Navigating the Legal, Policy, and Ethical Landscape of Adding Conditions to the State Newborn Screening Panel
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Adding new conditions to the Recommended Uniform Screening Panel (RUSP) based on recommendations from the Secretary’s ACHDNC presents significant challenges to state programs that conduct their population-based NBS program under a state authorized mandate.

The most recent conditions added to the RUSP: Pompe, MPS-1, and X-ALD, are fundamentally different from all other conditions included on the RUSP as these conditions have a late-onset phenotype. This group of disorders dramatically changes the potential for significant benefit from newborn screening. Once a condition has been added to the RUSP, state NBS programs face significant pressure to implement screening for the newest disorders from advocacy groups, state legislators, and citizens. An understanding of the natural history of these conditions in the context of population-based screening and the development of effective and beneficial treatments and therapies are clearly still in the experimental stages, and should be undertaken upon informed consent protocols for participating newborns. However, until pilot studies are embedded within the structure of newborn screening, the state cannot determine benefit to its population and thus is mandating a screen which may carry more harm than benefit.

Conditions with a late-onset type present challenges that impact the benefit obtained by newborn screening: Parents generally do not receive information about the natural history of these conditions; availability (or unavailability) of treatments or therapies for the conditions; false positive/false negative rates of screening tests; and long-term course. Therefore, families are not prepared to manage the care of their newborn who is at risk for a late-onset type condition and cannot make informed decisions about screening their newborn for these conditions. In addition, there are increased costs of maintaining the program due to additional needed resources for long-term follow-up for late-onset conditions. Iowa is addressing this issue by using a deliberative community engagement (DCE) model to convene meetings of representative Iowans and facilitate DCE members in providing recommendations to the Iowa NBS Program about processes for management of its newborn screening panel. Other states have taken different approaches. A dialog and sharing of successful strategies will assist state NBS programs in managing and evaluating their screening panels.
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**Working with Advocates: Breaking Down Barriers and Building Bridges**

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Newborn screening has a long history with advocate associations. Indeed, the advent of newborn screening came largely from the work of parent advocates who pushed for a better understanding of and treatment for phenylketonuria. This legacy of advocacy within newborn screening has only grown over the years, with a number of initiatives being driven by advocates – inclusive of a push to screen for more conditions, to improve public education about newborn screening and a variety of conditions, or to drive privacy or autonomy policies. This increase in the work done by advocate groups – whether it be national organizations like the March of Dimes and American Academy of Pediatrics, disease organizations, or individuals - has highlighted the vital importance for state newborn screening programs to be able to actively and respectively engage with organizations, individuals, and decision-makers. As a result, APHL’s Legal and Legislative Issues in Newborn Screening (LLINBS) Workgroup has embarked on a project to assess real and perceived barriers to advocate engagement, provide assistance and guidance in overcoming these barriers, and develop a toolkit on how best to engage and interact with different types of advocate groups.

This roundtable seeks to bring together a variety of advocate types and state programs in order to discuss successful case studies in engagement and to better define the challenges faced by states in this area. A survey and informant interviews will be conducted with a variety of states prior to the roundtable. The various themes identified in this work will be presented to participants and then participants will be asked to break out into groups to more fully explore state program barriers and needs for the various themes identified.

Outcomes of the roundtable will be used to develop a position statement on the importance of engagement for programs to use by programs with internal and external policy makers, as well as a toolkit for programs on how best to engage, educate and interact with newborn screening advocates if and when such opportunities arise.

**Presenter:** Amy Gaviglio, MS, CGC, Genetic Counselor/Supervisor, Minnesota Department of Health, Saint Paul, MN, Email: amy.gaviglio@state.mn.us
Detecting and Reporting Alpha Thalassemia in Newborns
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Focus: A report on a recent survey addressing the current status of alpha thalassemia screening in the US. Best practices and examples of how to detect this disorder are discussed.
Objective: To educate and improve alpha thalassemia detection and reporting.
Methodology: The APHL Hemoglobinopathy Laboratory Workgroup conducted a survey of state newborn screening programs to determine how they approach testing for alpha thalassemia. Questions revolved around ascertaining each program’s status, how Hb Bart’s is detected and the protein percentages used to ascertain Bart’s. Programs were asked about testing methods and types of alpha thalassemia reported.

Significant Results: Alpha thalassemia, through the detection of Hb Bart’s, is being reported in at least 79% of the newborn screening programs in the US. Of the programs that responded to the survey, 95% screen for alpha thalassemia (42 out of 44 programs). Reporting varies from classifying alpha thalassemia types to only identifying the presence of Hb Bart’s. 51% report alpha thalassemia trait, 49% report Hemoglobin H, 36% report alpha thalassemia major and 12% report Silent Carrier. HPLC percentage cutoffs are used by some programs to differentiate between silent carrier, trait, Hb H disease, and alpha thalassemia major. Hb constant spring is also identified and reported in a few programs.

Conclusion: The interpretation of Hb Bart’s results is not uniform between newborn screening programs. The spectrum of clinical severity and complexity of this disorder needs to be considered when reporting results.

Presenter: Tim Davis, BS, Microbiologist 3, Washington State Newborn Screening Program, Shoreline, WA, Phone: 206.418.5532, Email: tim.davis@doh.wa.gov

Connecticut’s Experience with Validation and Screening for X-linked Adrenoleukodystrophy Using a Negative Ion-Mode LC-MS/MS Analysis Method
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Newborn bloodspot screening (NBS) for X-linked adrenoleukodystrophy (X-ALD) was added to the US HHS Recommended Uniform Screening Panel (RUSP) in 2016. The CT Department of Public Health Newborn Screening Laboratory (CT DPH NBS) began the validation of a CDC-developed and published method for the extraction and analysis of C24:0-Lysophosphatidylcholine (C24:0-LPC) and C26:0-Lysophosphatidylcholine (C26:0-LPC) from dried blood spots (DBS) using a negative ion mode LC-MS/MS method¹ in September of 2015 following a legislative mandate to initiate screening. The CT DPH NBS Laboratory reviewed other methods for the analysis of C24:0-LPC and C26:0-LPC for the detection of X-ALD in DBS using tandem mass spectrometry methodology as a screening technique for the presence of

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biochemical markers of this disease in neonatal dried blood spots, however, the CDC method appeared to be most promising as there are no reported interference peaks as observed with the other published methods. The method validation for X-ALD in CT was carried out by the analysis of CDC-produced quality control reference material using an isotopically labeled Internal Standard (d4-C26:0-Lysophosphatidylcholine) to establish accuracy, precision, linearity, recovery, reportable range, carryover, drift, extract stability, internal standard storage stability as well as evaluation of CDC NSQAP Proficiency Testing (PT) specimens. Once completed, the screening of over 27,000 newborn screening patient samples of dried blood spots commenced for newborn samples collected over nine months from October 1, 2015 to June 29, 2016 to detect the levels of C24:0-lysophosphatidylcholine (C24:0-LPC) and C26:0-lysophosphatidylcholine (C26:0-LPC). During the validation, two male infants were identified and confirmed to have X-ALD, an older male sibling was also tested and identified to have X-ALD and a female infant was identified to be an X-ALD carrier. Connecticut officially began screening as of July 1, 2016. All newborns born in the state of Connecticut as of October 1, 2015 have been screened for X-ALD.


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Newborn Screening for Pompe Disease in New York State Identifies a Wide Spectrum of Variants in the GAA Gene
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New York State began screening for Pompe disease on October 1, 2014. The 1st tier assay for Pompe disease is the determination of GAA enzyme activity by tandem mass spectrometry. Infants who have GAA activity less than 15% of the daily mean are reflexed to a 2nd tier DNA sequencing assay. Sanger sequencing of all 19 coding exons and 20bp at the intron-exon boundaries of the GAA gene is performed on DNA extracted from a 3mm dried bloodspot. In addition, we perform a gap-PCR assay for detection of a commonly reported deletion of exon 18. Infants with low GAA enzyme activity and at least 1 pathogenic, likely pathogenic or variant of uncertain significance (VOUS) are referred to a specialty care center for diagnostic evaluation. From October 1, 2014 to March 15, 2017, 576,239 babies were screened for Pompe disease with 96 being referred for diagnostic testing. Four infants were diagnosed with classic (3) or non-classic (1) infantile-onset Pompe disease (IOPD). Two variants were identified in an additional 43 infants. These babies have been classified as having possible late-onset Pompe disease (LOPD), as none have developed symptoms of Pompe disease to date. Two previously reported pathogenic variants were detected in 15 of these infants, 19 had 1 pathogenic variant and 1 VOUS, and 9 had 2 VOUS. The remaining 49 infants referred for diagnostic testing had only a single variant identified and were reported as likely carriers. Forty-two of the 96 infants (43.8%) referred for Pompe disease diagnostic testing had at least one pseudodeficiency allele in addition to the other variants that were identified. Twenty-nine infants (30.2%) carried at least one copy of the c.-32-13T>G splice-site variant which is commonly reported in late-onset Pompe disease. Several other previously reported pathogenic variants in Pompe disease were identified in more than 1 infant; p.R854X in 10 infants, p.W746C in 5 infants, and p.S251L_p.S254L in 5 infants. Several VOUS were identified in more than one baby;
p.V222M in 9 infants, p.P690L and c.1888+5G>T each in 5 infants, p.P684L in 3 infants, and p.P475L and p.R837C each in 2 infants. Thirteen of the VOUS identified in our population have not previously been reported in the literature. Newborn screening for Pompe disease in the first 2 ½ years of testing in New York has revealed a wide spectrum of variants in the GAA gene. We identified 50 private variants, each detected only once in our population. Forty-four (45.8%) of the 96 infants referred for diagnostic testing had at least 1 VOUS identified in the GAA gene, making it difficult to provide guidance to clinicians based on genotype. A centralized database of GAA variants identified through newborn screening and long term follow-up data on these infants could provide essential information on genotype/phenotype correlations.

Presenter: Colleen Stevens, PhD, Research Scientist, New York State Newborn Screening Program, New York State Department of Health, Wadsworth Center, Albany, NY, Phone: 518.473.6805, Email: colleen.stevens@health.ny.gov

Newborns with Hypoxic Ischemic Encephalopathy Treated with Therapeutic Hypothermia Have Elevated TSH Levels on Newborn Screening
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Objectives: Therapeutic hypothermia (TH) has become standard care for the newborn with Hypoxic Ischemic Encephalopathy (HIE) at birth. It is biologically plausible that cold stress in newborns may cause Thyroid Stimulating Hormone (TSH) elevation. To test the hypothesis that there is an association between newborn treatment with TH and elevated TSH levels on NBS reports, we assessed newborn screen (NBS) TSH levels in a cohort of term newborns with HIE admitted to the NICU for TH and compared them to TSH values from non-cooled NICU term controls.

Methods: We collected the NBS results from a cohort of 82 infants cared for in the NICU at Brigham and Women's Hospital, Boston, MA, who had undergone TH for HIE, and 80 NICU controls who were contemporaneously matched by age, sex, and weight. TSH levels were categorized as normal or abnormal, based on a normal range of < 20 uU/ml.

Results: Of 82 HIE infants undergoing TH, 19 (23.2%) had an elevated TSH on NBS at some time during their hospital stay, as compared to 7/80 (8.8%) of matched controls (p=0.018). Newborns treated with TH had an average of 2.3 NBS TSH levels through their NICU course, and controls had an average of 1.7. Elevated TSH was identified in the first valid sample in almost all cases, and most elevations had resolved by time of NICU discharge in both groups. There was no significant difference between the two groups in the likelihood of having an elevated TSH level on discharge (4 TH vs. 3 controls, p=1.0).

Conclusions: To our knowledge, this is the first report of increased risk of elevated TSH levels on NBS in newborns with HIE treated with TH. The elevation appears to be transient. Although it is likely the higher TSH is related to TH therapy, it is possible that it could be related to the injury that caused the HIE. Because TH is now standard care for HIE, we did not have a control group of newborns with HIE not treated with TH for comparison. Given the propensity for the elevated TSH levels in cooled infants to normalize, the scenario can be considered a source of false positive for the concern of congenital hypothyroidism. Knowledge of the increased false positive risk will aid the clinician in assessment and counseling of parents. It is possible that a slight delay in sending the initial NBS (48–72 hours) in newborns with HIE treated with TH could minimize the likelihood of such false positive results.

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Session 2 – Quality Improvement and Assurance Activities in Newborn Screening

Implementation of a New Electronic Shipping System to Improve Timeliness
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Background: In 2011, the New Jersey Newborn Screening (NBS) Laboratory identified a delay in the time from specimen collection to receipt in the laboratory. According to this measure, NewSTEPs quality indicator (QI) 5b, only 86% of specimens were received in the laboratory within 3 days of collection despite the provision of United Parcel Service’s (UPS) overnight shipping to all of the state’s hospital submitters. A dedicated effort to educate hospital staff on the UPS system resulted in a modest improvement of QI 5b to 92% of specimens received within 3 days of collection. Despite continued efforts to train individuals throughout the shipping system, QI 5b has not improved beyond the 92% mark. A review of the shipping process identified an opportunity to improve timeliness through implementation of a new electronic shipping system.

Methods: The New Jersey NBS Laboratory collaborated with UPS to contact the State’s hospital submitters in an effort to identify areas for improvement with the laboratory’s online shipping system. The feedback was used to configure an off-the-shelf software solution, UPS Complete View®. While this shipping system is often utilized in the retail market, several features are applicable to a clinical laboratory. These enhanced features include laboratory control over label printing, specific package pickup times, dedicated package pickup points within each facility, improved shipment visibility, and more rapid response time in the event of system delays. Complete View® was deployed in a subset of hospitals to pilot test the shipping system. Lessons learned from the pilot hospitals will be incorporated when the system is deployed State-wide in the Spring 2017.

Results: The Complete View® system configured for the New Jersey NBS Laboratory has streamlined the specimen shipping process. Shipping label production, packaging, pick-up, transportation, and delivery are more synchronized between the hospital, laboratory, and UPS. Moreover, increased package visibility with the system allows hospitals to more easily track packages and the NBS Laboratory to anticipate incoming workloads, as well as, rapidly identify lost or delayed packages for immediate remediation. It is too early to evaluate an improvement with the timeliness quality indicators; however, State-wide use of the shipping system is expected to reduce the time from specimen collection to receipt at the laboratory.

Conclusions: Improvements in timeliness quality indicators do not necessarily require broad-scale changes to the NBS system. Deployment of a low-cost, enhanced shipping system that was configured based on the needs of the New Jersey Newborn Screening Laboratory and its hospital submitter resulted in system-wide process improvements, which will ultimately lead to improved quality indicators.

Presenter: Scott Shone, PhD, Senior Research Public Health Analyst, RTI International, Center for Newborn Screening, Ethics and Disability Studies, Research Triangle Park, NC, Phone: 919.485.5512, Email: sshone@rti.org
Infographics and Outreach used to Improve Newborn Screening Timeliness
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\textbf{Problem}: Although Iowa had put in place a structure that allowed timely delivery, testing, and follow up of samples, the facilities were not fully aware of their role(s) and how to best utilize these infrastructures to ensure timely newborn screening.

\textbf{Methodology}: As one of 8 states participating in NewSTEPS Newborn Screening Timeliness CoIIN, Iowa created and dispersed an info-graphic to communicate to hospitals the percentage of samples received at the newborn screening lab in 65 hours or less from birth for their facility as well as how other facilities are performing across the state. The CoIIN team set up site visits to review the timeliness reports as well as review the newborn screening process and provide technical assistance. These activities continued and expanded with Iowa's involvement with NewSTEPS 360.

