2016 Newborn Screening and Genetic Testing Symposium
February 29 – March 3, 2016 – St. Louis, MO

Oral Abstracts

Monday, February 29

Roundtables

Legislative Fact Sheet - Adding Conditions to State NBS Panels

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Many states have had to add newborn screening conditions to their state newborn screening panels based on legislative mandates, rather than on their defined process of utilizing evidence-based reviews of the specific condition and assessing the impact on public health and the populations served. Other states have had legislation introduced that requires the addition of conditions to the panel, but the laws have not passed yet.

This session will draw on the work of the Association of Public Health Laboratories Legal and Legislative Issues in Newborn Screening Workgroup (LLINBS), to create strategies and tools to explain and promote an evidence-based process for expanding screening panels. APHL launched the LLINBS Workgroup in 2013, to provide recommendations on law and policy and create practical tools to support newborn screening's mission. One of the first initiatives of the work group sought to help inform legislators about the official process states use to add conditions to their newborn screening panels.

A sub workgroup was formed to develop a fact sheet that state newborn screening providers can present to legislators, legislative agencies, and disease advocate organizations. This fact sheet is intended to educate policy makers about the established procedures their state uses to make evidence-based recommendations about adding conditions to the newborn screening panel; and to encourage the use of the state's procedures rather than a legislative mandate without an evidence-based recommendation.

The aim is to have disease or parent advocates, policy makers, newborn screening programs and public health departments work together to provide newborn screening for conditions that have the greatest potential for improving the lives of babies.

A small workgroup drafted the legislative fact sheet for review by the larger LLINBS workgroup. The fact sheet is available to any state through the APHL.

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Short-Term Follow-Up Roundtable: Successes and Challenges

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Short-term follow-up is an integral part of the newborn screening process. The APHL newborn screening symposium offers a unique opportunity to gather stakeholders in a roundtable discussion format. Attendees will meet counterparts, network and learn from each other while discussing their processes, challenges and triumphs. We will cover three topics during the roundtable: 1) models for fostering good communication with specialists, 2) successful initiatives to educate health care providers about newborn screening and 3) barriers/challenges to performing quality assurance activities within short-term follow-up programs. Moderators will be members of the NewSTEPs short-term follow-up workgroup and will sit at individual tables and lead discussion among the attendees. Twice during the exercise, participants will be asked to move to another table with a different topic, so by the end of the time, every non-moderator will be able to participate in discussion and give feedback on each topic. This will also benefit attendees in mixing together to meet and hear from new colleagues. The moderators will report back to the whole group during the final portion of the roundtable sharing highlights of their individual table's discussions. The three discussion topics are priorities identified through the NewSTEPs short-term follow-up workgroup's efforts. We hope that the discussion during this roundtable will provide guidance for future workgroup activities.

Presenter: John D. Thompson, PhD, MPH, MPA, Newborn Screening Program, 1610 NE 150th St, Shoreline, WA, 98155, Email: john.thompson@doh.wa.gov

Session 1 – Current Conditions in State Newborn Screening Panels

Status of Screening for Recommended Disorders in the United States

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Background: New disorders are added to the Recommended Uniform Screening Panel (RUSP) by the Secretary of Health and Human Services following a systematic review of the evidence by the Advisory Committee for Heritable Disorders in Newborns and Children (ACHDNC). Each state adopts new disorders to local panels according to state policies and resource allocation.
Objective: To provide a comprehensive review of the current status of state implementation for disorders recently added to the RUSP.
Methods: The NewSTEPs data repository was queried to obtain implementation status for each disorder on the RUSP. NewSTEPs is the Health Resources and Services Administration (HRSA) newborn screening technical assistance program and data repository. State NBS programs update their own NBS disorder implementation status. All programs were contacted to confirm data prior to reporting. Additional data were obtained from the Public Health System Impact surveys completed by the Association of Public Health Laboratories through the evidence review process of the ACHDNC. Data presented include the 50 states, Puerto Rico and the District of Columbia.
Results: NBS programs in the U.S. screen for between 26 – 32 disorders on the RUSP as well as a variety of other disorders. Most states universally screen for the 29 disorders that comprised the initial RUSP. The last three disorders added to the RUSP have been adopted by NBS programs after seeking

authority to screen and obtaining the necessary funding. As of August 29, 2015, 33 NBS programs report universal screening for Severe Combined Immunodeficiency (SCID), with 11 more scheduled to implement fully in 2016. Critical Congenital Heart Disease (CCHD) is screened nearly universally, offered in 42 programs, with 6 more implementing CCHD screening in early 2016; and 4 NBS programs do universal screening for Pompe. We estimate that by the end of 2016 87% of newborns will be born in states with universal screening for SCID, 87% will be born in states with universal CCHD screening, and 12% in states with universal Screening for Pompe. Implementation challenges in states for all of these disorders include gaining authority to screen and securing funding. Once funding and authority are in place, it takes roughly 1-3 years to fully implement screening for each of these disorders. Many NBS programs do not have authority to collect screening results following CCHD screening, resulting in varied data collection and public health oversight.
Conclusion: Implementation of new disorders on the RUSP requires funding and authority to screen. NBS programs add new disorders systematically, and the majority of newborns in the U.S. are screened for the 29 disorders on the initial RUSP, as well as SCID and CCHD. Implementation of Pompe NBS is currently being developed in most states."

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Building and Enhancing Laboratory Capacity for Screening and Diagnosis of Hemoglobinopathies

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Objective: To outline best practices for screening and diagnosis of hemoglobinopathies in newborns and adults. To assist new and developing laboratories with building capacity for hemoglobinopathy detection worldwide and to assist established laboratories in program enhancement.
Methodology: A joint workgroup between the Association of Public Health Laboratories (APHL) and the Centers for Disease Control and Prevention (CDC) was formed in December 2013 to create a document to detail current perspectives and best laboratory practices for hemoglobinopathy screening and confirmation in newborns and adults. The workgroup comprised of subject matter experts from six states conducting newborn screening (NBS) and/or adult testing, APHL, and CDC (National Center on Birth Defects and Developmental Disabilities and National Center for Environmental Health). Monthly conference calls and two face-to-face meetings were conducted to discuss current activities and testing practices. Each NBS program shared their unique experience and challenges with screening for abnormal hemoglobins and diagnosing hemoglobinopathies.
Significant Results: The members of the workgroup developed a comprehensive document describing the laboratory methods used by the majority of state NBS programs to screen for hemoglobinopathies, which included electrophoresis (citric acid and cellulose acetate), isoelectric focusing, high-performance liquid chromatography, capillary electrophoresis, and molecular methods, as well as the perspective of a diagnostic laboratory. The document also explains the advantages and limitations of each of these methods, screening algorithms, and the Quality Control and Quality Assessment protocols utilized by these laboratories. A recommended standardized follow-up procedure for positive test results—a necessity for all screening programs—is also included.

Conclusion: A 56 page document entitled "Testing for Hemoglobinopathies" has been developed, which we hope will serve as the foundation for improved hemoglobinopathy screening in both US and international settings. The free document will be available for download at www.aphl.org."

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Evaluation of Modified Newborn Screening Algorithms for Critical Congenital Heart Disease at Moderate Altitude

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Background: Colorado is poised to implement Critical Congenital Heart Disease (CCHD) newborn screening in all babies born below 7,000 feet elevation. With the known effects of altitude on oxygen saturation, which include increased CCHD screening false positives, modified CCHD screening algorithms were evaluated to determine if the false positive rate could be decreased at Colorado's elevation.
Methods: A retrospective study of newborns born at the University of Colorado Hospital (elevation: 5557 feet) between October 2012 and December 2013 using electronic medical records was conducted. Newborns who were prenatally diagnosed with CCHD or admitted to the neonatal intensive care unit were excluded. A total of 2,435 newborns were included for analysis. No newborns were identified with CCHD using the newborn screen during the study period. Therefore the failure rate was used as an approximation of the false positive rate. The false positive rates were calculated for the American Academy of Pediatrics (AAP), the Kohn (repeat screening every 4 hours following 3 failed screens while awaiting an echocardiogram or until passing saturation values), Tennessee (if post-ductal saturation at the first screen >97% considered pass, otherwise revert to the AAP algorithm), and the Tennessee+Kohn algorithms. These false positive rates were then compared to the historic false positive rate of 0.14%. (Thangaratinam, et al Lancet 2012)
Results: The false positive rates for the AAP, the Tennessee, the Kohn, and the Tennessee+Kohn algorithms were 1.11%, 1.07%, 0.78%, and 0.74% respectively. All of the false positive rates were statistically different from the historical false positive rate of 0.14% (p-value<0.001). The incomplete rates of the AAP, Tennessee, Kohn, and Tennessee+Kohn were 1.72%, 1.03%, 1.19%, and 0.49% respectively.
Conclusions: Around 70,000 babies are born annually in Colorado. If the AAP algorithm were implanted in Colorado we estimate that approximately 700 newborns per year would have false positive CCHD newborn screens. However, based on the Tennessee+Kohn algorithm we estimate that around 500 newborns per year would have false positive CCHD newborn screens. A lower number of false positive screens can decrease the burden placed on families and facilities. We recommend that the Tennessee+Kohn algorithm should be further evaluated at moderate and high altitude birthing facilities. The assessment of these algorithms can be used to inform Colorado Board of Health regulations for state wide CCHD newborn screening implementation.

Presenter: Leilani Russell, MPH, Colorado School of Public Health, 13001 E. 17th Place, Aurora, CO, 80045, Email: leilani.russell@ucdenver.edu

Screening for ALD and Pompe in New York, Expected the Unexpected

Presenters: Michele Caggana, ScD and Joseph Orsini, PhD, New York State Dept. of Health, 120 New Scotland Ave., Albany, NY, 12201-2002, Email: joseph.orsini@health.ny.gov

The two following abstracts have been combined into the single oral presentation above.

Screening for ALD in New York, Expect the Unexpected

M. Caggana, B. Vogel, M. Morrissey, C. Lubowski, S. Bradley, M. Nichols, A. Young, C. Saavedra and J. Orsini, Wadsworth Center, New York State Department of Health, Albany, NY

Objective: To provide an update from screening for X-linked adrenoleukodystrophy (ALD) and describe interesting findings from short term follow-up efforts.
Methodology: First tier screening is performed using MS/MS for C26:0 lysophosphatidylcholine (C26:0 LPC), the primary biomarker used for newborn screening of ALD. Second tier screening is accomplished using selective HPLC and MS/MS for C26:0 LPC in infants with a first-tier result of ≥ 0.40 µmole/L. Third tier DNA sequence analysis of the coding and promoter regions of the entire ABCD1 gene is done for all infants with C26:0 LPC values ≥ 0.4 µmole/L on the second tier assay. Follow-up at 1 of 9 Inherited Metabolic Disease Specialty Care Centers is recommended for all infants with a positive screen.
Results: Since December 30, 2013, approximately 400,000 infants have been screened for ALD; 39 were referred for a diagnostic evaluation. Fourteen boys have been confirmed with ALD and 17 female carriers have been identified. In addition, we identified one boy with Klinefelter syndrome who was heterozygous for an ABCD1 mutation. Seven infants were found with either Zellweger syndrome or another peroxisomal biogenesis disorder. Six additional family members were identified who are at high risk for ALD. One baby boy showed MRI changes consistent with progression of ALD and was transplanted at 10 months of age and another baby boy was diagnosed with adrenal symptoms at 6 months.
Conclusions: The NYS Newborn Screening Program has a low referral rate (0.0098%), and thus far has successfully detected 14 male infants with ALD (~1:14,000 males) in the first 20 months of screening.

New York's Experience: Screening for Pompe Disease

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Objective: To assess outcomes from the first months of newborn screening for Pompe disease in New York State.
Methodology: New York began screening for Pompe disease (acid α-glucosidase deficiency) October 1, 2014 using a two-tiered approach. In the first-tier test, tandem mass spectrometry is performed to measure acid α-glucosidase activity (GAA). Infants with low GAA activity [expressed as % of daily mean activity] are reflexed to second-tier DNA sequence of the GAA gene. Infants with low activity and at least one variant in the GAA gene, are referred to an Inherited Metabolic Disease Specialty Care Center for follow-up evaluation and diagnostic testing.
Results: During the first 11 months, ~220,000 infants were screened for Pompe disease and 35 were referred for a diagnostic evaluation. Thus far, no infantile cases of Pompe disease have been detected, however 10 of the 35 infants are at risk for late onset Pompe Disease. In addition, five infants with low GAA activity had only pseudo-deficiency alleles and thus were not referred for follow-up.

Conclusions: The NYS Newborn Screening Program has a low referral rate (0.016%), and thus far has detected ten infants at risk for late onset Pompe disease (incidence = 1 in 22,000). The tandem mass spectrometry method has only detected 5 infants with pseudodeficient GAA activity (1 in 44,000).

Session 2 – Prospective Newborn Screening Conditions

Missouri's Experience with Krabbe Screening Using a Simple Bench Fluorometric Assay

P. Hopkins, Missouri State Public Health Laboratory, Jefferson City, MO

After three years of contracting the New York (NY) Newborn Screening (NBS) Laboratory to conduct Krabbe testing on all of Missouri's NBS samples, Missouri (MO) has now developed a bench fluorometric assay for measuring Galactocerebrosidase (GALC) activity in newborns. This method was easily incorporated into the MO NBS laboratory and is a very straight forward assay. It requires overnight (17 hour) incubation of the sample extract with a 6-hexadecanoylamino-4-methylumbelliferone (HMU) modified substrate in microtiter plates. The resulting fluorescence measured from the product correlates with the residual GALC enzyme activity present in the sample. Validation of the assay included testing of 34 previous MO positive cases referred by NY testing (4 with two Krabbe mutations and 30 with one mutation). All flagged as abnormal except one carrier, which was slightly above our proposed cutoff. We tested blind positive samples provided by NY and results had excellent correlation. We tested 12 previous proficiency test samples and all correlated correctly. Accuracy, precision and linearity were good. On April 1, 2015, MO began our full population pilot testing using our own method and continued sending samples to NY for the following four months to track the parallel testing performance. All abnormal results detected by NY during the parallel testing were flagged as abnormal by MO also during this time period. On August 1, 2015, MO discontinued sending samples to NY for Krabbe testing and continued our full population pilot going solo. Second tier DNA testing for one Krabbe mutation (the 30 kb deletion) was established within Missouri State Public Health Laboratory (MSPHL) by our Molecular Laboratory Unit providing enhancement of sensitivity, specificity and timeliness for detecting infantile Krabbe disease. This presentation will provide data from seven months of full population pilot screening by MO using this primary screening method along with second tier testing for the 30 Kb deletion. It will describe MO's decision schemes for referral of the infant and will provide confirmatory testing outcomes up until the date of this conference along with lessons learned.

Presenter: Patrick Hopkins, Missouri State Public Health Laboratory, 101 N. Chestnut St., PO Box 570, Jefferson City, MO, 65102, Email: Patrick.Hopkins@health.mo.gov

Development of a 3-plex Assay by MS/MS to Detect the Lysosomal Storage Diseases MPS-II, MPS-IVA and MPS-VI

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We have previously developed tandem mass spectrometry screening methods for Fabry, Pompe, MPS-I, Gaucher, Niemann-Pick and Krabbe. These assays are simple to execute and are performing seamlessly within an existing newborn screening laboratory. We now present data from two additional pilot studies, one for a 6-plex and one for MPSII. We also introduce a 3-plex method for lysosomal storage diseases MPS-II, MPS-IVA and MPS-VI.

We are piloting the new Perkin Elmer 6-plex MS/MS assay for Fabry, Pompe, MPS-I, Gaucher, Neimann-Pick and Krabbe, which uses improved substrates, internal standards and optimized buffer conditions. We have assayed 35,000 anonymous newborn blood spots by the improved 6-plex assay and identified 34 with low activity. Six of these low-activity specimens have nucleotide changes consistent with a reasonable probability that the infant may eventually develop clinical symptoms of a lysosomal disease.

