening Panel (RUSP). The confirmed cases listed below are only those disorders that have been designated as primary disorders on the RUSP.

Disorder	**Cases Confirmed**
Biotinidase Deficiency (metab)	0
*Cystic Fibrosis (CF)**	4
Endocrine Disorders	
Congenital Adrenal Hyperplasia	3
Congenital Hypothyroidism	26
Galactosemia (metab)	0
Hemoglobinopathies	
Sickle Cell Disease	10
Non-Sickling Disease	7
Metabolic Disorders	
Amino Acid Disorders	3
2 PKU; 1 MSUD	
Fatty Acid Oxidation Disorders	8
5 MCAD; 1 SCAD; 2 VLCAD	
Organic Acidemias	1
Proprionic Acidemia	
SCID	2
TOTAL	**64**

Secondary Conditions or Incidental Findings

Disorder	Number Confirmed
Carriers of Various Metabolic Disorders/Incidental Findings	26
Cystic Fibrosis Carriers	38
Cystic Fibrosis Related Metabolic Syndrome (CRMS)*	6
Hemoglobinopathy Trait	544
SCID-Secondary/Incidental Findings	2
TOTAL	**616**

An Interesting Case

There are two cases we would like to highlight this year. We started screening for severe combined immunodeficiency (SCID) in June, 2013. During this time, we have identified babies that have t-cell lymphopenias (which is beneficial for them) but not "classic" SCID. The incidence rate is approximately 1:70,000 – 100,000 babies born, so in theory we should have identified a baby with classic SCID in our our second or third year of screening (2015-2016). In the last quarter of 2017 (confirmed in 2018), we identified a baby who was presumptive positive for SCID and requested that confirmatory testing be done. Confirmatory testing was concerning for significant t-cell lymphopenia/SCID. The baby was completely missing one of the common immunological markers, CD-8. The baby was evaluated and the decision was made to treat him like he had SCID while they were waiting on further genetic testing. He was started on infection control prevention as well as anti-viral, anti-fungal, and anti-bacterial medications and admitted to the hospital. Hospital personnel began the preparations to perform a bone marrow transplant, including testing family members to see if they were a suitable match. When taking the family history, the genetic counselor found out that this baby had a fraternal twin brother and that there was a family history of multiple deaths of children under the age of 2 on both sides of the family. It was also determined that the parents were related to each other.

We re-reviewed the twin brother's (Baby B) newborn screening result and found that it was reported as normal. The newborn screening lab was contacted and the screen was performed two more times and had the same normal screening results. We were concerned that we had missed a SCID case. However, the genetic testing results came back noting that Baby A had a ZAP-70 mutation. This is not a classic SCID mutation and is not typically identified through newborn screening. We were relieved that we didn't miss a true SCID case.

Meanwhile, the transplant staff was performing testing of Baby B to see if he could be a donor for his brother. The test results were shared with our medical director, who is also a geneticist. Based on the test results, she suspected these twins were not fraternal twins as had been reported, but identical twins. Fraternal twins typically each have their own placentas, which these twins did. Identical twins usually share a placenta. However, approximately 10% of

identical twins can have their own placentas. Testing was done on Baby B that day to determine if he might have SCID as well. Unfortunately for Baby B, his testing was markedly abnormal and identical to his twin brother. Therefore, he needed a bone marrow transplant as well.

Neither parent was deemed a good donor for transplant, so the medical team looked to a national cord blood repository to see if they could find a better match. This was made more difficult by the fact that the family was from a minority population that does not typically donate human tissues. One match was found, but there wasn't enough blood to transplant both babies. This presented an ethical dilemma. Which baby would be transplanted? Do you transplant Baby A because he has already been started on the treatment regime? Ultimately, they mixed the cells from the cord blood with the father's cells and transplanted both babies. The transplant was successful and the babies did well. It was a success story.
I am sad to report that in early 2019, Baby A passed away after an acute medical event nearly a year post transplant. The cause of his death was not determined. Thankfully, Baby B continues to do well.

This story illustrates the benefits of screening and treatment, the limitations of screening, the importance of obtaining a family history, the importance of reviewing test results carefully, and the ups and downs of clinical care and life in general.