\textbf{Results}: Statewide improvement with respect to timeliness with a 16\% increase of the number of initial samples in the state reaching the newborn screening laboratory in 65 hours or less from time of birth. Before outreach to multiple facilities and distribution of info-graphics statewide, 79\% of samples were received at the newborn screening lab within 65 hours of birth. Within 7 months of circulating the reports monthly or quarterly (depending on facility size) statewide and actively engaging with facilities, the state met its goal of receiving 95\% of samples within 65 hours of birth. The State has maintained that rate to date.

\textbf{Conclusions}: Iowa has over 80 birthing facilities and sending out a monthly or quarterly report showing them how they are performing compared to the state and other facilities is a powerful tool that can elicit improvement and maintain that improvement. The increased communication each month has strengthened our relationships with many facilities and has had impact beyond improving timeliness. The info-graphics gave an overall picture of performance and got many submitters engaged in finding out how the newborn screening process works at their facility and how they can make improvements. The increased communication allowed us to refer facilities to the newborn screening web portal that allowed them to look at their data in real time while working on quality improvement processes with respect to newborn screening. Partnering with the facilities and making sure we give them the right tools and information is key in successful outcomes.

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SCID Screening and Diagnostic Uncertainty: The California Experience Since 2010
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\textbf{Introduction}: The California Genetic Disease Screening Program (GDSP) has screened 3.5 million children for Severe Combined Immunodeficiency (SCID), a group of genetic disorders causing little or no immune response. GDSP targets SCID (classic SCID, Leaky SCID and Omenn Syndrome) specifically for intervention, but other conditions characterized by temporary or partially compromised immune function are also identified. We changed our T-cell receptor excision circles (TREC) assay mid-2015 which caused a perplexing increase in false screen-positive results, lowered our Positive Predictive Value (PPV), and identified more cases of other T-cell lymphopenias with poorly understood etiology and outcome.
In order to improve test performance and focus on SCID detection, we also needed to assess the consequence of missing non-SCID conditions that we previously identified.

**Methods:** 1) Using a retrospective cohort design we addressed recent test performance. 2) To ascertain the impact of screening indirectly we initiated an ongoing follow-up of screen-positive babies born from 2010-2013 to compare 1-year mortality outcomes using vital records and physician reports.

Results: 1) Prior probabilities of the true SCID positive rate were similar statistically whether newborns were tested in a Newborn Intensive Care Unit (NICU) or in a regular nursery, yet results among NICU babies had a very low PPV in multivariate logistic regression analysis. 2) In multivariate logistic regression of screen-positive babies controlling for NICU status and final diagnosis, children with SCID had one-third the death rate of those without SCID or those diagnosed with a T-cell lymphopenia; this difference was non-significant due to the small number of SCID babies included thus far. Children tested in a regular nursery had twice the death rate of NICU babies from causes other than SCID and this result was statistically significant.

**Discussion:** Analysis results led us to lower the TREC cut point and introduce policy changes. False positive results identified newborns in the NICU without SCID who were not at high risk of death, and babies in the regular nursery who had an increased death rate from causes other than SCID. Beyond an initial discovery period, is there a benefit to identify ambiguous results without clear interventions at the expense of reduced test performance? We have encountered similar questions for other newborn screening disorders where genetic variants of unknown significance are uncovered.

**Presenter:** Stanley Sciorino, PhD, MPH, Chief, Newborn Screening Outcomes Evaluation Section, California Department of Public Health, Genetic Disease Screening Program, Richmond, CA, Phone: 510.231.7464, Email: stanley.sciortino@cdph.ca.gov

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Analyzing Patterns in NewSTEPs Site Review Recommendations: The Big Picture for Newborn Screening Programs

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**Background:** NewSTEPs provides non-regulatory site visits upon request of State Newborn Screening (NBS) Programs. These site visits are aimed at assessing various components of the NBS system including the laboratory, birth facilities, and follow-up program for quality improvement purposes. As of April 30, 2017, NewSTEPs will have visited 6 state newborn screening programs. Each site visit is conducted by a Site Review Team (SRT) which is made up of at least one laboratory, follow-up, and clinical expert. SRTs also include additional experts when needed. These experts work with the NewSTEPs team to develop reports for each state after the visit, which includes recommendations for quality improvement.

**Objective:** Review reports and identify overlapping areas for improvement, recommendations, and opportunities across states/programs. The geographic and size distribution of the NBS programs that have received the Site Review Visit since the inception of NewSTEPs have been varied. The patterns identified across programs will be shared, in a de-identified manner, so that others who have not received a detailed Site Review may benefit from this knowledge and these patterns. Additionally, programs can learn more about the process and identify technical assistance needs that can be addressed by NewSTEPs. Additionally, a self-study tool developed by NewSTEPs will be shared with the participants, demonstrating how it can serve as an initial valuable step in performing a comprehensive internal assessment.

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Methods: The data is comprised of the six site review reports, from states representing varied geographic, size and demographic distributions. Using content analysis, two coders will identify strengths, opportunities, and recommendations noted. Any theme that exists in more than 50% of the reports will be shared. Because the SRTs are unique to each state, the insights in the report will be based on expert feedback received from at least 18 newborn screening experts. The emphasis will be on shared themes and, as a result, states will not be identified.

Results: The data has not been formally analyzed because there is a Site Visit in April. Formal data analysis consisted with what is noted in Methods will be conducted starting June 1, 2017.

Implications: NewSTEP Site Reviews are very helpful for states in identifying strengths and opportunities for improvement. The goal of this project is to identify NBS systems trends/deficiencies across states boundaries that can be addressed proactively on a national scale. To meet that goal, this presentation will share lessons learned so that states who are not able to formally invite NewSTEPs for a Site Review Visit can still strengthen their own programs, conduct a site review using the Site Review Self-Study Tool understanding what has been found in other sites, or identify their need for technical assistance from NewSTEPs as well as from peer programs.

Presenter: Yvonne Kellar-Guenther, PhD, NewSTEPs Program Evaluator, Colorado School of Public Health, Community and Behavioral Health, Aurora, CO, Phone: 303.724.7347, Email: yvonne.kellar-guenther@ucdenver.edu

The Relationship Between Newborn Screening Unsatisfactory Specimens and Unsatisfactory Results
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The Clinical and Laboratory Standards Institute (CLSI) publishes standards and guidelines for clinical and laboratory practices. Standard “NBS01-A6” covers blood collection on filter paper for newborn screening, including an explanation of appropriate dried blood spot (DBS) collection techniques and standards for specimen acceptability. The New Jersey Newborn Screening (NBS) Laboratory established its own specimen acceptability criteria based on the CLSI standard. Specimens considered unsatisfactory according to NJ NBS criteria are not tested. NJ NBS laboratory personnel immediately contact the specimen submitter to inform them that the specimen was invalid and to request a new specimen. In addition, unsatisfactory results reports are mailed to the hospital and physician of record requesting submission of a repeat specimen within two days. Delays in testing for time critical NBS disorders due to the submission of unsatisfactory specimens can have adverse effects on the newborns; repeat specimens can be substantially delayed. For some newborns, no repeat specimen is ever received, and the newborn remains unscreened. A systematic analysis of unsatisfactory specimens can help determine if these invalid specimens can be tested to provide “conditional unsatisfactory specimen results” while a new specimen is submitted, thereby reducing potentially harmful delays.

A study comparing NBS results of matched initial unsatisfactory specimens with acceptable repeat specimens was conducted. Unsatisfactory specimens were stored at -20 °C, under desiccant, to ensure analyte stability. After the arrival and screening of an acceptable repeat specimen, unsatisfactory and acceptable specimens from the same infant were paired, de-identified, and tested as part of the regular laboratory work flow. Test results were recorded and analyzed to evaluate trends and differences in interpretations.
A comparison of results between all unsatisfactory and all acceptable specimens showed age-related variations. Different types of unsatisfactory specimens showed no meaningful differences in analyte measurements. Visual inspection of unsatisfactory specimens revealed great variability in characterization, likely due to involvement of multiple staff members. When specimens were regrouped uniformly, differences were noted. Discrepant results between unsatisfactory and acceptable specimens were analyzed, with an emphasis on acceptable specimens that screened abnormal. While reducing invalid specimens by training providers on the correct collection method for DBS is the ideal solution, testing unsatisfactory specimens can provide valuable interim information. However, these unsatisfactory specimens results cannot be relied upon for final screening interpretations. Staff training to help minimize differences in characterization of unsatisfactory specimens is useful.

Presenter: Miriam Schachter, PhD, Ronald H. Laessig Memorial Newborn Screening Fellow, New Jersey Department of Health, Newborn Screening Laboratory, Trenton, NJ, Phone: 609.406.6892, Email: miriam.schachter@doh.nj.gov

Session 3 – Past, Present and Future Newborn Screening Conditions

Removing Short-chain Acyl-CoA Dehydrogenase Deficiency and Isobutyryl-CoA Dehydrogenase Deficiency from the Newborn Screening Panel: Michigan’s Experience
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Background: Michigan’s Newborn Screening (NBS) Program screens for all the disorders on the recommended uniform screening panel and many of the secondary targets. Increasing evidence suggests that two of those secondary targets, short-chain acyl-CoA dehydrogenase deficiency (SCAD) and isobutyryl-CoA dehydrogenase deficiency (IBD), may be benign, rather than disease-causing. These disorders are identified using the C4 analyte, so they can only be added or removed from a screening panel together. To evaluate the value of screening for these disorders, staff from Michigan’s NBS Program worked with clinical partners to assess the clinical course of patients and determine if identification through screening leads to tangible benefits for patients and their families.

Methods: All newborns who screen positive for SCAD/IBD are referred to one specialty center for confirmatory testing and treatment. The metabolic specialist at that center reviewed the cohort of NBS-identified SCAD/IBD patients for several outcomes, including number of ED visits/hospitalizations, developmental outcomes, and compliance with follow-up recommendations. A literature review was conducted to determine outcomes for SCAD/IBD patients in other states and countries. Finally, information was gathered about the potential harms associated with identifying benign conditions. Those detailed reviews were presented at the Metabolic Quality Improvement Committee, the NBS Technical Advisory Committee, and ultimately to the Quality Assurance Advisory Committee, a legislatively-mandated committee.

Results: A total of 89 newborns were diagnosed with SCAD or variant SCAD and 16 with IBD since screening began in Michigan in 2005. Of those, 77 SCAD patients and 13 IBD cases were included in the detailed clinical review. None of the SCAD patients had hypotonia, myopathy, or seizures. None of the IBD patients had hypoglycemia, acidosis, or other metabolic sequelae. Risk of secondary carnitine deficiency is very low to none for SCAD patients and low for IBD patients. Developmental outcomes among both disease groups were comparable to those in the general population. Evidence from the
literature supported the Michigan findings that SCAD and IBD patients are doing well with minimal medical intervention, with no significant morbidity or mortality.

**Conclusions:** After receiving the detailed information from the reviews and discussion, all committees unanimously supported removing SCAD and IBD from Michigan’s screening panel. This change will become effective once approved by Michigan’s legislature.

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**Development of a Multiplex Real-time PCR Newborn Screening Assay to Simultaneously Identify Spinal Muscular Atrophy, Severe Combined Immunodeficiency, and X-linked Agammaglobulinemia**

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Spinal muscular atrophy (SMA) is one of the most common lethal recessive genetic conditions, with an incidence of 1 in 10,000 births. The condition is associated with significant motor disability, respiratory and nutritional compromise, and death in infancy or childhood in more than 50% of affected children. Epidemiological data indicates that symptom onset before 18 months of age occurs in more than 80% of affected children. There is significant neuronal loss within the first six months in infants with SMA type I, the most severe form of SMA. The majority of undiagnosed affected infants who present in their first 12 months have medical crisis with acute respiratory failure. By the time a diagnosis is made, these infants are often severely nutritionally compromised, potentially exacerbating irreversible loss of neurological function and the resulting compromised respiratory reserve. There have been considerable advances toward the development of new therapies for SMA. The recently FDA approved new treatment for SMA will likely lead to increased interest in newborn screening (NBS) in public health contexts. A recent report demonstrated that SMA detection can be multiplexed, at minimal additional cost, with existing screening assays used to identify severe combined immunodeficiency (SCID) infants. A five-plex real-time PCR assay was developed to simultaneously measure copy numbers of five different loci using DNA extracted from a single 3.2mm punch of a dried blood spot. The PCR assay identifies the absence of exon 7 in the SMN1 gene while simultaneously evaluating the copy number of the SMN2 gene. This is achieved by using specific Locked Nucleic Acid (LNA®) Taqman® probes for both the SMN1 and SMN2 genes. The LNA® Taqman® probes for SMN1 and SMN2 differ in sequence by a single nucleotide. Elevated annealing temperatures and different fluorescent labels on the LNA® Taqman® probes permitted the simultaneous interrogation of both loci. To further demonstrate the capability of a multiplex assay, PCR primers and standard dual labeled Taqman® probes for T-cell receptor excision circles (TREC) and for K-deleting recombination excision circles (KREC) were included. Additionally, the amplification of a reference gene, RPP30, was included in the assay as a quality/quantity indicator of DNA isolated from the dried blood NBS specimens.

**Presenter:** Mei Baker, MD, Wisconsin State Laboratory of Hygiene, Madison, WI, Email: mei.baker@wisc.edu
Implementation of Newborn Screening for Duchenne Muscular Dystrophy (DMD)

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Duchenne muscular dystrophy (DMD) is one of the ten most severe and common pediatric genetic diseases and affects an estimated 1 in 5000 male births. CDC’s DMD surveillance reveals age of diagnosis of 4 years old (mean), with an average diagnostic odyssey of 2-3 years. DMD is a 100% fatal disease. The therapeutic landscape has changed dramatically with the establishment of practice guidelines recommending the early use of corticosteroid therapy and with the advent of some disease modifying treatments. FDA has approved the use of a corticosteroid (deflazacort) potentially appropriate for 100% of patients with DMD and a new treatment that targets the underlying cause of DMD in about 13% of patients (eteplirsen). The availability of these therapies, coupled with the opportunity to deliver treatments before the onset of clinical symptoms, accelerates the need for the development of technologies for DMD screening of newborns, as well as the creation of an infrastructure to select and deliver the appropriate therapy.

With the availability of these novel therapies, Parent Project Muscular Dystrophy (PPMD) recognized the critical need for DMD newborn screening (NBS) and initiated a national effort to build the public health infrastructure and support required to enable screening in the US. This session will present a summary of PPMD’s master plan and will report on three outcomes of the initiative: (1) Laboratory Workgroup’s assessment of available screening technologies by including two screening technologies, implementing a novel high-throughput assay that detects a biomarker of skeletal muscle injury, and incorporating targeted genomic sequencing to guide therapy selection; (2) Ethical and Legal Workgroup’s deliberations and conclusions related to the special considerations of screening for X-linked recessive conditions in which carrier females may exhibit clinical symptoms, and in a large gene with a high rate of novel mutations; and (3) Utilization of ACMG’s Newborn Screening Translational Research Network (NBSTRN) to coordinate the DMD NBS pilot including building a network of clinical experts working in concert with NBS laboratory teams and researchers. A key goal of the master plan is to generate the data needed to submit DMD NBS to a federal advisory committee for a formal evidence review. The DMD NBS will utilize the NBSTRN Longitudinal Pediatric Database Resource.

This session will present a summary of the master plan for the development of a pilot for newborn screening in the U.S. and workgroup activities accomplished to date. This effort will provide a roadmap for future NBS pilots of novel technologies for complex genetic conditions with emerging therapies.