Additionally, we have screened 36,000 anonymous newborn blood spots by a new MPSII assay and have identified five blood spots with low activity. Two have nucleotide changes that may predispose to clinical symptoms; two are pseudo deficiencies; and one sample has no detectable nucleotide alteration.

We are also evaluating a 3-plex assay for MPS-II, MPS-IVA and MPS-VI. This assay design utilizes a novel MS/MS method with a lower pressure LC column inserted into the flow injection stream. Preliminary data demonstrates the technology is robust and works well within a high-throughput environment. The incubation conditions required by the sulfatase enzymes (the 3-plex) differ from our prior assays, and must be quantitated separately from the 6-plex.

The work flow for performing either the 6-plex or the 3-plex is designed to utilize the evenings for incubation and MS/MS activity. The entire assay time from punch to report is 24 hours for one sample (6 or 3 enzyme assays respectively) using a single mass spectrometer. The MSMS assays generate a significantly lower number of screen positives compared to competing technology.

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Development of a New Bloodspot Screening Assay for Duchenne Muscular Dystrophy (DMD)

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Background: The Wales (UK) newborn screening programme for DMD was operational for 21 years (1990-2011) and utilised a bloodspot creatine kinase (CK) enzyme activity assay. A total of 343,170 boys were screened and 145 cases had raised CK activities, of these, 56 cases were confirmed to have DMD. The Wales programme was terminated following the withdrawal of the external quality assurance scheme and due to a lack of sustainability of the reagents used in the test. This programme was the second longest running in the world, but was the most comprehensive with respect to follow-up/outcome data. This long term study has so far identified 15 false negative cases. It is difficult to assess the false negative rates in other programmes as the vast majority were smaller and were operational for short periods or did not record such cases. A potential cause of these false negatives is that CK is unstable and activities can decrease by 30% within a week of sample collection. In addition,

the existing bloodspot CK assays are non-specific as total CK activity is measured. CK is an isoenzyme and it is the CK-MM isoform that is found predominantly in skeletal muscle and is elevated in boys with DMD. There is renewed interest in implementing screening for DMD as early intervention with steroids improves outcomes and the prospect of molecular therapies on the horizon.
Objectives: To develop a sensitive and specific immunoassay to detect CK-MM in bloodspots.
Results: CK-MM concentrations in the DMD bloodspot samples (1493-13,223 ng/ml) were higher than those observed in routine newborn bloodspots (114-240 ng/ml). The CK-MM concentrations in DMD samples correlated with the measured CK activity. CK-MM concentrations in the normal population separated well from background concentrations. This assay has been adapted onto the PerkinElmer GSP analyser with improved precision and sample stability compared to the enzyme activity assay.
Conclusion: CK-MM can be reliably detected in bloodspots. Adaption of this assay onto a commercial immunoassay-analyser would enable robust high-throughput screening for DMD.

Presenter: Stuart Moat, PhD, FRCPath, University Hospital of Wales, Heath Park, Cardiff, Cf14 4XW, United Kingdom, Email: Stuart.moat@wales.nhs.uk

Progress of Newborn Screening for Spinal Muscular Atrophy

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Background: Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder caused by defects in the SMN1 gene that leads to subsequent motor neuron degeneration. Because of the high incidence of SMA, and several promising treatment options, newborn screening for SMA is considered.
Methods: Dried blood spot (DBS) samples were obtained from routine newborn metabolic screening samples token at the age of day 3. DNA was extracted from a 3.2mm punch from each DBS sample. Real-time quantitative PCR assays using primers and probes targeting IVS7+100 were conducted in PCR plates. For newborns with positive screening result, showing no IVS7+100C, a second 3.2mm punch from the original DBS was subsequent to DNA extraction and tested by another set of primers and probes, and Droplet Digital PCR (ddPCR) if the 2nd result was still abnormal. At the same time, this newborn was requested to come to our clinics for clinical evaluation and to have blood sampling for MLPA test.
Results: Since Nov. 17, 2015, we have screened approximately 50,000 newborns. Four present no SMN1 gene, with 2, 2, 3, and 4 copies of SMN2 gene respectively. One newborn presented hypotonia and respiratory failure at birth. In addition, we found 3 false positive cases, one resulting from a nucleotide polymorphism at the target sequence (IVS7+100). A second tier assay by ddPCR showed presence of SMN1 in all three false positive samples.
Conclusion: Newborn screening provides the chance of early diagnosis to affected patients and provides genetic counseling and further pregnancy plan to the family. The incidence of SMA in our newborn population is 1 in 10,000. Further studies are necessary to explore the necessarily of modifying the screening method, and to understand if newborn treatment may be benefit to SMA patients.

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Inter-Laboratory Comparison of Assays to Measure SMN2 Copy Number in Dried Blood Spots from Patients with Spinal Muscular Atrophy

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Spinal muscular atrophy (SMA), a motor neuron disease and the leading genetic cause of infant death, results from the absence of a functional SMN1 gene. The paralogous SMN2 gene, which provides limited backup functionality, shows considerable copy number variation in the human genome. SMN2 copy number is the most significant known genetic modifier of SMA severity: fewer copies result in more severe disease. Newborns without an SMN1 gene who have only one or two SMN2 copies become symptomatic within the first month of life, never sit unsupported, and usually die before two years of age from respiratory failure. A new molecular therapy that increases SMN2 functionality has shown promising results in clinical trials and is currently under investigation in presymptomatic newborns, prompting pilot studies that use newborn bloodspot screening to identify affected infants at the earliest possible stage. In the absence of symptoms that would identify the most severely-affected newborns, SMN2 copy number is the major biological parameter used to determine eligibility for clinical trials and to assess therapeutic response. The usual method to quantifySMN2 copy number has been real-time qPCR, but a newer method, droplet digital PCR (ddPCR), has recently become available. We are conducting the first inter-laboratory comparison of SMN2 copy number measurements by both real-time qPCR and ddPCR assays on samples from SMA patients, carriers, and unaffected newborns. The study is focused on dried blood spot samples to prepare for rapid confirmation and follow-up of presumptive positives in newborn screening laboratories. In addition to comparison with real-time qPCR from a diagnostic laboratory, we are assessing within-method variance among the three laboratories using ddPCR. Preliminary results suggest that, in samples from SMA-affected patients where no SMN1 is present, SMN2 copy numbers measured by ddPCR agreed well with results from real-time qPCR.

Presenter: Robert Vogt, PhD, Centers for Disease Control and Prevention, 4770 Buford Hwy NE, MS F-19, Atlanta, GA, 30341, Email: rvogt@cdc.gov

Session 3 – International Perspectives

Toward National Newborn Screening in Australia

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Newborn screening began in Australia in 1964 with screening for phenylketonuria in one state (NSW). Today newborn blood spot screening is offered to all babies born (approximately 330,000 births per year) by one of 5 publically funded state based programs. One state (Tas) and 2 territories (ACT and NT) with births of less than 10,000 each per year contract for testing in one of the existing programs. Whilst guidelines for newborn screening practice are offered by professional societies (HGSA and ACP) it is up to each state program to decide what is included and therefore the screening pathway and disorders screened for a baby depends on where it is born.

In order to provide equity of service and set a clear pathway for deciding what should be included in the future there has been a national initiative under the Standing Committee on Screening (SCOS) to develop a policy framework. A Newborn Bloodspot Screening Working Group (NBSWG) was formed in 2013 with representatives from state and federal governments, professionals from screening for program and laboratory aspects, other health professionals, a bioethicist as well as a consumer representative.

The NBSWG has used a consultative approach, contacting health professionals and consumers and forwarding communiqués and providing a website* to provide updates on progress. As well it has conducted a survey and held 2 stakeholder meetings to further discuss identified issues. The policy, which includes program overview; program implementation; quality and safety; monitoring, evaluation and review; and decision-making framework will be submitted to SCOS by the end of 2015. It is anticipated that federal government will endorse the submission and a national policy will be applied from 2016.

In conclusion, a policy built on the strengths and successes of the last 50 years of screening in Australia will provide clear policy guidance, support consistency, with increased transparency as well as enable structured assessment of disorders.

*http://www.genomics.health.wa.gov.au/nbspf/

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Further Expansion of the Neonatal Screening Panel in the Netherlands

J.G. Loeber, International Society for Neonatal Screening, Bilthoven, Netherlands

In April 2015, the Dutch Health Council, on request by the Minister of Health, issued a report with recommendations for a further expansion of the neonatal screening panel in the Netherlands.
A much debated issue was the question whether untreatable conditions (such as DMD) should be included in the panel. Considering pros and cons, the Health Council believed such an expansion is not desirable.

In addition, the Health Council discussed how to deal with incidental findings especially carrier status. In its opinion, the child's right to later decide for himself/herself about knowing or not knowing about carrier status is more important than the interests of the parents in terms of making reproductive choices. Therefore, the Health Council recommended not to report carrier status.

The Minister adopted these recommendations. The Dutch programme will be (among) the first in Europe to formally include SCID and X-ALD. Other notable aspects are: 1. MPS1 will be included in contrast to Pompe and Krabbe; 2. DMD is not included; 3. HCY should be removed from the current panel since screening of more than 1 million Dutch newborns measuring methionine concentrations did not identify a single case.

Notwithstanding the Health Council report the Minister decided to explore the possibility of screening for untreatable conditions.

Implementation in the screening programme of all recommended conditions is expected to take at least three years.

The complete report including the list of all recommended conditions is available online at http://www.gezondheidsraad.nl/en/publications/preventie/neonatal-screening-new-recommendations

Presenter: J. Gerard Loeber, PhD, International Society for Neonatal Screening, Burgemeester Fabiuspark 55, Bilthoven, 3721CK, Netherlands, Email: gerard.loeber@gmail.com

The Prevalence of Hereditary Hemoglobin Disorders and its Implications for Newborn Screening in Germany

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Background: Some hemoglobin disorders are among those hereditary diseases with evidence that an early diagnosis and treatment improves the clinical outcome of affected children. So far hemoglobin disorders are not included in the German newborn screening program despite increased immigration from countries with populations at risk.
Design: To determine the birth prevalence in a major German metropolitan area we tested 17,018 newborns born in the State of Hamburg between January 2013 and May 2014. High pressure liquid chromatography (HPLC) and subsequent molecular-genetic testing were used for the detection and confirmation of hemoglobin variants.
Results: Out of relevant diseases the most prevalent was sickle cell disease with a frequency of disease-consistent genotypes of 1 in 2,385 newborns. Duffy-bloodgroup typing showed evidence that 90% of the affected children were likely of sub-Saharan ancestry.
Conclusion: Sickle cell disease (SCD) was found as prevalent as hypothyreodism, the most common disorder of the German routine newborn screening program. An inclusion of SCD into the national newborn screening program seems reasonable from medical and ethical viewpoints.

Presenter: Zoltan Lukacs, PhD, Hamburg University Medical Center, Martinistr 52, Hamburg, 20246, Germany, Email: lukacs@uke.de

Integration of SCID Screening into the Dutch Newborn Screening Program: Benefits and Shortcomings of the Available Screening Assays

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Introduction: Severe combined immunodeficiency (SCID) comprises a group of genetic disorders resulting in a severe cell-mediated and humoral immunodeficiency. Infants with SCID present with life-threatening infections during the first months of life and face a fatal outcome unless their immune system is replaced by hematopoietic stem cells transplantation (HSCT). Newborn SCID screening is based on the detection of T-cell receptor excision circles (TREC) in heel prick blood. B-lymphocyte deficiency-related SCID can be detected by the quantification of κ-deleting recombination excision circles (KRECs). In this study, we provide first experiences with two available detection methods.

Material and Methods: With the EnLite Neonatal TREC assay (PerkinElmer) and end-point PCR, 1295 fresh heel prick cards of the Dutch newborn screening program and heel prick cards stored for two weeks (n=61), one month (n=63), three months (n=33) and one year (n=33) were analyzed. Moreover, 155 heel prick cards of preterm infants, nine TREC reference dried blood spots from the CDC and peripheral blood spots of 19 confirmed and 30 potential SCID patients were included. With the SCREEN-ID assay (TRM Leipzig) and real time-qPCR, five fresh heel prick cards, seven cards of confirmed SCID patients and 18 cards of potential SCID patients were analyzed.
Results: The cut-off level, based on the distribution of TREC-levels in the 1295 fresh heel prick cards, was 39 copies/µl. A significant reduction in TREC levels was observed in heel prick cards stored for three months and one year. Preterm infants showed significant lower TREC levels and a high retest-rate than full-term infants. Finally, all 19 confirmed SCID-patients showed undetectable or low TREC levels.
Discussion: This study showed that the EnLite Neonatal TREC assay is a suitable method for SCID-screening in the Netherlands. Consequently, these findings will provide guidance in the decisions that have to be made during the incorporation process of SCID in the Dutch screening program.

Presenter: Peter Schielen, PhD, RIVM, PO Box 1, Bilthoven, 3720 BA, Netherlands, Email: peter.schielen@rivm.nl

Multiplex Screening for Treatable Lysosomal Storage Diseases (LSDs)
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Introduction: The interest in neonatal screening for LSDs has increased substantially because the need for early diagnosis improves the therapeutic efficacy of new developed treatments and because screening has been made possible by recent technical advances. The results of pilot LSD screening studies (USA, Austria, Taiwan) show that the current clinical prevalence is underestimated.
Method: Tandem mass spectrometry (MS/MS) has become an established tool for the detection of rare congenital metabolic disorders by newborn screening. The LC-based method has advantages for expanding the assays to include additional products and internal standards for multiplexing all nine currently available lysosomal enzyme assays in dried blood spots (Gaucher, Niemann-Pick A/B, Fabry, Krabbe, Pompe, MPS-I, MPS-II, MPS-IV and MPS-VI) as well as allowing other metabolites to be quantified (Spacil et al, 2012, Clin Chem). Validation of this method to the full set of treatable lysosomal storage disorders has been performed in our laboratory. We improved the pre-analytical steps and the enzymatic assay for ABG (Gaucher disease).
Results: ABG, GAA, GLA and IDUA enzyme activities in over 13,000 newborn samples were analyzed. Statistically significant higher GAA and GLA enzyme activities were observed in female newborns compared to male newborns. And newborns with a higher birth weight and gestation age have a statistically significant lower GAA and GLA enzyme activity compared to newborns with lower birth weight and gestation age. This proofs that it is of importance to define the reference intervals for lysosomal enzyme activities as well as cut-off limits for newborn babies with regard to birth weight, **gestational age and sex for each population. True positives were not yet found.**
Conclusion: We report for the first time results of a 7-plex enzymatic activity UHPLC-MS/MS assay for the lysosomal storage disorders Gaucher, Fabry, Pompe, MPS I, MPS II, MPS IV and MPS VI in Europe. This method is accurate, fast, has low cost and is easy to implement next to the routine newborn screening and therefore suitable for LSD newborn screening.

Presenter: Francois Eyskens, MD, PhD, PCMA vzw, Doornstraat 331, Antwerp, 2610, Belgium, Email: Francois.eyskens@pcma.provant.be

Tuesday, March 1

Joint Follow-up and QA/QC Session

Updating the National Newborn Screening Contingency Plan: Addressing the Gaps in the System
S. Shone[1], K. Taft[2]; [1]New Jersey Department of Health, Trenton, NJ, [2]Association of Maternal & Child Health Programs, Washington, DC

As part of the Newborn Screening Act of 2008 the CDC was required to develop a Newborn Screening Contingency Plan with input from subject matter experts, national organizations, state programs, and community stakeholders. Published in 2010, the national Newborn Screening Contingency Plan provides guidance on the formation of state-specific plans that need to be in place in order to continue critically important newborn screening and clinical management operations in the face of emergencies. The plan outlines the major supporting actions that each public health official should consider when planning and preparing for newborn screening contingency operations and responsible entities for each action.

This presentation will discuss a current effort to update the Contingency Plan to reflect the changing landscape in newborn screening since the initial development, incorporate lessons learned from state experience, and address systems gaps in areas such as laboratory and clinical follow-up to ensure diagnosis and treatment. Updates will take into account the variability of state newborn screening resources and processes.