False Negative Case - 0

When a baby is diagnosed with a disorder that we screen for, but the screening was reported as negative (normal), we refer to it as a "false negative". The program has to rely on individuals to report false negatives to the program because there is no other way to ascertain them. Often, we hear of these cases from the baby's PCP or through specialists. Although we strive to not have any false negatives, it is important to remember that newborn screening is indeed a screening test, *not* a diagnostic test. False negatives are a reality of newborn screening, particularly when the markers used to screen for risk are not fool proof such as in cystic fibrosis newborn screening. As an example, The medical community knew before we started screening for cystic fibrosis that there would be a minimum of a 3-4% false negative rate (some people will quote a 10% false negative rate). Immunoreactive trypsinogen (IRT), the marker used for cystic fibrosis newborn screening, does not have the sensitivity or specificity needed to be 100% accurate. However, it still is the best marker we have at our disposal to screen for cystic fibrosis.

Lost to Follow Up/Against Medical Advice – 27

Lost to Follow Up - 20

There were 20 cases categorized as lost to follow up. Lost to follow up is when a baby cannot be found by the baby's PCP or by the program (such as when a phone is disconnected and/or certified mail is returned) or when parents are contacted but do not bring the baby in for recommended repeat screen or confirmatory testing despite multiple attempts to get them to do so. There are some common reasons why lost to follow up occurs. Approximately half of the cases categorized as lost to follow up had an initial poor quality screen (not enough blood to do the testing, sample was layered or clotted, etc.). This is why it is so important that the first screen collected is a good quality sample.

There were also a few babies that were lost to follow up where their initial screen was deemed "early collection". Early collection is when the screen is collected prior to 24 hours of life. In these cases, the family chose to leave the hospital shortly after birth. As per protocol, the birthing center collected the screen before they left the hospital. However, when it's collected before 24 hours, a repeat screen needs to be collected *after* the 24 hour mark. The two screens together make a valid screen. In these cases, the parents did not bring the baby back in for their repeat screen.

We also had two babies move to another state or another country before the screening process could be completed. Therefore, further follow up was not able to be completed.

Before we close the case as lost to follow up, the PCP and the program have made multiple attempts by phone, mail and certified mail to reach the families. Often, the phone is disconnected and/or the mail cannot be delivered.

Against Medical Advice (AMA) - 7

We had 7 cases that were categorized as "against medical advice". These are situations where the PCP and/or program personnel have had an informed, educational conversation with the family about why they are recommending further testing as well as the potential ramifications/consequences if further testing is not done. In these cases, the parents still refuse further testing after being appropriately counseled about what might happen if they do not do further testing. Examples of our AMA cases this year are varied. One parent refused to take their baby to see a specialist. There were two instances where the initial screen was an early collection and an abnormality was seen on the screen. The parents decided not to pursue any further testing. One baby had an abnormal screen for cystic fibrosis. Education on the disorder was provided by the provider. There were 3 attempts to perform a sweat test, but the quantity of the sample was insufficient. The baby was not brought back for return appointments.

Poor Quality Screens – 457 – 1.3%

There are various reasons that newborn screening samples are considered to be "poor quality". The sample could be contaminated, there isn't enough blood within the circles on the card, the blood spot is layered or clotted, the blood spot card has expired, etc Screens are rejected when lab staff determines that the accuracy of the test results would be compromised for any of the reasons listed above.

Currently, the state percentage for poor quality samples is 1.3%. Compared to many other state programs, 1.3% is an acceptable number. However, the INSP would like the state average to be > 1.0%. The program provides technical assistance/education to reduce the percentage of poor quality screens in our state. It is imperative that a good quality screen be collected the first time. When it isn't, the baby's health could be impacted. Finally, poor quality screens negatively impact timeliness in newborn screening.

Refusals -95

On July 1, 2015, the Iowa Department of Public Health instituted a new rule in the Iowa Code that reads as follows: that ITEM 6. Amend paragraph **4.3(2)"b"** as follows:

b. Refusal of screening. Should a parent or guardian refuse the screening, said refusal shall be documented in the infant's medical record, and the parent or guardian shall sign the refusal of screening form. The birthing facility or attending health care provider shall submit the signed refusal of screening form to the central laboratory within six days of the refusal. The birthing facility or attending health care provider may submit refusal forms via the courier service established for the transportation of newborn screening specimen collection forms.

