2021 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 2022 so that we have complete data for calendar year 2021.

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 die 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; yet another reason why screening is so important. It is estimated that at least 13,500 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 either 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 we have diagnosed the baby with a 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 not ("false positive"). 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.

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 health providers 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 and 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 be 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*
- (SMA) Spinal Muscular Atrophy* – added 9/1/2022

* 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**

Conditions that are being reviewed at the time of the writing of this report:

- Pompe
- Mucopolysaccharidoses I (MPS 1)
- Adrenoleukodystrophy (X-ALD)

Screens Submitted

There were 39,147 newborn screening cards submitted to the newborn screening laboratory for testing (36,596 initial screens and 2,551 repeat screens).

Borderline and Presumptive Positive Cases for CY 2021

Disorder	Borderline/ Indeterminate	Presumptive Positive
Biotinidase	N/A	6
Cystic Fibrosis	N/A	
Presumptive Positive		6
Possible		50
Endocrine Disorders		
Congenital Adrenal Hyperplasia	289	23
Congenital Hypothyroidism	75	28
Galactosemia	0	3
Hemoglobinopathies	N/A	45
Metabolic Disorders	N/A	625
Severe Combined Immunodeficiency		
Indeterminate due to Prematurity	27	
Indeterminate Other	13	
Presumptive Positive		3
Spinal Muscular Atrophy	N/A	1
TOTAL		

Confirmed Cases for Calendar 2021

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.

The Iowa Newborn Screening added Spinal Muscular Atrophy (SMA) to our panel on September 13, 2021. Prior to that, we had been in a pilot for SMA since July 2020. SMA is an autosomal recessive neuromuscular disease resulting in the progressive degeneration of motor neurons. Symptoms of SMA type 1 usually occur between birth and 6 months and is the most common form of SMA**.** Symptoms of SMA type 2 usually occur between 6 months and 2 years. Symptoms of SMA type 3 usually occur between 18 months and 3 years. It is imperative to start treatment as soon as possible to reduce loss of motor neurons. Without treatment, SMA Type 1 babies will likely pass away before their first birthday. The prevalence of SMA is approximately 1 in every 10,000 babies born.

Disorder	**Cases Confirmed**
Biotinidase Deficiency (metab)	0
*Cystic Fibrosis (CF)**	10
Endocrine Disorders	
Congenital Adrenal Hyperplasia	2
Congenital Hypothyroidism	27
Galactosemia (metab)	1
Hemoglobinopathies	
Sickle Cell Disease	5
Non-Sickling Disease	0
Metabolic Disorders	
Amino Acid Disorders	8
1 ASA and 7 PKU	
Fatty Acid Oxidation Disorders	9
2 GA II, 5 MCAD, 2 VLCAD	
Organic Acidemias (1 3MCC)	1
SCID	0
Spinal Muscular Atrophy (SMA)	2
TOTAL	**65**

Secondary Conditions or Incidental Findings

Disorder	**Number Confirmed**
Carriers of Various Metabolic Disorders/Incidental Findings	26
Galactosemia Carrier	2
Cystic Fibrosis Carriers	39
Cystic Fibrosis Related Metabolic Syndrome (CRMS)*	8
Hemoglobinopathy Trait	561
SCID-Secondary/Incidental Findings	1
TOTAL	**637**

False Negative Case - 1

We had one false negative CH case reported during this calendar year. All false negatives are thoroughly investigated to determine any issues that may have arisen that were not detected during the screening process. Often, these samples are retested as well. This baby had a borderline first screen, a presumptive positive second screen, and a third screen that was within normal limits. The case was initially closed as a false positive. Serum fT4 and TSH were

obtained and reviewed by our medical consultant. This case was then deemed to be a true positive case of congenital hypothyroidism.

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

Against Medical Advice – 28

Against Medical Advice is defined as those situations where the PCP and/or program personnel have had an informed, educational conversation with the family about the need for a repeat screen, further testing and/or a referral to a specialty center. The conversation also includes information on why they are recommending further testing as well as the potential ramifications/consequences if further testing is not done.

Reasons	Number of Cases
(Initial) Poor Quality Screen	20
Early Collection	4
Refused Further Testing/Referral	3
Transfused; parent(s) declined screening after discharge	1

Lost to Follow Up - 19

Lost to Follow Up can be defined as those cases in which both the program and the PCP have made multiple attempts to reach the family by phone, mail and certified mail and no action and/or communication occurs.