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Communicating Incidental Findings of Sickle Cell Trait on the Newborn Screen: A Community Needs-based Assessment
M. Dreon, J. Tarnowski, N. Silva, P. Constant, A. Gaviglio, S. Rosendahl, and M. McCann, Minnesota Department of Health, St. Paul, MN

Background: Wide variation exists in the communication of positive newborn screening results for sickle cell trait (SCT). A lack of evidence in establishing guidelines for reporting SCT results highlights the need to investigate stakeholder perception of the communication of trait status from public health, and the capacity of screening programs to conduct effective follow-up.
Methods: We designed a quality improvement project to evaluate current and potential trait reporting processes in Minnesota. This project included a community needs assessment, pre and post policy change assessment, and continuous consumer satisfaction and quality assurance measurements. The new notification process adopted by Minnesota on June 19th, 2015 was developed from internal analysis of locally conducted focus groups to assess sickle cell trait notification and was guided by input from clinical newborn screening coordinators. Staff outlined specific quality improvement measurements for this new policy such as staff time necessary, consumer satisfaction, and long-term viability and efficacy.
Results: Community needs assessments revealed that a passive notification was against parental expectations of result reporting, and that incidental findings like trait have the potential to provide families with valuable information. Acceptable and effective trait notification was identified by parents as one that was facilitated by an individual knowledgeable on hemoglobinopathies, multi-faceted, and

which included the use of multiple modes of communication. Evaluation of staff time necessary to facilitate SCT follow-up processes in Minnesota as well as analysis of long-term efficacy and viability is still on going. The results of the consumer satisfaction survey are still pending.
Conclusion: Our findings suggest support for a multi-faceted approach to trait notification facilitated by newborn screening programs, and demonstrate the utility of policy development through community needs assessments. Further studies of the applicability of Minnesota's trait notification guidelines to other newborn screening programs need to be investigated.

Presenter: Maggie Dreon, MS, CGC, Minnesota Department of Health, 601 Robert St N, St. Paul, MN, 55164, Email: maggie.dreon@state.mn.us

Interactive Training Webinar for Newborn Screening Specimen Collection

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Background and Objectives: A successful newborn screening (NBS) program is dependent upon the pre-analytical phase of testing, specifically specimen collection and transport. Data from Wisconsin's monthly submitter quality assurance reports showed that improvements were needed in the area of specimen collection to reduce both the percentage of unsatisfactory specimens and the percentage of specimens missing key information. The Wisconsin NBS program sought to address these pre-analytic quality indicators by developing an interactive training webinar for specimen collection.
Methods: The objectives of the webinar were to detail procedures for proper specimen collection, suggest a review process for specimens prior to submission, describe the proper time-line for specimen re-collection in the event of an initial unsatisfactory specimen, and provide a framework for monitoring key pre-analytical quality indicators. The webinar contained five parts: a pre-test, an NBS success story, training in specimen collection, post-test, and an evaluation. Learners took an average of 60 minutes to complete the training. All submitters were provided access to the webinar on the Wisconsin newborn screening webpage with the intended audiences of phlebotomists, nurses, medical technicians, midwives, and other healthcare workers who participate in the screening process. The webinar was also offered for continuing education credit.
Results: The webinar was released to submitters in April 2015 and within the first two months, a total of 342 learners participated in the training. The average scores on the pre-test as compared to the post-test showed a statistically significant improvement, validating the effectiveness of the training for individual learners. Approximately 73% of all learners obtained the certificate for continuing education (PACE credit). The number of learners from each submitting facility was tallied and correlated to trends in the submitter's monthly pre-analytical quality indicators. Overall, submitters who had the largest number of learners participating in the training were able to achieve the bench marks for satisfactory specimen collection. An evaluation of the webinar was completed by 67% of all learners and the majority of the responses were favorable regarding the relevance of the material covered, the format of the webinar, and the ability to immediately put into practice the principles highlighted in the training.
Conclusion: The Wisconsin NBS program developed an interactive training webinar for newborn screening specimen collection. Individual learners, who participated in the training, enhanced their knowledge of proper specimen collection and as a result, improvements were seen in the pre-analytical quality indicators for submitting facilities.

Presenter: Patrice Held, PhD, Wisconsin State Laboratory of Hygiene, University of Wisconsin-Madison, 465 Henry Mall, Madison, WI, 53706, Email: patrice.held@slh.wisc.edu

Follow-up Status During First Five Years of Life for Select Primary RUSP Disorders Diagnosed Through California Newborn Screening

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Goals: For disorders to be included on the Recommended Uniform Screening Panel (RUSP) they have traditionally had to meet the criteria that treatment exists and, if initiated shortly after birth, before the newborn becomes symptomatic, it can halt or slow disease progression that would otherwise occur without early diagnosis. This necessitates that specialty care follow-up centers are available to provide disease management services and be accessible to families in the early years of life and ideally, over the life span. This study follows a cohort of newborns that were diagnosed with a metabolic disorder on the RUSP primary disorders list to determine the percent that were able to stay in active care at a specialty care clinic during the first 5 years of life and associated demographic characteristics of the mothers who had children that stayed in active care versus those that became lost to follow-up or refused care.
Method: Newborns screened between 2005-2009 and diagnosed with one 19 metabolic disorders were tracked to see which cases were still in "active" care at the completion of each year of life, through age five, as documented in the Annual Patient Summary (APS) data provided by California metabolic specialty care follow-up centers. Using linked California Birth Certificate data we examined the maternal characteristics of those cases that were more likely to stay in active care versus those that were lost to follow-up or where parents refused follow-up (LTFU/RFU).
Results: Of 448 newborns, 55.8% were in active care by the end of the fifth year of life. Over the course of five years, 117 (26.1%) were LTFU/RFU, and 18.1% were not in active care for other reasons (moved out of state, 8.7%; patient died, 3.3%; or treatment deemed no longer necessary, 6.0%). More cases dropped out of active care in the first year of life (n=39) compared to subsequent years and 28% of these were due to death of the child. Certain disorders were associated with a higher percent staying in active care through age five: 90% of PKU (n=60) vs. 54% for MCAD Deficiency (n=115) versus 44% for 3MCC Deficiency (n=61), for example. The percent of patients that stayed in active care was higher in mothers covered by private insurance and those who had >12 years of education. LTFU/RFU was associated with a higher percent of mothers that were Hispanic.
Conclusion: Equitable access to ongoing care is a critical feature of a successful state newborn screening program. Staying in care may be related to type of disorder as well as other complex life challenges including demographic characteristics of the family. Further study is required to fully understand the determinants that impact a family's ability to access ongoing care for newborns diagnosed with RUSP disorders.

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Improving Short- and Long-term Follow-up

Quality Improvement Strategies for a State Newborn Hearing Screening Program

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In 2014, the Hawai'i Newborn Hearing Screening Program (HNHSP) began a three-year grant cycle focusing on quality improvement (QI). The HNHSP grant activities are based upon the national Early

Hearing Detection and Intervention 1-3-6 plan, calling for newborn hearing screening by age one month, audiologic diagnostic evaluation by age three months, and enrollment in Early Intervention (EI) by age six months. As such, major aims of the HNHSP are to (1) decrease the loss-to-follow-up/documentation (LFU/D) rate of infants who do not pass newborn hearing screening from 24.6% (2011 data) to 10%; (2) decrease the proportion of children LFU/D for evaluation from 24.6% (2011) to 10%; (3) decrease the proportion of children LFU/D for EI services from 11.5% (2011) to 9.9%; and (4) increase the knowledge of physicians in meeting the needs of infants with hearing loss.

Grant activities use quality improvement (QI) methodology, specifically the PDSA (Plan-Do-Study-Act) model, to generate change. The development and implementation of talking points for midwives participating in Maui homebirths resulted in a hearing screening rate change from 18.5% to 55.6%. Working with institutional screeners to obtain secondary points of contact for infants not passing screening has prevented the LFU of a child via successful contact of the family's interpreter. A Family Resource Guide, parent brochures, and an online Providers' Manual have been developed and distributed to the community. Physician education has occurred at in-person presentations by the state American Academy of Pediatrics Hearing Loss Champion. On-going PDSA cycles involve (a) contacting homebirth families directly to schedule screening appointments, (b) contracting midwives to provide hearing screening to homebirths in rural areas and Neighbor Islands, (c) increasing the reimbursement rate for homebirth screening, (d) contracting providers to complete diagnostic evaluations in rural areas and Neighbor Islands, (e) contacting the medical home of children LFU/D for audiologic evaluation, (f) working with audiologists to ensure consistent EI referral recommendations on evaluation reports, and (g) developing talking points for EI care coordinators. Other activities include assessing institutional screener competencies, exploring tele-audiology to the Neighbor Islands, developing standardized protocols for the NHSP to follow-up on referrals, developing a memorandum of agreement with the state EI program to facilitate sharing of information, and launching a public awareness campaign about the 1-3-6 timeline during the Better Speech and Hearing month (May).

A significant amount of work has been done by the HNHSP to complete a program needs assessment, create a QI plan, develop PDSA activities, and implement interventions to reduce LFU/D rates. Future goals include expanding PDSA activities state-wide and continued education.

Presenter: Sylvia Mann, MS, Hawaii Department of Health Genomics Section, 741 Sunset Avenue, Honolulu, HI, 96816, Email: sylvia@hawaiigenetics.org

Using State Birth Defects Registries to Evaluate Outcomes of Critical Congenital Heart Disease Newborn Screening

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Objective: The present study was undertaken to determine whether the individual birth defects surveillance systems of five New England states (CT, ME, NH, RI, and VT) could provide sufficiently complete and timely data to assess: 1) Documentation of pulse oximetry screening (POx) for newborns with critical congenital heart disease (CCHD); 2) The proportion of CCHD cases that are detected prenatally, clinically or via screening; and 3) Outcomes of CCHD cases through the first year of life (e.g., CCHD-related surgeries, other procedures, and mortality).

Methods: Each of the five participating programs approach birth defects surveillance in a somewhat different manner, however, in general, records used for this analysis were identified by retrospective

searches through the state's birth defects database for all infants whose confirmed registry diagnosis included the specified diagnostic codes for the seven primary targets of CCHD screening born 2012-2013. Once identified, each child's electronic and/or paper medical record was reviewed by trained birth defects staff in order to abstract relevant information regarding how and when CCHD was diagnosed, types of medical treatment received and when it was given. Descriptive statistics are used to report results.

Results: From nearly 80,000 live births, 179 CCHD diagnoses were noted in the records of 159 children (10.0 per 10,000; 95% CI 8.7-12); of these, the most common diagnoses were tetralogy of Fallot (n=68, 43%), transposition of the great arteries (n=38, 24%), and hypoplastic left heart syndrome (n=24, 15%). Fifty-seven records indicated prenatal identification (36%). Of those not identified prenatally, newborn screening POx was noted in 41 (26%).

Information from states with active medical record abstraction was more complete than for the one state with passive abstraction: for example, information was available regarding prenatal diagnosis in 91% of records and age at first surgery in 85% among states with active abstraction compared to 35% and 75% in the state with passive abstraction.

Conclusions: Birth defects surveillance systems can provide information on health outcomes for infants diagnosed with CCHD, the contribution of prenatal, screening and clinical diagnoses to the identification of CCHD, and health services utilization after a diagnosis. However, this varies by the methods used by surveillance systems. In order to improve states' ability to provide these outcomes data, sources and quality of data should be carefully monitored, particularly for POx documentation.

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Minnesota Medical Foods Initiative: Building a Long-term Strategy for Assisting Families in Obtaining Medical Foods and Dietary Supplements for IBEM Management

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The Minnesota (MN) Medical Foods Initiative was formed to assess the status of medical foods and dietary supplement access and coverage in Minnesota and develop a feasible and sustainable strategy to assist families in navigating the processes available to obtain the recommended therapies for IBEM management.

Newborn screening is built on the premise that early detection and treatment of congenital diseases can prevent morbidity and mortality associated with the untreated disease. Achieving optimal health outcomes for individuals living with inborn errors of metabolism often relies on the availability of and lifelong adherence to the most basic, essential treatments consisting of medical foods and supplements. The Affordable Care Act (ACA) contains provisions for health insurance coverage of newborn screening as an essential health benefit preventive service. The ACA does not guarantee uniform health insurance coverage of commonly recommended/prescribed therapies for the lifelong management of many conditions identified through Newborn Screening. Children and adults with IBEM may be unable to gain the full benefits of newborn screening due to inequitable therapeutic access.

This session will present our findings from a nationwide survey on medical foods, formula, and supplement coverage used to manage IBEM. We will also present initial findings on potential

relationships between IBEM therapeutic coverage and adherence. Finally, we will discuss the formation of the MN Medical Foods Initiative and how this approach could expand regionally to help foster improvements in access to medical foods and dietary supplements for IBEM.

Presenter: Susan Berry, MD, University of Minnesota, 4209 Delaware St., Minneapolis, MN, 55455, Email: berry002@umn.edu

Congenital Hypothyroidism in Newborn Infants with Borderline TSH Screening Values

C.G. Abarquez, Newborn Screening Center Mindanao, Southern Philippines Medical Center, Davao City, Philippines

Background: Congenital hypothyroidism (CH) is one of the most preventable causes of mental retardation and has an incidence of 1 in 3000 to 4000 around the world. The TSH screening cut-off point used is >15 mIU/L. NSC Mindanao has been using a lower cut-off point of 12.5 mIU/L after observing that babies who had borderline levels of 15 mIU/L were confirmed to have CH and needed levothyroxine treatment.
Objective: The study aimed to evaluate the outcome of newborn infants who initially had borderline TSH results in newborn screening and were subsequently confirmed to have CH when further examination was carried out.
Methods: Between January 2011 and December 2014, a total of 786,175 newborn infants were screened by NSC Mindanao for the six (6) metabolic disorders. A chart review of newborn infants with borderline initial TSH values between 12.5 to < 14.5 mIU/L and subsequently confirmed to have CH was retrospectively done. Data from the Neometrics database of NSC Mindanao were obtained retrospectively. Relevant investigations were also gathered and these include serum TSH and FT4, and results of the thyroid gland imaging studies
Results: There were 784,661 newborn infants who tested normal for CH and needed no further action. Out of the total 1,514 elevated TSH levels on initial samples, 26.5% (or 401) babies had TSH values below the cut-off points but NBS results were reported as elevated TSH values. Of the 401 babies, 26 were confirmed to have CH and were started on levothyroxine treatment, The mean screening age was 5.58 days and the median was 2 days. The mean age of treatment was 35.3 days and the median was 28.5 days. The initial TSH values of the 26 cases ranged from 9.81 to 16.7 mIU/L with a median of 12.32. Eight cases had true CH, hence treated with levothyroxine.
Conclusion: The use of borderline TSH cut-off point has increased the detection rate of both true and subclinical CH. For appropriate screening outcome and to avoid missing any case of CH, it is therefore appropriate to lower the TSH screening cut-off point to >12 mIU/L.

Presenter: Conchita G. Abarquez, MD, Newborn Screening Center Mindanao, Southern Philippines Medical Center, JP Laurel Ave, 8000 Davao City, 8000, Philippines, Email: conchabarquez@yahoo.com

Arkansas Newborn Screening Long-Term Follow-up Cohort Study - Year 3

J.A. Bolick, University of Arkansas for Medical Sciences/Arkansas Children's Hospital, Little Rock, AR

Problem/Objectives: Every year approximately 38,000 Arkansas newborns receive a newborn screen for 29 primary core panel metabolic conditions, hearing loss, and Critical Congenital Heart Disease (CCHD); about 80 infants are diagnosed with a metabolic condition and 70 are diagnosed with hearing loss. Prior to January 2012, data systems were not in place to capture the long-term health outcomes of

the hundreds of infants diagnosed with a newborn screening (NBS) condition in Arkansas. The Arkansas NBS Long-Term Follow-up (LTFU) Cohort Study was established for the purpose of tracking and monitoring the clinical care and public health outcomes for children diagnosed with a NBS condition and to follow them until 21 years of age.
Methodology: The Arkansas NBS LTFU Cohort Study is a longitudinal, observational study conducted by the University of Arkansas for Medical Sciences (UAMS), Pediatric Genetics Section in partnership with the Arkansas Children's Hospital (ACH) and its Research Institute (ACHRI). The primary aim of the Study is to record demographics, characteristics of disease and treatment, utilization patterns, quality improvement measures, and clinical outcomes in Arkansas children with NBS conditions. The study database was developed using REDCap (Research Electronic Data Capture) hosted by the UAMS Translational Research Institute (NCRR/NIH 1 UL1 RR02988).
Significant Results: After receiving Institution Review Board approval September 2011, the database was implemented January 2012. Based on projections, the enrollment goal for the Study is a total of 3,000. At the end of Year 3, the database contained information on 576 subjects representing 580 newborn screening cases. Third year data (2014) and comparison data with Year 1 (2012) and Year 2 (2013) will be presented at the Symposium.
Conclusions/Implications: The Arkansas NBS LTFU Cohort Study will provide the opportunity to monitor and track health outcomes over time, and this could lead to improvements in health care for this population and ultimately the lives of children diagnosed with these conditions in the future.

