Newborn Screening Translation Research Network (NBSTRN): Recent Publications
Utilization of the Newborn Screening Translational Research Network to Advance Research and Clinical Applications in Lysosomal Storage Disorders

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Newborn screening programs in all U.S. states and territories screen over four million infants each year for at least thirty heritable disorders with the goal of early detection and treatment to reduce morbidity and mortality. The decision to add new disorders to screening programs occurs on a state-by-state basis and is based on several factors including an improved understanding of the disorder, the development of novel technologies to screen for the disorder and new therapeutic strategies for treatment. Expanded screening may also be the result of advocacy, legislation or recommendation by local, state and federal advisory boards. The Secretary’s Advisory Committee on Heritable Conditions in Newborns and Children (SACHDNC) advises the Secretary of Health and Human Services on a broad range of issues including newborn screening, and in 2007 SACHDNC established a system for nomination, external evidence-based review and recommendation/rejection of nominated disorders for screening in the newborn period. Successful implementation of screening for new disorders requires system-wide changes and encompasses not only screening but the diagnosis, short- and long-term follow-up of screen positive infants and, ideally, should advance understanding of the disorder and track patient outcomes based on early diagnosis and treatment. To support this systems approach and facilitate the translation of new technologies and treatments while fostering research, the Eunice Kennedy Shriver National Institute on Child Health and Human Development, National Institutes of Health established the Newborn Screening Translational Research Network (NBSTRN). NBSTRN work focuses on creating content and infrastructure, and establishes an analytical, clinical and research framework for use by the research, clinical and public health care communities. We present an overview of the NBSTRN and demonstrate its tools and resources as they are applied to advance newborn screening and research for a new group of conditions, lysosomal storage disorders (LSDs). Recent advances in the detection and treatment of some LSDs as well as legislative actions have led several state-based public health programs to begin screening for LSDs. The implementation of newborn screening for these six LSDs (Gaucher, Pompe, Mucopolysaccharidoses I/II, Fabry and Krabbe disease) provides a useful test case for the NBSTRN. The NBSTRN is involved in coordinating comparative evaluation of technologies for screening for LSDs and the development of diagnostic.
Planning for long-term follow-up data collection after newborn screening to advance research and improve service delivery and health outcomes

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Background: Newborn screening as a public health imperative has emerged over the last half-century. With the advent of tandem mass spectrometry, a need for a uniform panel for screening was defined and adopted. However, despite this major achievement, plans are lacking for long-term care and treatment strategies for the individually rare conditions detected by screening. In many cases, disorders are sufficiently rare that only national or international data will yield sufficient numbers to determine patient outcomes, quality of service delivery, appropriate practices and interventions, and deployment of direct care and resources. Only this ascertainment will identify populations robust enough for research trials needed to generate novel treatments. To provide the clinical history that will be necessary for translational research and program improvements leading to improving health outcomes, a uniform minimum data set with accompanying information collection, management and analysis tools is needed.

Methods: A broadly constituted workgroup comprised of content experts from laboratory-based specialties, departments of health, and clinical activities was convened under the aegis of the Joint Committee, described above. A series of national meetings was held to define a
uniform data set common to all screened conditions, and additional meetings were held with content experts to define condition-specific collection elements.

Results: A uniform minimum data set that comprises approximately 80% of desired immediate and longitudinal data collection elements in common across all screened disorders has been defined by consensus among the stakeholders represented in the Joint Committee. Additional workgroups to define condition-specific elements for metabolic conditions, endocrine conditions, and hemoglobinopathies detected by newborn screening have undertaken definition of condition-specific elements for initial encounter and follow-up measures for each screened condition. In addition, new groups have been convened to define elements for follow-up of lysosomal storage diseases, severe combined immunodeficiency, hearing loss, and cystic fibrosis.

Conclusions: A national community of specialty providers residing in public health, clinical centers and academic research centers can reach consensus regarding priorities for data collection for long-term follow-up. This effort lays an effective foundation for a uniform minimum consensus data set to ascertain the natural history of screened disorders and for both public health-related and research-related activities.

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Translational Research in Newborn Screening: Development of a Tool for the Clinical Validation of Severe Combined Immune Deficiency (SCID) Newborn Screening

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Background: A system of nomination and evidence review has resulted in the adoption of a uniform newborn screening panel of thirty-one core and twenty-six secondary conditions. The majority of these disorders are inborn errors in metabolism and tandem mass spectrometry is most often used to screen for these disorders. To enable and facilitate the clinical validation of cutoff target ranges for these metabolic disorders by tandem mass spectrometry, a web-based application for the collection and reporting of analytical results has been developed and widely adopted into the routine practice of newborn screening laboratories worldwide. This suite of information tools aggregates technical and clinical data enabling real time technology development and quality improvement. The use of these tools for pilots of new technologies which screen for disorders that are not yet part of newborn screening panels may be useful for analytical and clinical validation studies.

