Pulse Oximetry Screening for Homebirths: A Survey of Midwives and Follow-up to Address Barriers
K. Urquhart, M. Kleyn and J. Bach, Michigan Department of Community Health, Lansing, MI

Abstract

Objective: To assess midwives’ knowledge and attitudes related to screening newborns for critical congenital heart disease (CCHD) using pulse oximetry; and to address identified barriers to screening.

Methods: A survey including questions about use of pulse oximetry screening (POS) was sent to all midwives who attended 3+ homebirths in Michigan in 2011 to learn more about barriers related to newborn screening (NBS) among homebirths. Trainings and technical assistance were later provided to address identified barriers.

Results: Thirty-four midwives out of 51 (67%) returned the survey. Of the 34, nine (26%) indicated that they were currently either performing or referring clients for the POS. Midwives who ever delivered a newborn diagnosed with a disorder through NBS were significantly more likely to offer POS (50% compared to 14%). Midwives who discuss NBS with every client, have been practicing for <10 years, deliver 10+ clients per year, and work with other midwives were all more likely to perform POS, though none reached statistical significance. Twenty-five of the 27 respondents who provided a response (93%) stated that they would perform or refer for the screen if the state mandated screening for CCHD. The biggest barrier to performing the screen was lack of equipment, followed by knowledge of performing a POS.

Conclusions: This survey found that midwives were willing to perform or refer clients for the POS if mandated. Based on the survey results, Michigan NBS staff offered several trainings for midwives throughout the state. They expressed interest in offering screening, and we are now assisting with implementing screening and data reporting. We are also developing a program to supply POS equipment to midwives so that babies are screened appropriately. Based on Michigan’s experience, we believe state NBS programs will need to assist midwives with materials and training to ensure that all newborns have the opportunity to receive POS for early detection of CCHD.

Presenter: Janice Bach, MS, Michigan Department of Community Health, Lansing, MI, Phone: 517.335.8497, Email: bachj@michigan.gov

Summary

Approximately 1 in 100 babies is born with a congenital heart defect (CHD), making CHDs the most common of all birth defects.\(^1\) This means 40,000 infants with CHDs are born every year in the United States. Pulse oximetry has been shown to detect some forms of CHDs in the newborn based on low oxygen levels in the blood. This screening targets twelve specific anomalies classified as critical congenital heart disease (CCHD).\(^2\)
In 2011, pulse oximetry was recommended by the U.S. Department of Health and Human Services Secretary as an important screening tool for detection of CCHD in asymptomatic newborns. This recommendation was subsequently endorsed by the American Academy of Pediatrics (AAP) as a standard of care.

The AAP also released a policy statement, “Planned Home Birth”, which included a specific recommendation that screening for congenital heart disease should be performed using oxygen saturation testing; there is currently limited information about the involvement of midwives in state CCHD screening programs.

In Michigan, midwife-attended homebirths are much less likely to receive a newborn blood spot screen (65%) compared to the general population (99.6%). In January 2013, the Michigan Department of Community Health (MDCH) NBS Program was awarded a grant, “Improving Newborn Screening Rates within the Michigan Homebirth Community”, to identify ways to increase the number of infants born at home who receive a newborn screen in a timely manner.

To assess midwives’ knowledge and attitudes related to screening newborns for critical congenital heart disease using pulse oximetry, a survey was sent to all midwives who attended three or more home births in Michigan in 2011. The goal of the survey was to learn more about barriers related to screening for CCHD using pulse oximetry, as well as current practice in the homebirth community and their willingness to adopt the recommended screening protocol.

Thirty-four midwives returned the survey out of 51 (67%). Of the 34, nine (26%) indicated that they currently either perform or refer clients for the pulse oximetry screen. Midwives who ever delivered a newborn diagnosed with a disorder through NBS were significantly more likely to offer pulse oximetry screening (50% compared to 14%).

Midwives who discuss NBS with every client, have been practicing for less than ten years, deliver ten or more clients per year, and work with other midwives were all more likely to perform pulse oximetry screening, though none reached statistical significance.

If the state mandates pulse oximetry screening, 25 of the 27 respondents who provided a response (93%) stated that they would perform or refer for the screen.

The biggest barrier to performing the screen was lack of equipment, followed by not knowing how to perform a pulse oximetry screen.

This survey found that midwives were willing to perform or refer clients for the pulse oximetry screen if mandated. It is also important that state NBS programs provide midwives with materials and training in order to ensure that all newborns have the opportunity to receive a pulse oximetry screen. Follow-up of failed screens was not identified as an issue on the survey, however anecdotal conversations with midwives revealed that they were concerned about follow-up for a newborn with a low pulse oximetry reading and a possible CCHD. More work needs to be conducted to set up referral networks and plans for infants born at home who fail their pulse oximetry screen.

To assist midwives in screening for CCHD the MDCH has: (1) provided several regional trainings for midwives and homebirth attendants; (2) presented information on CCHD screening and provided...
training at Michigan Midwives Association Fall Conference; (3) created “Pulse Oximetry Screening for Critical Congenital Heart Disease in the Home Birth Community” –Toolkit for Implementing Screening; (4) developed training and educational materials for screening and follow-up for those infants born under the care of midwives and homebirth attendants; (5) designed a Pulse Oximetry Equipment Loan Program; as well as (6) implemented CCHD Screening Data Reporting for midwives. Including CCHD Screening data for those infants born at home is essential to effective public health follow-up, quality assurance and evaluation of the program.

Delayed diagnosis of CCHD is associated with increased morbidity and mortality in infants1 supporting the recommendation that all newborns, including those born at home, be screened using pulse oximetry.

References:

P-17

Use of Hospital-specific Cutoffs to Evaluate NBS Specimen Transit Time
M. Kleyn, L. Turbett, W. Young, K. Tomasko and J. Bach, Michigan Department of Community Health, Lansing, MI

Abstract

Background: Delays in blood spot specimen arrival at a state Newborn Screening (NBS) Laboratory may contribute to irreversible health problems for infants with a disorder requiring immediate diagnosis and treatment. Prompt pickup and delivery of NBS specimens reduces turnaround time from birth to reporting results. Michigan's NBS Program is improving transit times by working with birthing units to assure specimens are picked up by the state-funded courier services and delivered to the NBS Lab the next business day. All birthing units in Michigan have Monday-Friday and either Saturday or Sunday courier service.

Methods: A database has been created with the specimen pickup time for Monday-Friday and the weekend day and time for every birthing unit in the state. Since hospitals are advised to dry specimens for at least 3 hours and time may be needed to prepare specimens for shipping, we allowed for a 5-hour cushion between collection time and the earliest possible pickup time. We then developed hospital-specific cutoffs for determining whether specimens were received in the lab on the appropriate day based on collection time and each hospital’s courier pickup times.

Results: All initial specimens submitted by Michigan hospitals for infants born in the first quarter of 2014 were analyzed. Of the 26,523 initial specimens, 20,855 (79%) were received on the appropriate day. Of the 117 birthing units (including regular nursery, NICU, and SCN), 36 (31%) had >90% of their specimens received on the appropriate day.

Conclusions: NBS Follow-up Program staff provides technical assistance to hospitals with the lowest percent of specimens received on the appropriate day. This information will be added to the quarterly quality assurance reports sent to all birthing units. The use of hospital-specific cutoffs for assessing time from specimen collection to receipt in the State NBS Lab identifies hospitals that could improve their process for sending out specimens in a timely manner.

Presenter: Lois Turbett, MSN, Michigan Department of Community Health, Lansing, MI, Phone: 517.335.1966, Email: turbettl@michigan.gov

Summary

Delays in blood spot specimen arrival at a state newborn screening (NBS) laboratory may contribute to irreversible health problems for infants with a disorder requiring immediate diagnosis and treatment. Prompt pickup and delivery of NBS specimens reduces turnaround time from birth to reporting results. Michigan’s NBS Program works with birthing units to assure specimens are picked up by the state-funded courier services (Quest, A1, and UPS) and delivered to the NBS laboratory the next business day. All birthing units in Michigan have Monday-Friday and either Saturday or Sunday courier service.

The NBS Program provides each birthing unit with a quarterly report that includes data on performance metrics related to the NBS process. One measure was percent of specimens received in the State NBS Laboratory within three days of collection. Using one cutoff for the entire state limited the ability to adjust for weekends and varying specimen pickup days and times. Thus, the NBS Program created hospital-specific cutoffs for evaluating specimen transit time to allow better monitoring of transit time by both the NBS Program and birthing units.

Methods: NBS Program staff created a database that documents the specimen pickup time for Monday-Friday and the weekend day and time for every birthing unit in the state. The NBS nurse consultant maintains this database and updates the information when changes occur. Birthing units are advised to dry NBS specimens for at least 3 hours according to CLSI guidelines. Since additional time may be needed to prepare specimens for shipping and transport specimens to the designated pickup location in the hospital, we allowed a 5-hour cushion between specimen collection time and the earliest possible pickup time.

We then developed hospital-specific cutoffs for determining whether specimens were received in the NBS laboratory on or before the appropriate day based on specimen collection time and each hospital’s courier pickup days and times.

All initial NBS specimens submitted by Michigan hospitals for infants born from April 1 through June 30, 2014 were included.
Results: Of the 83 hospitals with birthing units in Michigan, 29 used Quest for Monday-Saturday pickup, 46 used Quest for Monday-Friday pickup and A1 International for Sunday pickup, and the 8 hospitals in the Upper Peninsula used UPS for Monday-Saturday pickup. One hospital used its own courier.