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QA/QC – Factors that Can Improve Screening Outcomes

The Effects of Gestational Age and Birth Weight on the Newborn Screening Activities of Enzymes Associated with Lysosomal Storage Disorders

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Newborn screening for some Lysosomal Storage Disorders (LSDs) has shown that preterm/low birth weight infants exhibit unexpectedly elevated enzyme levels. This phenomenon may affect proper evaluation of their disease status. The objective of this study was to evaluate variations in the activities of several lysosomal storage enzymes determined during newborn screening with respect to variations in birth weight and gestational age. We also examined the effect of postnatal age on the enzymes activities in preterm infants.
Methods: The Illinois state newborn screening program database was analyzed to determine enzyme activity levels in term babies and in babies with low birth weights. The lysosomal enzyme activity levels associated with five disorders – Pompe (α-glucosidase [GAA]), Fabry (α- galactosidase [GLA]), Gaucher (β-glucocerebrosidase [ABG]), Mucopolysaccaridosis Type I (MPS I) (α -L-iduronidase [IDUA]), and Niemann-Pick A/B (acid sphingomyelinase [ASM]) – were analyzed. Data were stratified into birth weight categories: 1-1000 g, 1001-1500 g, 1501-2000 g, 2001-2500 g, and >2500 g). In addition, to examine the effect of postnatal age on LSD test results, we examined GLA enzyme (the most elevated enzyme in preterm babies [<2500 g]) with respect to how this activity responded to postnatal age from 1-4 weeks after birth.

Results: Data from 60,510 neonates were reviewed. Infants with very low birth weight (VLBW <1000 g) comprised 1.75% of the study cohort; low birth weight (LBW 1000-2000 g) comprised 5.67%. For five disorders, Low birth weight babies ABG, GAA, IDUA and ASM results are close to normal birth weight. GLA results increased with decreasing birth weight/gestational age and were significantly increased in infants with VLBW compared with infants who weighed >2500 g, there are no When blood spots specimens were collected at a postnatal age of 1- 4 weeks in infants born <34 weeks of gestational age, a significant reduction in α- galactosidase activity was detected.
Conclusions: GLA (α- galactosidase) activity levels are disproportionately increased in VLBW infants. GLA levels fall after 3-4 weeks postnatal age and may only then reflect true activities of the enzyme. The data suggest that either a request for resubmission of specimens from birth weight <2000 g and <34 weeks of gestation age or a different cut-off should be applied to this subgroup.

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Normalization of Laboratory MS/MS Cutoffs Using CDC NSQAP Quality Control Materials

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Objective: Newborn screening laboratories cannot accurately compare analyte cutoff values and measurements because of differences in testing methodologies (i.e., derivatized vs. non-derivatized). To overcome these differences, a method comparison experiment can be performed in which specimens containing analytes covering the dynamic range of the methods are analyzed by each laboratory, and a linear regression equation is generated. The linear regression can then be used to normalize cutoff values (1). The NSQAP Quality Control Samples, which contain endogenous and three enriched levels of amino acid and acylcarnitines, are uniquely suited for a method comparison experiment and normalization of newborn screening MS/MS cutoffs.
Method: A subset of the NBS MS/MS analytes was evaluated: arginine (Arg), citrulline (Cit), phenylalanine (Phe), succinylacetone (SUAC), free carnitine (C0), octanoylcarnitine (C8), malonylcarnitine (C3DC), glutarylcarnitine (C5DC) and myristoylcarnitine (C14). Results submitted for NSQAP Set #2, 2014 QC materials and PT results from five different quarterly events were used for the method comparison experiments. The 8 NSQAP Quality Control Samples were tested in duplicate on five different days, providing 10 measurement results for each analyte for each control level. EP Evaluator software was used to perform the method comparison experiments and generate the linear regression and normalized cutoffs.
Results: Normalized cutoffs were generated for nine MS/MS-detectable analytes. Laboratory cutoffs for Phenylalanine ranged from 120 – 178 µM and normalized cutoffs were calculated to be 110 – 175 µM, showing little change. Laboratory cutoffs for SUAC ranged from 1.40 – 5.42 µM while normalized cutoffs were calculated to be 1.50 – 2.25 µM, suggesting a high degree of similarity in cutoffs which is not apparent when comparing non-normalized cutoff values. Other analytes (C3DC, C5DC) had significant differences in normalized cutoffs, regardless of analytical method. Using the CDC's derivatized method as the reference method and the measured concentrations and cutoff values submitted by participating laboratories for the NSQAP quality control (QC) and proficiency testing (PT) samples, regression lines

were generated and normalized cutoff values were calculated. Plots of participants' normalized cutoffs were prepared.
Conclusion: Normalized cutoff values enable accurate comparison of cutoffs regardless of testing methodology. The establishment of normalized cutoffs for participants provided a foundation for comparison and discussion. With these plots, laboratories could identify if their cutoffs were outliers, and could see where their cutoffs were relative to the other states.

Presenter: Mary Seeterlin, PhD, Michigan Department of Health & Human Services, 3350 N. MLK Jr. Blvd., Lansing, MI, 48906, Email: seeterlinm@michigan.gov

Variability in Biotinidase Screening Results between Filter Paper Lots

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A recent increase in in out-of-range (OOR) biotinidase results was noted to coincide with a change in filter paper (FP) lots produced by the same manufacturer. We investigated the effect of FP lots on biotinidase screening results.

Our laboratory screens for biotinidase with a visual colorimetric assay followed by quantitative confirmation of specimens manually selected by the visual screen. Results are reported as a percentage of the specimen OD over the average normal OD, which is calculated daily from 10 normal specimens. To investigate the effect of FP lot on biotinidase results, quantitative assays were run on two plates of specimens from different days (total 160) that contained approximately equal numbers from both FP lots.

The mean OD was 0.41 in specimens collected on new FP cards, and 0.47 in specimens collected on old FP cards, a 15% decrease. No differences were seen between FP lots in the mean values for T4, 17-OHP, IRT or SCID trecs. The new FP lot was distributed in late May 2015 and constituted 15% of specimens received in the lab in June, 48% in July and 60% in August. During this time, the number of OOR biotinidase specimens was 5 in June, 1 in July, and 1 in August. Of the 5 in June, 1 was a true positive while the remaining 4 were false positives all collected on new FP.

Variability in biotinidase screening results between filter paper lots has been noted in the past. Biotinidase activity was found to be significantly lower in specimens collected on the new lot of filter paper cards. Results of other newborn screening tests did not exhibit this difference. Since our assay reports biotinidase activity as a percentage of normal, calculated on a daily basis, any difference between lots would not be expected to affect the net result as long as all specimens were collected on the same filter paper lot. Our new lot was distributed to individual hospitals, and each hospital began using the new cards as they ran out of the old. When the majority of FP specimens used to calculate the normal standard were from old FP cards, such as was the case in June, specimens collected on new FP would be more likely to fall below the 30% cutoff. The resulting mix of new and old FP is a reasonable explanation for the increase in OOR specimens in June when 85% of the specimens were on old FP and all of the false positive results were collected on new FP.

Presenter: Roger Eaton, PhD, New England Newborn Screening Program, University of Massachusetts Medical School, 305 South St., Jamaica Plain, MA, 02130, Email: roger.eaton@umassmed.edu

Factors to Consider in Improving the Screening Algorithm for Congenital Adrenal Hyperplasia

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Introduction: Newborn screening for congenital adrenal hyperplasia (CAH) is recommended by the American College of Medical Genetics as part of a panel of 32 core conditions. Currently screening is performed in all states in the US as well as many countries worldwide. Screening is conducted for 21-hydroxylase deficiency which accounts for 95% of CAH cases, primarily by measuring 17α-hydroxyprogesterone (17-OHP). The positive predictive value for CAH screening is fairly low because 17-OHP values are elevated in low birth weight and premature infants as well as on the day of birth (DOB). Algorithms for screening should therefore adjust for these factors.

Methods: In New York State (NYS) between July 2010 and 2014 approximately 1.06 million babies were screened for CAH. 17-OHP concentration in dried blood spots was measured using the AutoDELFIA Neonatal 17α-hydroxyprogesterone (17-OHP) kit (Perkin Elmer, Turku, Finland). The NYS Newborn Screening (NBS) program's algorithm has set cut-off values for referring babies for follow up diagnostic testing or requiring a second specimen in borderline cases based on the age and weight of the newborn when the newborn's specimen is collected.

Results: From July 2010 to 2014, amongst the 1.06 million specimens submitted to the NBS program, 40,189 (3.8%) specimens were from infants with low birth weight (<2,250 g) and 21,429 (2.0%) specimens were collected on the DOB. Following testing, 6,541 infants had borderline results and a repeat specimen was requested. 1,144 babies were referred. 65 infants were confirmed with CAH: 53 with salt-wasting CAH, 6 with simple virilizing CAH (SV-CAH), 4 with non-classic CAH, and 2 with another enzyme deficiency. In addition, 14 cases were closed as possible CAH and one case of false negative SV-CAH was reported to the program. Of the 1,064 false positive cases, 743 (69.8%) were low birth weight infants, 234 (22.0%) were infants whose specimens were collected on the DOB and only 189 (17.8%) were normal birth weight infants whose specimen was collected 24 hours after birth.

Discussion: In general, more referrals were made in the winter when the average daily 17-OHP values were higher than in the summer. Male infants and Black infants were disproportionately represented in the false positive category. Our results indicate that in addition to weight of the infant and time of specimen collection, sex and race/ethnicity of infant and season of birth also affect 17-OHP values.

Presenter: Norma Tavakoli, Ph.D., Wadsworth Center, 120 New Scotland Ave., Albany, NY, 12201, Email: norma.tavakoli@health.ny.gov

Propionic Acidemia Screening in the Amish and Mennonite Populations

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Propionic Acidemia (PA) is found in Amish and Mennonite ("Plain") populations throughout North America. The founder mutation PCCB c.1606A>G has significant residual enzyme activity making acute neonatal presentations rare and leading to these cases often being described as phenotypically benign and not requiring medical intervention. However, episodic devastating ketoacidotic crises typically occur at times of illness or increased catabolism and can be associated with metabolic strokes resulting in movement disorders and other neurological complications as seen in some patients followed by two of the clinics providing care for Plain children with PA: the Community Health Clinic (CHC) in Indiana and the Clinic for Special Children (CSC) in Pennsylvania.

A cohort study performed by the CSC showed that at least 25% of the patients develop cardiac complications and heart failure, often following a minor illness without a metabolic crisis. Although dilated cardiomyopathy and congestive heart failure can be reversed with treatment in some patients, others may still suffer from metabolic crises, irreversible heart failure and sudden cardiac death when untreated.

MS/MS newborn screening (NBS) is expected to be positive despite the known low propionyl-carnitine levels in this PA variant. In 2013, however, a two-week old Amish female presented to the CHC for counseling after receiving DNA results confirming homozygosity for PCCB c.1606A>G. The patient had an initial NBS reported at 2 weeks of life with mild elevation of Tyrosine followed by a repeat NBS which was reported as normal. The C3 level was 3.60umol/L and 2.138umol/L respectively.

The idea of a high C3 cutoff as a reason for this false negative was considered but lowering it enough to detect all cases with the Amish/Mennonite variant would significantly increase the number of false positives in the general population. The utility of certain acylcarnitine ratios as secondary screening analytes was questioned. It was previously noted by the CSC that C3/C16 is usually < 2.2 in the confirmed positive Amish cases. The ratio was 1.11 and 3.01 on the first and the repeat screens, respectively, in our patient. C3/C2 was within normal limits while C3/C0 was slightly elevated on the initial screen with a level of 0.19 and normal on the second. These ratios, therefore, are not consistently diagnostic.

In addition to this confirmed missed case, we have received reports from community members of sudden cardiac death in young Amish adults with known family history of PA who were never diagnosed or treated. Their postmortem examination revealed dilated cardiomyopathy and heart failure.
These cases suggest that supplemental NBS for unique populations may be merited. Targeted mutation analysis with real-time PCR for the Plain community would enhance specificity for PA and other potentially life-threatening disorders with known founder mutations.

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Session 4 – Molecular Application

Development of a Multiplex CYP21A2 Genotyping Assay for Congenital Adrenal Hyperplasia Screening

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Objective: Develop a targeted multiplex genotyping method as a second-tier newborn screening (NBS) assay for congenital adrenal hyperplasia (CAH).
Background: CAH due to 21α-hydroxylase deficiency (21-OHD) results in adrenal insufficiency and has an incident rate of 1:15,000. All NBS programs in the U.S. screen for CAH. There are two phenotypes of the classic (severe) forms of CAH, salt-wasting (SW) and simple-virilizing (SV). The goal of newborn screening is to identify infants with classic SW- and SV-forms of CAH before either a life threatening salt-wasting and/or adrenal-crisis occurs, or a baby's gender is incorrectly assigned. CAH is the most common cause of ambiguous genitalia in the newborn. The primary screening method for CAH, a

fluoroimmunoassay measuring 17α-hydroxyprogesterone, a metabolite elevated in CAH, historically has the highest false-positive screening rate for all NBS tests, and as recent studies have shown, can also result in false-negative results. To address these issues, the Centers for Disease Control and Prevention (CDC) in partnership with the University of Minnesota and Minnesota Department of Health NBS program through a March of Dimes grant have developed a multiplex genotyping assay to identify CAH-causing CYP21A2 mutations to pilot as a second-tier assay in the Minnesota NBS program.
Methods: CDC developed an allele specific primer extension (ASPE) assay to detect CYP21A2 mutations present in the Minnesota population. A total of 59 families with at least one child with CAH were recruited from the University of Minnesota and blood specimens were used to create dried blood spots for method development. ASPE probes for the 18 CYP21A2 mutations in these families were designed for use with the Luminex bead array system as a single tube multiplexed assay. The ASPE reaction is used in conjunction with a long-range PCR assay to detect common 30 kb deletion and gene conversion alleles.
Results/Conclusions: Genotypes for the molecular CAH ASPE assay were determined by the signal ratio of mutant to normal alleles for each of the different CYP21A2 mutations detected in the Minnesota population. This genotyping panel represents the 12 mutations that are commonly included for CYP21A2 diagnostic genotyping panel and 6 additional mutations that were found in one or more Minnesota families. The allelic ratio cutoffs distinguish normal sequence from single heterozygous and homozygous genotypes of the mutant alleles, including compound mutations that result from intragenic gene conversion events. The turn-around time for the CAH genotyping assay is comparable to existing molecular NBS tests. This assay will be piloted in Minnesota in 2016 and compared to the current screening algorithm for CAH to assess its utility in NBS.