Reasons	Number of Cases
(Initial) Poor Quality Screen	15
Transfused; no response to request for further screening	4

Poor Quality – 3.1% for CY 2021 (previously 5.0% in CY 2020)

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 3.1%. The program saw a spike in poor quality samples during the COVID outbreak in 2020. The program heard from hospitals that staff members who normally collected the NBS samples were reassigned to other COVID-related jobs and then inexperienced people were tasked with collecting the NBS samples. At times during the early days of the pandemic, the poor-quality rates were about 5.0% The INSP would like the state average to be =< 1.0%. While the poor-quality rate is getting better, there is still much work to be done. The program provides technical assistance/education to reduce the percentage of poor-quality screens in our state and we continued to do so during the pandemic whenever possible. Staffing issues and visitor restrictions limited what we were able to do. We remind our collectors that it is imperative that a good quality screen be collected the first time. As you can see from the AMA/Lost to Follow Up information above, poor-quality samples have a very direct impact on babies being screened appropriately. We also remind them that a baby's health could be impacted by a poor-quality screen. Finally, poor-quality screens negatively impacts timeliness and resource utilization in newborn screening.

At the time this report is being written (in 2022), the program is working to combat rising poor-quality rates by introducing a "possible poor quality" category and developing new resources for internal and external education. This new category allows staff to attempt to perform initial testing before marking specimens as poor quality. This new status has already reduced the poor-quality rates. New educational resources have been created and are currently being "trialed" by a few select hospitals for feedback. The program plans to distribute these new resources to all birthing hospitals and midwives by the end of 2022.

Refusals – 135 (0.37%)

135 refusal forms were received on babies born in 2021

Reasons for Refusal	Number of cases	% Of Out of Hospital Births	Comments
Blank	43	83.7	4 of these cases went on to be screened on average at day of life 20 (range 9-57). The program assisted in getting all of these infants screen.
Prefer to screen later in life	21	4.8	20 of these cases went on to be screened on average at day of life 5 (range of 1-33 days). The program assisted in getting 4 of these infants screen.
Discharged before 24 hours	5	0	4 of these cases went on to be screened on average at day of life 6 (2-16 range). The program assisted in getting three of these infants screen.
Not necessary/personal choice	41	68.3	4 of these cases went on to be screened on average at day of life 32 (range 1-95). The program assisted in getting one of these infants screened.
Baby is healthy and will monitor health	5	100	None of these cases went on to be screened.
Cost	1	0	This baby went on to be screened at day of life 11. The program assisted in getting this infant screened.
Religion/culture	11	36.4	One of these cases went on to be screened on day of life one. The program did not assist in getting this infant screened.
No family history/other screens have been normal	8	100	None of these cases went on to be screened.

We continue to see a slight uptick in the number of refusals each year. Anecdotally, refusals are increasing across the United States. The program monitors the number of refusals along with the reasons for refusals. In Iowa, it is the parent's right to choose to screen or not to screen. We believe that better, NBS education to parents and providers, especially in the prenatal period, could reduce the number of refusals. We were awarded a continuous quality improvement grant to work on developing newborn screening educational materials for parents and providers. Please see more information about this project later in this report.

Baby Matching – 544 Cases

"Baby Matching" is a weekly QI process

In calendar year 2021 there were 544 baby matching cases (infants who did not match by the IDPH process or who had an IDPH refusal form)

- 74 cases were picked up by the baby matching process, but their screens simply had not yet arrived to the SHL yet.
- 48 cases were home births identified through baby matching after infant was 3 months of age. No further action was taken on these cases.
- 180 baby matching cases were screened either in Iowa and did not match for various reasons or were screened out of state

State screened	Number of Baby Matching Cases in 2021
Screened in Iowa	127
Screened in Illinois	3
Screened in Minnesota	7
Screened in Missouri	1
Screened in Nebraska	4

Screened in South Dakota	32
Screened in Wisconsin	6

- 2 infants were identified through baby matching and were deceased or went home with hospice care so no further follow up was completed

- 168 baby matching cases were closed out as refused.

Signed and returned the refusal form	99 (58.9%)
Returned the refusal form but did not sign the form	4 (2.4%)
Contacted by the program but did not return a refusal form	65 (38.7%)

- 36 baby matching cases were screened after our intervention through the baby matching process. Nine of these were classified as missed cases.