Presenter: Michele Lloyd-Puryear, MD, PhD, Consultant, Parent Project Muscular Dystrophy, Takoma Park, MD, Email: michele@parentprojectmd.org
**Congenital CMV – A Pilot Study**
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**Problem/Objectives:** Congenital cytomegalovirus (CMV) is the most common congenital viral infection and the leading non-genetic cause of deafness in children. It is estimated that one in 150 newborns is born with CMV, and 20% of affected births will experience some clinical manifestation from this infection. In collaboration with the Centers for Disease Control and Prevention (CDC) and the University of Minnesota (UMN), the Minnesota Department of Health (MDH) is engaged in a study to determine if dried blood spots (DBS) are an acceptable specimen for CMV universal screening.

**Method:** Five hospitals in the Twin Cities metro area are actively enrolling for this consented study. Families in postpartum or NICU settings are offered study enrollment and willing participants are consented. Saliva samples are taken at the hospital, and punches from their routinely collected DBS are sent by the MDH public health laboratory to two labs, one at the UMN and one at the CDC. The enrollment goal is 30,000 infants over 5 years.

**Significant results:** Within one year, participation expanded from one to five hospitals. Of all infants on the birth units during consenting times, 61.5% of infants that were present enrolled, which increased to 76.6% when the study was actively discussed with families. As of March 2017, approximately 1500 infants have been enrolled in the study. Results include negative (both saliva and DBS negative), inconclusive (saliva negative with DBS positive), or positive (Saliva positive with DBS positive or negative). A total of 3 infants were found to be positive for CMV. One infant was found to be inconclusive. Positives have been found in all possible cCMV infection categories: asymptomatic with normal hearing, asymptomatic with hearing loss, and symptomatic. All infants found to be positive or inconclusive are offered further evaluation with a specialist to confirm cCMV infection status.

**Conclusions:** Understanding the clinical utility and sensitivity of DBS for potential universal newborn screening is essential as more and more states are considering or enacting legislation related to CMV. These legislative efforts vary in their approach for addressing CMV: education only, targeted screening with failed hearing screen, or universal screening. This study will allow newborn screening programs to better understand the feasibility of a DBS-based methodology for possible universal screening for CMV. If DBS testing can identify the majority of those at-risk for developing CMV-associated disability and the use of a new specimen such as saliva would not be necessary, we could move a significant step closer to the possibility of universal screening for cCMV.

**Presenter:** Maggie Dreon, MS, CGC, Certified Genetic Counselor, Minnesota Department of Health, St. Paul, Minnesota, Phone: 651.201.5670, Email: maggie.dreon@state.mn.us

**Joint Follow-up and Quality Assurance/Quality Control Session – Cut-offs**

**A False Negative CPTII Case: Using the (C16+C18:1)/C2 Ratio to Improve both FN & FP Metrics**
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**Challenges:** Babies with CPT-II deficiency were previously screened at the Michigan Newborn Screening Laboratory using elevated acylcarnitines C16, C18 and C18:1. This successfully identified some CPTII cases. CPT II patients have widely variable clinical presentations, especially those with late onset CPT-II
deficiency. Literature review of CPT II cases suggests patients with the late-onset, myopathic form may have acylcarnitine results in dried blood spots within the normal range. Michigan encountered an initially missed CPT-II case with delayed clinical presentation, which prompted us to initiate an analysis of CPTII primary analytes, cutoffs and testing algorithm aimed at reducing both false negative and false positive results.

**Method:** A literature search and a review of the Region 4 Collaborative recommendations were used to identify potential primary analytes for CPTII. Scatter plots of these analytes for Michigan’s positive CPTII cases along with over 500,000 normal MSMS profiles were created and analyzed. The (C16+C18:1)/C2 ratio was found to be highly selective for CPTII. CPT-II False Positive cases from 2005 – 2016 were also examined. These cases all had elevated C2 and a normal (C16+C18:1)/C2 ratio. The Region 4 Collaborative Post Analytical Tool for CPT-II was used on Michigan cases. Many of the False Positive cases using the Michigan algorithm were also False Positives according to the Region 4 Collaborative Post Analytical Tool for CPT-II. Data from repeat specimens collected from two CPTII cases were reviewed. The C16 values were not elevated.

**Results:** Scatter Plot analysis of Michigan’s positive CPTII cases, false positive cases and over 500,000 normal specimens indicate that the (C16+C18:1)/C2 ratio is highly selective for CPTII. Using this (C16+C18:1)/C2 ratio as a primary analyte along with C16 allows for a significantly lower cutoff for C16 to be implemented. A confirmed severe CPTII patient was identified using the new algorithm with lower C16 cutoff. This case would have been missed by our old testing algorithm.

**Conclusions:** Using the ratio (C16+C18:1)/C2 greatly increases the sensitivity and specify of screening for CPT-II. CPTII analytes normalize with age of collection. CPTII presumptive positive cases should be referred to medical management rather than request a repeat screen.

**Presenter:** Mary Seeterlin, Scientist, Newborn Screening Section, Michigan Department of Health & Human Services, Lansing, MI, Phone: 517.373.9779, Email: seeterlinm@michigan.gov

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**Impact of Post-analytical Interpretive Tools on Newborn Screening for Three Lysosomal Disorders: First Year Prospective Experience in Kentucky**

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We have completed one year prospective screening for Mucopolysaccharidosis type I, Pompe disease and Krabbe disease using a 6plex MS/MS method combined with covariate-adjusted reference intervals, post-analytical interpretive tools created using Collaborative Laboratory Integrated Reports (CLIR; https://clir.mayo.edu), a novel multivariate pattern recognition software, and 2nd tier tests. A total of 55,161 initial and repeat blood spot specimens were collected from infants born in the Commonwealth of Kentucky over one year starting in February 2016. Specimens collected before 24 hours and after 1 week of age were 1,219 (2.2%) and 2,501 (4.5%), respectively. Age at collection and birth weight were provided for 99.4% of the specimens. A single repeat sample was requested in one year, the false positive rate was 0.0018% and the positive predictive value was 80%. Of five cases referred as abnormal, one was affected with Mucopolysaccharidosis type I, two were affected with Pompe disease, and one was affected with infantile Krabbe disease. The remaining case was a heterozygote for Mucopolysaccharidosis type I, a false positive outcome. Our testing and post-analytical protocol can improve performance for conditions recently included in the recommended uniform screening panel, and likely for all others as well. Downstream savings in health care expenditures and decrease in psychosocial harm experienced by caregivers could be realized if this freely available software is supported by greater collaboration and data sharing among programs.
Comparison of Traditional Fixed Cutoffs to Use of Collaborative Laboratory Integrated Reports (CLIR) Tools in Screening for Pompe Disease and Krabbe Disease

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Newborn screening assays for lysosomal storage disorders (LSD) are currently based on enzyme activity measurements, which are dependent on many variables. Since lysosomal enzymes reside in leukocytes, a primary variable is the leukocyte count of the newborn at the time of sample collection. Leukocyte counts vary from 9,400 – 34,000 leukocytes/mm³ in newborns (~24 hrs. of age). The variability continues with normal counts ranging from 5,000 – 21,000 leukocytes/mm³ in one-week old infants. Dried blood spot (DBS) enzyme assays do not normalize for this variable. Additionally, hematocrit levels impact measured activities. The blood volume in a punch is affected by the infant’s hematocrit and inhibitor effects impact activity measurements for some enzymes. In general, premature infants have lower birth weight and lower hematocrits when compared to full term infants. Thus an infant’s birth weight and age at the time of sample collection (i.e. leukocyte counts and hematocrit) can impact measured enzyme activities. Recently, it has become practical to analyze up to six lysosomal enzyme activities using a single DBS punch. The multiplexed enzyme activity measurements can act as a surrogate to normalize the measured activities to leukocyte counts. To this end, the Mayo Clinic has developed a tool (CLIR) that uses a combination of measured enzyme activities and a series of calculated ratios, adjusted for age and birth weight, to identify affected infants with a low false positive rate and a high positive predictive value. We have used CLIR tools to re-evaluate newborn screen results obtained in screening for Pompe disease and Krabbe disease applying traditional fixed cut-offs. By traditional screening, 83,211 infants were screened with 35 newborns requiring second tier DNA analysis (20 for Krabbe, 15 for Pompe). After second tier molecular testing 21 infants were referred for follow-up (8 for Krabbe, 13 for Pompe). All 8 infants referred for Krabbe disease were determined to be false positives and 9 of 13 Pompe cases were determined to be false positives. With CLIR tools, 10 would have required second tier testing for Krabbe and 10 for Pompe. The CLIR tool detected all of the possible Pompe cases identified through routine screening. This preliminary study will be expanded, results from the expanded study will be presented.

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North Carolina Mucopolysaccharidosis Type I (MPS I) Pilot Study: Screening for a Single Lysosomal Storage Disorder

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Mucopolysaccharidosis Type I (MPS I) is caused by a deficiency of the -L-iduronidase (IDUA) enzyme involved in the breakdown and recycling of glycosaminoglycans (GAGs). These sugars slowly accumulate in the lysosomes which can lead to progressive physical disease, shortened life span, and intellectual disability. Because new mass screening methods are available and treatment options have improved the
outcome for affected patients, MPS I was added to the Recommended Uniform Screening Panel (RUSP) in 2016. Currently, however, there are only a few states that have implemented full population screening. The National Institute for Child Health and Human Development awarded a contract to RTI International, the University of North Carolina at Chapel Hill, Duke University, and the North Carolina State Laboratory of Public Health to conduct a newborn screening pilot study for MPS I. We applied a stand-alone test using a flow injection analysis—tandem mass spectrometry (FIA-MS/MS) assay to determine the IDUA enzyme activity and identify patients at risk for MPS I. In the screening algorithm, specimens with low IDUA activity after the initial test were retested using a 3-plex FIA-MS/MS assay that added α-glucosidase (GAA) and β-glucocerebrosidase (ABG) enzyme activities to the analysis. The additional enzyme activities enabled the identification of unsatisfactory specimens and allowed us to process the data using Collaborative Laboratory Integrated Reports (CLIR), a web-based program that contains post-analytical interpretive tools developed at the Mayo Clinic. Samples that screened positive were sent for sequencing of the IDUA gene. A total of 63,545 specimens were screened with the initial single enzyme assay, 1,236 specimens were retested with the 3-plex assay from which 73 specimens were identified with low enzyme activity. After processing the data using the post-analytical tools in CLIR, 19 specimens were identified as at-risk for MPS I and requiring further follow-up, a 74% reduction in screen-positive specimens from the FIA-MS/MS assay only. Using the screening algorithm, our pilot study successfully identified one newborn with severe MPS I disease who was subsequently confirmed and referred for treatment. As been reported by other programs, a high rate of pseudo-deficiency alleles was observed in many of the specimens with low IDUA activity. In conclusion, the North Carolina Pilot study has successfully applied a screening method for one lysosomal storage disorder and has successfully identified a newborn with MPS I. Because of the high presumptive positive rate, we recommend that post-analytical tools such as CLIR or second-tier analysis for GAGs should be further developed to improve the positive predictive value of this test.

**Presenter:** Jennifer Taylor, Public Health Research Analyst, RTI International, Research Triangle Park, NC, Phone: 919.485.5787, Email: jltaylor@rti.org

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**Median Normalization of Newborn Screening Analyte Data to Improve Screening Performance**

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**Objective:** Using median normalization of newborn screening analyte data to create a uniform cut-off between states.

**Background:** Median normalization, or multiples of the median (MoMs) has been effectively utilized in prenatal maternal screening to allow fair and accurate comparison of data generated from separate laboratories by the application of a uniform cut-off. Use of MoMs also allows aggregation of data from multiple labs for true inter-laboratory comparisons to better define affected and unaffected populations, which informs cut-off selection and results in improved screening positive and negative predictive values.

**Method:** Newborn screening attempts to identify neonates at increased risk for genetic disorders based on the increase or decrease of biochemical markers associated with disease as compared to a reference range derived from the normal population. However, affected and unaffected population distributions may overlap, which makes cut-off selection challenging. In addition, programs identify only a few true positive cases each year per disorder, which makes it difficult to assess screening performance due to a lack of data to better define affected versus unaffected individuals. Standardization of testing data using MoMs allows merging of data from multiple laboratories which would increase the number of true
positive cases for analysis. Data standardization would result in improved stratification of affected and unaffected individuals and may also allow application of a uniform cut-off for all states following normalization of data.

Results: We investigated the use of MoMs to standardize screening data and investigate the application of a uniform cut-off for two separate labs. De-identified thyroid stimulating hormone (TSH) and T-cell receptor excision circle (TREC) data from the Minnesota and Iowa programs were median normalized using each state’s population median and then merged in order to assess analyte distributions and apply a uniform cut-off for each analyte. Prior to normalization, statistically significant differences in distributions of analyte values for each lab were observed. After normalization, analyte distributions were not statistically different. Further, application of uniform cut-offs for each lab resulted in similar percentages of cases identified as borderline and presumptive positive.

Conclusion: In this study, median normalization allowed standardization of data from two state programs and application of a uniform cut-off, despite differences in assay methods, instrumentation, and reagents. Use of MoMs in newborn screening may provide a means to better aggregate and summarize data not only for disease, but also healthy populations, which would ultimately improve screening performance and advance national newborn screening efforts.

Presenter: Travis Henry, PhD, Laboratory Scientist, State Hygienic Laboratory at the University of Iowa, Coralville, IA, Phone: 319.335.4364, Email: travis-henry@uiowa.edu

Joint Follow-up and Quality Assurance/Quality Control Session – Timeliness in Newborn Screening

Partnering with a University Data Science Department to Develop Innovative Tools for the Analysis and Reporting of Newborn Screening Data
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Background: The Virginia Newborn Screening (NBS) Program regularly conducts statistical analyses for epidemiologic and quality improvement efforts such as exploring disease prevalence, monitoring timeliness at various stages across the NBS process, and developing NBS hospital report cards. Due to limited resources, the analytical and reporting capabilities have often been restricted to manual and time-intensive procedures, using Microsoft Excel as the primary tool.

Objective: To propose university partnerships as a possible resource solution for NBS statistical analysis and quality monitoring.

Methods: The Virginia NBS Program collaborated with graduate students from the University of Virginia’s Data Science Department over the 2016-2017 academic year to develop innovative NBS statistical analysis and reporting tools. R Programming was used to create new procedures for analyzing data exported from the NBS Laboratory Information Management System (LIMS). This data included test results, sample quality information, turn-around time, patient diagnoses, and patient demographics. Over a period of eight months, weekly meetings were held to define the NBS program’s analytical needs. Scripts and reports were developed by the students, who also provided training in R software to the NBS team. New developments were rigorously tested, and feedback on the NBS hospital report cards was solicited from our hospital partners. The students also developed a module to study false positive rates in Virginia, and conducted an exploratory examination of the effect of total parenteral nutrition (TPN)
feeding, weight, and early collection (< 24 hours) on congenital adrenal hyperplasia (CAH) screening results.

**Results:** From this collaboration, a suite of analytical tools was developed. These included: (1) an automatically generated and electronically delivered hospital report card with improved visualizations and diagnosis information, (2) automated quality indicator calculations for inclusion in the NewSTEPs data repository, (3) visual mapping of diseases for a given date range, and (4) relationship modeling between various infant and sample factors to examine their effects on false positive rates.