Methods: A new module of the laboratory performance tool was developed in conjunction with a four-state pilot of newborn screening for Severe Combined Immune Deficiency (SCID). The SCID pilot assessed screening technologies for SCID, established confirmatory tests and procedures for presumed positive cases and created follow-up and treatment strategies for cases. The SCID screening test detects the presence of a by-product obtained during the development of an important part of a functioning immune system, the T cell. Patients with SCID have few or no T cells and the absence of this by-product, T-cell receptor excision circles (TRECs), identifies SCID regardless of the underlying genetic defect or DNA variation. The TREC test utilizes molecular methods to count the number of TRECs present in DNA obtained from dried blood spots. The SCID module includes technology details, assay controls, assay results, confirmatory diagnosis and participating laboratory details.

Results: As of December 8, 2011, three programs have entered a total of 480 data points, 28 analyte results of true positive cases with 8 conditions. The aggregation and analysis of data led to revised diagnosis categories and is expected to provide estimates of disease prevalence. The SCID module is available for use by interested stakeholders and provides a transparent process for clinical validation of new screening technologies.

Conclusions: The laboratory performance tool was successfully adapted to capture data related to the analytical and clinical validation of the TREC assay during a pilot of SCID newborn screening. This is a useful model for future investigations of new technologies and conditions.
Translational Research in Newborn Screening: Development of a Consensus Data Set for the Long-Term Follow-Up of Patients

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Background: The goal of newborn screening is the early identification, diagnosis and treatment of disease to improve health outcomes for affected infants. Once they are diagnosed, infants are followed by specialists for disease care and management throughout their lifespans, and a rich clinical history of observations, assessments and measurements is created for each individual. The information in patient records can be collected and harvested in a systematic way to better understand the natural history of newborn screen conditions, and new findings translated back into clinical practice and basic research. The interaction of clinical care and basic research to facilitate translational science is especially important as novel technologies and treatments emerge for conditions not yet part of newborn screening. To enable this collection and analysis of large, statistically robust data sets across the diversity of clinical practice and specialties a consensus data set with accompanying tools is needed.

Methods: A broadly constituted workgroup comprised of content experts was convened under the aegis of the Joint Committee, described above. The Joint Committee worked to define common and disease specific data elements for the thirty-one core and twenty-six secondary conditions on the Recommended Uniform Panel (RUSP). The Newborn Screening Translational Research Network (NBSTRN) defined additional disease specific data elements for conditions that are part of pilot projects.

Results: A consensus common data set of approximately 130 elements for use across all disorders, and individual disease specific data sets with a range between 30 and 200 individual elements were drafted. A data dictionary for all elements was generated and efforts to create standardized language for the data elements and a data capture tool are beginning.

Conclusions: The development of a consensus data set for the long-term follow-up of newborns facilitates the translation of new discoveries into clinical practice to improve health outcomes and further scientific understanding. The use of this approach in pilot studies serves a model for future initiatives as genomic technologies begin to be applied to disease screening and management across the lifespan.
Translational Research in Newborn Screening: Development of a Virtual Repository of Residual Dried Blood Spots

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Background: Samples collected within the first hours of birth for use in screening newborns for disease are a valuable resource with many uses including basic and translational research, clinical care, and programmatic improvements. The retention of and guidelines for usage of these residual samples outside of newborn screening vary by State and program. A tool to navigate this patchwork of policies and practices, and to identify populations of interest for research is needed.

Methods: A secure, centralized, web-based catalog of possibly available newborn screening samples was developed and is called the Virtual Repository of Dried Blood Spots (VRDBS). This catalog contains information about the stored samples in participating states and allows researchers to identify populations of interest and contact information for pursuing research with the samples. A four-state pilot of the VRDBS is in progress and the results will be described.

Results: The VRDBS lists information on all State programs and provides descriptions of key factors for each residual newborn sample. The data elements include birth year, birth weight, gender, sample storage conditions, age at collection, diagnosed condition and nutrition/feeding status at time of screening.

Conclusions: The development of a virtual repository of residual dried blood spots has been successfully piloted in four states. Future efforts will focus on additional state involvement and marketing of the resource to researchers and other key stakeholders.