Examples of hospital-specific cutoffs:

Saturday courier service:
Assume Hospital 1 has pickup Monday-Friday at 5:00 pm and Saturdays at 1:00 pm:

<table>
<thead>
<tr>
<th>Specimen Collection Time</th>
<th>Arrive on or before</th>
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<tbody>
<tr>
<td>Friday after 12:00 pm-Saturday at 8:00 am</td>
<td>Monday</td>
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<tr>
<td>Saturday after 8:00 am-Monday at 12:00 pm</td>
<td>Tuesday</td>
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<tr>
<td>Monday after 12:00 pm-Tuesday at 12:00 pm</td>
<td>Wednesday</td>
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<tr>
<td>Tuesday after 12:00 pm-Wednesday at 12:00 pm</td>
<td>Thursday</td>
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<td>Wednesday after 12:00 pm-Thursday at 12:00 pm</td>
<td>Friday</td>
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<tr>
<td>Thursday after 12:00 pm-Friday at 12:00 pm</td>
<td>Saturday</td>
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Sunday courier service:
Assume Hospital 2 has pickup Monday-Friday at 9:00 pm and Sundays at 3:00 pm:

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<th>Specimen Collection Time</th>
<th>Arrive on or before</th>
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<tbody>
<tr>
<td>Friday after 4:00 pm-Sunday at 10:00 am</td>
<td>Monday</td>
</tr>
<tr>
<td>Sunday after 10:00 pm-Monday at 4:00 pm</td>
<td>Tuesday</td>
</tr>
<tr>
<td>Monday after 4:00 pm-Tuesday at 4:00 pm</td>
<td>Wednesday</td>
</tr>
<tr>
<td>Tuesday after 4:00 pm-Wednesday at 4:00 pm</td>
<td>Thursday</td>
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<td>Wednesday after 4:00 pm-Thursday at 4:00 pm</td>
<td>Friday</td>
</tr>
<tr>
<td>Thursday after 4:00 pm-Friday at 4:00 pm</td>
<td>Saturday</td>
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</tbody>
</table>

All first sample specimens submitted by Michigan hospitals for infants born in the first quarter of 2014 were analyzed. Of the 26,523 first sample specimens, 20,855 (79%) were received on the appropriate day. Of the 117 birthing units (including regular nursery, NICU, and SCN), 36 (31%) had >90% of their specimens received on the appropriate day.

Conclusions: NBS Follow-up Program staff provides technical assistance to hospitals with the lowest percent of specimens received on the appropriate day. This information was added to the quarterly quality assurance reports sent to all birthing units in July 2014. The use of hospital-specific cutoffs for assessing time from specimen collection to receipt in the State NBS Laboratory identifies hospitals that could improve their process for sending out specimens in a timely manner.
Abstract

Background: Michigan’s Newborn Screening (NBS) Follow-up Program has linked NBS and birth certificate (BC) records since 2007. The web-based Michigan Care Improvement Registry (MCIR), first developed for immunizations, uses BC to populate MCIR for newborns. Using BC as the intermediate file, NBS records are uploaded into MCIR. If records match, the NBS laboratory report mailer can be viewed on MCIR. We set a goal of having mailers available within 2 weeks of birth, so providers can view the mailer on MCIR at the first well-child visit. This study evaluated whether the goal is being met.

Methods: Eligibility was defined as 2013 Michigan BC records to resident mothers where the infant was born in a hospital and not listed as deceased or adopted. One hospital system was excluded due to delays in releasing BC records to MCIR. We determined how many eligible BC records were linked to NBS records and matched with MCIR records. Date of BC receipt by NBS staff and date of NBS mailer availability in MCIR are recorded in databases. The time from birth to NBS mailer availability was calculated, and the percent of records meeting the 2 week goal was determined. We also examined the influence of time to BC receipt on meeting the goal.

Results: Of 112,654 infant birth certificate records, 101,215 (90%) were eligible, and 99% of the eligible records (n=100,651) had linked NBS/BC records uploaded in MCIR. NBS and MCIR records were linked for 98% of these infants (n=98,556). The median time from birth to NBS availability was 14 days. Nearly 60% of the infants had NBS mailers available in MCIR within 2 weeks of birth. The median time from birth to receipt of BC was 5 days for records that met the 2 week goal and 13 days for records not meeting the goal.

Conclusions: Earlier release of BC by hospitals decreases time to posting of NBS results on MCIR for access by primary care providers. Educating hospitals about the importance of timely BC release should increase the number of records meeting the goal.

Presenter: Kristy Tomasko, BS, Michigan Department of Community Health, Lansing, MI, Phone: 517.335.9296, Email: tomaskok@michigan.gov
Summary

Background: Michigan’s Newborn Screening (NBS) Follow-up Program has linked NBS and birth certificate (BC) records since 2007. The linkage process is conducted weekly and provides the NBS Follow-up Program information on potential missed screens. The process also provides data quality for BC compared to NBS and demonstrates the ability to match across other administrative datasets. The web-based Michigan Care Improvement Registry (MCIR) was first developed as an immunization registry and has expanded to include information from multiple programs, including lead screening and body mass index.

In 2009, NBS and MCIR staff collaborated to display the NBS mailer in its own tab as part of a child’s immunization record. The entire process consists of multiple steps: receipt of BC, preparation of BC and NBS files, linking files using Link Plus (free record linkage program from the Centers for Disease Control and Prevention), providing the unmatched BC records for follow-up, uploading linked NBS/BC file into MCIR, and manually linking unmatched records in MCIR.

Since BC records are used to populate MCIR records, the BC is an intermediate file that is used to link NBS and MCIR records (See Figure 1). The NBS tab becomes available when a successful link is created between the NBS and MCIR records. The MCIR NBS tab provides information such as specimen collection date, kit number, and a link to a pdf of the NBS mailer that contains the screening results (see Figure 2). The NBS laboratory report mailer includes demographic information on the newborn, the submitter name, infant’s physician and screening results by disorder category (see Figure 3). If records do not match, a file of unmatched records is downloaded from MCIR for manual linking by NBS staff. We set a goal of having mailers available within 2 weeks of birth, so providers can view the mailer on MCIR at the first well-child visit. This study evaluated whether the goal is being met.

Methods: Study eligibility was defined as 2013 Michigan BC records to resident mothers where the infant was born in a hospital and not listed as deceased or adopted. Non-hospital births were excluded due to (1) the delay in receipt of BC since they cannot be submitted electronically; and (2) increased

MCIR participation refusals among home births. Adoptions are excluded from the file uploaded into MCIR to protect the confidentiality of the birth mother. One hospital system was excluded from analysis of mailer availability due to its delays in releasing BC records to MCIR. However, it was included in calculations of the receipt of BC to the NBS program. We determined how many eligible BC records were linked to NBS records and how many linked BC/NBS records matched with MCIR records. Date of BC receipt by NBS staff and date of NBS mailer availability in MCIR are recorded in databases. If date of MCIR upload was not available, the record was removed from analysis of timeliness of mailer availability. The time from birth to NBS mailer availability was calculated, and the percent of records meeting the 2 week goal was determined. We also examined the influence of time to BC receipt on meeting the goal.

**Results:** Of 112,875 birth certificate records, 101,289 (90%) were eligible, and 99% of the eligible records (n=101,143) had linked NBS/BC records uploaded in MCIR. The median time from birth to receipt of BC records was 7 days. By two weeks of life, NBS staff received 85% of hospital BC records.

<table>
<thead>
<tr>
<th>Days to NBS receipt of BC</th>
<th>% of hospital births</th>
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<tr>
<td>0-7</td>
<td>45</td>
</tr>
<tr>
<td>8-14</td>
<td>40</td>
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<td>&gt;14</td>
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NBS and MCIR records were linked for 99% of infants with linked NBS/BC records uploaded in MCIR (n=100,721). The median time from birth to NBS mailer availability in MCIR was 14 days. Nearly 60% of the infants had NBS mailers available in MCIR within 2 weeks of birth excluding infants identified as adoptions, deceased or submitted by one hospital system.

<table>
<thead>
<tr>
<th>Days for NBS mailer available on MCIR</th>
<th>% of Births</th>
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<tbody>
<tr>
<td>0-14</td>
<td>60</td>
</tr>
<tr>
<td>&gt;14</td>
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The median time from birth to receipt of the BC record by NBS staff was 5 days for records that met the 2 week goal and 13 days for records not meeting the goal.

**Conclusions:** Timely notification to primary care providers with NBS results is important for (1) follow-up on positive, borderline, or missed screens, (2) providing results from all screening tests; and (3) the avoidance of unnecessary repeat screens. It also reduces manual labor for NBS staff. Making the NBS results accessible to the provider before the 2-week well-child visit allows discussion of the results at this visit. Earlier release of BC records by hospitals decreases time to posting of NBS results on MCIR for access by primary care providers. The availability of the NBS results on MCIR decreases the manual work load for provider offices and NBS staff. To improve the NBS result availability in MCIR within 2 weeks of life, NBS program staff plan to educate hospitals about the importance of timely BC record release.

**References:**

P-19

Newborn Screening Social Media Strategies in Minnesota
P. Constant, B. Roby, G. Caldwell and M. McCann, Minnesota Department of Health, St. Paul, MN

Abstract

The Minnesota Department of Health (MDH) Newborn Screening Program was interested in reaching our educational audiences through new platforms, namely social media sites such as Facebook and Twitter. Our goal for creating a social media presence was to increase awareness and general population education. Given the complex climate of newborn screening in Minnesota, we were unable to create our own Twitter or Facebook page and instead partnered with our Communications Department to build a presence via the Minnesota Department of Health’s Facebook and Twitter accounts.

To begin, we created a social media team made up of representatives from each section of the Newborn Screening Program. These representatives meet monthly to generate potential Tweets and Facebook posts, making a special effort to make posts timely and relevant. Often posts correspond to recognized national or international awareness days or months (e.g., Nurse Appreciation Day, Better Hearing & Speech Month, Cystic Fibrosis Awareness Month), and incorporate newborn screening messages into other relevant information for the general public. The team leader then works to fit the theme of the messages within character limits and finds or creates images to support the messages as appropriate. All social media posts are approved by the both team and the Program Manager before being sent to the Communications Department for posting. The team also evaluates the ‘Likes,’ ‘Shares,’ and ‘Favorites’ of each post to determine what types of messages are most effective and reach the greatest audiences, and makes an effort to monitor the social media accounts of partner organizations so that we can support/share their content with our audiences as well.

The Minnesota Department of Health currently has approximately 2,300 followers on Facebook and more than 6,000 Twitter followers. Several of our most popular posts have generated dozens of likes and multiple shares/retweets. Since launching our social media efforts in July 2013, the Newborn Screening Program has posted more than 100 unique newborn screening messages on social media.