Presenter: Christopher Greene, PhD, U.S. Centers for Disease Control and Prevention, 4770 Buford Highway, MS F-24, Atlanta, GA, 30341, Email: crg0@cdc.gov

Automation of the in situ Dried Blood Spot Screening Assay for Severe Combined Immunodeficiency
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Objective: Development of a high throughput automated method to process dried blood spot (DBS) samples in newborn screening (NBS) for severe combined immunodeficiency (SCID)
Background: NBS for SCID involves the quantitative detection of T-cell receptor excision circles (TREC), a DNA marker of T cell production. The novel in situDBS real-time PCR TREC assay by CDC eliminated the initial DNA extraction step, and has been adopted by eight US NBS programs to date. Meeting the demand of states with high birth rates requires an automated version that can process multiple PCR plates of samples concurrently to maximize throughput.
Method: We developed the protocol using a single bridge liquid handler that has an enhanced multichannel selective tip pipetting head. This allows the instrument to perform fast 96-channel operation as well as use a single row of tips to keep the dead volume to a minimum. With the pipet head in 96 tips format, 125 µl wash buffer was delivered to all PCR wells containing 2.0/1.5 mm DBS punches. After 10-second centrifugation to submerge all samples, the plates were returned to the liquid handler and the buffer in each plate was agitated by 20 repeated up-and-down pipetting, while the tips moved inside the wells to maximize mixing. After two mixing cycles through all the plates, the buffer was removed with a pipet tip movement pattern programmed to prevent accidental removal of the DBS punches. The pipetting head was then switched by software to single row operation and 15 µl of real-

time PCR reagent mixture was dispensed to each well. The plates were then sealed with optical film and were ready for thermal cycling. The protocol could process 1-4 full or partial PCR plates of samples simultaneously, with each run taking <30 minutes.
Results/Conclusion: Our primary goal was to develop an automated method comparable to the manual assay in performance. The main concerns in automation relate to uniformity, precision and reproducibility. Results of our automatic TREC assay, as measured in quantification cycle (Cq), for a single DBS sample processed in 96 individual wells all fell within 0.5 cycles from the mean. Such degree of uniformity was comparable to manual processing. Results measured across four PCR plates processed simultaneously were reproducible. The dispensed volume of PCR reagent ranged from 14.7- 19.5 µl by colorimetric measurement. However, such variation did not lead to significant difference in the Cq value (as the primers and probes were all in excess). Linear regression analysis of DBS TREC standards at 2-fold decreasing concentrations demonstrated linearity comparable to manual method in slope and intercept. This automated in situmethod has already been successfully implemented in the Virginia newborn screening laboratory and routine state-wide SCID screening for the past several months has produced very satisfactory results.

*LNH and JLT contributed equally to this project.

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Overview of the First Eight Years of Newborn Screening for Cystic Fibrosis: The California Experience
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California's unique 3-step cystic fibrosis (CF) screening model is based on first identifying newborns with an elevated IRT (Step1); followed by mutation panel testing for one of 40 mutations (Step 2); followed by sequencing of the cystic fibrosis transmembrane conductance regulator (CFTR) gene (Step-3) for cases that only had one CF causing mutation identified in Step-2. All newborns identified after either Step-2 or Step-3 are referred for sweat chloride confirmatory testing at one of 16 CF specialty care centers. A detailed flow chart will be presented representing the findings from the California experience from July 16, 2007 through June 30, 2015.

Among 4,054,917 newborns screened, 501 CF cases were diagnosed, representing 1 in 8,093 newborns screened; 57% were diagnosed after Step-2 and 43% were diagnosed after Step-3. In addition to CF, 2,581 carriers were identified (1 in 1,571 newborns screened) and 802 CFTR-Related Metabolic Syndrome (CRMS) cases were identified (1 in 5,056). CRMS represents the designation given to those who carry two CFTR mutations or variations but do not exhibit signs or symptoms of CF. The CF case detection rate was 93.8% and 33 cases (1 in 122,876) were missed through screening. Among the 33 missed cases, 49% were due to the initial IRT being less than the cut-off (62 ng/mL before 12/19/2012 and 67ng/mL since then), 36% had elevated IRT but no mutations identified on the California panel, and 15% did not have a second mutation identified during sequencing. Genetic counseling-only referrals started in May 2014 for newborns with one panel mutation and one non-CF-causing mutation (R31C, R668C with and without G576A, L997F, R1162L, V754M, and S1235R). In June 2011, the program stopped referring cases with one panel mutation and only a (TG)11-5T variant; and since July 2015, the program stopped referring cases with what was determined to be a benign variant (1525-42G>A). Ongoing program evaluation with our clinical and laboratory partners is required to fine-tune the California CF screening model. This evaluation includes monitoring of CRMS cases over time to

determine which mutations/variants are non-disease causing and which can be called out as benign variants. This effort has resulted in consistently high screening test performance that minimizes the number of unnecessary referrals of false-positive newborns.

Presenter: Tracey Bishop, California Department of Public Health, 850 Marina Bay Parkway, Rm F-175, Richmond, CA, 94114, Email: tracey.bishop@cdph.ca.gov

Second-tier Full Gene Sequencing for Follow-up of Positive Newborn Screening for Very Long-chain Acyl-CoA Dehydrogenase Deficiency and Glutaric Aciduria Type 1

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Second tier testing has been implemented by many newborn screening programs to reduce the false-positive rate and improve the positive predictive value. DNA confirmation is routinely performed as a second tier test for the common mutations for certain conditions, such as galactosemia, cystic fibrosis, MCAD deficiency and the hemoglobinopathies; however, not all newborn screening laboratories are equipped to perform molecular testing. Due to the high false positive rate for very long-chain acyl-CoA dehydrogenase deficiency (VLCADD) and glutaric aciduria type I (GA-I), second tier full gene sequencing of the ACADVL and GCDH genes, respectively, was implemented by the South Carolina Newborn Screening Program in cooperation with the Greenwood Genetic Center Diagnostic Laboratory in April 2013. Full gene sequencing was performed on the original dried blood specimen (DBS). To date, we have performed full gene sequencing for 162 infants (96 VLCADD and 66 GA-I). For VLCADD, we identified 47 carriers and one affected individual. For GA-I, we identified two carriers and one affected individual. A summary of the use of second tier full gene sequencing for VLCADD and GA1 in SC will be reported. We will review how implementation of this testing has significantly reduced the need for unnecessary blood collections, while still offering prompt reassurance for physicians and parents. Lastly, in addition to improving the positive predictive value for these disorders, the gene sequencing results have been used to make changes to the testing algorithm and further reduce the initial number of screen positives for each of these conditions. Plans are currently underway to perform full gene sequencing for additional conditions, such as galactosemia, biotinidase deficiency, carnitine palmitoyltransferase I (CPT I) deficiency and cystic fibrosis in screen positive infants.

Presenter: Neena Champaigne, MD, Greenwood Genetic Center, 106 Gregor Mendel, Greenwood, SC, 29646, Email: neena@ggc.org

Sequence Coverage of Genes for Inborn Errors of Metabolism by DNA Prepared from Residual Newborn Screening Dried Blood Spots

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Objective: To determine whether exome sequencing and targeted analysis of DNA prepared from residual newborn screening dried blood spots (DBS) provides mutation information for inborn errors of metabolism (IEM) on the RUSP to enable identification of disease and non-disease states.
Materials and Methods: De-identified residual DBS from 188 newborns identified through the California Newborn Screening Program as affected with IEM, false positive or control were provided to the UCSF NSIGHT project NBSeq. A protocol for automated extraction of DNA from two 3 mm DBS punches was developed, and library preparation with reduced sonication time was employed to generate appropriate sized fragments for exome capture and sequencing. Coverage for 63 specific genes was measured.
Results: High-quality sequence data were obtained from sequenced blood spot DNA for 184 of the 188 samples. Excluding 2 failed samples, all samples had > 40X median coverage depth in the target regions for metabolic disorder genes, and > 60% of these bases were covered at > 30X. Areas of lower coverage included first exons, an artifact common to the capture methodology also found on fresh blood samples; identifying variants in these regions may require other capture techniques or whole genome sequencing. Most quality control measures showed results comparable to those from fresh blood samples. For example, for PAH, the gene encoding for phenylalanine hydroxylase where defects cause PKU, all coding regions are covered well, while the longest annotated UTRs are not part of the capture region and are covered poorly. Of the 184 samples with good coverage, all but two samples covered every base at >10x and yielded variants for interpretation.
Conclusion: This pilot study demonstrates that deep sequencing of DBS DNA is feasible and can generate data that may substitute for or enhance existing diagnostic modalities to improve the precision of newborn screening for IEM.

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Session 5 - Screening for Special Populations

Improving the Entire Newborn Screening Process for Out of Hospital Births
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According to the Centers for Disease Control and Prevention, 1.36% of U.S. births were born outside of a hospital in 2012. Even though out-of-hospital (OOH) births make up a small percentage of the total births, it is important for Newborn Screening Programs to establish strong working relationship with out-of-hospital birth midwives and to alter typical protocols to account for the unique nature of OOH births.

Over the past few years, several initiatives have been undertaken to improve the screening process for lay midwives and their clients. These efforts are listed below and will be presented as possible solutions to improving screening and education in this population. As a result of the efforts listed below, our screening rate for blood spot improved from 51% in 2012 to 72% in 2014. Likewise, we have seen the hearing screening rate go from less than 50% in early 2012 to nearly 80% in 2014. Today, many of our midwives are also electronically reporting both EHDI and CCHD data.

Initiatives have included:
• Grant awards to the Minnesota Council of Certified Professional Midwives which allowed their organization to purchase newborn hearing screening equipment for their members.
• Free replacement specimen cards after unsatisfactory specimens, which has improved our rate of repeat specimen collection among the OOH birth community.
• Free specimen cards for OOH birth families that otherwise would not have screening completed because of the financial burden of paying for the card.
• Emphasis on parental choices after screening is completed.
• Creation of newborn screening education material especially for OOH births.
• Creation of a new Amish brochure and outreach to midwives who directly work with Amish families for input and feedback.
• Outreach, midwifery conference attendance, and trainings on completing screenings and reporting results
• Identification of midwife champions to help promote and disseminate new information and processes

Our work with lay midwives has led to several lessons learned which will also be shared with participants. These include, understanding the variability in midwifery practices, the importance of collaboration for best practices, and the need for flexibility and a greater understanding of the needs and concerns of this population."

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Newborn Screening in the NICU: Colorado's Experience with Screening Low Birth Weight Infants

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The Colorado Newborn Screening Program did not adopted the 2009 Clinical and Laboratory Standards Institute (CLSI) Newborn Screening for Preterm, Low Birth Weight, and Sick Newborns; Approved Guidelines for utilizing a three screen protocol for newborn screening collection for infants in the neonatal intensive care unit (NICU) setting. Instead, Colorado uses their standard two screen protocol for all infants, regardless of their weight, health, and gestational age. This study conducted a baseline evaluation of current NBS practices in Colorado to consider if NBS for this special population could be improved by adopting the CLSI guidelines or making other changes to the state's standard protocol. The study analyzed three years of newborn screening data from infants weighing less than 1800g to describe timeliness of screening and abnormal results. Since the NBS program does not collect specific data points such as gestational age or NICU status, low birth weight was used as a proxy. These newborns comprised 2% of births for the three-year period but represented a disproportionate number of the abnormal screening results. The study found that screening greater than 48 hours of age (late screening) was significantly higher for the NICU population than for the general population, less than 3% of screening in the NICU takes place after blood transfusion, and false positive results comprise the vast majority of abnormal screening results seen in this population. Based on the findings of the study , the following recommendations were suggested to the NBS program (1) Compare data from this study with data from states that have a three-screen NICU protocol in place or expanded fields on their specimen collection card. Such further analysis would provide insight for CDPHE's consideration of changing screening protocols for the NICU population and/or adding fields to the specimen collection card to assist laboratory personnel with analysis of results. (2) Implement procedures for following up on

infants who received screening after blood transfusion to include an additional screening at 120 days following last transfusion. (3) Adjust regulations to specify where the burden of screening lies when a newborn is being transferred to another facility. (4) Provide NICU-specific education addressing screening timing, completion of specimen collection cards, and responsibility for conducting first screening in the event of transfer. Collaborate with the NICU community to learn what types of training best suits their needs.

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Comprehensive Screening for Severe Combined Immunodeficiency in Manitoba, Canada

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Severe Combined Immunodeficiency (SCID) is the most profound form of the Primary Immunodeficiency Diseases (PID) and is usually fatal in the first year of life. Early pre-symptomatic detection and treatment lead to better outcome and, as a result, this condition has been included in the ACMG list of core conditions for Newborn Screening. Quantitation of T-cell receptor excision circles (TRECs) in the neonatal specimen is the test most widely utilized by newborn screening programs.

The overall incidence of SCID in Manitoba is three-fold higher than the Canadian national average and is overrepresented in two subsets of the Manitoba population, Mennonites and First Nations of Northern Cree ancestry. In these 2 groups, SCID results from homozygous mutations in the genes encoding zeta chain-associated protein kinase (ZAP70) and inhibitor of kappa light polypeptide gene enhancer in B-cells kinase beta (IKBKB) respectively. Infants affected with these conditions may not be detected by the TRECs assay as they have T-cells, the function of which is absent in those with the ZAP70 mutation and variable in infants with the IKBKB mutation. Retrospective analysis of previously identified patients homozygous for the ZAP70 or IKBKB mutations demonstrated that quantitation of TREC levels would have yielded false negative results in more than half of affected individuals.

To ensure detection of infants with these two specific conditions, we have developed multiplexed real time PCR high resolution DNA melt analyses that are run in parallel with the TREC quantitative assay to detect homozygous and heterozygous ZAP70 and IKBKB mutations in our population.

DNA was extracted from a single 3mm punch from the newborn specimen using the NucliSens EasyMAG automated extractor and separate aliquots were amplified in parallel on two CFX96 Touch Real Time PCR Detection Systems. The quantitative Trec/RNaseP is performed on one system and the genotyping multiplexed high resolution DNA melt on the second system. To ensure primer specificity and correct assignment of genotype, amplicons from each of the two primer sets were sequenced after the amplification of control specimens from individuals homozygous affected, heterozygous and homozygous normal with respect to the ZAP70 and IKBKB mutations.

A blinded study was performed (N=44) and heterozygous or homozygous unaffected status for each mutation was assigned with 100% accuracy. A sample from a confirmed homozygous affected individual was included in each blinded run.

Universal implementation of the multiplexed mutation specific screening strategy in addition to the TRECs assay on all newborns is being planned and will provide comprehensive detection of SCID in the newborn population of Manitoba."

Presenter: J. Robert Thompson, Cadham Provincial Laboratory, 750 William Ave, Winnipeg, MB, R3C 3Y1, Canada, Email: cgreenberg@hsc.mb.ca

Catching Blue Babies: Critical Congenital Heart Defects in Newborns

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Background: There is a lack of specific information on the oxygen saturation profile of newborns with critical congenital heart disease (CCHD). Advances in prenatal care and diagnosis have eliminated newborns with true positive diagnosis from the screening population. We aim to fill this gap by applying a novel approach of characterizing the pulse oximetry values of newborns already diagnosed with CCHD.
Methods: In this retrospective observational study, 343 newborns diagnosed with CCHD and treated at Children's Hospital Colorado (CHCO) from 2003 to 2013 were identified. Their medical charts were electronically reviewed (via EPIC) for demographic information and oxygen saturation values taken at approximately 24 hours after delivery as measured using pulse oxymetry technique. The American Academy of Pediatrics (AAP) screening algorithm was applied to collect these measurements from pre- and post-ductal sites. Data were analyzed using descriptive statistics.
Results: Annually, CHCO treated approximately 30 newborns with CCHD. Newborns were mostly male (69%), not Hispanic/Latino (64%), and white/Caucasian (69%). A majority was delivered in Colorado (78%). Hypoplastic Left Heart Syndrome (30%), Transposition of Great Arteries (26%), and Tetralogy of Fallot (18%) present as the three main diagnoses. There was no indication of risk factors such as having family history of CCHD, genetic abnormalities, and diabetic mother. Out of 343 cases, 159 of them had complete pulse oximetry measurements. Pre- and post-ductal oxygen saturation values and ranges were 87.1 ± 7.2 (70.0 – 100.0) and 87.8 ± 6.3 (67.0 – 100.0), respectively. Approximately two cases with CCHD produced negative screening results (7% false negative).
Conclusions: The average oxygen saturation values of newborns with CCHD were observed to be significantly lower and with wider range than their healthy counterparts at similar altitude (97.2 ± 1.9 with range of 88.0 to 100.0); based on previous literature). Applying the AAP screening algorithm to infants with CCHD treated at CHCO would result in a lower false negative rate than values reported in literature. Considering that 70,000 babies are delivered in Colorado annually, this may imply that CCHD screening at CHCO using current algorithm would miss approximately nine babies per year. Collectively, this information has not been previously described from a comprehensive electronic chart review of newborns with CCHD, and will help to inform cutoff values for CCHD screening in the region. This study design should be replicated at different altitudes to provide a more complete clinical assessment of newborns with CCHD.