**Conclusion:** The partnership between the Virginia NBS Program and the University of Virginia’s Data Science Department helped fill the gap between the program’s data needs and technical capabilities. The tools created will help the state identify underperforming hospitals to target with education and training, direct resources to areas with greater concentrations of disease, and ensure effectiveness of screening protocols.

**Presenter:** Rhonda West, Newborn Screening Informatics Scientist, Virginia Division of Consolidated Laboratory Services, Richmond, VA, Email: rhonda.west@dgs.virginia.gov

**It’s Time to be On Time**
L. Resto, S. Rivera, V. Perez, C. Rivera, S. Ramirez and S. Pardo, Puerto Rico Newborn Screening Program, San Juan, PR

**Background and Objectives:** Puerto Rico NBS Program was established 30 years ago when we began analyzing dried-blood samples for sickle cell disease, PKU and congenital hypothyroidism. Our Program currently tests for 28 of the RUSP core conditions with SCID being the recent one added to the panel in 2015. In our goal of decreasing the time of diagnosis for infants with a disorder identified by NBS, we have worked in different areas to improve timeliness following NewSTEPs 360 proposal initiative. One of our objectives is to increase the percentage of DBS samples received by the lab within 24 hours of sample collection. In PR, the transport of dried blood samples from birthing facilities to the NBS laboratory is not performed daily by the majority of hospitals. We serve 37 birthing hospital plus home births around the island. In order to address the ACHDNC recommendation of NBS specimens received at the laboratory ideally within 24 hours of collection, we developed strategies and made improvements in our NBS Program.

**Methods:** We improved our electronic health information system to obtain necessary information to monitor quality indicators such as the time from birth to sample receipt by our NBS lab among other indices. Visits to hospitals to discuss timeliness efforts with staff such as nursery, NICU and hospital medical director and administrative personnel have been delivered to 6 nearby hospitals and other hospitals are on the agenda. The mean number of days to submit samples was calculated for each hospital and home births for the last six months.

**Results:** Our monthly timeliness data suggest that the mean time from sample collection to receipt by our lab for all hospitals is 2.37 days (57 hours). After visiting 6 out of 11 nearby hospitals and analyzing their performance, we found three of them delivering samples within the 24-hour time frame (with one delivering samples as early as 15 hours after collection) and the other 3 hospitals taking two days to submit samples. Prior to our educational efforts, time from birth to submission was close to 5 days. Other strategies to create awareness about the importance of sample collection and transport have been implemented in our NBS Program. We developed a report for hospitals so we can provide feedback on their performance and recruited personnel to improve our follow up of presumptive positive cases for hypothyroidism.
Conclusions: We found an improvement in reducing time from sample collection to receipt by lab after visiting hospitals and will continue with the on-site visits for the remaining hospitals. We continue our feedback process to hospitals through their performance reports and continue developing and delivering educational and training activities to hospitals to improve newborn screening timeliness.

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The Impossible is Possible: Improving Timeliness in Alaska’s Newborn Bloodspot Screening
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Alaska was near the bottom in newborn bloodspot screening timeliness measures in the 2016 GAO report; the NewSTEPs goals seemed out of reach. Alaska has unique challenges due to its geography and climate; small, rural hospitals with low numbers of deliveries; long distances to the partner lab; and limited shipping options with high associated costs. Additionally, 7.5% of births occur outside of the hospital setting, at home or at birth centers. Expenses related to shipping are the responsibility of the birth provider. The state applied for and received funding from the NewSTEPs 360 project, focusing on improving the quality and timeliness of specimens. The Alaska 360 team began working with birthing facilities to improve internal processes that could reduce transit time, as well as building partnerships between facilities and out-of-hospital birth providers to decrease expenses. Alaska is now developing a state-wide courier system that transports specimens 7 days a week to the Northwest Regional Screening Laboratory in Oregon via an overnight flight, allowing specimens to reach the lab less than one day after collection; costs are covered by NewSTEPs 360 funding during this trial period. By engaging on a personal level, educating staff, and working within existing systems, areas for improvement could be identified for all birthing providers. Finding partners, identifying and empowering non-management champions, and promoting buy-in for newborn bloodspot screening works in Alaska: when everyone from hospital staff to couriers understands why timely results are critical to the health of Alaska’s infants and how they, individually, play a role in the process, success ensues. Alaska’s NewSTEPs 360 team and state-wide partners are proving that what seemed impossible is not.

Presenter: Sabra Anckner, RN, Perinatal Nurse Consultant, Alaska Division of Public Health, Anchorage, AK, Phone: 907.334.2295, Email: sabra.anckner@alaska.gov

Towards Improved Timeliness, Accuracy, and Operational Efficiency: Utah Newborn Screening Program’s Journey

Newborn screening (NBS) is critically depending on timeliness and efficiency to save lives. The Utah NBS program is 100% kit fee based. The more efficiently the NBS programs operate, the more conditions can be included for screening. A high level of technical and quality sophistication further ensures ongoing quality monitoring and improvement for testing algorithms. Since 2014, the Utah NBS program has been undertaking significant efforts to improve operational efficiency. Focusing on timeliness, the program
measured overall turn-around-time (TAT) for the entire process. Rather than focusing on the respective isolated sub-processes or only looking at the process beginning with sample receiving and ending with report generation, the program defined the life-cycle of screening beginning with birth and ending with NBS report consumption by providers and families. This global process measure is complemented with precise measurements of all sub-processes. With this life cycle analysis we identified TAT delays in the transit process; sample receiving and accessioning; and laboratory testing. We also identified process inefficiencies in the reporting process. We significantly improved transit timeliness through the introduction of a courier program for underperforming hospitals. This reduced mean transit TAT to less than 1.5 days. We significantly improved laboratory testing through implementation of 7-day operations. Specimens are received through Saturday; the laboratory performs full testing on Sundays. Because the Utah NBS program is entirely kit fee based, expanded operating hours were implemented through strategic rehiring when attrition occurred. Same day data entry completion was implemented through expanded scanning of SECOND specimens. Integration of the NBS Follow-up group within the division has resulted in resource consolidation and cost savings. This has allowed hiring of a fulltime PhD trained health informaticist. Implementation of SCID in the NBS laboratory has further reduced mean TAT to 4.7 days and 6.1 days from the life cycle perspective. The implementation of CF mutation testing in-house has resulted in improved time-to-diagnosis for CF (27 days).The last iteration addresses the introduction of a new LIMS with a complete chain-of-custody solution for all specimens. This system allows electronic laboratory ordering (ELO), electronic laboratory reporting (ELR), and real-time notification of providers regarding specimen receipt and delays. It will also eliminate data entry requirements. A data warehouse with clinical and operational data will further improve transparency of key operational and clinical indicators.

**Presenter:** Andy Rohrwasser, Utah Department of Health, Salt Lake City, UT, Email: arohrwasser@utah.gov

**CQI Texas – Improving Timeliness through a Systematic Investigation of Process Workflows**

B. Reilly, P. Trevino Gonzales, T. Odums, A. Vinyard and R. Lee, Texas Department of State Health Services, Austin, TX

**Objective:** In continuing efforts to improve timeliness of newborn screening, the Texas Newborn Screening Laboratory sought to reduce overall laboratory turnaround times by conducting a constraints analysis of workflows to identify bottlenecks and developing a system workflow that maximizes the laboratory’s ability to complete the punching process and initiate testing on the day of specimen receipt. **Methodology:** The laboratory followed the Lean Six Sigma process (Define, Measure, Analyze, Improve, Control) to remove the identified system constraints and allow earlier initiation and completion of downstream processes. The percent of initial specimens sampled (punched) the same day as received in the laboratory was defined as the primary metric and the Texas NBS Program adherence to ACHDNC recommendations for timeliness as secondary measures. Quantitative data on courier delivery times, specimen volumes, specimen receipt, and accessioning, and punching initiation and completion times were collected. Laboratory staff provided extensive qualitative input on system issues and potential options for improvement. Lean tools, statistical analyses, data projections, and staff mapping diagrams were used to analyze quantitative and qualitative measures and project outcomes for various workflow adjustments. Proposed adjustments and projected outcomes were reviewed by laboratory management. An improvement plan with estimated timeline, developed based on management recommendations and laboratory staff feedback, was implemented. Outcomes of primary and
secondary measures and processes were monitored to ensure stability, coordinate adjustments, and identify new targets for improvement.

**Results:** Process changes resulted in an improvement of the percent of specimens punched the same day received from ~16% to over 90%. Secondary measures also significantly improved:

- Percent of presumptive positive 1st screen results for time critical disorders released within 5 days of life increased from ~30% to ~70%
- Percent of presumptive positive 1st screen results for time sensitive disorders released within 7 days of life increased from ~70% to ~85%
- Percent of all 1st screen specimens reported within 7 days of life increased from ~15% to ~60%

Subsequent analysis of outcome systems identified additional potential projects to further improve quality measures.

**Conclusions:** Workflow evaluation and change management are complicated processes in a high volume newborn screening laboratory. A systematic continuous quality improvement approach incorporating goal-setting, communication, and workflow analysis and redesign can successfully identify inefficiencies, reduce resistance to change, and minimize unintended consequences.

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### Session 4 – Follow-up Activities in Newborn Screening

**High Presumptive Positive Rates in Neonatal ICU Babies - The Texas Experience and How to Fix It!**

L. Fitzgerald, K. Hess, M. Shaffer, K. Wolf and D. Freedenberg, Texas Department of State Health Services, Austin TX,

**Problem:** Newborn screening false-positive results (FPRs) are disproportionately higher among sick, premature, and low birth weight (LBW) infants, most of whom are cared for in the neonatal intensive care unit (NICU). FPRs lead to additional repeat screening and/or confirmatory testing, which places further burden on the infant, the infant’s family, the NICU staff, and the NBS staff. Current protocols in Texas require that for any infant with an abnormal NBS result, a verbal notification be made to a clinical staff person of the infant’s current provider, typically a hospital nursery/NICU or primary care provider. If the current provider cannot be found, then verbal notification is made to the parent. The Texas NBS program makes a high volume of outbound phone calls to our state’s NICUs to report abnormal NBS results. Some Texas NICUs have voiced concerns about the large number of calls. The NBS program is aware of the potential strain this places on NICU clinical staff. Moreover, the high rate of FPRs among sick, premature, and LBW infants may lead to desensitization of NICU staff to abnormal results.

**Methodology:** Texas conducted an internal study to determine the number of presumptive positives and confirmed diagnosed cases over a 42 month period for endocrinopathies (congenital adrenal hyperplasia and congenital hypothyroidism) and over a 6-year period for inborn errors of metabolism (aminoacidopathies, organic acidurias, and fatty acid oxidation defects) tested via tandem mass spectrometry (MS/MS). Results will be used to guide updates to current notification protocols.

**Results:** Annually, the Texas NBS program tests approximately 750,000 dried blood spots, which yield about 20,000 abnormal results. Roughly 48% percent of these abnormal results are generated from NICU infants. Texas will present a summary of findings, including the false positive rate and positive
predictive value for endocrinopathies and inborn errors of metabolism and by birth weight category. Texas will also present surprising findings with regard to TPN/General Elevation abnormal results.

**Conclusion:** Using metrics, Texas will be able to safely change protocols and predict how those changes will result in the desired outcomes of decreasing call volume to our state’s NICUs.

**Presenter:** Lori Fitzgerald, MSN, Public Health Prevention Specialist, Texas Department of State Health Services, Austin TX, Email: lori.fitzgerald@dshs.texas.gov

**North Carolina Mucopolysaccharidosis I (MPS I) Pilot Study: How Incorporating Sequencing Data Impacts Follow-up**

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**Background:** MPS I is caused by a deficiency of a-L-iduronidase (IDUA) and results in progressive storage of glycosaminoglycans (GAG) in affected tissue leading to physical disease, shortened life span and, in the severe form (Hurler syndrome), progressive cognitive impairment. MPS I was added to the Recommended Uniform Screening Panel in February 2016. The objective of this study was to conduct a state-wide pilot study of newborn screening for MPS I in North Carolina to provide outcome data for broader implementation.

**Methods:** MPS I enzyme activity was measured in DBS using a flow injection analysis - tandem mass spectrometry (FIA-MS/MS) assay followed by retesting with a 3-plex FIA-MS/MS assay and analysis of the data using the Collaborative Laboratory Integrated Reports (CLIR) tool. To provide further diagnostic information to the follow-up team, the screening algorithm incorporated Sanger sequencing of the IDUA gene on screen-positive DBS specimens. Clinicians received both the enzyme activity and the sequencing results prior to the follow-up and confirmatory testing. Confirmatory testing was performed through measurement of urine GAG and IDUA enzyme activity in whole blood.

**Results:** Out of 63,545 specimens screened, positive results included one newborn with homozygosity for a known pathogenic variant associated with the severe form of MPS I, 4 newborns with variants of unknown significance, 2 likely carriers of pathogenic or likely pathogenic variants and 18 newborns with suspected pseudodeficiency variants. Follow-up and confirmatory testing has been provided for nineteen newborns. The infant with homozygosity for a pathogenic variant associated with the severe form of MPS I had elevated urine GAG on confirmatory testing and early clinical signs consistent with MPS I. The affected newborn was referred for hematopoietic stem cell transplantation. Of the other 18 infants, urinary GAG was not elevated in 14 infants and urinary GAG is pending in the remaining 4.

**Conclusions:** The North Carolina NBS pilot study for MPS I successfully identified an infant with the severe form of MPS I, however the pilot study also identified and provided follow-up for several infants with suspected pseudodeficiency variants and variants of unknown significance. The pilot provided further evidence that newborns with pseudodeficiency alleles do not have urine GAG or evidence of disease.

**Presenter:** Lisa Gehtland, Public Health Research Analyst, RTI International, Research Triangle Park, NC, Email: lgehtland@rti.org
An Update on Newborn Screening for Adrenoleukodystrophy in New York State: A Review of Management Protocol Changes and Confirmed Cases  
B. Vogel, S. Bradley, J. Orsini and M. Caggana, New York State Department of Health, Wadsworth Center, Albany, NY

New York State developed diagnostic and surveillance protocols and treatment guidelines for newborns with a positive screen for adrenoleukodystrophy in anticipation of screening implementation. These protocols have now been used to follow boys with a confirmed diagnosis of X-linked adrenoleukodystrophy since December 30, 2013 and have been modified based on this experience. Originally the first brain MRI without contrast was recommended at six months of age for asymptomatic boys. The specialty centers across New York State report difficulty with interpretation and challenges with coordinating the brain MRI prior to six months of age. Based on this feedback, the recommendation in New York State has changed to the first brain MRI occurring at twelve months of age. The treatment guidelines have also been modified to recommend that the ALD MRI score of a boy with a diagnosis of X-linked adrenoleukodystrophy be independently confirmed by experts in ALD prior to recommendation for assessment for hematopoietic cell therapy. For endocrine surveillance, the original recommendation was to perform ACTH and cortisol testing every six months. However, the endocrinologists in New York State report difficulty interpreting these values in newborns prior to the regulation of the circadian rhythm. Discussions are ongoing about the best approach to monitoring for adrenal disease prior to one year of age, including the utility of a cosyntropin stimulation test. These protocols will continue to be evaluated over time. Long-term follow-up is currently being implemented in New York State, which will provide valuable data for ongoing evaluation of these protocols.