Presenter:  Patti Constant, MPH, Minnesota Department of Health, Newborn Screening, St. Paul, MN,
Phone:  651.201.4517, Email:  patti.constant@state.mn.us

Summary

The Minnesota Department of Health (MDH) Newborn Screening Program continually seeks to reach our educational audiences through new platforms, including social media sites such as Facebook and Twitter. Our goal for creating a social media presence is to increase awareness and general population education. Given the complex climate of newborn screening in Minnesota, we were unable to create our own Twitter or Facebook page and instead partnered with our Communications Department to build a presence via the Minnesota Department of Health’s Facebook and Twitter accounts.

To begin, we created a social media team made up of representatives from each section of the Newborn Screening Program. These representatives meet monthly to generate potential Tweets and Facebook posts, making a special effort to make posts timely and relevant. Often posts correspond to recognized
national or international awareness days or months (e.g., Nurse Appreciation Day, Better Hearing & Speech Month, Cystic Fibrosis Awareness Month), and incorporate newborn screening messages into other relevant information for the general public. The team leader then works to fit the theme of the messages within character limits and finds or creates images to support the messages as appropriate. The following is an example of a recent Facebook post:

All social media posts are approved by both the team and the Program Manager before they are sent to the Communications Department for posting. The team also evaluates the Likes, Shares, and Favorites of each post to determine what types of messages are most effective and reach the greatest audiences, and makes an effort to monitor the social media accounts of partner organizations so that we can support/share their content with our audiences as well.

As of September 2014, the Minnesota Department of Health has approximately 2,750 followers on Facebook and more than 6,700 Twitter followers. Several of our most popular posts have generated dozens of likes and multiple shares/retweets. Since launching our social media efforts in July 2013, the Newborn Screening Program has posted more than 100 unique newborn screening messages on social media.

Most recently, we have been working to expand these efforts by following and liking the pages of other newborn screening partners, colleagues, and supporters. We have also been more diligent about retweeting and reposting partners’ messages. Our goal is to increase the number of people likely to see and/or share our posts/tweets. Ultimately, these efforts promote general newborn screening awareness and visibility.
Clarification and Branding of Newborn Screening in Minnesota
P. Constant, B. Roby, S. Rosendahl and M. McCann, Minnesota Department of Health, St. Paul, MN

Abstract
Before hearing screening and pulse oximetry screening were added to Minnesota’s newborn screening panel, the term “newborn screening” was used to describe both the overall screening program and the blood spot testing process. Because newborn screening only involved the heel stick and subsequent testing, the term could be used interchangeably. Yet as newborn screening has expanded to include hearing and pulse oximetry screening over the years, using the term “newborn screening” to ambiguously refer to both one part of the screening process (blood spot screening) and the program as a whole made for unclear public health educational materials. Furthermore, allowing one part of the screening process to be called “newborn screening” often created the appearance that pulse oximetry and hearing screening were not as important as blood spot screening, but rather just “add-ons.”

To resolve this issue, we made a decision to rebrand our program so as to make it clear that “newborn screening” is not synonymous with “heel stick” or “blood spot screening,” but rather refers to a three-part screening process: blood spot screening, hearing screening, and pulse oximetry screening. We have begun the process of revising all of our educational materials to be consistent with this new language and program structure. We have also designed three icons to use on our materials and website that correspond with each of the three screening components to help visually represent everything that “newborn screening” encompasses. Each icon corresponds with a unique color scheme as well, to help “brand” that part of the screening process. Finally, our team has worked to simplify and reorganize our website based on both audience and screening component, so that information and materials are easily accessible and understandable. By the end of this project, we were able to reduce the clutter of our website from 864 to 240 files. These changes have so far been positively received.

Presenter: Patti Constant, MPH, Minnesota Department of Health, Newborn Screening, St. Paul, MN, Phone: 651.201.4517, Email: Patti.Constant@state.mn.us

Summary
Before hearing screening and pulse oximetry screening were added to Minnesota’s newborn screening panel, the term “newborn screening” was used to describe both the overall screening program and the blood spot testing process. Because newborn screening only involved the heel stick and subsequent testing, the term could be used interchangeably. Yet as newborn screening has expanded to include hearing and pulse oximetry screening over the years, using the term “newborn screening” to ambiguously refer to both one part of the screening process (blood spot screening) and the program as a whole made for unclear educational materials. Furthermore, allowing one part of the screening process to be called “newborn screening” often created the appearance that pulse oximetry and hearing screening were not as important as blood spot screening, but rather just “add-ons.”

To resolve this issue, we made a decision to rebrand our program to make it clear that “newborn screening” is not simply synonymous with “heel stick” or “blood spot screening,” but rather refers to the
three-part screening process in Minnesota: blood spot screening, hearing screening, and pulse oximetry screening.

We have begun the process of revising all of our educational materials to be consistent with this new language and program structure. We have also designed three icons to use on our materials and website that correspond with each of the three screening components to help visually represent everything that “newborn screening” encompasses. Each icon corresponds with a unique color scheme as well, to help “brand” that part of the screening process.

Blood spot screening materials include an icon of a newborn footprint to represent the heel stick, hearing screening materials include an icon of an ear, and pulse oximetry screening materials include an icon of a heart.

To further promote this new branding structure, we integrated these icons and terms into our program website. As we began to review webpages, it also became clear that the website was not clearly organized according to the variety of audiences that use it. Our team worked to simplify and reorganize our website based on both audience and screening component, so that information and materials are easily accessible and understandable. The new organizational structure of our website is as follows:
Throughout the process, we sought to reduce duplication, ensure materials and content would be easy to maintain and keep current, and create a more intuitive navigational structure. In the end, we were able to reduce the clutter of our website from 864 to 240 files.

We continue to work to represent each of the program components equally and with the same level of importance in all of our communication and educational campaigns so that no piece of the screening process is left behind or subsumed by another. These changes have so far been positively received.
SCID Screening in Minnesota: Program Changes after Implementation
B. Warman, C. Wolf, K. Bye, A. Hietala, M. McCann, Minnesota Department of Health, St. Paul, MN

Abstract

Severe combined immune deficiency and other T-cell lymphopenias can be identified early in infants by quantitation of T-cell receptor excision circles (TRECs). We present program changes implemented after a few months of screening for SCID in Minnesota. Screening for SCID and other T-cell lymphopenias officially began for all Minnesota infants on January 7th, 2013. After months of screening, evaluation of specimen, quality control, and outcome data was performed and the following program changes were made ensuring quality testing:

Elimination of standards:
• Discontinue the use of TREC and RNaseP standards in each run
• Replace the use of TREC and RNaseP copies/µL of whole blood cut-offs with TREC and RNaseP Cq cut-offs to determine if a specimen is normal or abnormal
• Increase the TREC Cq internal laboratory repeat cut-off from 32.70 to 33.00

Reporting changes:
• Eliminate the reporting of TREC values on the final report
• Report specimens as “Unsatisfactory” for children older than 1 year of age
• Close a potential SCID case once a negative SCID screen is obtained on newborns with multiple specimens

Assay improvements:
• Extracted DNA from the SCID assay is shared with the cystic fibrosis mutation assay
• 96-well aspirator manifolds are used to remove washing solutions from the 96-well plates to reduce tip cost and time

These changes decreased the internal laboratory repeat rate (from 2.72% to 1.38%) as well as the presumptive positive rate (from 0.26% to 0.12%), thereby decreasing screening costs, reducing unnecessary tests for the newborn, and minimizing the burden on families.

The MDH Newborn Screening Program has successfully implemented SCID as a routine test for all Minnesota babies. To date 5 infants were confirmed as positive, including one SCID case. We continue to monitor our testing and further refine the SCID screening assay, laboratory reporting algorithms, and follow up of babies with presumptive positive results.

Presenter: Carrie Wolf, MBS, Minnesota Department of Health, Newborn Screening Laboratory, St. Paul, MN, Phone: 651.201.5458, Email: carrie.wolf@state.mn.us
Summary

Severe combined immune deficiencies (SCID) is a lethal disorder when there is no early medical intervention. SCID and other T-cell lymphopenias can be identified early in infants by quantitation of T-cell receptor excision circles (TREC). Screening for SCID and other T-cell lymphopenias began for all babies born in Minnesota on January 7, 2013. After months of screening, evaluation of specimen values, quality control, and outcome data was performed that resulted in program changes. The following changes ensure high quality and timely testing for SCID in Minnesota.

Eliminating Standards and Converting to Cq Cut-offs:
The SCID validation was performed to use either copies/μL of whole blood or Cq (cycle of quantification) as the cut-off. A conservative approach was taken in that all results below the copies/μL of whole blood cut-off value or above the Cq cut-off value were repeated. Quantification of TREC and ribonuclease P (RNaseP) was based on their respective standard curves. For the first 3 months of screening, results were expressed in copies/μL of whole blood. Analysis of data obtained during this period showed that the standards introduced more variability and the Cq cut-off values were more accurate and precise. Therefore, the decision was made to use the TREC and RNaseP Cq cut-offs for result determination of all specimens. The elimination of the standards also allowed space for an additional 48 specimens to be included in a run. This change did not impact testing accuracy based on the results obtained when running samples from the SCID pilot proficiency testing program (CDC Newborn Screening Quality Assurance Program) and the TRECs Model Performance Evaluation Survey (MPES), as well as outcome tracking of actual patient results.

Increasing the TREC Cq Internal Laboratory Repeat Cut-off
The internal laboratory repeat cut-off triggers the repeat of the SCID assay on the original specimen in triplicate. Four months of data analysis indicated that changing the repeat cut-off from a Cq of 32.70 to 33.00 cycles would not change result classification (positive or negative) of the specimens. This change decreased the internal repeat rate from 1.89% to 1.39%, thereby reducing the screening cost while maintaining the correct classification of the specimens tested.

Decreasing the RNaseP Cq Cut-off for the Blank Control
A Blank Control (blank filter paper punch) is used on each plate to monitor contamination during punching and/or DNA extraction. Occasionally, runs were failing due to RNaseP amplifying in the Blank Control. RNaseP is at a background level in the environment including filter paper and is expected at an insignificant level in the Blank. An evaluation was performed with the Blank Control results obtained from six months of data. Data analysis showed that changing the Cq cut-off value from >33.00 to >30.00 would allow for some background RNaseP while not jeopardizing the integrity of the assay. This change decreased the rate of failed runs, and reduced screening cost and employee time.