Presenter: Merlin Ariefdjohan, PhD, Colorado School of Public Health, University of Colorado, 13123 E. 16th Ave., Suite D4152, Aurora, CO, 80045, Email: merlin.ariefdjohan@ucdenver.edu

Wednesday, March 2

Roundtables

Strategies for Implementing Newborn Screening for Adrenoleukodystrophy (ALD)

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Adding a new disorder to a state newborn screening program is a dynamic, complex process. With the recent recommendation of the Advisory Committee on Heritable Disorders in Newborns and Children to add adrenoleukodystrophy (ALD) to the Recommended Uniform Screening Panel, many states are in the process of addressing the complexities of newborn screening for this disorder.

Participants will meet in small groups to brainstorm strategies for dealing with program implementation challenges. These topics include: ALD screening test methodology; short-term follow-up coordination and managing referrals to metabolic, endocrine and neurology specialists; diagnostic testing and secondary targets; identification of heterozygotes, affected siblings, and variable presentation; very long-term follow-up and strategies for follow-up of long-term asymptomatic cases; access to hematopoietic stem cell transplantation and monitoring of clinical outcomes following transplantation; how to track, who will track, and how long to track.

The common contextual theme for all group discussions will be the need to build an evidence base through the collection of data that can demonstrate the impact of early diagnosis for newborns diagnosed with ALD and whether screening makes a difference in outcomes. California program staff will partner with program staff in other states to lead these strategy discussions and summarize findings.

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Solutions for Implementing Newborn Screening Surveillance Case Definitions

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Background: Approximately four million newborns are screened for over 32 rare genetic conditions every year in the United States. Each diagnosis is confirmed in a manner determined appropriate by state consultants and clinicians. Recognizing that clinical work-up may vary and each diagnosis is made based on clinical judgment, there are different diagnoses that may occur for individual newborns. Uniform surveillance case definitions for newborn screening (NBS) are critical to understand the frequency of the disorders and to guide public health surveillance activities. Surveillance case definitions for NBS conditions have been developed with the purpose of harmonizing the reporting of confirmed cases within and across programs.

Clinical experts developed consensus statements on the criteria for the minimal essential elements to diagnose a case after an abnormal screen. Criteria included the minimal reasonable evaluation panels for confirming a diagnosis. The consensus statements were further developed into surveillance case

definitions by experts. Based on retrospective reviews of cases and comparisons to established criteria, cases can be categorized by Definite, Probable, Possible or Unlikely diagnoses. NewSTEPs performed pilot testing of these initial case definitions and sought feedback from a variety of stakeholders, including state NBS programs and clinicians.
Discussion: The implementation of the surveillance case definitions at the state public health level can be challenging and time consuming. The data required to assess the certainty of a diagnosis must be ascertained through communication between state newborn screening programs and clinical specialists. Data elements must be recorded in local and/or national data resources and evaluated against the case definition tables.
A brief overview of the public health surveillance case definitions will be presented. States who have implemented case definitions at the local level will share utility of the case definitions, challenges to collecting the data and solutions to assist with implementation. The NewSTEPs Toolkit for case definitions will also be presented.
Conclusion: This is the first time uniform surveillance case definitions have been developed for disorders detected through NBS. These definitions will facilitate data harmonization across state and regional NBS programs for public health surveillance and outcomes assessment. These data, when collected in a uniform fashion, will enable tracking of disorder frequency and show trends across time within and across programs.

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Session 6 – Health Information Technology

HIT the Ground Running: Statewide Implementation of Electronic Demographics and Reporting of Point-of-Care Newborn Screening Results

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The relatively recent addition of Critical Congenital Heart Defects (CCHD) to the Recommended Universal Screening Panel (RUSP) in 2011 caused many newborn screening programs to re-examine how point-of-care testing results (for both Early Hearing Detection and Intervention (EHDI), and CCHD) are delivered from the birth facility to the program. Minnesota was one such program that took the addition of CCHD as an opportunity to also improve upon the EHDI program by implementing an electronic reporting system that would allow for real-time demographic receipt from Electronic Health Records (EHRs) and result reporting in order to improve upon follow-up efficiency and data integrity.

We will present Minnesota's point-of-care electronic reporting implementation planning, successes, and lessons learned. Utilizing a number of key steps has allowed the Newborn Screening Program to get buy-in for implementation from IT staff and ensure preparedness by birth facilities and attendants.

We will discuss:
- Hospital survey outcomes and development of educational materials and training
- General messaging terminology to prepare states to discuss needs
- Interoperability Tools used in implementation
- Project management tactics

• Implementation steps, including stakeholder meetings and process planning
• Status of implementation with lessons learned
• Update on Meaningful Use as incentives for implementation

The addition and implementation of new reporting modalities often follow very different paths in different states. Because each state faces different challenges, and may enjoy different opportunities, sharing state experiences in implementation of electronic data systems is critical to improving the public health practice of Newborn Screening nationwide.

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Past, Present, Future - Health Information Technologies in the Texas Newborn Screening Laboratory

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Objective: To develop a roadmap to sustainable implementation of Health Information Technology (HIT) solutions for reducing public health laboratory turnaround time constraints and expediting delivery of test results to healthcare providers.

Summary: Health Information Technologies have the potential to introduce efficiencies into public laboratory systems by:
• Automating patient demographic (order) entry
• Eliminating barriers and delays to timely delivery of laboratory test results.
• Streamlining communications between public health entities and healthcare providers.

Sustainable and scalable implementation of these technologies, however, continues to present unique challenges to public health programs.

The Texas Department of State Health Services (DSHS) Laboratory initiated the use of Health Information Technology for Newborn Screening in 2006. In the ten years since, Texas has enjoyed successes, experienced multiple obstacles and learned a variety of lessons.

An analysis of currently implemented HIT solutions will focus on quantifiable impact on demographic entry and result reporting, lessons learned from previous implementations, system integration within the overall public health laboratory organizational structure, deficiencies in current systems, human resource needs for implementation and maintenance, and required adjustments to process workflows.

Various possible models / solutions for future implementation or expansion of HIT solutions will be assessed. Findings from these analyses will be used to develop a roadmap to serve as a structural guideline for future public health laboratory health information technology solutions.

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Increasing Newborn Screening Health Information Interoperability: A Systems Approach

H. Brand, C. Wolf, J. Simonetti, A. Gavigilo, M.R. Harsha and M. McCann, Minnesota Department of Health, St. Paul, MN

The Minnesota Department of Health's (MDH) newborn screening program is in the process of replacing an Oracle based laboratory developed information management system (LIMS) to increase the timeliness of information transferred and collected for public health. We have undertaken a two-fold approach to integrate systematic program practices from point-of-care (POC) screening all the way through blood spot screening. MDH has implemented OZ Systems™ Intelligent Newborn Screening services to integrate with hospital based electronic health records (EHR's) and handle the results for point-of-care hearing screening and heart screening from the device level to public health reporting. This now functional system has been named MNScreen. The second approach will utilize Natus Medical's Incorporated data management solution Software-as-a-Service (Saas) for public health newborn screening practice that will interoperate with MNScreen. MDH's newborn screening program has identified three key components to improve newborn screening system performance:

- Interoperability among many systems
- Vendor hosted
- Software-as-a-Service

Both systems once fully implemented, will meet these criteria allowing the MDH newborn screening program to achieve full system interoperability of blood spot test results, hearing results, heart screening results, hospital demographic information from the electronic health record (EHR), and birth certificates from the MN Department of Vital Records.

Tools include remote diagnostic tools for our primary care providers and specialists that will allow them to log-in to the system to enter and retrieve diagnostic results. Both our hospital based system partners and out-of-hospital specimen submitters will have the option for remote demographic entry and secure remote viewing of test results. The program will have enhanced capabilities to monitor timeliness and many other quality control indicators by achieving interoperability of our systems. This will greatly improve many facets of the entire MDH newborn screening program.

Presenter: Heather Brand, Minnesota Department of Health, 601 Robert Street North, St. Paul, MN, 55164, Email: heather.brand@state.mn.us

Proof of Concept Project Using Electronic Birth Notification to Improve Surveillance and Quality of Newborn Screening Pre-Analytic Processes: Implementation of NANI in Select Indiana Hospitals

V. Buchanan, Indiana State Department of Health, Indianapolis, IN

Problem Studied/Objectives: High quality newborn screening (NBS) depends on timely collection of clinical information on the newborn infant and timely collection and transport of quality specimens to the testing laboratory. However, the laboratory usually does not receive information about new births or specimens until the filter paper cards arrive at the laboratory.

This proof-of-concept project tested the feasibility of establishing birth notification using Integrating the Healthcare Enterprise's (IHE) Newborn Admission Notification Information (NANI) technical framework for the Indiana State Department of Health's (ISDH) Genomics and Newborn Screening (NBS) program's pre-analytics. NANI improves data quality, reduces data entry errors, and decreases duplicate data entry burden on birthing facilities.

Methodology: In Phase 1, the Indiana project expanded the use of their NANI system from 8 to 12 hospitals. ISDH's NBS program currently has a contract in place with OZ Systems to establish and maintain individual connections between several of Indiana's birthing facilities and the ISDH data system. This connection is made so that data related to birth notification can be sent electronically from a birth facility to OZ Systems, and then on to ISDH. Data related to birth notification is sent electronically from a birth facility to OZ Systems, and then on to ISDH. Funds from this project were contracted to OZ Systems in order to provide hospitals with small stipends to set up the necessary interface and messages to implement NANI. In Phase 2, Indiana will attempt similar conversations with at least 5 other facilities to have them implement NANI.
Significant Results: In Phase 1, agreements to participate in the project were signed by 3 hospital systems and 4 hospitals, however due to other priorities at the hospitals, NANI was implemented at only 2 of those recruited hospitals. It was found that the data matched on the Last name: 71%; First name: 40%; Medical Record Number: 97%; Date of Birth: 100%; Time of Birth: 81%; Mother last name: 97%; Address: 57%; and City: 64%. Phase 2 will have a total of 4 new hospitals and data similar to Phase 1 will be collected.
Conclusions/Implications: The data is not yet available in the laboratory, so the utility for improving preanalytical quality metrics was limited. However, the data was being used to find missing data fields for future programming improvements and to find missing specimens for further follow up. The presentation will highlight how the follow-up programs are using the data and how the data will be shared with the laboratory to improve preanalytical quality metrics.

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Session 7 – Education

Baby's First Test: 5 years of a National Educational Initiative

Presenter: Jaclyn Seisman, MPH, Genetic Alliance, 4301 Connecticut Ave NW Suite 404, Washington, DC, 20008, Email: jseisman@geneticalliance.org

The two following abstracts have been combined into the single oral presentation above.

Tell Us More: Stakeholder Evaluation of the Newborn Screening Clearinghouse
N. Bonhomme, Genetic Alliance, Washington, DC

In September 2011, the Newborn Screening Clearinghouse was fully launched as Baby's First Test (www.BabysFirstTest.org). Created in response to the 2008 Newborn Screening Saves Lives Act, Baby's First Test provides healthcare professionals and new and expecting parents access to reliable information and resources on newborn screening policies and procedures. Just three years after its initial launch, the number of visitors to the Baby's First Test website had grown exponentially and was continuing to grow each quarter. Yet, despite this growth in traffic, it was hard to assess the impact of the program from the perspective of the newborn screening community.

To assess the program's impact, the project team conducted in-depth evaluation interviews with key stakeholders to determine perceptions of the Clearinghouse as well as areas for further improvement. Four key groups were interviewed: 1) Consumer Task Force members; 2) Challenge Award recipients; 3)

newborn screening thought leaders; and 4) newborn screening laboratory and follow up representatives. These interviews were confidential and conducted by a third party evaluator. In total, 40 participants were recruited, representing a mix of parents, leaders from non-profit organizations, and health professionals engaged in the newborn screening field.

Key findings from the qualitative analysis varied depending on the category or field the interviewee was from, but overall, stakeholders found the Clearinghouse to be a helpful resource that supported local programs, especially through social media. Respondents across all four categories wanted more specific strategies for engaging families, including those who are low-income and non-English speaking. Further, stakeholders recommended that Baby's First Test reach out to obstetricians, pediatricians, and other healthcare providers that connect with parents in the prenatal stage. This presentation will provide an in-depth analysis of the key findings, opportunities for growth as identified by each category of stakeholders, as well as the strategies in place to address them.

The Newborn Screening Clearinghouse: Four Years of a National Education Initiative
N. Bonhomme, Genetic Alliance, Washington, DC

Newborn screening is one of the most successful public health programs in the United States. However, with the introduction of new technology and the ability to screen for more conditions at lower costs and with greater accessibility, the scope and depth of newborn screening has rapidly evolved since its inception, causing gaps in both education and in information and clinical services.

In an effort to address these educational gaps, Baby's First Test (www.BabysFirstTest.org), the nation's newborn screening clearinghouse, was created to provide the public with access to reliable information and resources on newborn screening policies and procedures at the local, state, and national levels. Over the past 4 years, Genetic Alliance has built, expanded, and maintained BabysFirstTest.org. This has led to more than 1 million sessions on the site by nearly 900,000 users. With key target audiences of healthcare providers and new and expectant parents, Baby's First Test has implemented numerous strategies to increase traffic, expand its reach, and to evaluate the impact of this reach.

Based on an analysis of the site's web analytics over the past 4 years, this presentation will focus on four key areas: 1) the statistical changes of site visits and visitors; 2) key web-based partnerships and their potential affect on usage of the site; 3) demographics of site users; and 4) expansions of the program based on this data, including mobile development and additional content creation. Furthermore, the presentation will discuss lessons learned through continued user evaluation and specific strategies for increased dissemination of NBS education in an ever-changing newborn screening system.

Impact of Continuing Medical Education on Primary Care Providers' Knowledge and Confidence in Caring for Patients with Congenital Hypothyroidism
E. Bezar[1], N. Rosenthal[2], L. Feuchtbaum[2]; [1]Public Health Foundation Enterprises, City of Industry, CA, [2]California Department of Public Health, Richmond, CA

Goal: Primary Congenital Hypothyroidism (PCH) is the most common disorder diagnosed through the California Newborn Screening Program and is one of the "Recommended Uniform Screening Panel" disorders that can potentially be managed well by primary care providers (PCP) with support from endocrinologists. Although treatment can be viewed as relatively simple (parent administration of a daily dose of levothyroxine), if PCPs do not know the basics of disease management, they could

inadvertently deliver less than optimum care. During a 2014 survey conducted among PCPs in California and Hawaii, we identified a significant knowledge gap in treating patients with PCH. Therefore, we developed a course entitled "Congenital Hypothyroidism: What Every Pediatrician Needs to Know" to address the gap. This study will assess the impact of the course on improving PCPs' knowledge and confidence in caring for patients with PCH.
Methods: In 2015, the course was presented at 6 hospital Grand Rounds in California (5) and Hawaii (1) for CME credit. A pre- and post-course evaluation was conducted among participants of each session. Changes in knowledge and confidence in initiating treatment and conducting long-term case management were evaluated.
Results: Approximately 300 providers attended the course and over 50% completed both the pre- and post-course evaluation. Among the 171 respondents, 56% were pediatricians and 21% were nurse practitioners/physician assistants. After attending the course, 70% had improved confidence in PCH case management; 80% indicated being more confident in initiating treatment; 69% indicated being more confident in conducting follow-up care; and 75% said they would make changes in their management of PCH patients in the future. 88%, 87% and 86% rated the course outstanding in content, course organization, and usefulness to clinical practice, respectively. For 6 of 8 clinical knowledge questions, more than 70% of participants improved their scores on the post-course evaluation.
Conclusion: The educational course has been shown to be effective in improving PCPs' knowledge and confidence in caring for patients with PCH. Newborn screening programs may consider offering such educational courses to PCPs who provide care for patients with PCH.