Presenter: Beth Vogel, MS, CGC, Research Scientist 3, New York State Department of Health, Wadsworth Center, Albany, NY, Email: beth.vogel@health.ny.gov

Long-Term Follow-Up of Sickle Cell Disease in California  
P. McLendon, S. Sciortino and L. Feuchtbaum, California Department of Public Health, Richmond, CA

Objective: In California, the most common types of sickle cell disease (SCD) subtypes (HbSS, Hb SC and HbS beta thalassemia) impact 1 in 6,000 births and SCD is the second most common disorder diagnosed through the California Newborn Screening Program (NBS). We describe long-term follow up (LTFU) data to evaluate clinical outcomes and to determine if children receive appropriate care and recommended disease treatment and management.

Methods: NBS systematically collects LTFU data on all SCD patients identified through newborn screening each year on their birthday, through age five. A web-based system allows follow-up centers to enter information about the patients after each completed year of life. Data is collected on number of visits and services provided, reasons for missed appointment (barriers to care), emergency room visits and hospitalizations, symptoms and complications, treatments and tests ordered, and morbidity/cause of death data. Information will be presented by hemoglobin subtype and by patient age. We include LTFU data for children screened from January 1, 2009 through December 31, 2015.

Results: Data on 948 LTFU reports from 372 patients are described. Nearly 10% of all patients were lost to follow-up, most frequently during the first year. Four patients died by 5-years of age, 1 in the first year of life. One death was known to be due to complications of SCD. Patients reported at least one episode of febrile illness (63%), anemia (44%), and pain requiring medication at home (27%). Sixty-nine percent of children required emergency department care, mostly for fever (79%) and pain (38%). The majority of patients received penicillin prophylaxis during all 5 years of follow-up and 31% received...
hydroxyurea treatment. Less than a quarter of all patients were vaccinated for influenza (annually), pneumonia, and meningitis. At least one-third of patients had annual transcranial Doppler (TCD) screening beginning at 2 years of age.

**Conclusions:** These findings demonstrate the value of collecting LTFU data for patients with SCD and can be used to enhance our understanding of the post-screening healthcare experience for children diagnosed with these hemoglobinopathies. These data can also be used to explore if established standards of care for disease treatment and management are being provided.

**Presenter:** Patricia McLendon, California Department of Public Health, Richmond, CA, Email: patricia.mclendon@cdph.ca.gov

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### Session 5 – Financial, Legal, Ethical, Policy and Social Implications (FLEPSI)

**Benefit-Cost Analysis for Adding Newborn Screening for X-linked Adrenoleukodystrophy**

J. Thompson, Washington State Department of Health, Shoreline, WA

**Background:** One of the five criteria for adding a newborn screening condition in Washington State is that the benefits must justify the costs of screening. A benefit-cost analysis for adding newborn screening for X-linked adrenoleukodystrophy (X-ALD) was performed during 2015 in preparation for formal consideration by the advisory committee. The intent of this presentation is to give a brief overview of how the benefit-cost analysis was performed and share its findings.

**Methods:** A decision tree analysis was created comparing the morbidity and mortality associated with X-ALD in hypothetical no-screening and screening cohorts. The primary medical literature and expert opinion informed the estimates used for the following parameters included in the model: disease prevalence, screening performance (sensitivity and specificity), morbidity and mortality rates for early diagnoses versus late diagnoses, percent of cases with a family history, costs of newborn screening, costs of early versus late treatment, costs of serial testing and the value of a life saved. One-way sensitivity analyses were performed with ranges for these parameters to understand which assumptions have the biggest impact on the overall benefit-cost analysis.

**Results:** The model predicted approximately 3 babies born in Washington State each year with X-ALD (birthrate = 88,000 births per year). The costs of testing were estimated at $8 per baby (for two routine screens). The model predicts that about one life will be saved through screening every three years. The final benefit-cost ratio was favorable at 3.95, with a total net benefit of $1.8 million per year and an incremental cost-effectiveness ratio of about $88,000.

**Conclusion:** The costs of implementing X-ALD screening are similar to many other conditions currently being screened by many programs. The model’s favorable benefit-cost analysis for adding newborn screening is driven by the lives saved through early identification and treatment. Washington's model (Excel spreadsheets) can easily be used and modified by other programs to provide information to decision makers about X-ALD newborn screening.

**Presenter:** John Thompson, PhD, MPH, MPA, Newborn Screening Office Director, Washington State Department of Health, Shoreline, WA, Phone: 206.418.5531, Email: john.thompson@doh.wa.gov
Development of a State Condition-readiness Tool for Disorders Not on the Recommended Uniform Screening Panel
K. Karasinski, M. Kleyn and J. Bach, Michigan Department of Health and Human Services, Lansing, MI

**Background:** Michigan’s process for adding disorders to the newborn screening (NBS) panel relies on a recommendation from the NBS Quality Assurance Advisory Committee (QAAC) established under the state public health code in 2006, followed by legislative approval. Typically, the decision to add a new disorder follows the recommendation of the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC). Occasionally, the NBS Program is approached by families, state legislators, or clinicians to consider adding other disorders to Michigan’s panel. The need for a more systematic approach to reviewing these requests was identified by NBS Program staff. Over the past year, staff members developed criteria to assist in the decision-making process for adding disorders to the screening panel that are not on the federal Recommended Uniform Screening Panel (RUSP). This tool allows for an internal assessment of Michigan’s readiness for adding disorders that have been brought to the ACHDNC but not recommended for approval by the U.S. Secretary of Health and Human Services.

**Methods:** Criteria for the tool were selected based on a thorough review of the document, “Newborn Screening: Toward a Uniform Screening Panel and System” that was used to determine the disorders on the initial RUSP; the current process for evaluating disorders for the RUSP in terms of determining benefits compared to readiness; and examples of criteria from other states that have implemented similar processes. The proposed tool was first reviewed and approved internally by Michigan Department of Health and Human Services NBS Program follow-up and laboratory staff. It was then shared with the NBS Technical Advisory Committee and the QAAC. Their feedback was incorporated into the final version of the tool.

**Results:** The tool will be used when a stakeholder requests that a new disorder be added to the Michigan NBS panel. The readiness criteria framework assesses the feasibility of screening and follow-up for disorders that have been brought to the attention of the ACHDNC but not recommended for RUSP inclusion. These guidelines will be used to assess Michigan’s readiness for adding the disorder to the state screening panel. Seven required criteria must be met before a disorder can move forward to the supporting factor categories that include: condition characteristics, laboratory/screening, follow-up/diagnosis, clinic/treatment availability. Depending on the scores for all these categories, the disorder is classified as ready, developmental, or unprepared. Disorders meeting the ready or developmental stages can be discussed and moved through Michigan’s formal approval process.

**Conclusions:** The development of the criteria included on the readiness tool was viewed as useful by staff and advisory committees. It will clarify factors that need to be considered and provide a way to standardize review of proposed disorders.

**Presenter:** Kristy Karasinski, Michigan Department of Health and Human Services, Lansing, MI, Email: karasinkik@michigan.gov

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**Updating the National Newborn Screening Contingency Plan to Facilitate Preparedness for Newborn Screening**
S. Shone\(^1\), K. Taft\(^2\), J. Ojodu\(^3\); \(^1\)New Jersey Department of Health, Trenton, NJ, \(^2\)Association of Maternal & Child Health Programs, Washington, DC, \(^3\)Association of Public Health Laboratories, Silver Spring, MD

**Background:** The national newborn screening (NBS) contingency plan (CONPLAN) was developed in 2010 by the Centers for Disease Control and Prevention (CDC) and the Health Resources and Services Administration (HRSA) as required by the Newborn Screening Saves Lives Act of 2008. The CONPLAN
serves as a manual for maintaining NBS operations during a public health emergency. In 2015, the Association of Maternal and Child Health Programs (AMCHP) and the Association of Public Health Laboratories (APHL) partnered with CDC and HRSA to form an Advisory Committee of NBS and emergency preparedness experts and stakeholders to update the CONPLAN.

**Methods:** AMCHP conducted a public comment survey from January 1 – February 15, 2016 to review gaps in the existing CONPLAN, and solicit feedback on how the CONPLAn could incorporate the entire NBS system. Survey results gathered from NBS programs, preparedness programs, hospitals, families and other stakeholders were analyzed during committee conference calls and an in-person meeting. The outcomes were incorporated into CONPLAN revisions.

**Results:** The updated CONPLAN addresses laboratory and follow-up operational gaps in the original document, includes point-of-care screening, and emphasizes communication and family engagement. New appendices including a flowchart, contingency planning checklist, and resource list were designed to help states develop their own continuity of operations plan (COOP) and to incorporate the emergency management assistance compact (EMAC). The revised CONPLAN is currently being vetted through HRSA and CDC, however, approval is anticipated in advance of the Symposium.

**Conclusions:** The CONPLAN was updated to ensure all aspects of the NBS system are included in preparedness planning. In addition, the updated document includes several new resources that will enable states to be better prepared for the next public health emergency.

**Presenter:** Scott Shone PhD, Public Health Research Analyst, RTI International, Research Triangle Park, NC, Email: sshone@rti.org

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**A Systematic Review of the Research Uses of Residual Newborn Screening Dried Blood Spots: A Scoping Protocol**

E. Rothwell¹, N. Riches¹, E. Johnson¹, J. Zhao², M. Fiander¹, M. Lackey¹; J. Botkin¹; ¹University of Utah, Salt Lake City, UT, ²Huntsman Cancer Institute, Salt Lake City, UT

**Objective:** To systematically review the published literature using a scoping review protocol (per Arksey & O’Malley) to identify, categorize and describe secondary research uses of residual dried blood spots (DBS) from newborn screening (NBS) programs. Research using DBS is acknowledged as providing valuable information to guide improvements in population health, treatment, diagnosis, as well as quality control in laboratories. Despite this acknowledgement, there is no documented summary of the extent or uses of DBS in research.

**Methods:** A librarian searched the following databases in August 2015: Pubmed, EMBASE, CINAHL, PsycInfo, Academic Search Premiere, and Web of Science, Theses and Dissertations index; no limits were applied. The search identified 9,613 unique citations; 7828 were excluded during title/abstract screening that resulted in 1785 full-text publications for inclusion. Full-text of the 1785 publications were screened independently by two PhD research assistants for inclusion/exclusion using the software program Covidence. This resulted in 526 publications that fulfilled the inclusion criteria with a 92% interrater reliability. Conflicts were resolved by the lead author. Data was extracted from the 526 publications by one of the PhD research assistants, but consistency and accuracy were reviewed by two independent investigators for 10% of the data, and no discrepancies were found.

**Results:** Three study designs were identified: observational, 42.4%; case-control, 38%; and, cross-sectional, 16%. Year of publication was from 1973-2015. The majority of research, 74.6%, focused on quality assessment or quality control; 21.5% investigated quality improvement strategies for known diseases and clinical procedures; and 72.5% were on conditions not currently screened or not related to NBS. Consent was obtained in 32.4% of the studies; 3% stated no consent was sought; and in 64.6% of
studies, status of consent was not reported. Data was described as anonymized in 14.9%, as identified in 11%, and 53.9% of research did not record this information. Commonly used procedures used to analyze the DBS targeted analytes (58.7%), DNA (35.6%) and enzymes (5.7%). Most of the research focused on a genetic disease (57.6%) with 15.4% studying infectious disease, 3.8% toxicological and 2.7% cancer related. About 28% of the studies were conducted in the U.S., 7% were from multiple countries, 6.9% were from United Kingdom; 6.5% were from Italy, 6.1% were from Denmark, and 5.3% were from Australia. Overall 46.3% were funded by federal agencies.

**Conclusions:** Outcomes of this research indicate that residual DBS are used extensively and worldwide for research addressing health and public health issues. Future analyses will summarize outcomes of disease-specific research and provide detailed evidence of effectiveness from the use of residual DBS in research on health outcomes.

**Presenter:** Erin Rothwell, PhD, Associate Professor, College of Nursing, University of Utah, Salt Lake City, UT, Email: erin.rothwell@nurs.utah.edu

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**Equality and Equity in Newborn Screening**

N. Bonhomme¹, A. Gaviglio², A. Goldenberg³, B. Tarini⁴; ¹Genetic Alliance, Washington, DC, ²Minnesota Department of Health, St. Paul, MN, ³Case Western Reserve University, Cleveland, OH, ⁴University of Iowa, Iowa City, IA

Newborn screening is often heralded as a universal public health program that affords each infant the opportunity to benefit from early detection and treatment. Indeed, nearly all infants in the United States currently receive newborn screening, which has resulted in life-saving treatment for thousands of children each year. However, the discussion of universality and equity in newborn screening needs to extend well beyond the number of conditions on the RUSP and testing methodologies within the laboratory to include disparities in education, follow-up services, and treatment. This discussion is particularly salient given the mandatory nature of newborn screening. In this session, a discussion of newborn screening will be presented utilizing a health equity lens, focusing on identifying and addressing the existing and potential health disparities facing the Newborn Screening System.

Presenters will include representatives from Clinical, Advocacy, Ethics, and State program perspectives and will report on work from a variety of initiatives examining the Equity implications of NBS programs. Presenter One will discuss disparities in short and long-term follow-up, presenting a systems map of the newborn screening process with a focus on potential failure points. Presenter Two will discuss equity with regards to the availability of, and access to, treatments and other interventions. Presenter Three will discuss disparities in educational initiatives, focusing on needs and learning styles of particular consumers. Finally, Presenter Four will look to future expansion of NBS programs and discuss the potential for disparities associated with the integration of genomic applications in newborn screening. As newborn screening continues to expand both in terms of the use of molecular applications as well as in conditions that may need longer monitoring or more expensive treatment, it is imperative that the newborn screening community begins examining the system and services beyond the disorders offered.

This presentation aims to engage multiple stakeholders of newborn screening in a crucial discussion to identify potential areas for improvement and opportunities to address health equity within programs. Through this panel, we hope to encourage future activities aimed at ensuring that both access and system-wide health equity are considered in order to preserve the universality of newborn screening throughout the entire process.

2017 APHL Newborn Screening & Genetic Testing Symposium, New Orleans, LA, September 10-13, 2017
**Roundtables**

**Is a Voluntary Panel of Non-RUSP Conditions a Viable Future for Newborn Screening?**

For the most part, newborn screening in the U.S. is done without consent, although most states allow parents to opt-out for moral or religious reasons. The fundamental argument for non-consented screening is that there is an urgent public health need to identify babies with certain treatable health conditions before symptoms appear. The rigorous evidence review conducted before a condition is added to the Recommended Uniform Screening Panel (RUSP) is intended to provide assurance that pre-symptomatic screening for a condition would result in significant net benefit for affected children.

A possible future scenario for newborn screening is a secondary panel of conditions that could be offered on a voluntary basis for parents who want it. The fundamental argument for a secondary panel is that there are many conditions that do not meet the rigorous requirements of the RUSP but for which there is likely to be some degree of medical, developmental, and/or family benefit. Voluntary screening for those conditions would help address growing advocacy demands for a more rapid expansion of newborn screening and could provide evidence for determining whether a disorder should become part of standard newborn screening. Despite its conceptual appeal, however, a voluntary secondary panel would be challenging and expensive to implement. Some have argued that it might also adversely affect standard newborn screening.

Our team is developing and preparing to implement Early Check, a voluntary statewide newborn screening program designed to test the benefits of pre-symptomatic treatment for conditions that need such evidence before RUSP approval. If successful, Early Check could also provide the foundation for an envisioned future in which states offer screening for a voluntary panel of “non-RUSP” conditions. This roundtable session is designed to facilitate an open dialogue with conference participants about the desirability and feasibility of a secondary panel of conditions. The session will begin with a brief introduction to the issue, followed by a team-facilitated interactive discussion designed to elicit and address both the opportunities afforded and challenges evoked by a voluntary secondary panel offered in conjunction with regular newborn screening.