Improving Reporting
Based on the experience gained in the first six months of screening and analysis of the data, the following reported changes were implemented:

- Numeric TREC values for positives are no longer reported
- Specimens with abnormal values received from older children are reported as “Unsatisfactory” as SCID screening is not appropriate for children older than 1 year of age.
- Infants that are in our Low Birthweight Protocol receive multiple screens at 24-48 hours, 14
days, and 30 days or at discharge. These infants have more false positive SCID results. Therefore, once a negative SCID screen has been obtained no further action is taken.

**Improving the Assay**

Improvements to the SCID assay are made in order to save time, reduce cost, and make it easier for analysts to perform the testing. A few assay improvements are:

- The DNA extract from the SCID assay is shared with the cystic fibrosis mutation assay.
- 96-well aspirator manifolds are used during DNA purification and extraction to remove washing solutions from the 96-well plates containing the blood spot punches.

These measures also reduce the cost and time for cystic fibrosis mutation screening.

**Conclusions**

These changes decreased the internal laboratory repeat rate from 2.84% to 1.35% and the presumptive positive rate from 0.28% to 0.19%. This not only reduces the cost to screen for SCID, but also minimizes the burden on families by eliminating unnecessary tests for the newborn.

The MN Newborn Screening Program has screened over 123,000 specimens for SCID since screening began on January 7, 2013. Ten infants have been identified with T-Cell Lymphopenia or SCID, as shown in the table below:

<table>
<thead>
<tr>
<th>Identified Cases of Positives in Minnesota</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCID RAG1</td>
<td>1</td>
</tr>
<tr>
<td>SCID ADA</td>
<td>1</td>
</tr>
<tr>
<td>22q11.2 Deletion Syndrome</td>
<td>4</td>
</tr>
<tr>
<td>Combined Immune Deficiencies (CID)</td>
<td>1</td>
</tr>
<tr>
<td>T-Cell Lymphopenia</td>
<td>3</td>
</tr>
</tbody>
</table>

The MDH Newborn Screening Program has successfully implemented screening for SCID as a routine test for all Minnesota babies. We continue to monitor our testing and further refine the SCID screening assay, laboratory reporting algorithms, and follow up of infants with presumptive positive results.
California Sickle Cell Disease Provider Survey: Assessment of Patient Management Approaches, Barriers to Care and Educational Needs
L. Feuchtbaum¹, N. Rosenthal¹, C. Hutchinson¹, S. Paulukonis²; ¹California Department of Public Health, Richmond, CA, ²Public Health Institute, Oakland, CA

Abstract

Introduction: Sickle Cell Disease (SCD) is a group of inherited disorders characterized by production of abnormal hemoglobin with complex clinical manifestations that can be challenging to manage & treat. This study investigates how California providers manage care for patients with SCD, the barriers they face when providing care, and their SCD-related educational needs.

Methods: A survey was mailed to 1,539 physicians who were listed as the contact doctor of at least one confirmed patient with SCD identified through the California Newborn Screening Program (2009-2012) and/or the MediCal claims data files (2004-2008). We asked providers about who manages the care of their patients with SCD, how familiar they are with SCD treatment & management, whether they experience barriers in providing care, and if they encounter challenges coordinating care with other specialists. Providers also indicated the SCD-related topics they want more information about and how they prefer to receive this information.

Results: Among primary care providers, 40% indicated that their SCD patients are mainly managed by other providers/specialists, 28% manage patients mainly by themselves but other providers are involved, and 20% manage patients on their own. 38% said they are very familiar with SCD treatment & management standards and 52% are somewhat familiar. Among those that acknowledged that barriers to care exist (64%), the most common barrier was “Patients are not adherent with treatment regimens” (48%), followed by “need more staff time to coordinate care” (34%) and “low reimbursement rate for the type of services provided” (32%). Only 22% indicated that they have experienced challenges when coordinating care with other specialists. The most common topical areas that providers want more information about were guidelines for care & management (61%), health educational materials for patients (46%), and complications & clinical outcomes (33%). Providers said they would like to receive these materials through mailed newsletters (54%), or by e-mail (31%).

Conclusions: This survey provided valuable insight into how California providers manage care for patients with SCD, the barriers they face when providing care, the SCD-related education topics they want more information about and how this information can best be disseminated.

Presenter: Lisa Feuchtbaum, DrPH, MPH, California Department of Public Health, Genetic Disease Screening Program, Richmond, CA, Phone: 510.412.1455, Email: lisa.feuchtbaum@cdph.ca.gov

Summary

California Genetic Disease Screening Program received funding from the Centers for Disease Control (Division of Blood Disorders) to implement the Public Health Research, Education and Epidemiology for Hemoglobinopathies (PHRESH) project. The project was funded from September 2012 through September 2014. The primary focus was a detailed evaluation of a population-based surveillance effort targeted towards sickle cell disease (SCD) and thalassemia in California. The surveillance methods were developed and implemented as part of the prior-funded, Registries and Surveillance for...
Hemoglobinopathies (RuSH) project. A second focus of the PHRESH project was to disseminate data (developed under RuSH funding) to promote SCD and thalassemia disease awareness among California primary care providers.

Several of the PHRESH-related disease awareness-raising activities included the development of a California Sickle Cell Disease Fact Sheet. The Fact Sheet provided disease definitions by type of SCD, birth prevalence estimates by race, a map showing counts of diagnosed cases among California newborns by California counties (2004-2008), and graphical displays of health care utilization patterns by age for the five-year cohort, including hospital in-patient and emergency room visits; common medical treatments; procedures; complications and comorbidities; and age at death for people with SCD. Other health promotion materials included a SCD Resource Guide and a postcard promoting the PHRESH project website (see CaSickleCell.org).

All three educational materials were mailed to 1,539 primary care providers along with a 17-question survey. The survey was sent to the provider of record for newborns diagnosed with SCD though the California newborn screening program and those identified through the MediCal claims database (2004 and 2008). The survey contents included questions asking providers for feedback on the Fact Sheet and Resource Guide; physicians’ capacity to care for patients with SCD, barriers to providing care to affected patients; educational needs and best methods for providing this information; and demographic information. Of the 1,539 surveys mailed and 111 completed surveys were returned.

Survey respondents represented providers in the following areas of medical practice: pediatricians (49.5%), internal medicine (18%), family medicine (10.8%), hematology (9%), emergency medicine (4.5%) and nephrology (2.7%). Eight-two percent of respondents practiced medicine for more than 15 years; 50% reported having between 1 and 5 current patients with SCD in their practice and 15% reported having 6 or more current patients with SCD in their practice.

Reaction to the SCD Fact Sheet was very positive: over 90% considered the overall appearance excellent or very good, and the information on the Fact Sheets very clear or clear; 75% considered the Fact Sheet very useful or useful to their clinical practice, and would share it with their patients. All of the following messages were rated as communicated clearly or very clearly by over 80% of the respondents, respectively: the burden of SCD in CA is substantial; SCD affects more than just the Black community; individuals with SCD have a low life expectancy; hospital and emergency room utilization spikes during transition from pediatric to adult care; red blood cell transfusion is the most common procedure among individuals with SCD of all ages; pneumonia/acute chest syndrome is the most common complication observed among SCD patients.

When asked what information about SCD is needed, providers shared the following information needs: guidelines for care and management (61.3%); continuing education opportunities (46.8%); need for health education materials for patients (45.1%); complications and clinical outcomes (33.3%); sickle cell trait (27.9%); clinical trials (23.4%); general genetics (11.7%) and SCD epidemiology (7.2%). When asked to state how they would prefer to receive the needed information, responses included: mailed newsletters (48.6%); emailed newsletters (34.2%); the CasickleCell.org website (27.9%); one on one consultation/conversation with experts (5.4%); and an electronic listserve to discuss individual cases (4.5%).
When asked how the primary care providers (PCP) go about managing care for their patients with SCD, responses included: 42.2% of patients are mainly managed by other providers/specialists; 31.3% are managed by the PCP with specialist involvement; 7.2% say that patients are managed solely by other providers/specialists; and 19.3% managed patients solely by themselves. As far rating their own familiarity with SCD treatment guidelines, 39.8% considered themselves very familiar; 51.6% somewhat familiar; and 8.6% were not familiar.

When asked to identify barriers to providing optimal care for patients with SCD, providers identified the following issues: Patients not adherent with treatment regimens (41.1%); low reimbursement rate for services provided (28.8%); need guidance or support from hematologists (28.8%); need more staff time to coordinate care (27.4%); and lack of familiarity with treatment standards (21.9%).

Despite a low survey response rate, providers gave high marks to the quality and content of the SCD Fact Sheet and they provided important information about their SCD-related information needs, practice patterns and barriers to care.

P-23

California Newborn Screening Program Quality Control Sample Production and Application
Y. Hou and T. Ho, California Department of Public Health, Richmond, CA

Abstract

The Genetic Disease Screening Program (GDSP) has been recognized as an international leader in genetic disease screening. On an annual basis, approximately one million pregnant women and newborns in California are screened for nearly 80 disorders.

As the central laboratory, the Genetic Disease Laboratory Branch (GDLB) conducts a statewide program of adult, prenatal and newborn testing for detection of genetic diseases in support of the clinical initiatives of the GDSP to ensure that these tests are reliable, accurate and cost-effective. GDLB oversees the testing of several contract laboratories that perform newborn and prenatal screening testing, and is responsible for quality assurance, data review and release, method validations, chemical research and training, supply of equipment and reagents to contract laboratories, maintain blood spot specimen bank, vendor services, and inspections for compliance.

As part of the quality assurance program, GDLB makes many different types of quality control samples made from adult human blood that mimics newborn blood samples and maternal blood samples, which are “tray controls”, “proficiency test controls”, or “reference controls”, and all have different concentrations and uses depending on the requirements in each screening program. The tray controls are used with each patient run on a daily basis and results have to fall within limits predetermined by GDLB. Analytical runs with patient samples can pass or fail depending on the results. Contract laboratories assay surrogate specimens at predetermined intervals. Acceptability limits are set by GDLB and are the same for all laboratories. Laboratory staffs are trained using these quality control samples while learning the equipment. The proficiency samples contain expected target levels that are known to GDLB but not to the contract laboratories. When scores are unsatisfactory, GDLB directs the contract laboratory to undertake corrective action. By distributing samples and scoring results biweekly, GDLB is
able to direct corrective actions on a timely basis. New reagents kits are tested using these quality control samples to verify that there is no significant change in patient results when the new lot of reagents is switched.