Reason for Refusal Data

- 17 forms were blank
- 20 prefer to screen later – 94.7% of these screens were obtained (only 1 did not). On average, these infants were screened on day of life 8
- 4 were transferred; 100% of babies were screened
- 28 said the screen was not necessary and/or it was a personal choice; only 2 of these babies went on to be screened on an average of day of life 13
- 6 said that their baby was healthy and they would monitor their health; none were screened
- 2 stated cost was the reason they refused; none were screened

- 5 cited religious beliefs; 2 cases went on to be screened on an average of day of life 4. There was no program intervention
- 11 said that there was no family history of any of these disorders in their family and/or that their other children were healthy/normal. None of these babies were screened
- 2 stated that they did not want their baby's heel pricked; none of these babies were screened

There were 37,641 babies born in Iowa that were eligible to be screened. This is a rate of refusal of 0.25% and is slightly up from 0.20% last calendar year.

Genetic Counseling

Genetic counseling is offered to all patients who have abnormal test results through the newborn screening process. The counseling is completed either face to face or over the phone. Genetic counseling is performed for the conditions we screen for. The only exception is congenital hypothyroidism. Most cases of congenital hypothyroidism are sporadic, which means they occur in people with no history of the disorder in their family. When inherited, the condition usually has an autosomal recessive inheritance pattern, which means both copies of the gene in each cell have mutations.

Quality Improvement Activities

Baby Matching

Baby matching is the process of "matching" a newborn screening result or an official NBS refusal form with birth certificates to make sure that all babies born in the state have been screened. Matching is completed by the IDPH and then a list of babies who do not appear to have a NBS are sent to follow up staff to reconcile. If NBS results cannot be found, the birthing hospital is contacted to see if a screen was collected. If not, the baby's PCP is notified and asked to obtain the screen as soon as possible. Often we find that a baby has been screened in a bordering state. On occasion we find that a baby did not get screened. This process reduces the number of babies who do not get screened. Initially, baby matching was done about every 30 days. We now perform baby matching each week.

Baby Matching Quality Indicators

- 430 Baby Matching Cases – these are babies who did not match by the IDPH process or who had a refusal form
- 90 cases were identified through the matching process where the sample simply hadn't gotten to the newborn screening lab yet. This began to happen when we moved to doing baby matching each week.
- 41 cases were home births identified through baby matching after infant was 3 months of age. No further action was taken on these cases.

- 122 baby matching cases were screened either in Iowa and did not match for various reasons or they were screened out of state. Sixty two of these babies were screened in Iowa; 1 baby was screened in Illinois; 14 babies were screened in Minnesota; 4 babies were screened in Missouri; 7 babies were screened in Nebraska; 30 were screened in South Dakota and 4 were screened in Wisconsin.
- 2 infants were identified through baby matching and were deceased or went home with hospice care so no further follow up was completed.
- 123 baby matching cases were closed out as refused; 70 of these signed a refusal form and 53 were contacted by the program and did not return a refusal form.
- 18 baby matching cases were screened after our intervention through the baby matching process.
- 4 cases remain open at this time.

Timeliness/Sample Quality

The lab sends birthing facilities and midwives monthly or quarterly reports (based on volume) that provide information about timeliness and sample quality . These parameters are monitored, and the quality control officer will reach out to facilities or individuals if we see values that are below our threshold. We provide technical assistance over the phone. If this doesn't rectify the problem, we ask to do a site visit. We find this often improves performance. As an added benefit, relationships are built between the program and facility staff. People are more likely to reach out if they know you and if they know they will not be judged for asking questions.

Case Closure Meetings

Case closure meetings now occur for CF, hemoglobinopathies, metabolic and SCID. The case closure meetings include the medical consultant, short and long term follow up staff and disorder specific lab staff. The frequency is dictated by the disorder. Metabolic case closure occurs monthly, CF and hemoglobinopathies every 6-8 weeks (volume dependent) and SCID case closure During this meeting , cases are reviewed and discussed. We find that some cases can be closed and that some cases are still pending. Education on disorders is also provided from the clinical staff. This process allows us to ensure that cases are closed in a timely manner and that NBS cases are not lost during the follow up process. On occasion, cases are closed prior to the scheduled case closure meeting. If they are closed prior to the meeting, we still review the case with the entire team. We do not do a case closure meeting for the endocrine disorders as they are closed very quickly and there really is no need to meet.

Protocols and Educational Materials

Protocols and educational materials for each disorder are reviewed on a yearly basis, but can also be reviewed and altered on an as needed basis. Often, case experience brings an issue to light and changes to the protocols need to be made. Because this is a large undertaking (over 120 protocols and related educational material), follow up staff work on protocols all year long.