- 35 baby matching cases screened without INSP intervention.

Genetic Counseling

Genetic counseling is offered to all patients who have abnormal test results. The counseling is completed either face to face or over the phone. While genetic counseling is offered to the patient via their PCP, the uptake of this service varies, especially by disorder. One of the many topics on our educational outreach plan is to teach PCPs, allied healthcare providers and parents the importance of genetic counseling. We hypothesize that once healthcare providers and parents understand the importance, additional buy-in will occur and these numbers will increase even further.

Disorder	# of Babies	# of Individuals Present	In-Person or Telephone	Interpreter Utilized
Cystic Fibrosis	23	63	17/6	0

Hemoglobinopathies	156	97	24/132	7
Metabolic Disorders	69	74	154/0	3
TOTALS	248	234		10

An interpreter was utilized to assist with communication to families whose primary languages include Arabic, Burmese, French, Karen, Spanish, Swahili, and Vietnamese.

Genetic Counseling Family Contact Calls

The Family Contact Call (FCC) initiative was implemented by the Iowa Newborn Screening Program in September 2020 as a way to improve family experiences and communication about newborn screening results. The FCC initiative connects families with a genetic counselor who can explain the newborn screening process, the baby's abnormal result, answer parent/guardian questions, and review next steps. Based on the Iowa experience, families appreciate the timely contact, education, and support during this emotional time. The questions that are asked during these calls also highlight the importance of reducing anxiety and explaining things more thoroughly than was done (for the most part) by the PCP or PCP office staff. These questions also highlight the lack of newborn screening and genetic literacy in our population. The following are some of the questions asked by parents to the genetic counselor:

General Questions Asked by Parents

- Would the NBS pick up if we as parents were carriers?
- What are they looking for with the different tests?
- Which analytes would be abnormal?
- Why is the genetics (metabolic) appointment necessary?
- What is this condition?
- Where did it come from since I have 5 healthy kids?
- Is this serious?
- How much blood is needed for these tests? Will the blood be taken from the heel or vein? What were the previous labs looking for?
- Will those labs give a diagnosis?
- Does it matter if he has a twin brother?
- How could they get the result when the sample was poor quality?
- Can the parents have bloodwork instead of the baby?
- Did maternal diet during pregnancy cause this?
- How soon will we know the answers?
- Do carriers need treatment?
- Do baby's older siblings need tested?
- Is there a cure?
- Is it possible this test is wrong?
- Are there any symptoms in infancy? Would we see anything different now?
- What is her result? Told metabolic screen was abnormal.

Condition Specific Questions:

Cystic Fibrosis:

- What are the treatments for CF? When will she start treatment? Is this manageable? What does this look like long-term? We did IVF – shouldn't we have been tested for this?
- How is the sweat test done?
- Was my shortness of breath/sneezing during pregnancy related to CF? I wasn't told much about CF.
- How is it that she tested positive and her brother was a carrier?
- Is the sweat test safe? Will he be uncomfortable?

Hemoglobinopathies (Sickle Cell Disease):

- How can two of our three children have sickle cell disease when we were told a ¼ recurrence risk?

Metabolic (PKU):

- Our understanding is that he can't have PKU, right?
- Am I still able to breastfeed if he has PKU?

Parent did not know anything about newborn screening:

- If you don't know what my doctor said, why are you calling me? What program are you calling from? What is NBS? What is MSUD? Why are you saying my baby might have this? Where did you get this information, because I didn't enter my baby into any program?

The following are excerpts of family experiences reported to or by the genetic counselor:

- The PCP was very timely and the referral was completed within hours of receiving the NBS results
- Mom was very anxious and has read a lot on-line
- Informed and not particularly concerned
- Mom was not aware of the abnormal NBS and was told everything was fine. She did not want any more information and just wanted to wait to see the specialist

The first FCC call was made on September 28, 2020. The genetic counselor continued to do these important calls in 2021. The following is a table showing which disorders calls were made for:

Disorder	**Number of Calls**
Biotinidase	0
Cystic Fibrosis	

Presumptive Positive	4
Possible CF	50
Endocrine Disorders	
Congenital Adrenal Hyperplasia	4
Congenital Hypothyroidism	0
Galactosemia	3
Hemoglobinopathies	
Sickle Cell Disease	20
Hemoglobin VV	4
Metabolic Disorders	
Amino Acid Disorders	32
Fatty Acid Disorders	35
Organic Acidemias	18
Miscellaneous	4
SCID	2
SMA	N/A
TOTAL	176