**Presenter:** Yu Hou, PhD, Genetic Disease Laboratory Branch, California Department of Public Health, Richmond, CA, Phone: 510.231.1735, Email: yhou@cdph.ca.gov

**Summary**

California statutes provide for universal access to quality genetic medical services. Accurate laboratory testing is a key component of these services. As the central laboratory of the Genetic Disease Screening Program (GDSP), the Genetic Disease Laboratory Branch (GDLB) has the responsibility to assure that laboratory tests are conducted with uniform standards of high quality.

Most of the GDLB's genetic testing for birth defects and congenital disorders is performed in the private sector by laboratories who work under contract to GDSP. GDLB has maintained a productive public-private partnership with the laboratories that carry out the testing as well as with the vendors of test instruments that provide reagents and equipment. As part of the quality assurance program, GDLB makes many different types of quality control samples that are made from adult human blood that mimics newborn blood samples and maternal blood samples.

Various proteins, hormones and human red blood cells as ingredients for the controls are purchased from outside vendors. A few drops of blood are placed on filter paper cards, dried overnight, and then tested for background activity on the same equipment that is used for actual newborn babies. The blood then is “spiked” with various amounts of ingredients to reach certain levels, some of which could even be heated to reduce excessive enzyme activity. The process to test the “spiked” blood is repeated until the target levels are reached before blood pools are spotted on approved cards. The dried blood spot cards are then placed in the freezer for long-term storage.

Depending on the purpose of usage, these controls are called “tray controls”, “proficiency test controls”, or “reference controls”, and all have different concentrations and uses depending on the requirements in each screening program. The tray controls are used with each patient run on a daily basis and results have to fall within limits predetermined by GDLB. Analytical runs with patient samples can pass or fail depending on the results. Contract laboratories assay surrogate specimens at predetermined intervals. Acceptability limits are set by GDLB and are the same for all laboratories. GDLB can detect when the wrong reagents are used, or when improper mixing of samples are done, plus many other reasons that cause the quality control samples to give different results. Laboratory staffs are trained using these quality control samples while learning the equipment. They are required to perform periodic testing (called “proficiency testing”) to verify that they are qualified for the work. GDLB fabricates these samples to be surrogates for patient specimens. The proficiency samples contain expected target levels that are known to GDLB but not to the contract laboratories. When scores are unsatisfactory, GDLB directs the contract laboratory to undertake corrective action. By distributing samples and scoring results biweekly, GDLB is able to direct corrective actions on a timely basis. New reagents kits are tested using these quality control samples to verify that there is no significant change in patient results when the new lot of reagents is switched. GDLB also uses the reference samples when developing new assays for screening programs.

Newborn screening is rapidly expanding because of new technologies and genetic discoveries. The implementation of these new technologies and scientific findings requires newborn screening program to set higher standards on the preparation and appropriate use of quality control materials for the newborn screening tests.

P-24

Identification of Galactose-1-Phosphate Uridyl Transferase Gene Common Mutations in Dried Blood Spots

M. Sartippour, R. Doroudian, G. Frampton, F. Lorey, G. Helmer, T. Ho, A. Bhandal, California Department of Public Health, Richmond, CA

Abstract

The California newborn screening program uses newborns’ dried blood spots (DBS) to screen for genetic disorders. The deficiency of galactose-1-phosphate uridyltransferase (GALT) results in an inherited metabolic disorder, classic galactosemia. Common mutations of the GALT gene are well-identified. To avoid the stress of drawing an intravenous blood sample from newborns identified as presumptive positive for galactosemia, we evaluated a method to use the initial DBS collected for newborn screening and test it to identify common mutations in the GALT gene.


Conclusions: This method will decrease the follow-up turnaround time of GALT positive patients and potentially reduce emotional stress on the families.

Presenter: Maryam Sartippour, PhD, Genetic Disease Laboratory, California Department of Public Health, Richmond, CA, Phone: 510.231.1718, Email: msartipp@cdph.ca.gov

Summary

1 - Importance and relevance of the project and results
Deficiency of galactose-1-phosphate uridyl transferase (GALT) is one of the metabolic genetic disorders screened in California using newborn dried blood spots. During follow-up tests, common mutations of the GALT gene are identified using whole blood samples. To avoid the stress of drawing an additional
blood sample from newborns who are identified as presumptive positive for galactosemia, we developed a method to test common mutations in the GALT gene using blood spots.

With our method of extracting DNA from dried blood spots, the newborn’s initial blood spot can be tested for 9 common GALT gene mutations/variants. This method needs less specimen volume and provides a convenient and efficient test for newborns that have demonstrated initial positive screening results. Early detection of mutations, heterozygosity, and homozygosity helps the physicians to make prompt diagnosis and provide counseling to parents of newborns.

Due to the relatively high percentage of Hispanics in California, we had an interest in detecting the IVS2-2 mutation which has been reported as being prevalent in the Hispanic population. A literature search showed no previously reported studies on IVS2-2 patients using dried blood spots.

This blood spot method decreases the genomic test turnaround time of GALT screened positive patients and potentially reduces emotional stress on families required to bring an additional blood draw and on the newborn identified as presumptive positive who might be severely sick. The results of these experiments offer new insights into the design of future pilot studies.

2 - Broad Interest of the Topic
Galactose-1-phosphate uridyl transferase (GALT- EC 2.7.7.10) is required for the conversion of galactose to glucose. GALT deficiency caused by gene mutations leads to physical complications including growth failure, renal and hepatic dysfunction, cataracts, sepsis, and mental retardation. More than 230 mutations have been identified for the GALT gene. Nine common GALT gene mutations/variants account for most of the galactosemia alleles. The newborn screening program at the California Department of Public Health screens for GALT deficient newborns as part of the newborn genetic defect screening panel. Our cut-off limits are set conservatively to prevent any false negative results. Presumptive positive cases are followed by DNA testing. Poor specimen handling, environmental factors and GALT enzyme bio-instability, and the presence of the Duarte N314D variant may potentially result in the increase of false positives in the initial enzymatic deficiency screen. Follow-up DNA testing methods have been developed to identify true positive cases. In 2007 combination of biochemical analysis of GALT enzyme activity and analysis of the most common mutations have been developed and also a well-defined method using single nucleotide extension to identify common GALT gene mutations in whole blood were published. Newborns identified as presumptive positive for galactosemia in the California Newborn Screening Program are referred to an out of State contracted laboratory to test for these seven GALT gene mutations: IVS2-2A>G, p.S135L, p.T138M, p.Q188R, p.L195P, p.Y209C, p.K285N, and these two variants: p.L218L and p.N314D. The DNA testing method requires a few milliliters of venous blood which can be a burden on newborns and their parents. In 2003, a Light Cycler technology was described to determine four common mutations and one Duarte variant using blood spots. The goal of our study is to develop a reliable method to extract DNA from the initial dried blood spot taken from the newborn for Newborn Screening and to detect nine GALT gene common mutations/variants in these blood spot samples.

3 - Educational Value
This method is useful for newborn screening programs providing test results for Galactose-1-Phosphate Uridyl Transferase (GALT) enzyme activity and referring presumptive positive newborns to confirmatory laboratories for identification of common mutations in the GALT gene. Our method provided the following new insights:

We developed a method to identify GALT gene common mutations/variants by Single Nucleotide Extension amplification using dried blood spots. We tested the effect of homozygosity for mutations/variants S135L, Q188R, and N314D. We evaluated our method by spotting whole blood confirmed for 2 mutations Q188R and K285N and by testing the dried blood spots for expected results. We detected the IVS2-2 mutation in samples from actual patients. If successful, this method may exempt the newborn identified as presumptive positive from the need for a blood redraw. This method may conserve time and effort, reduce financial costs, and reduce emotional stress for substantial number of families.

4 - Design and Layout
In a double-blind study specimens from newborns were provided by the Genetic Disease Screening Program of the California Department of Public Health. Two punches of dried blood spot were subjected to DNA extraction using “Generation” DNA Purification Solution 1 and “Generation” DNA Elution Solution 2 (Qiagen Sciences, Maryland, USA). Extracted DNA (5-10 ng/µl) were subjected to the polymerase chain reaction in 20 µl of final mixture, using a GeneAmp 9700 Thermal cycler (Applied Biosystems, Foster City, CA), EmeraldAmp Max HS PCR Master Mix (Takara Bio Inc/Clontech Laboratories, Mountain View, CA) and one µmol/l of each forward 5’-GCCTGTCCAGTCTTTGAAGC-3’ and reverse primer 5’-CATTTCGTAGCCAACCATGA-3’ obtained from Applied Biosystems (Foster City, CA). Single Nucleotide Extension was then performed using nine primers (Integrated DNA Technologies, Inc., Coralville, IA) directed at GALT gene common mutations/variants and SNaPshot Multiplex GeneScan (Applied Biosystems, Foster City, CA). Single nucleotide extension products were injected into the ABI Prism 3100 capillary electrophoresis instrument using performance-optimized polymer -6 on a 50-cm array (Applied Biosystems).

We used one hundred eighty-four newborn specimens from the Genetic Disease Screening Program. Our results from newborn dried blood spots show 100% concordance with the genotypes of galactosemia-positive whole-blood specimens previously tested by reference laboratories and documented in the Genetic Disease Screening Program. Newborn specimens identified as negative for the nine mutations/variants (n=111) showed expected normal peaks (Figures 1A and 2A). Figure 1 (B-H) shows the genotyping of common mutations/variants of the GALT gene (IVS2-2, S135L, Q188R, L195P, Y209C, L218L, K285N, and N314D) detected in dried blood spots in comparison to the normal peaks detected in a negative sample. Since we didn’t receive any dried blood spots with detectable T138M mutation, we requested samples from Emory University School of Medicine which were kindly provided by Drs. Bradford Coffee and Nick Hjelm. Nine of our specimens were homozygous for S135L (n=2), Q188R (n=4), and N314D (n=3). Figure 2 shows the effect of homozygosity with our method. In comparison with wild type, no distinguishable normal peak was detected and the mutated peak was significantly bigger for these homozygous cases (Figure 2: B-D). To further validate our method using dried blood spots, heparinized whole blood with known mutations Q188R and K285N (Virginia Medical Research, Virginia Beach, VA) was spotted on filter paper following the established laboratory protocol and was tested by the current method. Figure 2E shows the Q188R and K285N mutations expected for this specimen.