Presenter: Emily Bezar, MA, Public Health Foundation Enterprises, 12801 Crossroads Parkway South, Suite 200, City of Industry, CA, 91746-3505, Email: emily.bezar@cdph.ca.gov

Health Communication Strategies for Newborn Screening
P. Constant, S. Rosendahl, M. Dreon, B-A. Bloom, B. Roby, J. Cavazos and M. McCann, Minnesota Department of Health, St. Paul, MN

In general, public health does an insufficient job of educating the public on the importance and significance of our work. In particular, Newborn screening has relied on medical providers to directly educate new parents on the benefits of screening. Many stakeholders, providers and public alike, struggle to understand the rationale and importance of educating people about a program that is considered 'routine' and a 'standard of care'.

People have an ever increasing desire to understand medical practices and information. At the same time, there is an increased focus on parental / patient autonomy. In order to empower new and expectant parents, we need focused efforts on increasing general awareness about newborn screening. In Minnesota, we have made significant efforts to increase visibility, program transparency, and general awareness of newborn screening.

In this presentation, we will discuss educational efforts implemented in Minnesota, such as:
- Social media efforts
- Billboard campaign that included both metro and outstate advertisement
- Exhibits at multiple medical conferences
- Customized trainings for medical providers with an outreach 'push' to providers and clinics
- State Fair presence including a booth, fans, restroom advertising, and media presence
- Prenatal outreach in multiple formats, including birth and baby fair displays, and outreach to childbirth

educators
- Diverse photography project to increase availability of culturally appropriate pregnancy and newborn photos for educational materials
- GovDelivery as a means to increase informal communication

These combined efforts have increased general awareness of screening and span an array of cost, time, and audience reach, including unique challenges. These efforts represent initial measures to increase awareness in Minnesota with the hope to inspire further engagement on behalf of public health.

Presenter: Patti Constant, MPH, Minnesota Department of Health, 601 Robert St. N, St. Paul, MN, 55164, Email: patti.constant@state.mn.us

Development of the NC NEXUS Decision Aid: Implications for Parental Education and Newborn Screening

M. Lewis, R. Paquin and D. Bailey, RTI International, Research Triangle Park, NC,

Advances in genomic sequencing technology raise fundamental challenges to the communication of genomic information. These will get even more complicated as this information is incorporated into newborn screening (NBS) practice in the future. Doctors and public health officials will need to decide what type of information to test for and which results incidental to NBS targets should be returned to parents. This will be a vexing challenge for policy, clinical practice and public health systems. We need evidence-based and validated tools that can support informed decision making for parents who may be faced with making decisions about the type of results they want to learn. The North Carolina Newborn Exome Sequencing for Universal Screening Study (NC NEXUS) is addressing this challenge by examining parental knowledge, beliefs and values about genomic sequencing for newborns and using this information to develop a decision aid to support informed decision making as part of a research study. We will provide an overview of the evidence-based approach we are using to develop an electronic decision aid that will deliver tailored information to support parental decision making about the types of genomic sequencing information they want to learn as part of NC NEXUS. We will describe the theoretical bases for the aid from decision science, the process of development, the qualitative (qualitative interviews with parents) and quantitative data (national survey of parents) used to inform content, and best practices in user design principles being applied. How the decision aid will be tested, and the implications for educational materials that support parents and newborn screening programs will be discussed.

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Session 8 – Parent/Patient Panel (no abstracts)

Session 9 – Financial, Legal, Ethical, Policy and Social Implications (FLEPSI)

Parental Interest in Genomic Sequencing (GS) of Healthy Newborns: Experiences from the BabySeq Project

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The NIH funded BabySeqTM Project explores the impact of genomic sequencing (GS) on the healthcare of newborns and the well-being of their families. Well newborns (240) are being randomized to receive either standard of care (SOC) (state-mandated newborn screening) or SOC plus GS that will evaluate genes with strong evidence for causing childhood disorders. Detection of both disease and carrier status is reported. After receiving results, enrolled families and their baby's Pediatrician are monitored over time. Prior work published from our group, based on a post-partum survey regarding the theoretical offer of newborn GS, suggested that 82% of parents would have a significant interest in this type of testing.

Our protocol requires that we obtain parental consent and a newborn blood sample in the short time between birth and discharge from the birth hospital. We assessed how often and why parents who expressed an initial interest in the BabySeq Project chose to decline consent.

Enrollment began in May 2015. Of the first 113 parents expressing interest in participation, 13 could not be consented either due to exclusion criteria or study logistics. Of the remaining 100 families approached, 73% declined participation after the first cursory explanation of the study. Of the 27% who agreed to review the consent form in the context of a 1 hour genetic counseling session, 55% consented to participation. The final overall decline rate was 85% of interested families and slightly less than half of those who started the consent process. In an exit survey of 59 families, reasons for declining included: too overwhelmed to decide (12%), worries regarding genetic discrimination (10%), concern about confidentiality and privacy of information documented in the medical record (10%) and desire not to receive any potentially unfavorable information about their new child's status (15%). Parents also cited issues related to the protocol structure, including the need to draw extra blood from the baby (14%) and requirement to return to the hospital for results disclosure and/or commit time to surveys (28%).

In approaching families for consent, we confronted constraints of both the protocol (e.g. time of stress for parents, blood collection from the newborn, randomization outcome, requirement for surveys and return to hospital for result disclosure) and perceived negative impacts of genetic information. Actual participation was only a fraction of that anticipated by the pre-BabySeq Project survey. While some parental reasoning is artificially influenced by protocol constructs (50%), 20% of interested parents expressed enough concern about privacy and insurability that they steered away from consideration of potential newborn GS benefits. These initial findings provide valuable insights into parental thoughts and feelings regarding GS as well as feasibility of newborn GS implementation on a population-based level.

Presenter: Richard Parad, MD, MPH, Brigham and Women's Hospital, 75 Francis Street, Boston, MA, 02115, Email: rparad@partners.org

The Michigan BioTrust for Health: Impact of Parental Consent Process on Robust Population-based Research Using Residual Newborn Screening Blood Spots

M. Kleyn, C. Langbo and J. Bach, Michigan Department of Health and Human Services, Lansing, MI

Background: The Michigan BioTrust for Health (BioTrust) was established in 2009 to optimally preserve, and increase utilization of residual newborn screening blood spots in medical research while emphasizing a greater need for transparency and improved parental decision-making opportunities. We conducted an analysis to assess whether adequate blood spots are available for robust population-based research after implementation of the BioTrust parental consent process in 2010.
Methods: Following a hospital or home birth, parents record their BioTrust consent decision on a form in the newborn screening kit that is returned to the Michigan Newborn Screening Laboratory for linkage with their newborn's blood spot sample. Outcomes of this process include a signed form documenting either consent ("yes" checkbox marked) or active refusal ("no" checkbox marked). Alternatively, forms may be incomplete or not returned at all, which is considered passive refusal, rendering the blood spots ineligible for research (unless future consent is obtained). Logistic regression was used to determine the association between characteristics of interest from the birth certificate and a response of active refusal or passive refusal, compared to consent for all newborns screened between 2011-2014. Characteristics examined included metro status of maternal county of residence, birth place, race, ethnicity, maternal age, maternal education, admitted to neonatal intensive care unit (NICU), birth weight, and multiple birth status.
Results: Completed BioTrust consent forms were received for 353,536 of 447,482 (75%) newborns. The consent rate was 61% for all newborns screened (18% of all newborns screened had an active refusal and 21% a passive refusal); and 77.5% amongst those with a completed BioTrust consent form. After adjustment, certain groups were significantly more likely to have an active or passive BioTrust refusal including non-hospital births, minority races, Hispanic ethnicity, mothers ≥35 years of age, maternal education ≤high school, and NICU admission. The strongest association was seen among non-hospital births which were 3.4 times more likely to have no consent obtained. When compared to the general population, black newborns were under-represented in the consented pool by <4%.
Discussion: Further analyses are needed to tease out the effects of hospital compliance with the consent process on demographic characteristics of consented samples, particularly focusing on race. If asked, parents of NICU newborns were significantly less likely to refuse the BioTrust, but they are significantly less likely to be asked, due in part to hospital staff trained not to burden parents with the consent process during such a tumultuous time. Overall, it is reassuring that demographic characteristics of those consenting to the BioTrust are relatively consistent with those of the screened population.

Presenter: Mary Kleyn, MSc, Michigan Department of Health and Human Services, 201 Townsend St, Lansing, MI, 48909, Email: kleynm@michigan.gov

Analysis of Four Lysosomal Storage Disorders within the Context of Newborn Screening in Washington State

M. McCrillis, M. Glass and J.D. Thompson, Washington State Department of Health, Shoreline, WA

Background: Heritable lysosomal storage disorders (LSDs) have emerged as a compelling group of candidate conditions for newborn screening (NBS), largely due to advances in therapeutic interventions such as enzyme replacement therapy and bone marrow transplantation. These interventions can reduce

morbidity and mortality in patients, particularly when administered pre-symptomatically or early in disease progression.
Problem: In the wake of these developments, Pompe disease was added to the Recommended Uniform Screening Panel (RUSP) and the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children recommended adding mucopolysaccharidosis type I (MPS-I) to the RUSP. In recent years, the committee conducted an External Evidence Review on Krabbe disease and voted not to recommend screening for Fabry disease and Niemann-Pick disease. A small number of newborn screening programs have already expanded screening to include LSDs, but the majority faces the decision to add one or more these complex conditions using their own advisory committees and review processes.
Methods: Summary documents were compiled for the following LSDs: Pompe disease, MPS-I, Krabbe disease, and Fabry disease. To develop these documents, a literature review was conducted to capture the existing scientific evidence for the conditions as it pertains to NBS. Next, the acquired data was parsed and structured for comparison of each condition against the following four Washington NBS criteria: Available Screening Technology, Diagnostic Testing and Treatment Available, Prevention Potential and Medical Rationale, and Public Health Rationale. (The final Washington NBS criterion pertaining to Cost-benefit/Cost-effectiveness was not systematically reviewed.)
Results: We will share highlights and preliminary analysis from the summary documents. Specifically, we will present how the four disorders measure up to the Washington NBS criteria and where robust data exists, where evidence is lacking, as well as unique social, legal, and ethical issues.
Conclusion: This was a Masters Practicum project, prepared in anticipation that these LSDs would be formally considered in Washington State in the future. When they are, the documents will be updated and provide advisory committee members with a valuable resource upon which to initiate discussion. As the majority of states have yet to add a LSD to their screening panel, these shareable documents could serve as a springboard to use in their own process for considering screening for these four LSDs. Furthermore, more than static documents, this project highlights the importance of systematically evaluating existing evidence for a considered NBS condition.

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Thursday, March 3

Session 10 – Quality Improvement - Timeliness

Meet Your Match: The Importance of Vital Record Matching in the Realm of Timely Newborn Screening

A. Dahle, A. Gaviglio, H. Brand, M. Zerby and M. McCann, Minnesota Department of Health, , St. Paul, MN

Having timely access to vital records is an important process within a state's Newborn Screening program to ensure all infants are being given the opportunity to have effective newborn screening. In Minnesota, we are able to view almost real-time vital record information (through an Internal Data Use Authorization) that allows us to match our newborn screening specimens to a birth certificate typically around 5 days after date of birth (DOB). The ability to match specimens so quickly has several benefits – it aids in timely screening for individuals who may have otherwise been missed, it allows program staff

to have more reliable contact information when following up on abnormal screening results, and it allows program staff to receive death certification information in order to tailor follow-up. This session will present the infrastructure and process of matching with our office of vital records, outcomes from 2014 and 2015, and lessons learned from our practice of following up on unmatched vital records. In addition, we will discuss educational initiatives taken to reduce the numbers of infants whose screens get missed and increase the receipt of required refusal paperwork. Our efforts have included handouts for hospital staff about collecting a pre-transfer specimen, contacting submitters via phone and mail for missing refusal documentation, and contacting midwives regarding missing specimens or refusal forms. In 2014, there were 69,196 birth certificates filed in Minnesota. Of the 69,196 birth certificates, 164 infants died prior to specimen collection, 156 infants did not receive blood spot screening due to parental refusal, and 327 infants (115 hospital births/212 out-of-hospital births) were unable to be matched to a birth certificate.

Of the 115 unmatched infants from hospitals, only 8 remain unscreened. Notification of a potentially missed infant was able to occur at a median of 13 days post DOB, with a specimen subsequently received at a median of 17 days after DOB. These results indicate that we successfully obtained screening results from 99.7% of eligible infants with a MN birth certificate filed in 2014. More recently, we have implemented initiatives to improve upon our missing specimens, which include a new protocol to work with midwifery practices and an effort to reduce time to notification of potentially missed infants to 7 days of age. Outcomes of this work will also be shared.

Presenter: Amy Gaviglio, MS, CGC, Minnesota Department of Health, 601 Robert Street North, St. Paul, MN, 55164, Email: amy.gaviglio@state.mn.us

What Predicts NBS Specimen Timeliness in a State-based Cohort of Birthing Hospitals?

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Background: Newborn screening (NBS) is a system whose effectiveness depends on the timely collection, processing, and transport of NBS specimens. There have been no published analyses of hospital and birth characteristics that might influence the timeliness of the NBS process.
Methods: Using data from the Michigan NBS Program, we examined the timeliness of the NBS process for first NBS specimens (i.e., not repeat or follow-up specimens) collected in Michigan from April 2014 to March 2015. We conducted univariate analyses on hospital characteristics (number of first NBS specimens, time from birth to NBS specimen collection, NBS specimen transit time from birth to state lab) and birth characteristics (day of birth, hour of birth). Our main outcome was appropriate day of NBS specimen pickup from the hospital. A NBS specimen is deemed as an appropriate day pickup if it is collected after the previous NBS specimen pickup and >5 hours before the next NBS specimen pickup. All NBS specimens in Michigan are transported from the hospital by courier or UPS and arrive at the state lab the day following pickup. We then used multiple regression (specifically, a generalized linear mixed model) to determine which characteristics were significantly associated with appropriate day pickup.
Results: We analyzed data from 110,851 first NBS specimens across >80 birthing hospitals in Michigan during the analysis period. Overall, NBS specimen transit time relative to the hospital average was the best predictor of appropriate day pickup, with an approximate 17.6% [95% CI: 16.7%-18.1%] increase in the relative risk of an untimely NBS test for every hour a patient exceeds the hospital average (P<0.001). Average transit time by hospital, ranging across hospitals from 28.1 to 64.6 hours, was also highly

predictive of appropriate day (17.4% [95% CI: 14.2%-21.1%] increase in relative risk per hour; P<0.001). Even though hospitals range in their average time to collect NBS specimens (24.4-33.4 hours), this variable was not significant factor in the regression (P=0.665); nor was NBS specimen collection time relative to hospital average (P=0.154). Interestingly, the day of the week when a NBS specimen is collected is significant (P<0.001), where Monday is associated with the greatest risk for an untimely NBS test and Friday is associated with the least risk.
Conclusions: To improve NBS specimen timeliness, NBS programs might consider working with hospitals to optimize processes related to NBS specimen transit time and the day of the week that the NBS specimen was collected.

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A Lean Six Sigma Approach to Continuous Quality Improvement in Texas Newborn Screening Program
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Objective: Utilization of Lean Six Sigma concepts in reducing laboratory turnaround times and improving overall system timeliness and efficiency in the Texas Newborn Screening (NBS) Laboratory.
Methodology: A combination of Lean Six Sigma and Theory of Constraints concepts were used to analyze the system of processes contributing to Texas NBS Laboratory turnaround times. Lean Six Sigma uses Define-Measure-Analyze-Improve-Control – a five-step approach to process improvement. Processes from the arrival of NBS specimens in the laboratory to the final result reporting step were examined in an effort to remove delays, duplications and bottlenecks. Baseline data was collected over a 2-week period capturing information for major time points in the process.