Newborn Screening Stories

A baby was born in 2021 that was presumptive positive for VLCAD, a fatty acid oxidation disorder (FAO). It is important that individuals with a FAO never fast, as fasting can cause life-threatening hypoglycemia. This family celebrates Ramadan, a religious holiday in which fasting is a part of the religious practice. The screening and diagnosis of this baby was important for this baby's life; but also important for the lives of the 5 older siblings who are expected to fast once past puberty. Luckily for the 5 older siblings, the diagnostic testing for VLCAD was negative.

A baby was born to a mother with CF. Through a conversation with the baby's provider, mother understood her baby had CF. Through the Family Contact Call, the program was able to provide some reassurance that the result was "possible CF" and educated the mother that until sweat testing was done, we couldn't say whether or not her baby had CF. Baby was a carrier for CF, but did not have classic CF. Mother was relieved that her baby did not have classic CF.

The parents of a baby born in 2021 had opted not have carrier screening. They had a baby with classic CF, which in their words, was a surprise. Parents received genetic counseling and because of the information that was received, have now had carrier screening done and are considering IVF for future pregnancies.

"Baby Z" was born in 2021 and had a presumptive positive galactosemia newborn screening result with 0.0 enzyme activity which is indicative of classic galactosemia. Galactosemia is a time-critical disorder where minutes/hours and days can make the difference between a

normal life vs permanent disability or death. When confirmatory testing was done, Baby Z was found to have elevated bilirubin and liver enzymes. This is indicative that not only did Baby Z likely have galactosemia, but that Baby Z was nearing a catastrophic medical event.

Quality Improvement Activities

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 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.

Grants

Opportunities Through Training and Educational Resources – "OTTER". The OTTER grant was awarded in 2019 to the Iowa Newborn Screening Program from the Association of Public Health Laboratories (APHL). The grant is a quality improvement project aimed at engaging prenatal providers to educate their patients about newborn screening. We understand that prenatal offices are busy places, and we knew for this to be successful, we had to come up with a quick

and easy way for the education to be accomplished. To do this, we developed an application that can easily be accessed through mobile devices or a computer that is geared towards expectant parents. We have two surveys to assess parental knowledge of newborn screening. The first survey is done prior to any educational intervention to assess baseline knowledge of newborn screening. The second survey is completed after the expectant parent has utilized our application and assesses what the parent learned from the educational intervention. If this works, our goal is to implement this educational tool with prenatal providers across the state. We believe that the first time that a parent hears about newborn screening should not be when they are receiving a call stating that their newborn baby's screen is abnormal. The first educational opportunity should be in the prenatal setting; the second when the baby's screen is collected; and the third time in the PCP's office where newborn screening results – even if they are normal – should be discussed with parents.

We had recruited a site to be our "beta" site, but COVID really impacted their ability to do this project. We eventually had to call a halt to this collaboration and look elsewhere. We identified a new site and have been successful in beginning this project at that site. Based on the number of patients and surveys returned, we may make the decision to add additional beta sites to this project.

Continuation of Operations (COOP) – The COOP grant was awarded to the Iowa Newborn Screening Program in 2021 from the Association of Public Health Laboratories (APHL). All newborn screening programs are required to have a COOP plan; however, the focus is often on the newborn screening laboratory and not on Follow-Up activities. This grant is the beginning of focusing on an overall program communications plan as well as on Follow-Up activities. We plan to work with beta sites (both birthing facilities and clinics) to determine best practices to contact them in an event of a disaster. It also will help us develop a hierarchy of notification and defines each person's role in the event of a disaster.

Center for Disease Control and Prevention (CDC), Spinal Muscular Atrophy (SMA) Implementation Grant. The program applied for and received funding from the CDC to develop and implement screening for SMA. The grant provides funding for two years to develop and implement the SMA screening test, follow-up protocols, educational materials, and to develop and monitor quality indicators and benchmark those indicators against other newborn screening programs screening for SMA.

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, "Unresolved Issues in Newborn Screening: Quantifying the Harms of a False Positive Result". This is a five-year grant and includes the Iowa and Virginia Newborn Screening Programs. Key personnel in Iowa include Dr. Amy Calhoun, Carol Johnson and Emily Phillips. Work on this grant started in 2019 and continues through 2022.