Our method of extracting DNA from dried blood spots needs less specimen volume and provides a convenient and efficient test for newborns that have demonstrated initial positive screening results. With our method the newborn’s initial dried blood spots can be tested for 9 common GALT mutations/variants, which allows a faster reporting of results. Early detection of mutations,
heterozygosity, and homozygosity helps the physicians to make prompt diagnosis and provide counseling to parents of newborns. The results of these experiments offer new insights into the design of future pilot studies.

Figure 1
What Factors Influence the Decisions of Parents Regarding Residual Dried Blood Spot Storage and Use in an Opt in System
B. Reilly, C. Bresette, S. Arshadmansab, R. Lee, S. Tanksley, J. Wallace, Texas Department of State Health Services, Austin, TX

Abstract

Objective: To examine residual specimen storage and use decision form statistics to determine what factors may influence the rate of form return. This investigation will consider whether there are demographic, regional, or other trends in parental decisions, and what aspects investigators would need to consider if requesting access to bloodspots in Texas.

Background: In 2011, the Texas Legislature passed a new law regarding the storage and use of residual dried blood spots. By default under this law, all specimens collected on or after June 1, 2012 may be stored for up to 2 years and are not allowed for research uses external to the Texas Department of State Health Services (DSHS). However, the parents may opt to have specimens stored for up to 25 years and allow de-identified blood spots to be used for external research. Texas DSHS developed a system where parents receive a “Decision” form upon the collection of each newborn screening specimen. Parents make a selection of “OK” or “NO” and return the form either to the healthcare provider or directly to DSHS. DSHS tracks and acts upon the latest Decision form received by the laboratory for all specimens associated with any particular patient.

Methodology: The Texas Newborn Screening Laboratory Information Management System has been configured to track which specimens the laboratory has received an associated “Decision” form for and whether or not the parent selected ‘OK’ or ‘NO’. Texas DSHS compares the Decision form data for each specimen with the patient and submitting facility data provided on the specimen collection kit. Analyses
have been developed to focus on and monitor trends associated with region, urban vs. rural location, submitting facility type, ethnicity, health status, birth weight, and Medicaid eligibility.

**Significance:** Findings from this analysis can provide insight into the effect that an opt-in residual dried blood spot storage and use policy may have on the stored sample set's accurate representation of a particular population. It may also provide additional information for potential investigators regarding the appropriateness of available dried blood spots in Texas for any proposed study. Finally, public health programs may gain insights into targeted submitting facility education that may be considered to ensure parents' understand their options.

**Presenter:** Brendan Reilly, Texas Department of State Health Services, Austin, TX, Phone: 512.776.2477, Email: breandan.reilly@dshs.state.tx.us

**Summary**

**Objective:** To examine residual specimen storage and use decision form statistics to determine what factors may influence the rate of form return. This investigation will consider whether there are demographic, regional, or other trends in parental decisions, and what aspects investigators would need to consider if requesting access to bloodspots in Texas.

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**Methodology:** The Texas Newborn Screening Laboratory Information Management System has been configured to track which specimens the laboratory has received an associated “Decision” form for and whether or not the parent selected ‘OK’ or ‘NO’. Texas DSHS compared the Decision form data for each specimen with the patient and submitting facility data provided on the specimen collection kit. Texas staff analyzed data from all of 2013. Analyses were completed to determine specimen volume, form return rate and percentage OK of returned forms by region, county, submitting facility type, payor, ethnicity, birth weight, sex, mother’s age, and health status.

Texas is a two screen state and specimen linking success is approximately 90%. Patient level data was analyzed based on first screens only in order to remove possible duplicates. Since a single decision form applies to all specimens for an individual patient, submitter level data can only be used to estimate effect of submitter type on return rates. Submitter and submitter location analyses were based on all specimens.

Summary of Results:
The Texas laboratory received 752,176 newborn screening specimens in 2013 including 386,715 first screens. 47.3% of these specimens had an associated Decision form returned to DSHS. Of the returned forms, 74.5% indicated OK to store for up to 25 years and allow for external research purposes.

Submitter Type
The Texas laboratory receives specimens from hospitals (67%), doctor’s offices or clinics (30%), laboratories (2%), midwives or birthing centers (1%), and County Health Departments (0.1%).

Return rate by submitter type varied. Return rate for forms applicable to specimens submitted by midwives or birthing centers (73.0%) were 1.56 times the rate for forms applicable to specimens submitted by hospitals (44.3%). Clinics also had higher than average return rates (54.9%) while laboratories had poor return rates (19.8%).

With the exception of midwives / birthing centers, parental decision by submitter type showed little variation, ranging from 69.3% to 76% with “OK” response. Forms distributed by midwives or birthing centers were 1.91 times more likely to indicate NO than a form distributed by a hospital.

The percentage of specimens OK to store for up to 25 years and allow for external research purposes from hospitals, midwives / birthing centers, and health departments is representative of all specimens received by the Texas laboratory. Specimens submitted by doctor’s offices or clinics are 17% over-represented. Specimens submitted by laboratories are 60% under-represented.

Submitter Location
The state of Texas is divided into 11 health service regions and 254 counties. Approximately 2/3 of all NBS specimens are received from the 10 counties containing the population centers of Houston, Dallas / Fort Worth, San Antonio, Austin, the Rio Grande Valley, and El Paso.

Analysis of return rates by health service region showed considerable variability, ranging from 7.4% to 75%. The highest return rate was from the Texas Panhandle (Region 1) with the majority of specimens from Lubbock County. Due to very low return rates in El Paso County, the lowest return rate was from far west Texas (Region 10).

Parental Decisions overall by region varied little from the statewide average. All regions had percent OK rates between 69% and 84%, with the lowest percent OK from the Austin metropolitan area (Region 7) and the highest percent OK from the Rio Grande Valley (Region 11). The lower than average percent OK for forms distributed by midwives or birthing centers was consistent regardless of region or county.

Regional distribution of specimens OK to store for up to 25 years and allow for external research purposes varies across regions. Region 8 (including San Antonio metropolitan area) and Region 9 (rural near west Texas) accurately represent overall populations. Region 10 is the most under represented region due to very low return rates from the population center of El Paso. Region 1 is the most over – represented due to high return rates from the region.

Payor
There are two types of newborn screening collection forms in Texas, Medicaid/CHIP and Insurance/Self-pay.

Forms for patients with insurance are 1.2 times more likely to be returned to DSHS than forms for patients who are eligible for Medicaid or CHIP. Parents of Medicaid-eligible patients are slightly more likely (1.04 times) to indicate OK on the form.

The percentage of specimens OK to store for up to 25 years and allow for external research is slightly over-representative of insurance-eligible patients.

**Ethnicity**
53.4% of forms for White patients are returned to DSHS. This is a rate >1.30 times more likely than both African American and Hispanic patients.

Percent OK rates for Hispanics (76.3%) and Whites (75.0%) were consistent with the 74.5% statewide average. African Americans (68.2%), Asians (69.1%), and American Indians (70.6%) were the least likely to indicate OK.

A random sampling of specimens OK for 25 year storage and de-identified research would moderately under-represent African Americans, slightly under-represent Hispanics, and moderately over-represent Whites. Asians and American Indians would be accurately represented.

**Birth Weight and Health Status**
Form return rate was significantly lower than average for both low birth weight patients and patients with a health status listed as sick or premature. Forms for normal weight patients are 1.62 times more likely to be returned than forms for low birth weight patients. Forms for Normal status patients are 1.63 times more likely to be returned than forms for sick/premature status patients.

Neither birth weight nor health status influenced the percent of specimens OK for 25 year storage and de-identified research use.

A random sampling of specimens OK for 25 year storage and de-identified research would significantly under-represent low birth weight and sick/premature patients.

**Patient Sex/Mother’s Age**
Neither patient sex nor mother’s age demonstrated significant effect on either form return rate or percent OK.

**Conclusions:**

**Return Rates**
Submitter type and location, payor, ethnicity, birth weight, and health status may affect form return rates. Sex and mother’s age did not influence return rates. To improve return rates, Texas should focus education efforts on hospitals in El Paso County, hospitals commonly providing for Medicaid-eligible patients, and Neonatal Intensive Care Units.

**Percent OK of Returned Forms**
Parent sentiment (74.5% OK) is consistent across almost all measures independent of return rate. Payor, birth weight, health status, sex, and mother’s age do not appear to influence the parent decision. Variation occurs by Region and Ethnicity, but OK rates remain consistently between 68% and 80% for
both measures. OK rates for specimens submitted by midwives or birthing hospitals are significantly lower than other submitter types.

Specimens approved for long term storage and de-identified research uses are generally representative of the statewide population. However, potential researchers should carefully consider that a random sampling of specimens would under and over represent various subgroups.

<table>
<thead>
<tr>
<th>Over Represented</th>
<th>Under Represented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimens submitted by doctor's offices</td>
<td>Specimens submitted by laboratories</td>
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<tr>
<td>Region 1 - Panhandle</td>
<td>Region 10 - Far west Texas</td>
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<tr>
<td>Insurance patients</td>
<td>Medicaid /CHIP patients</td>
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<tr>
<td>Whites</td>
<td>African Americas and Hispanics</td>
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<td></td>
<td>Low birth weight patients</td>
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<td>Sick/Premature patients</td>
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P-26

Newborn Screening for Severe Combined Immunodeficiency: The First 17 Months of the Texas Experience
R. Lee, M. Nolen, C. Corrigan, D. Luna, D. Freedenberg, S. Tanksley, Texas Department of State Health Services, Austin, TX

Abstract

Objective: To evaluate the first 17 months of newborn screening for severe combined immunodeficiency (SCID) in the Texas Department of State Health Services Newborn Screening Program.

