Received: 8 September 2022 | Accepted: 12 September 2022

DOI: 10.1002/ajmg.c.32007

COMMENTARY

AMERICAN JOURNAL OF medical genetics PART C Seminars in Medical Genetics WILEY

Special issue: Newborn screening research

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Funding information
Eunice Kennedy Shriver National Institute of Child Health and Human Development

Abstract

This Special Issue provides a wide-ranging update from the front lines of newborn screening (NBS) research and is the result of conversations and collaborations facilitated by the Newborn Screening Translational Research Network (NBSTRN) across the NBS community and their extended networks. For 14 years NBSTRN has accelerated research efforts to advance NBS by creating a research infrastructure available to the NBS community to discover novel technologies to screen, diagnose, and treat newborns.Authors in this Special issues share their innovative and impactful efforts to advance NBS to include additional conditions, populations, genomics, and information sharing.

1 | INTRODUCTION

The 200th anniversary of the birth of the "father of modern genetics," Gregor Mendel, affords us the opportunity to consider how advancements in genetics and genomics have led to almost every newborn in the United States (U.S.) receiving screening. Today, we use our knowledge of genetics to inform the screening and guide the care of an estimated 12,500 newborns each year who are born with a rare genetic disease. We are also on the cusp of realizing the promise of using genomics to not only screen, but to diagnose, treat, and manage an ever-increasing list of diseases. Today molecularly designed therapies are revolutionizing care and incrementally, and in some cases, dramatically improving health outcomes in conditions like cystic fibrosis and spinal muscular atrophy. In this era of gene-targeted therapies and presymptomatic diagnosis, newborn screening (NBS) has emerged as a potential mechanism to screen, diagnose and treat all of the estimated 7,000 genetic conditions. These rapid advancements in genomic technologies to detect and treat disease within the newborn period have led to a number of research and public health initiatives.

Neonatal screening of ~4 million newborns each year in the U.S. leads to the diagnosis of over 12,500 infants with genetic conditions that require referral to clinical care and, in most cases, lifelong management. This unselected cohort of newborns reflects the racial, geographic, economic, and education diversity of our nation. Newborns may be the perfect cohort to help advance disease understanding, because although every newborn receives essentially the same screen, other factors, including treatment choice and the course of disease, vary. In addition, many of the screened conditions have comorbidities, including intellectual disabilities, and these children receive a variety of interventions that can be tracked and analyzed to identify critical periods of development and intervention. Because the NBS system in the U.S. effectively screens over 99% of newborns, it has the potential to provide a unique platform for understanding rare diseases and lifelong outcomes. In fact, the process of neonatal screening followed by a coordinated transition to clinical care facilitates the collection of health information beginning just hours after birth. And because the majority of NBS conditions require life-long care and management, we have the opportunity to conduct prospective, longitudinal natural history studies on a population basis with unbiased ascertainment. For six decades, NBS has saved countless lives through early identification and treatment. While groundbreaking investigations by researchers have delivered new technologies, including informatics and information exchange, that enable the early detection and treatment of disease in newborns, NBS is a diverse community that includes researchers, healthcare professionals, families, advocacy groups, and state NBS programs working together to use genetics and genomics to save and improve lives.

The Hunter Kelly Newborn Screening Program at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports research in NBS. A key component of these

efforts is the Newborn Screening Translational Research Network (NBSTRN), led for 15 years by the American College of Medical Genetics and Genomics. NBSTRN accelerates efforts to advance NBS by creating a research infrastructure that fosters collaborations and information sharing across the NBS community. Over the last decade, NBSTRN has developed data tools to support several landmark research projects. NBSTRN data tools are designed to help plan research studies, facilitate efforts, accelerate discoveries, and foster collaborations with key stakeholders and partners. Let us take a detailed look at some of the key aspects. As NBS in the U.S. marks its 60th anniversary this year, the goal of this special issue is to provide readers with an informative tour of innovative efforts across the NBS community.

2 | NICHD HUNTER KELLY NEWBORN SCREENING RESEARCH PROGRAM

NBS research is an important program of the *Eunice Kennedy Shriver* NICHD Hunter Kelly Newborn Screening Research Program. The first article of the issue, "Newborn Screening Research Sponsored by the NIH: From Diagnostic Paradigms to Precision," written by Dr. Melissa Parisi and Dr. Mollie Minear, describes NICHD efforts to foster the development of novel technologies, treatments, and interventions through the development of resources, tools, and expertise.

3 | FAMILIES AND ADVOCACY GROUPS

Parents, families, and advocacy groups play important roles in advancing NBS research. The first article in the issue, "Why Must the Debate Continue on Krabbe Disease Newborn Screening?" from Stacy Pike-Langenfeld, Executive Director of the Legacy of Angels Foundation, highlights the important role families play in communicating the benefit of early diagnosis and treatment from NBS. Dr. Matthew Ellinwood's article adds the perspective of an advocacy group to establish the evidence-base for NBS with "Newborn Screening and the Recommended Uniform Screening Panel: Optimal Submissions and Suggested Improvements based on an Advocacy Organization's Decade-Long Experience." The involvement of families and clinicians is key to advancing NBS research. To illustrate this point, the patient advocacy group, Parent Project Muscular Dystrophy, presents two studies, "Duchenne expert physician perspectives on Duchenne newborn screening and early Duchenne care" and "Diagnostic experiences of Duchenne families and their preferences for newborn screening: A mixed-methods study" detailing the experiences from families and physicians on Duchenne NBS.