**Presenter:** Don Bailey, Director, Center for Newborn Screening, Ethics, and Disability Studies, RTI International, Research Triangle Park, NC, Phone: 919.541.6488, Email: dbailey@rti.org

**What’s Next? Follow Up on Best Practices from the Beyond the Bloodspot: Education and Engagement Summit**
N. Bonhomme and J. Seisman, Baby’s First Test, Genetic Alliance, Washington, DC
The Newborn Screening Clearinghouse, launched in 2011 as Baby’s First Test (www.BabysFirstTest.org), provides the public with access to reliable information and resources on newborn screening policies and procedures at the local, state, and national levels. In an effort to increase knowledge and awareness of newborn screening, in June 2017 the Clearinghouse will bring together a diverse group of families, advocates, newborn screening and public health professionals, and health educators for Beyond the Bloodspot: an Education and Engagement Summit. The goals for the summit are to: 1) identify and evaluate best practices that improve family and healthcare provider understanding of the newborn screening system; 2) identify best practices that increase family and healthcare provider involvement; and 3) evaluate family and healthcare provider involvement throughout the system. Attendees will work together to identify support needs and priorities for educational efforts by both populations and content type (prenatal, postnatal, out-of-range, etc.), and identify specific strategies for an evolving newborn screening system. The Clearinghouse will develop a white paper on evaluating best practices in education and engagement directed towards educators, policymakers, advocates, and funders of newborn screening education activities. The purpose of this roundtable discussion is to gather more input from newborn screening stakeholders. Specifically, we will 1) discuss the outcomes of the summit, including identified best practices and support needs; 2) elicit additional feedback and comments from the group on developing and sharing best practices; and 3) identify how these activities can build off of other initiatives, including the Follow Up Work Group and other state/regional/and national education efforts. Participants will have an opportunity to view a draft of the white paper and provide comments and feedback.

Presenter: Jackie Seisman, MPH, Assistant Director of Maternal and Child Health Programs, Genetic Alliance, Washington, DC, Phone: 202.966.5557, Email: jseisman@geneticalliance.org

Newborn Screening for Alpha Talassemias
M.C. Dorley1, T. Davis2, C. Yusuf3, J. Ubaike4, C. Moore5, M. Chan6, L. Nayak7, M. del Pilar Aguinaga8, 
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The Problem Studied and/or Objective: Alpha Thalassemia (a-thal) is a hemoglobin disorder with varying clinical significance. Currently, this disorder is not a core disorder on the Recommended Uniform Screening Panel (RUSP). However, some state newborn screening programs have opted to screen for a-thal through detection of Bart’s hemoglobin. As the Association of Public Health Laboratories (APHL) Hemoglobinopathy Laboratory Workgroup, our objectives are threefold. First, we want to hear from states that report Bart’s hemoglobin what motivated the decision to screen for a-thal beyond the RUSP. Secondly, we anticipate identifying unique and shared barriers as well as challenges encountered by states and how these were overcome since these same barriers and challenges may limit other programs from screening and reporting for this disorder. Lastly we endeavor to highlight state experiences as a result of screening for a-thal.

Methodology: Open discussion with states that have adopted screening for a-thal versus states that report a-thal as an incidental finding versus those that do not screen so as to fulfill the aforementioned objectives.

Significant Results: Undetermined.
Conclusion: Collation of results from the discussion will be used to identify gaps in screening for a-thal and aid future educational opportunities and recommendations that the APHL Hemoglobinopathy Laboratory Workgroup can develop.

Presenter: M. Christine Dorley, MSP, BS, MT (ASCP), Assistant Director Newborn Screening, Tennessee Department of Health: Laboratory Services, Nashville, TN, Phone: 615.262.6352, Email: m.christine.dorley@tn.gov

Session 6 – International Perspectives in Newborn Screening

Neonatal Screening of Duchenne Muscular Dystrophy in Zhengjiang China
G. Qian and R. Yang, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, China

Objective: To establish and perform the screening network for neonatal DMD. To provide a service of genetic consultation for the family of patient who is screened out in order to avoid a second birth of this type of child patient and to reduce the social and family burden, to manage the patient who is definitely diagnosed and to offer a comprehensive, reasonable and normalized therapy.

Method: a total of 18330 cases of male neonate born in Zhejiang province from 2016/5/16 to 2016/6/23 was taken as an object of study. All of them met the condition of neonatal screening and their blood was sampled with a filter paper 72 hours after birth. The suspicious patient was screened out by a measurement of CK value of dry blood spot of sample. The GSP was used to detect the concentration of CK-MM by the DELFIA method. The experiment reagent is freely sponsored by the PerkinElmer. The cut-off value was set based on 99.5 percentile of sample measurement value and the suspicious patients were recalled for a biochemical detection of blood CK value, the highly suspected patients were performed with a gene detection combined (or not combined) with muscle biopsy for definite diagnosis. The diagnosed patients were documented for management and to be clinically intervened at an appropriate time.

Result: the cut-off value (99.5 percentile value) of this experiment method, CK-MM, approximated 400ng/ml, 94 out of 18330 cases of male neonate were found to be suspicious and recalled after screening, among whom, there were 81 cases whose CK-MM fell between 400ng/ml and 700ng/ml (99.9 percentile value) and 13 cases whose CK-MM fell beyond 700ng/ml. 52 out of 81 cases of patient whose CK-MM fell between 400ng/ml and 700ng/ml were recalled, their reexamination results were all normal. 12 out of 13 cases of patient whose CK-MM fell beyond 700ng/ml were recalled, among whom there were 4 cases of patient whose CK value was found to be significantly elevated by repetitive reexamination of blood biochemistry, finally they were definitely diagnosed as DMD/BMD by gene detection. All the genotype of 4 cases definitely diagnosed were defect in large segments, which accorded with the mutational hot pot of this gene that had been reported previously.

Conclusion: among 18330 cases of male neonate born in a random consecutive period in Zhejiang, China, 94 cases are found by screening of CK-MM to exceed the threshold, 4 cases have been definitely diagnosed, incidence rate is about 1:4240. This screening method is easy to operate with a high specificity and accuracy, and it deserves a further study of greater-size sample and a gradual official popularization. Now we have finished the other part of the test from October 26th 2016 to December 30th 2016. Totally 24230 boys were screened, and 95 cases out of them whose CK-MM are in range between 400ng/ml and 700 ng/ml, 25 cases whose CK-MM fell beyond 700ng/ml. The suspicious patients are now being recalled in succession.
Timeliness of Newborn Screening Activities in the Mindanao Region
C.G. Abarquez, Southern Philippines Medical Center, Davao, Philippines

**Background:** Newborn screening (NBS) is a public health program which aims to detect certain metabolic disorders, which if not detected and appropriately managed early in the neonatal period can lead to severe complications. The effectiveness of the newborn screening system depends on the proper and timely collection of samples and the timely diagnosis and appropriate management of cases.

**Objective:** The study aimed to evaluate the timeliness of newborn screening, to identify areas in the newborn screening system that can be shortened to improve timeliness and to identify issues that impact timeliness and how these issues can be addressed by stakeholders.

**Methods:** Between January 2011 and December 2016, a total of 1,429,578 newborn infants were screened by NSC Mindanao for the six (6) metabolic disorders. Timeliness of newborn screening activities which includes screening age, transit time, time when NBS results are reported out and the turnaround time for immediate notification of medical providers, confirmation of the diagnosis and treatment of cases were reviewed. A six-year data (2011-2016) from the Neometrics database of NSC Mindanao were obtained retrospectively.

**Results:** The six-year data showed that the percentage of babies screened by Day 2 ranged from 65.41% to 76.14%. The percentage of specimens collected beyond 7 days of age decreased from 7.61% in 2011 to 5.7% in 2016. From 2011-2016, the percentage of samples received within the set target of 2 days was only 26.6%. However, 95.4% and 99.85% were received within 7 and 14 days, respectively. In 96.8% of cases, normal NBS results were reported out within 5 days from specimen receipt while 98.23% of out-of-range results were reported out by day 3. Age of confirmation and treatment age for the 6 disorders varied.

**Conclusion:** It is important to routinely monitor the timeliness of NBS activities because this can potentially improve the NBS program performance. The effectiveness of the NBS system can only be achieved if all stakeholders namely the families, NBS coordinators, health care professionals, newborn screening center staff and couriers will work collectively as a team.

**Presenter:** Conchita G. Abarquez, Southern Philippines Medical Center, Southern Philippines Medical Center, Davao City, Davao del Sur, Philippines, Phone: 63.918.990.5857, Email: conchabarquez@yahoo.com

The Importance of Partnerships - Strengthening Newborn Bloodspot Screening in Victoria, Australia
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Australia’s states and territories fund and implement separate newborn bloodspot screening programs, with five laboratories providing testing services for the country’s six states and two territories. In the state of Victoria screening is funded by the State Government of Victoria, with laboratory services provided by Victorian Clinical Genetics Services, a private, not-for-profit organisation that provides a range of clinical and laboratory services. Newborn screening has been in operation in Victoria for more than 50 years, expanding over time to screen approximately 79,000 babies each year for 25 conditions. Historically the screening service has functioned relatively autonomously, but in recent years a
combination of factors has led to a strengthening of the link between the screening service and state policymakers. This in turn has contributed to a concentration of effort towards newborn bloodspot screening on the part of maternity service providers. Concurrently, Victoria has contributed to national efforts to increase consistency between state and territory programs through participation in a working group developing Australia’s first national policy framework for newborn bloodspot screening. This has provided a valuable opportunity to review and update our local service and structures. While there is still much to achieve, this presentation will describe the shared effort to strengthen newborn screening policy and practice in Victoria, with the aim of improving screening quality for the babies and families at the heart of the service.

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Preparing to Expand the National Newborn Bloodspot Screening Program in the Netherlands with Fourteen Conditions
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Background: In 2015 the Health Council (HC) of the Netherlands published a policy advice to expand the national newborn bloodspot screening (NBS) program from seventeen to thirty-one conditions. The Minister of Health, Welfare and Sport agreed to this advice through a policy decision and gave the Centre for Population Screening (CPS) the assignment to study the feasibility of adding these fourteen conditions in three phases. To initiate the feasibility study the HC review was complemented with additional information on aspects such as: Dutch prevalence numbers, test characteristics and consensus in clinical follow-up. The CPS facilitated a stakeholder process to gain insight in these aspects. Here we describe the stakeholder process that took place in the Netherlands and the implications for the implementation of an expanded NBS program.

Methods: First an evaluation framework was developed based on international frameworks of criteria to assess conditions for NBS to gain more detailed insight in test properties, clinical findings, follow up and implementation. Then the advised conditions that needed extra information were selected. For each group of conditions experts were selected for participation in expert meetings including pediatricians, clinical geneticists, clinical chemists, epidemiologists and patient advocates. Prior to all expert meetings an elaborate background document was prepared with information from academic literature and policy reports, conference presentations and information from the project team’s network. The expert meetings resulted in advisory documents for each condition, with information summarized for each topic from the evaluation framework and suggestions for follow-up research. These advisory documents were provided to and discussed with a large group of stakeholders at a stakeholder meeting. Finally, the outline of feasibility study was compiled to be considered by the Minister of Health, Welfare and Sport.

Results: Eight expert meetings were held, reviewing eleven conditions. For most conditions pilot studies were advised by the experts, mostly focusing on validation studies in the Dutch context. For example, cut-off values relevant for the Dutch population, the number of false positives and false negatives should be evaluated. Furthermore, some additional condition-specific research was suggested, such as
for X-linked adrenoleukodystrophy and organic cation transporter 2 deficiency. The additional information from both the Dutch experts and international experience led to a shift in the previously suggested phasing: three conditions are expected to be implemented sooner, and one later.

**Conclusion:** Overall, the process illustrated the need for additional information on feasibility prior to the policy advice on such rare conditions. Therefore it should be strived for to gather this information prior to the evaluation by an independent organization.

**Presenter:** Marleen Jansen, Centre for Health Protection, National Institute for Public Health and the Environment, Bilthoven, Utrecht, Netherlands, Email: marleen.jansen@rivm.nl

**Screening on X-ALD in the Netherlands - An Ethical Perspective**

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**Background:** In 2015 the Dutch Health Council published a policy advice to expand the national newborn screening (NBS) program from seventeen to thirty-one conditions, including X-linked adrenoleukodystrophy (X-ALD). The Minister of Health, Welfare and Sport accepted this recommendation. In a recent policy decision the Centre for Population Screening (CPS) was asked to study the feasibility of adding the fourteen new conditions to the program. With regard to X-ALD, the Health Council advised to screen only boys. In the current NBS program, all newborns are screened for all conditions. The council reasoned that whereas girls do not develop the treatable forms of X-ALD that are found in boys, they may develop untreatable symptoms, mostly at a later age.

**Objective:** To describe the expert considerations on X-ALD screening in the Netherlands and the implications for the implementation of an expanded NBS program. Methodology CPS selected multidisciplinary experts for participation in an expert meeting, to discuss the ethical dilemma’s and possible solutions concerning screening only boys, the screening method, diagnostics and follow up of newborns referred with a positive screening result for X-ALD.

**Results:** The expert group discussed that a positive X-ALD testing result for male newborns reveals carrier status in the mother and possible sisters of the boy. Of the female carriers, 80% develops an untreatable variant of the disease. The expert group considered the health gain for male newborns with X-ALD large enough to outweigh the disadvantages of finding carriers in the relatives of the affected boys and having to inform the parents about this in this phase of their lives. The clinical experts stated that there is sufficient experience in the academic expertise center to provide good support to the families with X-ALD carriers. Another ethical issue the expert group discussed is that from an ethical perspective it is indeed better to avoid screening girls for X-ALD. There is a serious potential for harm that is not outweighed by any benefits for these girls. Screening girls for this condition would therefore be at odds with criteria for responsible screening that also govern the Dutch NBS program. Since at present all newborns are screened for all conditions in the program, stratifying between boys and girls is a practical challenge. Currently, the sex of the newborn is only registered on the heelprick card by the screener, and this information is not processed in the screening laboratories. Furthermore, the
information on sex may not be completely reliable. Screening all newborns for X-ALD and determining the sex only for the screen positive newborns, followed by selectively informing only the parents of screen positive boys, might be regarded as a solution for this problem. However, this approach comes with ethical challenges of its own, as it involves generating information about screen positive girls that caregivers would be supposed not to share with the parents. For this reason, the expert group advises to only consider this solution if alternatives involving prescreening sex-determination have more thoroughly been investigated.

**Conclusion and implications:** Parents should be informed that the benefits of finding X-ALD positive boys comes at the price of revealing female carriers who may develop an untreatable disease. Efforts are needed to find a robust way to select and register male newborns before the laboratory analysis for X-ALD is done. "

**Presenter:** Eugenie Dekkers, Programme Manager, Newborn Bloodspot Screening Program, RIVM, the Netherlands, Bilthoven, Utrecht, the Netherlands, Phone: 31.3.0274.4310, Email: eugenie.dekkers@rivm.nl

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**Session 7 – Communicating with Families and the Public**

**MinneStories: The Importance of Newborn Screening Storytelling**

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**Objectives:** To highlight the importance of storytelling by families impacted by newborn screening.

**Background:** Storytelling is one of the most powerful forms of communication. Storytelling helps create a personal connection and makes meaning of our lives. Everyone has a story to tell, especially families of children with a newborn screening condition. Many families impacted by newborn screening recall the first time they found out, that moment, as the moment that changed everything. The Minnesota Department of Health (MDH) sought to uncover these unique stories to bring together a community resource of strength and hope for families impacted by newborn screening. This one-of-a-kind collection of audio stories is named MinneStories that specifically lays out the impact, significance, and resilience of our newborn screening families.