Based on the data collected, laboratory staff initiated a series of projects aiming to minimize the time from receipt of the specimen in the laboratory to:

- Release of presumptive positive results for critical disorders
- Release of presumptive positive results for non-critical disorders
- Reporting of complete results

Identified projects focused efforts on analytical area processes for Galactosemia Screening, Hypothyroidism Screening, and Tandem Mass Spectrometry as well as support area procedures for specimen receiving, punching, demographic entry, and result reporting. Additional matrices and process data were collected and analyzed to identify opportunities and recommendations for improvement for each project.
Results: The baseline data indicated that overall turnaround time is meeting established expectations and process flow appears predictable and stable. The Texas NBS Laboratory will examine the recommendations, implementations and outcomes of these projects. The individual and collective impact on Texas's ability to meet timeliness measures will be evaluated. This presentation will summarize lessons learned and discuss the suitability of Lean Six Sigma to the newborn screening process.

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Collaborating Across States to Improve NBS Timeliness: An Overview of the CoIIN (Collaborative Improvement and Innovation Network) for Timeliness

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Problem Studied: In 2013, a report in the Milwaukee Journal Sentinel found evidence of delays in newborn screening programs across the country. These delays can have serious, if not deadly, implications for the newborn and their family. Since that time, newborn screening programs in public health departments across the country have undertaken quality improvement initiatives to improve timely submission and testing of newborn blood samples.

Methods: Since January 2015, 8 states have been actively working together as part of a NewSTEPs (Newborn Screening and Technical assistance and Evaluation Program) Newborn Screening Timeliness CoIIN (Collaborative Improvement and Innovative Network) to identify barriers to timely newborn screening. As part of this CoIIN, states have been asked to undertake activities to overcome barriers and improve their processes as well as report on quality indicators monitoring: • Time between birth to specimen collection.

• Time between specimen collection to receipt by lab.

• Time between specimen receipt to reporting out results [reported by analyte] as well as average time between birth to reporting out if the lab collects that data.

The states have met face-to-face once and continue to meet monthly for educational purposes and to provide progress reports.

Results: Currently we have data for the first 4 months of the project but will have data for 13 of the 15 months of the program to present in February. At this time (a) 4 of the 7 states providing QI data saw an increase in the percentages of births where the specimen was collected between birth and 48 hours; (b) all 4 of the states who could look at percent of samples received same day as collection or on day 1 after the sample was collected saw an increase in the percent of samples received by the lab within 1 day after collection; (c) both of the states who looked at time elapsed between specimen collection and receipt by lab from 0 to 2 days saw an increase in the percentages of specimens received within 2 days from collection. The percentages increased from January to April were 21.3% and 33%; (d) one of the two states who reported specimen receipt to reporting out complete results saw an increase in how quickly they could report out the complete results after the specimen was received (from 94.2% to 97.4% within 72 hours and 73.5% to 74.7% within 48 hours) while the other saw a decrease; and finally the one state who was able to report changes in how quickly time critical results were reported out from specimen collection to receipt by lab showed no difference between time 1 and time 2 for critical results.

Goal of Presentation: The goal of this presentation is to provide an overview of CoIIN with an emphasis on the group-level activities. Results across all 8 states will be shared. Individual states have been invited to submit abstracts that will highlight their individual activities."

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Collaborative Improvement and Innovation Network (CoIIN) for Timeliness in Newborn Screening in Colorado and Wyoming

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Colorado and Wyoming are two of the 8 states that have been participating in NewSTEPs CoIIN for Timeliness in Newborn Screening. The CO/WY CoIIN team consists of newborn screening program staff, hospital laboratory staff and a midwife. Initially, the CO/WY team worked to identify the strengths and weaknesses of their newborn screening programs. Their strengths included statewide courier services in both Colorado and Wyoming; utilization of quarterly performance "report cards" to birth facilities and midwives; a strong history of collaboration with hospitals; the expansion of NBS follow-up with focus on education and quality improvement; and the expansion of weekend laboratory hours in April 2015. Despite these strengths, both states still struggle with transit times of specimens. Barriers include the large geographical region with rural communities served by small community hospitals. Also, more than 1 percent of infants born in Colorado and Wyoming are homebirths. The CO/WY CoIIN team established SMART goals including: reducing transit time of 1st NBS screens to meet the national recommendations that specimens are received within 24-72 hours after collection, ensure all 1st NBS are collected prior to 48 hours of age, reduce number of unsatisfactory specimens, and develop an education program aimed at quality improvement. The CO/WY CoIIN team completed a survey of all birthing facilities throughout Colorado and Wyoming to better understand the screening processes at each hospital, identify barriers to transit time, and educational needs of hospital staff. In April 2015, the CDPHE NBS laboratory began processing specimens on Saturdays. CDPHE's contracted courier has extended service to six days a week and hospitals not yet using the state courier were strongly encouraged to switch to the state courier. The CO/WY CoIIN team has revised its quarterly performance report cards as a means to improve feedback to hospitals and midwives in meeting goals and expectations of the NBS program. Additionally, the CO/WY CoIIN team is working to assemble an educational toolkit for hospitals and midwives to aid them in achieving quality improvement. Overall, Colorado and Wyoming have seen marked improvement in timeliness of newborn screening. Successes include an increase in the percentage of specimens received within two days of collection, improved completion of essential demographics and the development of multi-media educational materials for hospitals and midwives. The team attributes its success to its evolving relationship with the contracted couriers, as well as a strong partnership with both hospitals and midwives. The CO/WY CoIIN team credits NewSTEPs for moving Colorado and Wyoming's quality improvement processes forward. Collaboration with the other CoIIN states has generated both ideas and practical solutions and has contributed to maintaining enthusiasm over the term of the initiative.

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Session 11 – Quality Improvement – Getting it Right

Does Every Baby Get Screened? - Overhauling Birth Monitoring in Washington State

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Background: A goal of the Washington State (WA) Newborn Screening (NBS) program is to ensure every baby born in WA receives screening (or the option to refuse screening.) Success hinges on obtaining a comprehensive record of every birth in WA and receiving that record in a timely manner. For the past twenty years, birth hospitals across WA have provided NBS with a weekly birth roster of babies born in their hospital. NBS reviews and matches these birth rosters to screening specimens received and follows up on any baby that did not receive a newborn screen (or refusal). Due to changes in recent years to hospital procedures and an increasing number of out-of-hospital births, the previous birth roster process is no longer a comprehensive method for obtaining birth records in WA.

Process: We will tell the story of our systematic review to improve the birth monitoring process and show how we now are able to answer two critical questions: Is every baby born in Washington getting screened? and How many babies receive newborn screening in Washington? We made two elemental changes to the database structure to improve birth monitoring and program statistics: 1. Every birth record should be matched to a screening specimen and 2. Every screening specimen received should be matched to a birth record. In our presentation, we will highlight the significant changes in data collection and processes including adding fields to the collection form, incorporating new sources of birth data, and creating monitoring queries in the database to generate statistics and identify cases that require attention.

Challenges: NBS experienced several challenges in meeting the goals. The routine second screen in WA adds a layer of complexity when matching specimens to births. Additional challenges that were addressed included accounting for adoptions/foster care, 'border babies', out-of-hospital births, delayed and duplicate birth certificates, name changes/incorrect demographics, and database restrictions.

Impact: In the first year since implementation of the new birth monitoring process, NBS has seen significant improvement in the reliability and accuracy of the data. Birth rosters are now supplemented by extracting birth records from vital statistics birth certificates. As before, each birth record is matched to a screening specimen and, when the baby was not screened, the PCP or family is contacted in an attempt to get the child in for testing. With the new process, 73 babies that missed screening at birth were later screened, compared to 20 babies from the previous year. In the year prior to implementation more than 3,500 specimens were not matched to a birth record. With the new birth monitoring process all but 31 specimens were matched to a birth record. Changes in birth monitoring allow NBS to accurately identify babies that missed screening and account for all babies that received screening in Washington State.

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Multi-analyte Data Analysis Reduces False Positives in Cystic Fibrosis

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Approximately 4 million newborns are screened each year in the United States for disorders that can cause developmental deficits or death if left untreated. Iowa screens for 46 conditions, including expanded screening using tandem mass spectrometry (TMS), which results in approximately 65 data points for each newborn specimen tested. While TMS analysis utilizes patterns of increases or decreases in acylcarnitine or amino acid concentrations to assess disease risk, other screening methodologies rely solely on single analyte measurements, such as cystic fibrosis (CF). Immunoreative trypsinogen (IRT) is used as a marker for CF due to pancreatic and hepatobiliary involvement. Increases in IRT may be indicative of CF disease, CF-related metabolic syndrome (CRMS), or CF carrier status. Most states use a two-tier screening method for CF which utilizes IRT as the primary screen followed by cystic fibrosis transmembrane regulator (CFTR) mutation analysis. However, more than 2,000 mutations in the CFTR gene have been identified with only a small percentage of those correlated with known clinical significance. Thus, CFTR mutation testing may not provide a final diagnostic answer and some newborns may be subjected to sweat testing as a confirmatory method which adds burden to clinical follow-up as well as stress to the affected family. Since CF causes damage to multiple organ systems, it may be possible to identify secondary markers of true CF disease from the 65 data points collected for each specimen, which would result in improved discrimination between true CF cases and CF carriers. Data from CF diagnostic groups comprised of known positives, CRMS, CF carriers, and normals (total dataset n=27,000) was analyzed to identify significant increases and decreases in markers other than IRT to potentially improve stratification of true CF as compared to CF carriers. Following median scaling of all newborn screening analyte data, ANOVA analysis was performed between CF diagnostic groups. Statistically significant changes in IRT, C8, and the citrulline/arginine ratio were identified which allowed clustering of true CF patients in a clade distinct from CF carriers and CRMS patients. IRT combined with C8 and the cit/arg ratio allowed segregation of 27 of 28 CF carriers from true CF patients. CRMS patients were grouped with CF carriers and normal controls were grouped separately from CF carriers and CRMS patients. Application of multi-analyte data analysis to CF can improve stratification and reduce false positives. Further, this analysis approach can be applied to all other newborn screening disorders to potentially identify additional markers to reduce false positive rates for other disorders.

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Use of Quality Initiative to Increase CCHD Screening

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Objective: Utilize quality improvement (QI) and community partnerships to implement a comprehensive screening program for critical congenital heart disease (CCHD). As one of the most common birth defects among infants in the US, CCHD accounts for 30% of infant deaths. Infants born with a CCHD are at a significant risk for death or disability. The objective was to implement a well-designed program to screen for CCHD, ensuring prompt care, follow-up, and connections to resources, improving health outcomes for infants with CCHD.

Methods: This comprehensive approach addresses population-based screening in Kansas to ensure all babies are screened for CCHD after birth. The Kansas Department of Health and Environment Newborn Screening (KDHE-NBS) Program launched a QI initiative, providing training and technical assistance to

birthing facilities, to increase awareness of CCHD through collaborative partnership and community engagement.
Results: In approximately eight months significant progress in the implementation of CCHD screening increasing the percent of birthing facilities from 30% to 97.4% and the approximate number of newborns screened annually from 78% to 99.6%. Additionally, an online reporting mechanism was established, a critical component to assuring short- and long-term follow up, including appropriate referrals for diagnostic evaluations and resources for families.
Conclusion: Quality improvement supports community partnerships and stakeholder engagement, identifies and addresses barriers, and creates opportunities to raise awareness and develop educational interventions. Through this initiative, Kansas has increased capacity for screening and reporting, while implementing an effective system to support hospital-based data collection and quality assurance of appropriate and effective screenings.

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Using Lean Process for Improvement in Newborn Screening
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Background: The Washington State Newborn Screening (NBS) program is responsible for receiving and testing an average of 3000 newborn specimens per week. The timeliness of test results is crucial to babies' survival and it is therefore essential to continually seek improvements in the process of tracking and recording specimens received.
Lean is a process created by Toyota to help identify cause and effect relationships within the daily workflow. Their goal was to reduce steps and increase efficiency in order to save time, money, and manpower. The Lean process can be used in all aspects and types of business, including newborn screening.
The NBS program decided to use Lean techniques to focus on three areas for improvement: metabolic treatment product logistics, billing for specimens, and receiving/accessioning specimens.
Objective: The objective of the Lean project was to identify areas of the newborn screening specimen receiving/accessioning process that could be improved upon. This presentation will highlight our experience using lean process improvement to determine a better way to track the received specimens and reduce the likelihood of misplaced specimens.
Methods: A team of three NBS lab members, one lead worker, a supervisor, and one NBS follow up staff member worked together to identify and address areas of improvement for the receiving and accessioning of couriered specimens project. Using the Lean process, the team decided on ways to change the current processes. An improved way of tracking specimens received was created and put into effect immediately. When receiving NBS specimens, the Washington State Public Health Laboratory receiving unit staff is required to count the number of samples upon receipt and log that number of samples. Upon pick up, a member of the NBS laboratory confirms the number of cards received against the count of the receiving unit. Additionally, hospitals and clinics were asked to submit a tracking log of all samples sent with their specimens. The receiving unit and NBS staff checks the list and immediately report any discrepancies to the given submitter.
Results: NBS follow up QC staff is able to immediately resolve these issues with the submitters. Using the lean process, key performance indicators were established and those goals were met. The tracking log and double counting method allows for Newborn Screening staff to quickly identify any mislabeled

or unsent samples. This process is ongoing and will require continuous monitoring to assure that every sample is received and tested on time.
Conclusion: The Lean process is an effective tool to improve laboratory processes and identify potential areas to solve problems and eliminate wasted effort. Improvements can be made quickly and results can be measured. Involvement by staff at all levels in the process ensures different perspectives and needs are recognized.

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The Wisconsin Experience Getting In-Step with NewSTEPs Quality Indicators
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As a part of continuous quality monitoring effort, the Wisconsin newborn screening program decided to incorporate the eight quality indicators, established by the Newborn Screening Technical assistance and Evaluation Program (NewSTEPs), into routine newborn screening (NBS) practice. The experience of the Wisconsin NBS Program preparing for and entering quality indicator (QI) data for 2014 and 2015 into the NewSTEPs repository will be shared.

Preparation of the data for submission began with a review of the patient database. In-house procedures were followed to reconcile discrepancies in order to accurately count the number of infants receiving a NBS test, and correctly identify initial and subsequent screens. From this information, the QI denominator was derived. To facilitate reporting on the timeliness of NBS activities, fields were added to the laboratory information management system (LIMS) to capture the instant of any key events that were not initially stored discretely, such as the date and time specimens are physically received in the laboratory (distinct from when they are entered into the LIMS), and the date and time providers are notified of presumptive positive results by telephone. Additionally, improvements to capturing short-term follow-up information, such as when confirmatory results are obtained, and when treatment is initiated, were implemented. With the instant of all key events (i.e. birth, collection, receipt, result notification, case confirmation, treatment) populated in the LIMS, it became possible to calculate the time interval between events for various timeliness QIs (e.g. birth to collection, collection to receipt, receipt to reporting, reporting to intervention). Collecting data on the percent of specimens missing essential information, and the percent of invalid specimens due to improper collection and/or transport was enabled by building into the LIMS means to flag such specimens. The percentage of eligible babies not receiving a newborn screen could not previously be determined, but through the recent implementation of a policy and procedure to collect the not-screened status for every infant born in Wisconsin, this QI will be able to be reported in the future. SAP SE Crystal reports were devised to extract information from the LIMS for export into Microsoft Excel. Pivot tables were then employed to determine the summary counts required for most of the NewSTEPs QIs. The case template provided by NewSTEPs was populated and used to upload standardized case information to the repository, from which the remaining case-specific QIs were auto-calculated.

For the Wisconsin NBS Program, participation in the NewSTEPs repository has promoted more efficient and comprehensive practices for data management that facilitate quality indicator reporting. The established data file templates will streamline data extraction and data entry for the subsequent years.

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