4 | NBS PILOT STUDIES

NBS is often referred to as the "PKU test" because it began with screening for a single condition, phenylketonuria. The expansion of NBS to include additional conditions is based on evidence for a net benefit of early identification and treatment and requires the discovery of novel technologies to screen in the neonatal period. The introduction of novel screening technologies into NBS requires pilots to determine the detection rate, positive predictive value, clinical validity, and false-positive rate. These factors demonstrate the feasibility and benefit of screening and establish an evidence-base. The generation of this evidence is usually in the form of prospective studies, called pilots, and the goal is to identify at least one case in an unselected population. NICHD established a pool of states to pilot conditions that are part of, or candidates for, the Recommended Uniform Screening Panel, and since 2015 has funded pilots of 10 conditions that have screened over 550,000 newborns. The next two articles highlight one of these states, Georgia. In the first article, "Proximal Urea Cycle Defects Are Challenging to Detect with Newborn Screening: Results of a Prospective Pilot Study Using Post-Analytical Tools," Dr. Patricia Hall describes efforts to improve screening for proximal urea cycle disorders. The second article, "Georgia State Spinal Muscular Atrophy (SMA) newborn screening experience: screening assay performance and early clinical outcomes," shares details on the screening, diagnosis, and treatment during a 2-year pilot. In "Newborn Screening for Duchenne Muscular Dystrophy-Early Detection and Diagnostic Algorithm for Female Carriers of Duchenne Muscular Dystrophy," Dr. Dorota Gruber outlines an approach to the identification of female carriers and subsequent cascade testing of family members in a 2-year pilot of an X-linked disorder.

5 | LONG-TERM FOLLOW-UP

The longitudinal follow-up of newborns identified with a condition through NBS not only provides evidence of the benefit of NBS, but also has the potential to advance disease understanding. In the article "Newborn screening for Fabry Disease in Oregon: Approaching the iceberg of A143T and variants of uncertain significance" from Sarah Viall, describes a larger than expected number of cases and highlights the challenge of a missense variant in the galactosidase alpha gene.

6 | NBS EXPANSION

Discoveries and innovations lead to an increase in the number of conditions that benefit from NBS. Up to 81 conditions are screened in the U.S., and Melis Yilmaz reports on an effort to expand screening for Severe Combined Immune Deficiency to include screening for Warts, Hypogammaglobulinemia, Infections, Myelokathexis (WHIM) syndrome in "Can we identify WHIM in infancy?". In "Newborn Screening for Neurodevelopmental Diseases: Are We There Yet?", Dr. Wendy Chung outlines a framework for piloting NBS for neurodevelopmental disorders that includes the key technical, practical, and ethical considerations and challenges. Researchers are working to identify NBS conditions during pregnancy, and in "Prenatal phenotyping: a community effort to enhance the Human Phenotype Ontology,"

Ferdinand Dhombes provides guidelines for using Human Phenotype Ontology for prenatal phenotyping. The advancement of sequencing technology and the drop in the cost of sequencing has paved the road to use genome sequencing to advance genomic medicine within NBS. In "Beginning BeginNGS: Rapid newborn genome sequencing to end the diagnostic and therapeutic odyssey" Dr. Stephen Kingsmore proposes the Begin NBS which stands for BeginNGS™ (Newborn Genomic Sequencing to end the diagnostic and therapeutic odyssey), a new international, precompetitive, public–private consortium that proposes to implement a self-learning healthcare delivery system for screening all newborns for hundreds of genetic diseases by rWGS, diagnostic confirmation, implementation of effective treatment, and acceleration of drug development worldwide. NBSTRN is a partner in these efforts where data tools such as Longitudinal Pediatric Data Resource and Ethical, Legal, and Social Implications (ELSI) Advantage will assist in data repository and exploration of ELSI of genomic sequencing in newborns.

7 | ENGAGING THE NETWORK OF KEY STAKEHOLDERS

This Special Issue provides a wide-ranging update from the front lines of NBS research and is the result of conversations and collaborations across the NBS community and their extended networks. NBSTRN hosts regular events and forums to provide a platform for NBS researchers to learn from each other, communicate new findings and build new partners between academia, researchers, clinicians, health systems, industry, non-profit, and advocacy organization. Through these discussions, NBSTRN has focused its effort in creating tools, databases, forums, and resources to help advance NBS research, which is available at www.nbstrn.org. NBSTRN can help researchers build new connections and strengthen partnerships across government, academia, clinical care, public health, and industry; support collection, analysis, storage, and sharing of phenotypic and genomic data; guide NBS research studies and pilot studies; and support the validation of new technologies and treatments for NBS. The research community has an unprecedented opportunity to realize the promise of Mendel's discoveries in genetics by developing genomic technologies available to every newborn.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: Brower, A., & Chan, K. (2022). Special issue: Newborn screening research. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, *190*C: 135–137. https://doi.org/10.1002/ajmg.c.32007