**Method:** Following professional training by StoryCorps Legacy staff, we recorded conversations of people impacted by newborn screening. Participants were either known families to our program or were recruited with the help of our external partners. In pairs, these individuals had free-flowing conversations circling around their shared experience of a child, loved-one, or patient with a condition identified through newborn screening. Original recordings are 40 minutes in length. We then make shorter clips to be used, with the participants’ permission, on our website and through other program activities. Participants receive a copy of their full-length recording, which may be used as they please.

**Results and Conclusion:** To date, 18 interviews have been recorded, including stories about people with CCHD, hearing loss, MCAD, and CAH just to name a few. As of March 2017, all participants have given permission for us to share their story and six have been posted on the MDH website for other families to listen to and find shared experiences. Additionally, 204 individuals have subscribed to receive notifications when new stories are added. Families have reported that they look forward to having their memories and experiences preserved and have found this experience to be almost therapeutic. One mother wrote to us about her experience saying, "We have never made the time to sit and talk about [our son’s] hearing loss the way we did yesterday so it was actually a great experience and pretty eye
opening for us.” MinneStories is an on-going public health initiative and recordings continue to be collected and published. MDH will continue to explore additional avenues for sharing these invaluable stories and view this as a resource for newly diagnosed families, established families, medical providers, and legislators alike.

**Presenter:** Sondra Rosendahl, MS, CGC, Genetic Counselor, Minnesota Department of Health, St. Paul, MN, Email: sondra.rosendahl@state.mn.us

### Improving Communication of Negative Newborn Screening Results

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The purpose of newborn screening is to triage at-risk infants into the medical system in order to aid in early detection and treatment of affected children. Thus, communication of abnormal results is often the primary focus of newborn screening programs and has evolved into a relatively consistent and streamlined process. In addition, public health programs meet regulatory compliance with accurate and timely reporting to specimen submitters but have varying approaches as to how normal newborn screening results are reported to front-line medical providers, which often results in a more haphazard process. Recent media attention, however, has highlighted the importance of accurately relaying normal results to primary care providers and the need for improved discussion with providers and parents about the limitations of screening and the meaning of normal newborn screening results. A Quality Improvement (QI) project has been initiated to further understand as well as identify where improvements are needed for the efficient and effective communication of negative results to physicians and families.

The following components of this QI project will be presented and discussed:

- Assessment of how normal newborn screening results are handled at several hospitals and clinics with a discussion of what is and is not working well in terms of dissemination and communication of normal results
- Results of a parental survey used to determine if families received and understood their normal screening results
- Proposed improvement of communication processes based on the information collected and the capacity of a newborn screening program
- Identification and recommendation for newborn screening programs to adopt continuous quality improvement (CQI) measures regarding effective reporting and communication

The ultimate aim of this project is to increase the likelihood that all newborn screen results are successfully communicated to both providers and families, including negative ones. The hope is that this will lead to better equipped and more well-informed physicians and parents who can better understand newborn screening results and their limitations.

**Presenter:** Whitney Thompson, University of Minnesota Medical School, Minneapolis, MN, Email: thom2711@umn.edu

### Assessing Parental Attitudes about Newborn Screening for Late Onset Disorders

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2017 APHL Newborn Screening & Genetic Testing Symposium, New Orleans, LA, September 10-13, 2017
The first late onset disorder, X-linked adrenoleukodystrophy, has been added to the Recommended Uniform Screening Panel. Historically, state newborn screening systems have existed to screen, diagnose, treat and manage newborns with serious conditions that occur early in the newborn period. Adding late onset disorders to our newborn screening panels adds new considerations as we plan implementation and follow-up activities. The Western States Genetic Services Collaborative (WSGSC) sought to ascertain parental attitudes towards newborn screening for late onset disorders and if and how parents want the state programs to contact them for follow-up outside the newborn period.

**Methodology:** A survey was developed to assess parental attitudes towards newborn screening for late onset disorders over various ages in their child’s life. The survey also asked parents how they wish to receive newborn screening information and if and how they wanted to be contacted in the future with reminders about their child’s recommended follow-up. The surveys were administered at Baby or Kid’s Expos in Hawaii, Washington, and California. The survey results were analyzed for overall findings in the three states and similarities and differences among the states.

**Results:** Results are only available for Hawaii and Washington at the time of this abstract submission. Over 600 parents completed the surveys. Over 70% of the respondents knew about newborn screening. An overwhelming majority were either glad or relieved that newborn screening was being done. Over 75% of the respondents wanted newborn screening for late onset disorders regardless of whether there was a known treatment for the disorder. The number of respondents supporting newborn screening where symptoms would start at various stages in life declined as onset of symptoms moved towards adulthood (18+ years old). However, interest still remained high with approximately 40% approving of screening for adult onset disorders. The overwhelming majority of respondents (approximately 90%) wanted the Department of Health to contact them with reminders about care for their child either once or twice per year. The most popular form of contact reported was e-mail, followed by mail, phone calls, and text messages.

**Conclusions:** The parents taking our survey support newborn screening for late onset disorders with onset of symptoms throughout the child’s life. They also want the public health system to remind them about follow-up for their child detected with a late onset disorder. The preferred method of contact is by e-mail or mailing.

**Presenter:** Sylvia Mann, Project Director, Western States Genetic Services Collaborative, Hawaii Department of Health, Honolulu, HI, Phone: 808.733.9063, Email: sylvia@hawaiigenetics.org

**Redefining Public Engagement in Newborn Screening and its Impact on Education and Policy**

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Effective parental education and public engagement are essential components of efforts to increase understanding of newborn screening goals and to maintain trust in the public health system. The Newborn Screening Clearinghouse, which was launched in 2011 as Baby’s First Test (www.BabysFirstTest.org), is dedicated to working with the newborn screening community to support these efforts. Baby’s First Test provides healthcare professionals and new and expecting parents, who remain relatively unaware of the newborn screening system, access to reliable information and resources on newborn screening policies and procedures. With the addition of new conditions to State newborn screening panels and the introduction of new communication technologies since 2011, gaps in both education and in information and clinical services have illustrated the need for new and innovative approaches to newborn screening education and engagement. In response, the Clearinghouse launched
two new initiatives on BabysFirstTest.org: the Newborn Screening Public Square and Ask an Expert. The Newborn Screening Public Square is an online space where families, professionals, and advocates can engage in conversations and stories about newborn screening. The Public Square was designed to be more than just a forum – it was designed to share new ideas and knowledge, and bring together a range of communities and experiences within newborn screening to improve education and awareness. Ask an Expert is a tool designed for parents and the public to engage with experts and have their specific questions about newborn screening answered. In this session, Aaron Goldenberg, Director of Ethics, Policy and Practice for the Newborn Screening Clearinghouse, will discuss existing and new efforts aimed at promoting authentic public engagement around newborn screening. More specifically, he will detail the development of the Newborn Screening Public Square and Ask the Expert initiatives, including a review of the public squares hosted since August 2016 and an analysis of questions submitted by parents and the public. To date, the Ask the Expert tool has received over 100 questions from the public on various topics, including but not limited to: timing and access to newborn screening results, clinical follow up, research, and advocacy. These questions, along with dialogue in the public square, may help States and other organizations to refine their own educational efforts in ways that are responsive to current parental concerns. Therefore, Dr. Goldenberg will conclude by discussing how the results of these initiatives may impact the future of education, policy, and engagement efforts with the public on newborn screening.

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Session 8 – Parent/Patient Panel (No Abstracts)

Session 9 – Health Information Technology

Understanding an HL7 Implementation Guide – A Primer on IT Nerd-dom for Newborn Screening Nerds
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Background: Health information technology (HIT) continues to play a crucial role in improving newborn screening (NBS) processes. A key component of HIT is utilizing Health Level 7 (HL7) to send laboratory orders and test results between providers and the NBS laboratory. HL7 standards specifications are developed to be generic and adaptable, and therefore require an implementation guide (IG) to ensure conformity and that specified requirements are satisfied. However, knowledge gaps may exist among NBS management and informatics staff on how to utilize and apply an IG to fit specified needs of their state program.

Objective: To provide newborn screening management and informatics staff with a high-level understanding of the purpose, content, and applicability of an HL7 IG.

Methods: In 2016 and 2017, the NewSTEPs HL7 Taskforce updated the original Public Health Informatics Institute (PHII) Newborn Dried Blood Spot (NDBS) IG for laboratory orders and results to fit the wider ranging framework of the HL7 Laboratory Results Interface (LRI) and Laboratory Orders Interface (LOI). The Taskforce focused on developing an IG that provides an outline for message construction but allows
states flexibility to further constrain the IG to develop state specific guides that still adhere to the overall standard.

Results: The balloted HL7 NDBS IG for laboratory orders and results will be officially released for use by September 2017. As such, it is important that appropriate NBS staff understand how to apply this IG to fit their specific state needs in implementing electronic messaging. An HL7 message can be thought of as a package that has specifically designed and organized sets of compartments and sub-compartments. These compartments hold the data and information about the data that exchanging partners need to share in a very specific and standardized way. The HL7 NDBS IG sets ideal limits on the layout of the overall package, the configuration of the compartments, and the size, shape, and quantity of data that can be stored in each.

Conclusion: The successful development and use of an HL7 implementation guide requires a blend of expertise and understanding of Health Information Exchange and Newborn Screening Program nomenclature, practices, and standards. This presentation will discuss these attributes, provide examples specific to newborn screening, and present concepts regarding the approach informaticists and laboratory professionals might consider when developing a state specific implementation guide.

Presenter: Brendan Reilly, Program Specialist, Texas Department of State Health Services, Austin, TX, Email: brendan.reilly@dshs.texas.gov

Challenges and Benefits of Implementing Electronic Messaging in Newborn Screening Laboratories
A. Ragsdale and J. Thompson, Washington State Department of Health, Shoreline, WA

Background: Utilization of Health information Technology (HIT) to modernize the workflow of newborn screening (NBS) processes has been touted as a comprehensive solution for many challenges NBS programs face. One of these solutions is implementing electronic messaging for NBS orders and results using Health Level 7 (HL7) and Logical Observation Identifiers Names and Codes (LOINC). However, the transition to electronic messaging is complex, time consuming and is often a new and challenging process for NBS programs to understand.

Objective: To provide an overview of how electronic messaging can be implemented and beneficial for NBS programs, including laboratory workflows, dataflow, and system architecture, and to identify some of the challenges of implementation. Methods: The Washington State NBS program has successfully developed HL7 results messages, and has adopted Department of Health’s middleware and the State Health Information Exchange (HIE) as an efficient data exchange pathway for sending the messages. This success required the initial development of a process map encompassing system architecture, changes to laboratory workflows, and the design of data exchange pathways that posed several challenges requiring innovative solutions.

Results: NBS programs should customize electronic messaging specific to their program needs. There are several challenges to consider prior to implementation. Once such challenge is the substantial impact on the operation of the laboratory information system, by changing the way orders are placed and results are sent. In addition, developing data exchange pathways can become quite complex and may include a middleware program, an integration engine, a HIE, and/or direct connections between the lab and hospital. Other challenges include potential change to laboratory workflows, identifying internal support and expertise, and obtaining hospital buy-in. However, overcoming these challenges can lead to reducing the need for data entry staff, integrating results into the patient electronic medical record (eliminating transcription) and minimizing the necessity to print, fold and mail paper results (improving turnaround time).
**Conclusion:** Several HIT components have the capacity to greatly improve the NBS system, but perhaps none more so than electronic messaging. There are many ways to establish electronic messaging for NBS orders and results, but all will pose similar challenges. However, overcoming these challenges will not only benefit the implementing NBS program, but will also have a positive impact on the internal agency IT program, the hospital IT program, and ground level hospital staff.

**Presenter:** Ashleigh Ragsdale, MPH, QA and Development Supervisory, Newborn Screening Program, Washington State Department of Health, Shoreline, WA, Phone: 206.418.5534, Email: ashleigh.ragsdale@doh.wa.gov

**Baby’s First Message: Next Steps and Lessons Learned after Achieving Statewide Implementation of Electronic Demographics and Point-of-Care Result Reporting**

K. Houlihan, A. Gaviglio, H. Brand, J. Simonetti, J. Durbin and M. McCann, Minnesota Department of Health, St. Paul, MN

In early 2017, the Minnesota Department of Health Newborn Screening program achieved statewide implementation of MNScreen, a three prong IT solution based on using OZ Systems that allows for electronic receipt of newborn demographic information as well as Hearing Screening and Critical Congenital Heart Disease Point-of-Care screening results. As the implementation phase of the MNScreen project winds down, several new projects are being undertaken to improve and expand upon the existing infrastructure to enhance patient, provider, and program services. The first project seeks to further refine workflow improvements in order to enhance the end-user experience and our program’s ability to efficiently collect and analyze data.

To this end, the following will be presented:

- The importance of ongoing stakeholder engagement
- The ongoing need for monitoring of submissions and continuous improvement of processes.
- Improvements seen as a result of electronic reporting as well as limitations to HIT solutions
- The integration of clinical decision support tools for accurate CCHD screening

The second project is linking MNScreen with the Minnesota Newborn Screening program’s LIMS through an Internal Exchange Hub. This linkage will increase accuracy and timeliness of information and allow for less manual data entry both on the side of the submitter as well as by data entry staff in the program. Utilizing this linkage allows the facility and program to reduce manual entry fields from 28 to 7. The remaining 7 fields and various approaches for collecting this information as well as improvements in processing of specimens after this change will also be discussed. The movement towards electronic solutions for newborn screening present a multitude of opportunities and challenges. This presentation will serve as a guide for other states looking to implement electronic laboratory ordering and reporting.

**Presenter:** Amy Gaviglio, MS, CGC, Minnesota Department of Health, St. Paul, MN, Email: amy.gaviglio@state.mn.us
Session 10 – Molecular Technology in Newborn Screening

A Targeted Next Generation Sequencing (tNGS) Screening Assay for Menkes Disease and its Implications for Primary DNA-based Newborn Screening
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Problem/Objectives: With advances in genomic sequencing, early identification of infantile-onset inherited disorders that are clinically actionable is now feasible by DNA sequence analysis from dried blood spots (DBS). Menkes disease (MD) is a X-linked recessive disorder of copper metabolism with onset in early infancy (6-8 weeks postnatally) associated with high morbidity and mortality in the absence of early diagnosis and treatment. The impact of existing and emerging medical remedies for this illness would be enhanced by early detection via newborn screening (NBS); affected infants appear normal at birth and their brain degeneration is irreparable once begun. To date, it has not been possible to develop a biochemical screening assay for MD detection that is suitable for existing NBS platforms (e.g. tandem mass spectrometry).

Methods: We developed and validated a DBS-based targeted next generation sequencing (tNGS) method with rapid turnaround time for prompt, accurate identification of affected newborns with MD. We applied this method to characterize 24 blinded DBS specimens from apparently healthy control or MD subjects enrolled in a current clinical trial (ClinicalTrials.gov number, NCT0081785).

Results: Of the 23 samples from subjects with MD, 21 had previously characterized ATP7A variants that were correctly identified by our assay (100%). For samples from 2 MD subjects for which clinical sequencing had not previously revealed variants, a causative variant was identified in one. No pathogenic variants were identified in the one normal control sample.

Conclusions: Our results provide proof-of-principle that a tNGS algorithm can be applied to DBS samples with high sensitivity and specificity to detect ATP7A variants predictive for MD, a medically actionable disorder. Early detection by genomic screening in concert with advances in ATP7A gene therapy suggests the potential to transform the natural history of Menkes disease.