Cystic Fibrosis (CF) Timeliness Initiative

We officially began our work on a timeliness initiative for CF NBS on 1/1/2018. One of our follow up nurses, Melody Hobert-Mellecker was the primary person working on this project. It is now known that very early nutritional intervention improves outcomes for patients with CF. A data analysis performed by the Cystic Fibrosis Foundation discovered that in the US, the average time from presumptive positive NBS results to the baby actually getting a sweat testis 45 days. This is too long for optimal outcomes. We reviewed our CF NBS algorithm and determined that we could potentially reduce the time from when the PCP was notified of an abnormal CF NBS result to when the baby gets a sweat test by enabling the referral process. Coordinating the appointment with the CF Center and the family was burdensome for the PCPs and often didn't get completed until 8-10 days after the PCP was notified of the abnormal result. Our plan is to ask permission of the PCP to contact the local CF Center of the case and then have the CF Center reach out to the family to schedule the sweat test/appointment. The PCP knows that they have 24 hours to contact the family prior to the CF Center reaching out to the family. We are hopeful that this reduces time to sweat test and improves outcomes. We will report on the outcome of this project in the CY2019 Annual Report

Database

The INSP is in the middle of switching over to an integrated database for the three newborn screening programs called the Iowa Newborn Screening Information System (INSIS). We continue to work on identifying needs as OZ Systems continues to build the blood spot newborn screening module

Laboratory Information System – OpenELIS

The NBS laboratory and follow up continue to work on a new laboratory information system. OpenELIS will be the vehicle that reports results to INSIS and provides HL-7 reporting to hospitals. This is a long range project and we anticipate working on this project at least until the end of 2019.

Projects

NewSTEPs Repository

Confirmed cases are entered into this national repository by our follow up staff. At this time, NewSTEPS is still working on case definitions for hemoglobinopathies and SCID, so any confirmed cases of these disorders are not currently in this repository.

Other Projects and Relevant Information

Inborn Errors of Metabolism Collaborative Research Project – this is a natural history, consented patient registry for those patients with metabolic conditions. Emily Phillips is the research coordinator.

Clinical Trials/Patient Registries – the metabolic and lysosomal storage clinical teams participate in various clinical trials being conducted at the University of Iowa Stead Family Children's Hospital for these disorders.

NIH Grant – Dr. Beth Tarini is the Principal Investigator on a NIH funded grant that is looking into the potential harm of false positive newborn screening results, This is a five-year grant and includes the Iowa and Minnesota Newborn Screening Programs. Key personnel in Iowa include Dr. Amy Calhoun, Carol Johnson and Emily Phillips. We anticipate starting to work on this grant in 2019.

Educational Activities

The newborn program is dedicated to education. Our scope of education includes the education of parents, PCPs (including midwives) the birthing centers, the public, advocacy groups and the legislature. We have found that education is key to understanding the processes, the disorders we screen for, and compliance with recommendations. We also believe that continuing education of our staff is key, as newborn screening is an ever-changing activity and you must actively participate in education in order to keep up with the changes and do the job to the best of your abilities.

As mentioned above, we provide technical assistance and education to providers and facilities upon request, and we provide education daily when carrying out follow up activities

Program staff continue to be active as "vendors" at public events such as community baby showers and health fairs. We also attend professional meetings where our NBS audience will be present. These meetings include the Statewide Perinatal Meeting, the state AWONN meeting, the Iowa Healthcare Collaborative, and various meetings of pediatricians and family medicine physicians.

.MD Consultants often do Grand Round presentations on NBS disorders in various departments at University Hospitals and will also do presentations at other facilities when requested. Our MD consultants do platform and/or poster presentations of NBS related information at disorder specific national meetings, such as the North America Cystic Fibrosis Conference.

Program personnel are very active on the national stage with poster, platform, and roundtable presentations at newborn screening meetings. Several members of the program have also been asked to moderate sessions at the national meeting.

Follow up staff are actively engaged with NBS education of medical students, residents and fellows that rotate through the Division of Medical Genetics. Presentations and lectures on NBS are given by the medical consultants and follow up staff at the Carver College of Medicine at the University of Iowa and in residency programs throughout University of Iowa Hospitals and Clinics. Presentations were also given this year to the Unity Point Family Medicine Residency Program in Des Moines. Follow up staff give a presentation on NBS to each new orientation class of NICU nurses at University of Iowa Hospitals. Program staff also participate in Genetics Journal Club in the Division of Medical Genetics and present NBS based articles.