Methodology: The State of Texas Newborn Screening Program tests two separate specimens for each newborn, with a 1st screen performed on specimens generally collected at 24-48 hours of age, and a 2nd screen on specimens collected 7-14 days of age. The baby’s blood is collected by heel stick onto filter paper and the dried blood spot is screened for SCID through an automated DNA extraction method followed by a RT-qPCR assay to detect the presence of TREC’s, the primary marker, and RNaseP, the reference gene. For all 1st screen specimens reported as other than normal, a repeat specimen is requested. A referral to immunologists is recommended if the TREC quantity is below Limit of Blank or if the newborn has repeated non-normal results.

Results and Conclusion: From December 2012 to April 2014, approximately 1,051,955 specimens were screened for SCID. Of these specimens, 2,848 were reported as Abnormal or Borderline. Of ~542,930 newborns screened, 446 were referred to immunologists, and 14 SCID cases and 247 secondary cases were diagnosed. Data analysis including the incidence rate by ethnicity will be presented. Using TREC quantities vs. Ct values as analyte cutoffs will be compared. To evaluate the usefulness of testing all 2nd screens, diagnosed cases with 1st screen normal TREC and 2nd screen non-normal TREC will also be reviewed. In addition, the potential effect of transfusion, birth weight, and age of collection will be discussed for quality improvement.
**Summary**

**Objective:** To evaluate the first 17 months of newborn screening for severe combined immunodeficiency (SCID) in the Texas Department of State Health Services Newborn Screening Program.

**Background:** In December 2012, the Texas Newborn Screening Program added Severe Combined Immunodeficiency to the screening panel. The State of Texas Newborn Screening Program tests two separate specimens for each newborn, with a 1st screen performed on specimens generally collected within 24-48 hours of age, and a 2nd screen on specimens collected 7-14 days of age. The baby’s blood is collected by heel stick onto filter paper and the dried blood spot is screened for SCID.

**Methodology:** The dried blood spot is screened for SCID through an automated DNA extraction method followed by a RT-qPCR assay to detect the presence of T-cell Receptor Excision Circles (TRECs), the primary marker, and RNaseP, the reference gene. All specimens with TRECs <200 copies/µL of blood were retested in duplicate using the same specimen. If the final TREC was <110 copies/µL, the specimen was reported as abnormal. For low birth weight babies (<2,000g), TREC quantities between 110-150 copies/µL were reported as borderline. For normal birth weight babies, TREC quantities between 110-150 copies/µL were reported as abnormal. For all 1st screen specimens reported as other than normal, a repeat specimen is requested. A referral to immunologists is recommended if the TREC quantity is below the Limit of Blank or if the newborn has repeated non-normal results.

**Results and Conclusions:** From December 2012 to April 2014, approximately 1,051,955 specimens were screened for SCID. Of these specimens, 2,848 were reported as Abnormal or Borderline. The overall presumptive positive rate is 0.27%. Of the approximately 542,930 newborns screened, 446 (0.08%) were referred to immunologists, resulting in 14 SCID cases and 231 secondary cases being diagnosed. The positive predictive value for true SCID cases is 3.1%. The negative predictive value is 100%. Clinical sensitivity is 100%. Clinical Specificity is 99.9%. The false positive rate is 0.08%. The false negative rate is 0%.

Several factors were evaluated to determine their effects on the TREC quantities and/or SCID screening results.

**Birth Weight:** Low birth weight babies (<2,000g) account for approximately 3.3% of the total newborn population; however, close to half (48.2%) of non-normal SCID screening results were collected from low birth weight newborns. For normal birth weight babies, the presumptive positive rate was 0.14%. For low birth weight babies, the presumptive positive rate increased 28 fold to 4.0%.

**Age:** The median TREC value of different age brackets were evaluated. Although the scatter chart showed a slight decrease in TREC quantities with age, statistical analysis performed indicated there was no significant difference.

**Newborn’s Status:** 30.0% of presumptive positive specimens were from newborns with normal (healthy) status, 43.9% from newborns that were sick without transfusion, and 26.2% from newborns who had received a transfusion. For babies with normal status, the presumptive positive rate was 0.09%. For babies sick without transfusion, the presumptive positive rate increased 14 fold to 1.3%. For babies receiving a transfusion, the presumptive positive rate increased another 10 fold to 13.3%.

**Ethnicity:** The ethnic distribution of the 14 diagnosed cases is 21.4% whites, 50% Hispanics, and 28.6% unknown. Overall, the SCID incidence rate is 1 in 38,780 (1 in 62,600 for whites, 1 in 37,080 for Hispanics, and 1 in 8,590 for unknown).

Overall, birth weight, sick/transfusion status, and ethnicity have an effect on SCID screening results.

The potential use of TREC Ct, instead of TREC quantities, as the cutoff was reviewed. The median TREC copy numbers/µL of whole blood for each month of the 17 months period ranged from 764 to 1,362. The median TREC Ct values ranged from 33.885 to 34.436. Median TREC copy numbers/µL of whole blood varies with standard preparation lots over time while median TREC Ct remains more constant over time. Currently, the TREC quantity cutoff of 150 is set conservatively to allow for the TREC standard lot changes. We will continue the evaluation of using TREC Ct to set cutoffs.

The effectiveness of testing all second screens was reviewed. Texas Newborn Screening Laboratory tests all 2nd screens even if the 1st screen was normal. Over the 17 months, 737 newborns had 1st normal SCID screening results and 2nd non-normal results, the majority (89.8%) of which was cleared. 10.2% had secondary diagnoses, and no classical SCID cases were found. All classical SCID cases were non-normal on both first and second screens.

**P-27**

**Affordable Care Act Web-based Resource Tool**
S. Mann, L. Hasegawa and J. Boomsma, Hawaii Department of Health, Honolulu, HI

**Abstract**

**Background:** The Western States Genetic Services Collaborative (WSGSC) is one of seven Health Resources and Services Administration (HRSA) funded Regional Genetic Service Collaboratives (RCs) across the country. The WSGSC consists of Alaska, California, Guam, Hawaii, Idaho, Oregon and Washington. Understanding the possible impact of the Affordable Care Act (ACA) to the families with or at risk for genetic disease is a priority activity for HRSA and the RCs. The WSGSC has developed a web based resource to help health care providers, public health staff, and families learn about the various aspects of the ACA.

**Methodology:** Based on HRSA’s focus on the life course and Milton Bradley’s Game of Life, the website is presented as a path of life segmented with major life activities. ACA information pertinent to that stage of life is accessible by clicking on the stage of life box. Some examples of the life activities include: You already have health insurance; Your baby has newborn screening; and You have a child with special health needs. The inside of the path contains a town square with links to general information about the ACA including: Insurance marketplace/exchange; essential health benefits; and Medicaid. Information is linked to state specific information when applicable. There is also a link to allow users to share stories about their experiences with the ACA.

**Results:** The website was launched to the public with e-mails to the WSGSC partners, other RCs, the National Coordinating Center for the RCs, and our various RC partners on October 22, 2013.
**Discussion:** The website is a valuable tool to help providers and families learn more about the ACA in an easily accessible manner.

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**Presenter:** Sylvia Mann, MS, Hawaii Department of Health Genomics Section, Honolulu, HI, Phone: 808.733.9063, Email: sylvia@hawaiigenetics.org

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**P-28**

**Technology Transfer Among NBS Programs within SCID NBS Pilots**

J. Gerstel-Thompson\(^1\), J. Hale\(^1\), R. Lee\(^2\), S. Tanksley\(^2\); \(^1\)New England Newborn Screening Program, Jamaica Plain, MA, \(^2\)Texas Department of State Health Services, Austin, TX

**Abstract**

**Background:** Technology transfer and quality assurance among newborn screening laboratories implementing emerging technologies is essential to quality improvement and expansion of technical capacities. Detection of Severe Combined Immunodeficiency (SCID) requires high-throughput DNA testing. With funding from the Centers for Disease Control and Prevention, the New England Newborn Screening Program (NENSP UMMS) of the University of Massachusetts Medical School sought to make available its screening assay and algorithm to other public health Newborn Screening (NBS) programs. Beginning in 2009 and continuing for three years, a series of hands-on four-day technical trainings were provided on-site at NENSP UMMS to colleagues from approximately ten independent centers.

**Objectives:** To test the quality of technology transfer of NENSP’s SCID NBS technology and knowledge experience. To validate methodology prior to its implementation in another state. To enhance understanding of TREC copy numbers within the neonatal period.

**Methodology:** NENSP UMMS and the Texas newborn screening program of the Texas Department of State Health Services (TXNBS DSHS) entered into an agreement to perform parallel testing on a set of coded specimens. TXNBS DSHS put forth a pilot program, implementing SCID NBS as a supplemental research protocol in select hospitals. After TXNBS completed routine NBS testing, a coded aliquot of each specimen was sent to NENSP. SCID NBS was performed by NENSP in a manner and timeframe for clinical reporting. TXNBS later tested other aliquots from the same specimens. TREC Cq values, and result interpretations from NENSP UMMS and TXNBS were compared.

**Results:** 5,569 specimens from 3,267 infants were tested by the NENSP and TXNBS. Of the 3,267 infants, 2,270 had at least two serial specimens tested. Interpretations of SCID NBS data were consistent between programs. Additionally, 40 newborn specimens retrieved after consent from known SCID cases or other primary immunodeficiencies were coded and tested by the NENSP. Data consistent with diagnoses were observed.

**Conclusion:** Collaboration between NBS programs facilitates expansion of screening services with confidence. Following the completion of this project, Texas began statewide SCID NBS on December 1, 2012.

**Presenter:** Anne Marie Comeau, PhD, New England Newborn Screening Program, University of Massachusetts Medical School, Jamaica Plain, MA, Phone: 617.983.6324, Email: anne.comeau@umassmed.edu or jacalyn.gerstel-thompson@umassmed.edu

The 15-year Experience of Newborn Screening for Medium Chain Acyl-CoA Deficiency in Massachusetts
I. Sahai, J. Bailey, J. Hale and T. Zytkovicz, New England Newborn Screening Program, Jamaica Plain, MA

Abstract

Background: Massachusetts began screening neonates for medium chain acyl-CoA deficiency (MCAD) in February 2009 and approximately 1.2 M neonates have been screened since then.