Projects

NewSTEPs Repository

Confirmed cases are entered into this national repository by our follow up staff through a MOU between the Association of Public Health Laboratories and the Iowa Department of Public Health.

Database

Laboratory Information System – OpenELIS

Development of the OpenELIS laboratory information system came to a screeching halt because of the COVID pandemic. The State Hygienic Laboratory's IT resources had put toward responding to the pandemic and reporting out COVID test results.

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.

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

Many educational outreach activities were put on hold due to the pandemic. Activities were limited primarily due to lack of staff time as well as travel and access restrictions. We considered doing outreach via Zoom and other meeting platforms but found that it wasn't feasible due to staffing issues.

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. All meetings were virtual this year.

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. Again, this was performed virtually this past year.

The Pandemic - Continuation

What Went Well:

Follow-Up staff were sent home on March 13, 2020 when COVID-19 became a crisis. Follow-Up staff continued to work remotely until mid-July 2021. Since we are a 365/24 operation, Follow-Up staff had all the necessary tools to work remotely as well as in person.

Impacts and Adaptations:

Shortly after the pandemic started, we did notice reluctance from parents to take their babies back in for repeat screens and/or confirmatory testing. While this situation was better in 2021, it still was an issue from time to time. This was especially true if the family had been exposed or had an active case of COVID within their family. We worked with our medical consultants and parents on a case-by-case basis to find solutions that worked best for everyone. This took more time and more communication than what typically happens, but overall things worked very well.

The program saw poor quality rates increase during the pandemic. This phenomenon was not limited to Iowa; it was an issue present on the national level as well. This increase can be directly attributed to skilled blood spot collection staff at hospitals being reassigned to other jobs during the pandemic, resignations, retirements and staffing issues. New staff brought in to do blood spot collections did not have experience performing this nuanced procedure nor was education on how to collect a newborn screen a priority.

An increase in poor quality samples also increases the amount of work that both the NBS lab and Follow-Up staff have to do, adds more work to stressed local laboratories and PCPs, increases parental anxiety, and reduces the number of babies who have a completed screen.

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.

ACHDNC
Secretary's Advisory Committee on Heritable Disorders in Newbo rns and Children

Communication Guide

THIS GUIDE WILL HELP YOU EFFECTIVELY COMMUNICATE [POSITIVE]* NEWBORN SCREENING RESULTS TO PARENTS.

Because this type of communication is not a routine activity for the primary care provider, the information below may be used to help frame the discussion with families to improve understanding of the screening result, adherence to follow-up recommendations, and the family's overall experience with newborn screening.

Families who have had [positive]* newborn screening results have suggested that the following key points are important in helping families cope with the uncertainty of a [positive]* newborn screening result and understand the next steps needed to gain certainty.

Sharethe specific [positive]* newborn screening result and associated condition(s) with the family.

- Help the family understand that a [positive]* newborn screening result is serious, but that you are there to help guide them through the next steps.

Comprehension:Assess the family's understanding of newborn screening.

- Assess if the family recalls and understands the process of newborn screening.

Reiterate what screening is and is not.

- Remind the family about the purpose of newborn screening and that it is not a diagnostic test, so it is important that timely follow-up confirmatory testing oe done.

Engagewith the family and provide information at their desired level and pace.

- Offer to provide the family additional result-specific information provided by the state newborn screening program.
- Discuss information using non-medical terms, at the family's pace and desired level of detail.

Explorethe family's emotions.

- Explore with the family how they might use their support system or other support resources now and as they go through the diagnostic process.
- Remember there is a wide spectrum of how families may cope with this result (anxiety to denial). Tailor your discussion to help the family hear and retain the information discussed.

Next steps: Discuss a shared plan and provide resources.

- Discuss with the family a shared plan that is concrete, specific, and includes the following:
  - Where, when, and with whom is the next appointment?
  - What testing will be considered and/or done?
  - What should they watch for in their child while they wait?
  - Who can they contact if they have additional questions or concerns?
- Assess the family's understanding of the visit and information provided using teach-back methods, and provide valid websites for them to get more information.

A positive newborn screening result can also be referred to as an abnormal result, an out-of-range result, or presumptive positive result.

For more information about the Advisory Committee on Heritable Disorders in Newborns and Children, please visit https://www.hrsa.gov/advisory-committees/heritable-disorders