Other Notable Items

Dr Mary Beth Fasano, our SCID medical consultant, served as the Secretary-Treasurer of the American Academy of Allergy, Asthma and Immunology and will advance to President-Elect of this national organization in March of 2019.

Summary

Please feel free to contact the Iowa Newborn Screening Program Follow up for further information or if you have any questions. Our contact information is listed below.

Contact Information

Iowa Newborn Screening Follow Up	319-384-5097 iowanewbornscreening@uiowa.edu
Carol Johnson Iowa Newborn Screening Follow Up Coordinator	319-356-7248 carol-johnson@uiowa.edu

Appendix A

Terms and Definitions Used in Newborn Screening and in this Report

Against Medical Advice – Refers to a situation where medical advice is not followed by a patient/parent/guardian despite being educated about why it is important and the ramifications of not following medical advice

Amino Acid Disorders – Babies born with one of these disorders cannot process certain amino acids in their body. The amino acids, along with other toxic substances, build up in the body and cause serious effects on health, growth and learning. Treatment may include a special diet for life, close monitoring and/or vitamin and amino acid supplements. An example of an amino acid disorder is phenylketonuria (PKU). Babies with PKU cannot process a substance called phenylalanine. Left untreated, phenylalanine builds up in the bloodstream and causes brain damage, intellectual disability, depression, and other problems. If PKU is detected early and the special diet is started by Day 10 of life, these problems can be greatly reduced or prevented. PKU occurs in about 1 in every 12,000 births.

Baby Matching – A term used in newborn screening where a birth certificate is "matched" with a newborn screening result or an official NBS refusal form to make sure that all babies born in the state have been screened.

Beta Thalassemia – *Beta thalassemia major* usually causes severe anemia that can occur within months after birth. If left untreated, severe anemia can result in insufficient growth and development, as well as other common physical complications that can lead to a dramatically decreased life-expectancy. Fortunately, in developed countries beta thalassemia is usually identified by screening in the newborn period, before symptoms have developed. Children who are identified early can be started on ongoing blood transfusion therapy as needed. Although transfusion therapy prevents many of the complications of severe anemia, the body is unable to eliminate the excess iron contained in the transfused blood. Over time, the excess iron deposits in tissues and organs, resulting in damage and organ failure. Another medication must be administered to help the body eliminate the excess iron and prevent iron-over-load complications. *Beta thalassemia intermedia* describes the disease in individuals who have moderate anemia that only requires blood transfusions intermittently, if at all

Biotinidase Deficiency – Babies with biotinidase deficiency cannot reuse the vitamin biotin. Biotin helps maintain the normal body functioning. Without treatment, this disorder can lead to seizures, developmental delay, eczema and hearing loss. Biotin has to be added to the diet for treatment of this disorder. This disorder occurs in about 1 in every 60,000 births.

Borderline - a term used for some newborn screening disorders where the results are not normal, but are not high enough to be considered presumptive positive. A repeat screen on the baby is requested when the results are "borderline".

Card – a card/form that contains circles with filter paper to deposit the blood from the baby's heel on. This card also contains demographic information regarding the baby, mother, and sample information. Also called the "dried blood spot card".

Carrier – a person that has inherited a genetic trait or mutation but has no symptoms of the disease

Confirmatory/Second Tier Testing – specific testing that is recommended and performed post newborn screening to determine if a baby has a specific disorder or not, e.g. a sweat test for cystic fibrosis.

Confirmed – used to convey that the newborn screen and/or confirmatory testing determined that a baby had a disorder.

Congenital – a condition or problem present at birth.

Congenital Adrenal Hyperplasia – Babies born with this disorder have adrenal glands that cannot make enough of the hormone cortisol, and sometimes not enough of the hormone aldosterone. Sometimes this disorder affects the development of the genitals. You treat this disorder by taking medication that replaces the hormones that are deficient or eliminating the source of excess hormones. Without treatment, severe cases of this disorder can cause death. This disorder occurs in about 1 in every 16,000 births.

Congenital Hypothyroidism – Babies with this disorder are born with a thyroid gland that does not make enough thyroid hormone. This can lead to poor growth and abnormal brain development. If it is detected in time, a baby can be treated with medication. This disorder occurs in about 1 in every 4,000 births.