Methods: Octanoylcarnitine (C8), the primary marker for MCAD, is analyzed as part of the acylcarnitine panel by MS/MS. All results with C8>0.5 uM (6 SD above mean) are considered screen positive. Diagnostic testing on neonates with positive screens performed by / under the guidance of the specialist. The New England Newborn Screening Program (NENSP) tracks all positive screens until resolution of diagnosis; as determined by the specialist, and tracks confirmed cases periodically. Targeted scanning for the 985A>G mutation on the ACADM gene is performed by NENSP on positive screens.

Results: Sixty infants with confirmed MCAD were identified by screening. C8 values in the initial specimen (collected 24 -96 hrs after birth) in the cases ranged from 0.56 uM to 37.44 uM. A C8 > 30 uM on the initial screen was noted in 4 neonates; all were 985A>G homozygotes. 3/4 had symptoms attributable to MCAD within 96 hrs of birth. C8>20 & <30 uM was noted in 9; six were 985A>G homozygotes & one a compound heterozygote with 985A>G. Two had symptoms within 96 hrs of birth, one of these infants died at 11 months. C8>10 & <20 uM was noted in 13; 6 were 985A>G homozygotes & two compound heterozygote with 985A>G. Three infants had symptoms within 96 hrs of birth; one died on day of life 3 and one survived the neonatal period but died a few months later. C8>0.5 & <10 uM was noted in 34; 3 were 985A>G homozygotes & 22 compound heterozygote with 985A>G. One infant (C8 of 6.98 uM) had symptoms within 96 hrs of birth. Majority of cases in the cohort were Non-Hispanic Whites with the exception of 3 Black Non-Hispanic, 2 Asians and 2 Hispanic. 3/7 cases among the Non-Whites were compound heterozygote with 985A>G. Breast fed neonates had higher C8. All 985A>G homozygotes had C8>5uM. Neonates with initial C8>15 were at increased risk of developing carnitine deficiency on follow-up and required supplementation.

Conclusions: Newborn screening for MCAD has been a successful initiative, however severe phenotypes can present very soon after birth. Furthermore identification by screening does not automatically signify a successful outcome and the importance of continued vigilance and treatment is imperative.

Presenter: Inderneel Sahai, MD, New England Newborn Screening Program, University of Massachusetts, Jamaica Plain, MA, Phone: 617.983.6300, Email: nderneel.sahai@umassmed.edu
Newborn Screening for Galactosemia: The New England Newborn Screening Program Experience
I. Sahai, A.M. Comeau, J. Hale, T. Zytkovicz and D. Britton, New England Newborn Screening Program, Jamaica Plain, MA

Abstract

Background: The New England Newborn Screening Program (NENSP) has been screening neonates for Galactosemia since 1964.

Methods: The NENSP utilizes a two-tier (Tgal + GALT) approach. TGal of > 5mg/dl prompts GALT analysis. T-Gal of < 14 mg/dl and GALT > 50% is reported as normal. Specimens with (1) GALT < 25%, (2) T-gal > 30mg/dl, or (3) GALT > 25 & < 50% AND T-gal > 20 & < 30mg/dl prompt an immediate phone contact (“High” positive). Results with (4) GALT > 25 & < 50% AND T-gal < 20 mg/dl, or (5) GALT > 50% AND T-gal > 14 & < 30 mg/dl prompt a request for a repeat screen (“Moderate” positive). Specimens with a high positive, and those from neonates with two moderate positive results with GALT > 25 & < 50, are tested for 9 common mutations of the GALT gene.

Results: Of the 264,490 initial specimens from neonates born Jun 2009 to Dec 2012 in Massachusetts, 6140 prompted a second-tier GALT analysis. 80 were considered positive and prompted further intervention. GALT < 25% was noted in 8; these were subsequently confirmed as 1 classical galactosemia (Q188R/ Q188R), 2 Duarte variant galactosemia (Q188R/N314D), 3 carriers & 2 false positives (FP). 33 positive screens had GALT > 25 & < 50% AND T-gal < 20 mg/dl; in this group were 19 Duarte variants, 17 carriers & 17 FP. 19 positive screens had GALT > 50% AND T-gal > 14 & < 20 mg/dl and prompted a repeat screen. Only 3 of these neonates had a positive screen on the follow-up specimen, none with galactosemia. The 33 cases of classical galactosemia cases identified by NENSP since 1999 were reviewed; GALT activity was < 10 % in 20; > 10 & < 25 % in 12. The lowest T-gal amongst the classical cases was 5.8 mg/dl. Interestingly the T-gal values in the initial specimen from a set of twins were substantially different (8.5 mg/dl and >50 mg/dl). Since 1999, NENSP has identified 3 cases of GALE deficiency. We are not aware of any false negative screening results for classical galactosemia during this period.

Conclusion: The report summarizes our most recent experience and adds to the limited information available on screening for galactosemia.

Presenter: Inderneel Sahai, MD, New England Newborn Screening Program, University of Massachusetts Medical School, Jamaica Plain, MA, Phone: 617.983.6300, Email: inderneel.sahai@umassmed.edu

Summary

Abstract: Newborn screening (NBS) for classical galactosemia has a long history and provides the opportunity for early diagnosis, intervention and improved outcomes. The New England Newborn Screening Program (NENSP) retrospectively analyzed 10 years of screening data and diagnostic outcomes from our two-tiered testing algorithm. Additionally, we reviewed all diagnosed cases of classical galactosemia and kinase and epimerase deficiencies that had been reported to our program over a 15 year period.
**Introduction:** Identification and early treatment of infants with Classical Galactosemia has long been a focus of NBS programs in order to mitigate the acute life threatening complications associated with this disorder. The initiation of a lactose restricted diet within the first days of life will typically resolve neonatal complications such as feeding problems, failure to thrive, liver failure, and sepsis, ultimately preventing death. Impairment of galactose metabolism can result from a deficiency of any one of three enzymes of the Leloir pathway that catalyzes the conversion of galactose to glucose: Galactokinase (GALK), Galactose-1-phosphate uridylyltransferase (GALT), or UDP-galactose-4-epimerase (GALE). Most NBS programs target the identification of infants with Classical Galactosemia caused by a deficiency of the GALT enzyme. Population-based NBS programs measure total serum galactose or GALT activity (or some combination of the two) eluted from newborn dried blood spots as markers of the disease. When the screening strategy uses total galactose as the primary marker, infants with GALK or GALE deficiencies may also be identified by screening.

**Methods:**

**Study Subjects**
We reviewed screening outcomes from a 10 year cohort of all New England infants screened by the NENSP for galactosemia from June 10, 2004 – June 10, 2014 (n = 1,200,640). In addition, we reviewed characteristics of all diagnosed cases of GALK, GALT, and GALE deficiencies that have been reported to the NENSP since 1999.

**Laboratory Screening Algorithm**
The NENSP galactosemia screening algorithm used total galactose (TGAL) as a primary marker. The GALT enzyme activity is measured in a subset of infants (those with a TGAL >=5 mg/dL or by request due to clinical concern) as a second tier test. GALT testing was performed in ~3% of samples. Specimen results showing a TGAL <5 mg/dL or a “TGAL <14 and GALT activity >=50%” are reported to be within normal limits. Any specimen with a “TGAL >=14 mg/dL or GALT activity <50%” have screening results that are reported to be out of range. Supplemental GALT DNA testing is provided for a subset of infants with out of range biochemical screening results.

**Out of Range Reporting Algorithm**
All out of range galactosemia results are reported by phone to the infant’s primary care provider (PCP). Using a screening result profile comprising TGAL concentration and measured GALT activity, the NENSP categorizes out of range NBS results as high or low probability for classical galactosemia. Recommended follow up actions for out of range galactosemia results are based on the categorization of the infant’s biochemical results. Experience-based relative risks are provided by NENSP to the PCP.

**Results:** Over the 10 year period, 563 infants (0.05%) of the over 1 million infants screened had an out of range NBS result suggestive of one of the three types of galactosemia (Table 1). Seventeen infants with confirmed Classical Galactosemia were identified (1 in 70,626) with no known false negative screening results. An additional 10 infants with confirmed GALE deficiency and 2 infants with confirmed GALK deficiency were also identified by the screening program.

**Confirmed Case data since 1999**
Over the past 15 years of screening, the NENSP has identified 34 infants with GALT deficiency, 12 infants with GALE deficiency, and 2 infants with GALK deficiency.

• Of the 10 cases of classical galactosemia with WNL TGAL: 5 on breast or regular formula; 4 on soy due to family history; 1 feeding status unknown. The lowest observed TGAL among classical cases was 5.8 mg/dL (Q188R homozygote breast feeding at time of NBS collection)
• A set of fraternal twins (Q188R homozygotes) were identified with markedly different TGAL levels of 8.5 mg/dL (DOL 2) and >50 mg/dL (DOL 3) on their initial specimens.
• The GALT activity in 21 of the confirmed cases of classical galactosemia was <10% and 11 cases had GALT activities ranging from >=10% and <25% including 6 Q188R homozygotes. The percentages for two cases are only known to be <25%.
• Of the 12 confirmed cases of GALE deficiency detected, one was diagnosed with the severe generalized form. This infant’s NBS specimen was collected on DOL 3 and showed an extremely elevated total galactose level of >50 mg/dL. At the time of the NBS report (DOL 4), the infant had received four feedings of milk-based formula but had been switched to soy formula after reducing substances were detected in the urine and a known family history. The infant also had elevated liver function tests and the NBS sample showed elevated tyrosine levels suggesting liver involvement. Before the age of one month, the child went into fulminant hepatic failure and died despite aggressive efforts.

Conclusions:
• Categorization of the risk associated with positive biochemical screening results minimizes the number of infants that require urgent referrals and recommended dietary intervention.
• Total galactose levels are not always elevated in neonates with classical galactosemia. If measurement of total galactose is used as the primary screen, a conservative prompt for second-tier GALT testing is needed.
• The presence of the N314D variant does not exclude the possibility of classical galactosemia requiring dietary lactose restriction and should not alter the interpretation of a biochemical screening result.
• Some kinase and epimerase deficiencies identified incidental to screening for classical galactosemia can be clinically significant.