Presenter: Richard Parad, MD, MPH, Director of Neonatal Genomic Medicine Program, Brigham and Women’s Hospital, Connors Center for Women, Boston, MA, Phone: 617.732.7371, Email: rparad@partners.org

Design and Validation of a 2nd Tier Next Generation Sequencing (NGS) Panel for Newborn Screening for Severe Combined Immunodeficiency Disease

Background: Newborn screening (NBS) for severe combined immunodeficiency disease (SCID) is performed by quantification of T-cell receptor excision circles (TRECs). Although the sensitivity of the assay for detection of immune deficiencies is high, it does not provide information on the underlying genetic etiology, potentially delaying initiation of optimal treatment.

Objective: We sought to design and validate a multi-gene NGS panel for two different platforms and assess them for ease of use, turn-around time, and accuracy. We also aim to determine if
implementation of such a panel in the NBS setting could improve patient outcomes for infants who screen positive for SCID by the TREC assay.

**Methods:** TruSeq Custom Amplicon (TSCA) and AmpliSeq (AS) panels targeting 39 immunodeficiency associated genes were designed. DNA extracted from a single 3-mm dried blood spot was used to prepare both TSCA and AS libraries. Twenty samples with a positive screen for the TREC assay were included. Samples were multiplexed and TSCA libraries were run on an Illumina MiSeq instrument and AS libraries were run on an Ion Torrent Personal Genome Machine (PGM). Sensitivity and precision was assessed using published high confidence genotypes derived from HapMap sample NA12878 (“Genome in a Bottle” 3.3.2). Receiver operating characteristic curves (ROCs) were used to determine thresholds to effectively filter out false-positive calls, while retaining true-positives. Complete Sanger sequencing for the 39 genes was performed for eight samples, and confirmation of reportable variants was performed for the remaining 12 samples.

**Results:** A read depth of 30X or greater was obtained for 90.3±3.4% (81.1% - 93.0%) of targeted bases with TSCA and 90.8±2.8% (84.7% - 92.7%) of targeted bases with AS. Sensitivity and precision based on comparison to the publicly available sequence for NA12878 were 92.4% and 96.0% for TSCA and 94.1% and 87.7% for AS. Both panels identified the correct molecular diagnosis for 7/8 samples for which the genetic defect was known. We identified 106 and 161 regions with low coverage for the TSCA and AS panels, respectively, prompting us to request additional bioinformatic and wet-bench optimization.

**Conclusions:** Initial results for a second tier multi-gene NGS panel for SCID suggest that both platforms, Illumina MiSeq and Ion Torrent, are suitable for identification of the underlying molecular defect in infants screening positive by the first tier TREC assay. A consented study for infants referred for a positive SCID screen is underway. The goal is to determine the percentage of infants for whom a molecular diagnosis is obtained, and to assess whether identification of the underlying genetic defect early on improves patient outcomes.

**Presenter:** Colleen Stevens, PhD, Research Scientist, New York State Newborn Screening Program, New York State Department of Health, Wadsworth Center, Albany, NY, Phone: 518.473.6805, Email: colleen.stevens@health.ny.gov

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**Implementing Next Generation Sequencing as a Third-Tier Newborn Screen for Cystic Fibrosis in New York State**


The current newborn screening testing algorithm for cystic fibrosis (CF) in New York State (NYS) includes a first-tier screen for elevated immunoreactive trypsinogen (IRT; top 5%) followed by a second-tier DNA test (Luminex) consisting of a panel of 39 of more than 1,900 known mutations in the CFTR gene. NYS refers all babies with at least one mutation or a very high IRT (VHIRT; highest 0.1%) in the absence of mutations to CF specialty care centers for confirmatory diagnostic testing. We hypothesized that a more comprehensive mutation panel would allow us to refer only infants with two CFTR mutations. We validated use of DNA extracted from dried blood spots with the Illumina MiSeqDx CF Clinical Sequencing Assay (CSA). A pilot study to prospectively assess the feasibility of implementing next generation sequencing as a third-tier CF screen in NYS is underway. Infants with one Luminex panel mutation, or no mutations and VHIRT were blinded and comprehensively tested for mutations using the CSA. We had previously identified mutations not detected by the CSA, and developed a panel of supplemental assays to test for common deletions and/or duplications determined to be most relevant to the NYS population, to be run concurrently with the CSA. From January 23, 2017 – March 16, 2017, 33,733
infants were screened for CF using the first-tier IRT test and 1,903 infants screened positive, requiring the second-tier DNA test. 106 infants were referred for follow-up testing using the current algorithm. DNA from 103 of 106 with fewer than two Luminex mutations were anonymized and reflexed for third-tier analysis. Seven different pathogenic/likely pathogenic, 18 different variants of uncertain significance (VOUS) and 14 different benign/likely benign variants not on the Luminex panel were identified. Had third-tier testing been utilized, 20 (18.9%) infants would have been referred, and 86 (81.1%) would have screened negative. The average turnaround time (TAT) for completing the third-tier was five days, increasing the overall average TAT to eight days for samples requiring third-tier analysis (~870/year). The addition of the CSA and deletion/duplication analysis as a third-tier screen for CF would increase the positive predictive value by decreasing the false positive referral rate in NYS by 81.1%. Though the cost and TAT would increase, the reduction in false positive referrals would reduce health care costs and parent anxiety.

**Presenter:** Denise Kay, PhD, Research Scientist, New York State Department of Health, Wadsworth Center, Albany, NY, Email: denise.kay@health.ny.gov

### Challenges of Severe Combined Immunodeficiency Screening in a Two Screen State

**A. Coleman, Maryland Newborn Screening, Baltimore, MD**

**Background:** The State of Maryland began screening all babies for Severe Combined Immunodeficiency (SCID) on April 1, 2016. All truly new endeavors bring unexpected difficulties, but we were unprepared for the quantity and scope of the hurdles we faced, as our findings were not predicted by the current literature.

**Results:** We will present our experience and summary data from our first year of SCID screening using the in situ TREC assay developed at the Centers for Disease Control and Prevention. Maryland is a two screen state, and in screening all specimens we found previously unreported data trends. Though taken from the same babies, only weeks apart, we found significant differences between the performances of the first and second specimens in the TREC assay. These results were unexpected, as they did not match the changes in circulating T cell counts that have been previously observed by flow cytometry. Our preliminary screening algorithm was updated to account for these differences. More perplexing still, we then found that even the observed differences themselves were in flux, causing seasonal variations that challenged our new cutoffs and required an overhaul of our screening algorithm.

**Conclusion:** These previously unreported trends in the data contributed to a tumultuous but successful first year of screening, and our hope is that our observations and experience can help other organizations better understand and improve their SCID screening algorithms.

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Newborn Screening for Spinal Muscular Atrophy: Current and Alternative Assay Methods

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Type 1 or infantile-onset spinal muscular atrophy (SMA) is a genetic disease that causes progressive degeneration of motor function and a high mortality rate among children ages 2 and younger. In December of 2016, an anti-sense oligonucleotide (ASO) therapeutic was approved by the FDA to treat SMA. Although a clinical trial of the ASO therapeutic in pre-symptomatic infants is still ongoing, early detection and pre-symptomatic treatment is expected to provide even greater benefit because of the rapid and irreversible loss of motor neurons in symptomatic children. Newborn screening for SMA could therefore become very important in preventing the death and disability caused by Type 1 SMA. Fortunately, the genetic cause for most cases of SMA has been well characterized and several different tests to identify these genetic variants have been developed. The majority of SMA cases are caused by a homozygous deletion or gene conversion of the SMN1 gene, which results in a deficiency of the SMN (survival of motor neuron) protein. The paralogous SMN2 gene also produces a small amount of SMN protein and, depending on genomic copy number, can partially compensate for the loss of SMN that would otherwise cause Type 1 SMA. SMN1 and SMN2 differ by only 4 nucleotides in the region of the SMA-causing mutation (exon 7, intron 7, and exon 8). While having this “backup” gene is critically important from a clinical perspective, it can complicate molecular screening tests for SMA since special care must be taken to avoid misidentifying SMN2 amplification in assays designed to detect SMN1 genomic loss. This issue can be largely overcome in real-time PCR by the use of SMN1 sequence specific probes containing locked nucleic acids (LNA) nucleotides, which can differentiate single nucleotide mismatches between the two genes. In addition, background amplification from SMN2 can be reduced further by utilizing an LNA primer that will preferentially anneal and amplify from SMN1 sequence and discriminate against SMN2. For newborn screening of SMA, test specificity and sensitivity have to be the primary considerations when choosing the most appropriate assay method. In addition to providing a summary of existing methods to screen for SMA, we present data generated from the use of a new method that incorporates both an LNA probe and an LNA primer in a real-time PCR assay. It can be multiplexed into the current TREC assay for SCID for minimal additional cost. We also address the importance of using a method to identify the loss of SMN1 sequence at exon 7 rather than intron 7 to reduce the likelihood of a false positive or false negative result in the presence of an SMN1/SMN2 hybrid gene. We will compare results from two methods and discuss the benefits and drawbacks of using either approach in a newborn screening assay.

Presenter: Kristina Mercer, MPH, PhD, ORISE Postdoctoral Fellow, Centers for Disease Control and Prevention, Newborn Screening, Atlanta, GA, Phone: 404.498.0866, Email: kmercer@cdc.gov

Evaluation of Multiplexing Spinal Muscular Atrophy Identification with a Laboratory Developed Severe Combined Immunodeficiency Assay in Minnesota

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Objective: To evaluate and validate the addition of spinal muscular atrophy (SMA) to the laboratory developed severe combined immunodeficiency (SCID) assay currently being run in Minnesota.
**Background:** Spinal muscular atrophy (SMA) is considered the most common lethal autosomal recessive genetic disorder in infants. It is a motor neuron condition caused by the deletion or conversion of the SMN1 gene resulting in severe and progressive neuromuscular degeneration. Approximately 1:6000 to 1:10000 individuals are affected with SMA and 1:40 are carriers. On December 2016, for the first time, the FDA approved a treatment option for therapy for SMA. To achieve optimal outcomes, medical interventions should start soon after birth before symptoms develop, making SMA a good candidate for newborn screening.

**Methods:** The SMA assay developed at the CDC’s Newborn Screening & Molecular Biology Branch was transferred to the Minnesota Newborn Screening Program. This assay uses a SMN1 Taqman probe based on the novel locked nucleic acid (LNA) technology, and has been proven to yield good results when multiplexed with laboratory developed SCID real-time PCR assay. Minnesota has been screening for SCID since January 2013. T-cell receptor excision circles (TREC) and RNaseP are multiplexed in the current SCID assay. Changes to the SCID assay would include the addition of the SMN1 Taqman probe and primers in the master mix solution and an increase in the annealing temperature of the reaction. The assay will be run using a real time quantitative PCR instrument (ViiA). The CDC has provided blood spots derived from SMA patient cell lines for validation.

**Results and Conclusions:** Preliminary data suggests that the SMN1 Taqman probe and primers can be added to the current SCID assay with minimal changes. A full validation of the combined SCID–SMA assay will be completed. By multiplexing this assay, cost is greatly minimized with no additional laboratory scientists needed to run the assay. SMA is likely the next candidate for consideration by the Advisory Committee on Heritable Disorders in Newborns and Children for the national recommended universal screening panel. In the future, SMA screening will be reviewed by the Minnesota Advisory Committee on Heritable and Congenital Disorders for recommendation of inclusion to the Minnesota newborn screening panel.

**Presenter:** Carrie Wolf, MBS, Minnesota Department of Health, Saint Paul, MN, Email: carrie.wolf@state.mn.us

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**Spinal Muscular Atrophy Screening in New York State: Feasibility and Prospective Pilot Study**

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**Background:** Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease. Predominant features include severe and progressive muscle weakness and atrophy, resulting from lower motor neuron degeneration. SMA is the most common genetic cause of death in infancy, with an estimated incidence of 1 in 5,000 to 1 in 11,000 live births. Approximately 95% of SMA results from homozygous deletion of exon 7 of the survival of motor neuron 1 (SMN1) gene. In 2008, the Health and Human Services Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) declined to review a proposal to add SMA to the Recommended Uniform Screening Panel (RUSP), citing a lack of effective treatment and an absence of pilot studies demonstrating feasibility of newborn screening (NBS) for SMA by a public health lab.

**Methods:** Using severe combined immunodeficiency (SCID) screening as a model for conditions lacking a biochemical biomarker, we validated a real-time qPCR assay for detection of the recurrent SMN1 exon 7
The assay was optimized to detect both homozygous and heterozygous deletions. The validation study included positive controls with known SMN1/SMN2 genotypes and >4,000 de-identified dried blood spots (DBS). A prospective pilot study using an opt-in model for SMA screening began at three New York Presbyterian hospitals in January, 2016.

**Results:** The SMN1 assay is sensitive, specific and robust. Lab turnaround time is within recommended federal guidelines. During the first year of the pilot study, 3,826 infants were screened for SMA. Fifty-nine carriers were detected and reported, corresponding to a carrier frequency of 1.5% or 1 in 65, which is similar to published estimates. One infant with a homozygous SMN1 deletion was referred for clinical evaluation and confirmatory testing. This infant is predicted to have severe, type I SMA with two copies of SMN2.

**Conclusions:** We have validated a robust molecular assay for SMA, demonstrated feasibility of screening in the NBS setting, and are in the midst of a prospective pilot study. These data, coupled with the FDA approval of Spinraza (nusinersen)™ in late 2016 suggests that SMA should be reconsidered for addition to the RUSP. With a birth rate of 250,000, each year, approximately 25-40 New York State infants with SMA remain undiagnosed until symptomatic. NBS for SMA will facilitate identification of pre-symptomatic infants, for early initiation of therapy, when it may be most beneficial.

**Presenter:** Denise Kay, PhD, Research Scientist, New York State Department of Health, Wadsworth Center, Albany, NY, Email: denise.kay@health.ny.gov

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**Clinical Challenges of Providing Nusinersen for Spinal Muscular Atrophy and the Implications for Newborn Screening**

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Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by degeneration of motor neurons in the spinal cord leading to profound muscle weakness and atrophy. The recent FDA approval of a novel antisense oligonucleotide for SMA treatment, nusinersen (SPINRAZA™) has generated excitement because clinical trials show dramatic improvements in strength and function in those with the most common and severe form of SMA. The treatment should be initiated early in the course of disease, suggesting that SMA newborn screening could significantly improve outcomes. Yet nusinersen is very expensive, needs to be administered intrathecally several times per year, and requires specialized medical resources to administer safely. These health care burdens need to be considered if this disorder is to be recommended for widespread newborn screening (NBS). We present the experience of one medical center that was the first in their region to provide and administer nusinersen to SMA patients. Soon after FDA approval in late December, frequent discussions took place between many levels of hospital administration, finance, and numerous clinical departments and programs including Neurology, Pharmacy, Orthopedics, Radiology, Anesthesiology and Pediatric Critical Care. As a treatment program, nusinersen administration for SMA is complicated by the variability in weakness, respiratory compromise, scoliosis, limb contractures, and prior spine instrumentation seen in current SMA patients. Conversations with other neuromuscular programs nationally show that the issues encountered in this single center are similar to those seen across the United States. Nusinersen is an exciting treatment for SMA that profoundly alters the disease course when initiated early. The value of NBS in this disorder seems clear, but the high cost of the drug and the need for specialized medical services to provide intrathecal administration will need to be considered.

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