Courier – the contractual entity that travels to Iowa birthing facilities on a daily basis to pick up newborn screening cards and delivers them to the newborn screening laboratory.

CRMS - When a person has a sweat test that gives an intermediate (borderline) result or a genetic test that shows only one CF gene, he or she is said to have CFTR-related metabolic syndrome (CRMS). People with CRMS can be at a higher risk of having problems in the airways and sinuses; the intestines and pancreas; or the reproductive tract.

Cystic Fibrosis – Cystic fibrosis (CF) is the most common inherited (genetic) disorder, affecting about 30,000 children and adults in the US. A defective gene causes lung infections and digestive problems with malnutrition. CF can be life-shortening[5]. It's important to diagnose CF early, so that CF health care providers can help parents learn ways to keep their child as healthy as possible and delay problems related to CF. Research shows that children who receive CF care early in life have better nutrition and are healthier than those who are diagnosed later. Good nutrition in CF is important for overall health and well-being.

Early Collection – the newborn screen was obtained prior to 24 hours of age. The newborn screen is not valid if collected before 24 hours of age. A repeat screen will be requested on the baby by program staff.

False Negative – a term used when the newborn screen was negative, but a baby is found to have a disorder that we are screening for. As stated above, the newborn screen is a screening test, not a diagnostic test. Every attempt is made to reduce the number of false negatives, but it is understood that some cases will be missed. It is an inherent part of newborn screening.

False Positive – the newborn screen was positive for a particular disorder, but further testing was negative for the disorder.

Fatty Acid Oxidation Disorders – Babies with fatty acid disorders are unable to breakdown stored fats for energy. People who have this disorder cannot fast, and need prompt medical intervention when they have the stomach flu, fevers, etc. One example of a fatty acid disorder is Medium Chain acyl-CoA Dehydrogenase Deficiency (MCAD). Babies born with MCAD cannot break down fat into energy because an enzyme is missing or does not work correctly. People with MCAD should not fast (go without food) for very long or they can experience low blood sugar, seizures, coma and even death. MCAD occurs in about 1 in every 12,000 births.

Galactosemia – Babies with this disorder cannot convert galactose, a sugar present in milk, into glucose, a sugar the body uses as an energy source. Galactosemia can cause death in infancy, or blindness and intellectual disability. A baby will this disorder is not able to drink milk and/or eat other dairy products. They have to drink special formula and follow a special diet for their lifetime. This disorder occurs in about 1 in every 70,000 births.

Hemoglobin E Disease - is an inherited blood disorder characterized by an abnormal form of hemoglobin, called hemoglobin E. People with this condition have red blood cells that are smaller than normal and have an irregular shape. It is thought to be a benign condition. The mutation that causes hemoglobin E disease has the highest frequency among people of Southeast Asian heritage (Cambodian, Laotian, Vietnamese and Thai). However, it is also found in people of Chinese, Filipino, Asiatic Indian, and Turkish descent.

Hemoglobin H Disease - Hemoglobin H disease is a relatively mild form of thalassemia that may go unrecognized. It is not generally considered a condition that will reduce one's life expectancy. Transfusions are rarely needed in this disorder, except in a variant of this disorder called constant Spring. Occasionally additional medication is required for treatment.

Hemoglobinopathies – Hemoglobinopathies are inherited red blood cell disorders. Hemoglobin is the protein in the blood that carries oxygen from the lungs to the body. The most common hemoglobin disorder is sickle cell disease. When sickle cell shaped cells block small blood vessels, less blood can reach that part of the body. Sickle cell anemia occurs in about 1 in every 375 African Americans.

Iowa Department of Public Health – state agency that administers and oversees newborn screening processes in Iowa.

Long Term Follow Up - fundamentally, long-term follow-up comprises the assurance and provision of quality chronic disease management, condition-specific treatment, and age-appropriate preventive care throughout the lifespan of individuals identified with a condition included in newborn screening. Integral to assuring appropriate long-term follow-up are activities related to improving care delivery, including engagement of affected individuals and their families as effective partners in care management, continuous quality improvement through the medical home, research into pathophysiology and treatment options, and active surveillance and evaluation of data related to care and outcomes.

Lost to Follow Up – refers to situations where the baby cannot be located (moved with no forwarding address, guardian doesn't respond to phone calls or certified letters) or when the guardian is contacted about further testing but doesn't bring the baby in for further work up.

Medical Consultant – A physician who makes medical recommendations for a specific disorder to the newborn screening program, state health department, and health care providers throughout the state. They may also assist with development of protocols and provide education.

Newborn Screening Laboratory - The newborn screening laboratory is part of the State Hygienic Laboratory at the University of Iowa (Ankeny campus). This is the laboratory where the testing is performed.

Organic Acidemia – Babies born with organic acid disorders have a chemical imbalance in their bodies which can be toxic. Organic acids play an important role in the breakdown of fats, sugars and protein for the body's use and storage. Muscle wasting, seizures, developmental delays and even death can occur if untreated. Treatment may include a special diet, monitoring and medications.

Outcome – the final determination of a newborn screen, such as "confirmed, false positive, false negative, etc.

Poor Quality – a term used to describe that the sample was not able to be tested. A sample is called "poor quality" when the blood does not soak through the filter paper layers, when the sample is clotted, when too much blood is placed on the card, etc. A repeat screen will be requested by program staff.

Presumptive Positive – a term used by the laboratory and follow up personnel to identify a screen that was positive. The term "presumptive" is used because until further testing is done,

the result is considered positive until the disorder is confirmed or determined to be a false positive.

Primary Care Provider/Local Care Provider – also known as "PCP". The physician who is taking care of the baby, or is listed as the baby's physician.

Rejected Sample – similar to early collection and poor quality determinations. This term is usually used in association with a screen that was submitted after the 30 day cut off time frame. It is also used when the screening card does not have enough information recorded on it to determine who the baby really was.

Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) - The committee advises the Secretary, U.S. Department of Health and Human Services on the most appropriate application of universal newborn screening tests, technologies, policies, guidelines and standards. Specifically, the committee provides to the Secretary, the following: Advice and recommendations concerning grants and projects authorized under the Heritable Disorders Program administered by the Health Resources and Services Administration; technical information to develop Heritable Disorders Program policies and priorities will enhance the ability of the state and local health agencies to provide screening, counseling and health care services for newborns and children who have or are at risk for heritable disorders; and recommendations, advice and information to enhance, expand or improve the ability of the Secretary to reduce mortality and morbidity from heritable disorders in newborns and children. The committee was chartered in February 2003.

Short Term Follow Up - refers to the process of ensuring that all newborns are screened, that an appropriate caregiver is informed of results, that repeat testing on a new specimen or confirmatory testing has been completed, and that the infant has received a diagnosis and, if necessary, treatment.

Sickle Cell Disease/Trait – Sickle cell anemia is caused by an abnormal type of hemoglobin called hemoglobin S. Hemoglobin is a protein inside red blood cells that carries oxygen. Hemoglobin S changes the shape of red blood cells. The red blood cells become shaped like crescents or sickles.The fragile, sickle-shaped cells deliver less oxygen to the body's tissues. They can also get stuck more easily in small blood vessels, as well as break into pieces that can interrupt healthy blood flow. These problems decrease the amount of oxygen flowing to body tissues even more. Sickle cell anemia is inherited from both parents. If you inherit the sickle cell gene from only one parent, you will have sickle cell trait. People with sickle cell trait do not have the symptoms of sickle cell anemia. Sickle cell disease is much more common in people of African and Mediterranean descent. It is also seen in people from South and Central America, the Caribbean, and the Middle East. About 90,000-100,000 residents of the US have sickle cell disease. One in every 500 blacks/African American's have disease. One in every 36,000 Hispanics have sickle cell disease. One in every 12 blacks/African American's have sickle cell trait.

Tandem Mass Spectrometry (MS/MS) - Tandem mass spectrometry, also known as MS/MS or MS2, involves multiple steps of mass spectrometry selection, with some form of fragmentation occurring in between the stages. In a tandem mass spectrometer, ions are formed in the ion source and separated by mass-to-charge ratio in the first stage of mass spectrometry (MS1). Ions of a particular mass-to-charge ratio (precursor ions) are selected and fragment ions (product ions) are created by collision-induced dissociation, ion-molecule reaction, photodissociation, or other process. The resulting ions are then separated and detected in a second stage of mass spectrometry (MS2). This is the technology used for most metabolic disorders.

Trait – a distinct, observable change in a person that might be inherited, such as sickle cell trait which can possibly be determined by newborn screening. It is not true sickle cell disease.

Unsatisfactory Specimen – a term used to state that there was not enough blood placed on the card to perform the newborn screen.