

PIONEERING THE NEW ERA OF NEWBORN SCREENING

**Collaborative Insights and
Recommendations for
Modernizing NBS Systems**



Executive Summary

The newborn screening (NBS) system has grown from screening for a single disease in a few states to a system capable of screening every newborn in the United States for more than 60 genetic conditions. NBS has expanded over time due to discoveries of novel technologies and therapies to screen, diagnose, treat, and manage life-altering conditions, but the current system is unequipped to meet the demands that therapeutic advances offer newborns. While often considered one of the most successful public health programs in the country, in a 2021 RTI International survey of NBS experts, 100 percent of participants acknowledged that change, either small or large, was needed within the current NBS system. Modernization of the NBS system is necessary to ensure that newborns with treatable conditions can be identified and offered life-saving interventions at the earliest moment possible to optimize their health outcomes.

A group of more than 100 NBS stakeholders participated in the Newborn Screening Modernization Roundtable Series in 2022 with the goal of developing policy solutions to transform and optimize the existing NBS system. The Roundtable brought together a broad collection of NBS stakeholders including academic researchers, state public health officials, patient advocacy organizations, industry, and government officials to identify key priority areas and the actions needed to achieve those goals. Through small group discussions, targeted questions, and issue prioritization to facilitate consensus, the following policy priorities were identified:

1. Increase federal leadership, accountability, and transparency within federal newborn screening programs
2. Establish a regional lab network that provides state newborn screening programs with the opportunity to work together to ensure efficient and faster addition of newborn screening conditions
3. Increase access to population-level data both before and after newborn screening to facilitate the development and adoption of newborn screening conditions to federal and state panels
4. Integrate next-generation, evidence-based neonatal sequencing into newborn screening in a manner that can be broadly implemented in all state newborn screening programs

This first-of-its-kind initiative brought stakeholders together to develop actionable policy recommendations designed to achieve NBS modernization. Those actions will help transform the NBS system to remain one of the most successful public health programs.

Study Support Provided By:

American Society of Gene and Cell Therapy	PTC Therapeutics
Biomarin	Orchard Therapeutics
Expecting Health	Sarepta Therapeutics
NBSTRN, American College of Medical Genetics and Genomics	Sanofi
	Traverse Therapeutics

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Introduction

Newborn screening (NBS) is part of the early moments of life for the approximately four million babies born in the United States every year. Considered one of the most successful public health programs in the country, NBS has the unique ability to provide timely identification of serious health conditions early in a newborn's life, allowing for immediate, and often lifesaving diagnosis and treatment to begin. Approximately 1 in 300 newborns have a condition that can be diagnosed through NBS, and annually more than 12,000 infants receive life-altering treatment due to this public health program.¹

Current Challenges in Newborn Screening

Despite many successes within the NBS system, challenges remain within the program. The Recommended Uniform Screening Panel (RUSP) was created in 2009 to guide states on which conditions they should be screening for within their NBS program. Currently, the Advisory Committee for Heritable Disorders in Newborns and Children (ACHDNC), the Committee within the U.S. Department of Health and Human Services charged with overseeing and recommending NBS policies, is limited to conducting only two evidence reviews per year of conditions nominated for the RUSP.² In addition, once conditions are deemed eligible for addition to the RUSP, implementation of the condition to a state panel takes an average of an additional five to six years.³ These delays occur in large part because most state laboratories are struggling to keep up with the growing list of conditions on the RUSP due to insufficient funding and staffing shortages, as well as infrastructure challenges. This system is further complicated as the needs of any individual state laboratory are subject to that state's annual budget process, whose political nature and variability creates uncertainty for both the public health and patient communities.

States do receive guidance and limited financial support from the federal government including screening recommendations from the ACHDNC, quality assurance testing through the Centers for Disease Control and Prevention (CDC) Newborn Screening Quality Assurance Program (NSQAP), and grants from the Health Resources and Services Administration (HRSA) to assist states in adding new conditions and improving the existing programs. Currently, the federal government provides important resources such as the RUSP, CDC and HRSA grants, CDC and National Institutes of Health (NIH) data collection, and NIH research efforts. However, only a small percentage of the states are receiving federal support, with 13 percent of states utilizing Title V funding and only 2 percent of states reporting using federal funds in 2019.⁴

The ability to make changes to federal NBS programs has been stalled with the recent failure to pass federal legislation. The Newborn Screening Saves Lives Reauthorization Act is a federal bill that would reauthorize key NBS programs, expand and improve state grants providing for support, educational resources and follow-up services, ensure quality assurance for laboratories, and help to improve federal data collection to better understand best practices within NBS. Despite its importance, the bill remains stalled, failing to pass in the United States in the previous two Congressional sessions.

Additionally, recent decisions made by the ACHDNC against moving specific conditions through the RUSP nomination process have also stalled efforts to expand NBS at the state level.^{5,6} The Advisory Committee's initial decisions at the February 2023 ACHDNC meetings to not recommend Krabbe disease for addition to the RUSP and to not move Duchenne Muscular Dystrophy forward to full evidence review illuminated the changing landscape in how conditions are reviewed within newborn screening. Patient advocacy organizations often serve as the lead organizer and nominator for conditions nominated to the RUSP, spending many years and millions of dollars developing the infrastructure and evidence needed to support the addition of a new condition. Although votes to move Duchenne Muscular Dystrophy to evidence review and allow Krabbe Disease an expedited



NBS has the unique ability to provide timely identification of serious health conditions early in a newborn's life, allowing for immediate, and often lifesaving diagnosis and treatment to begin.

¹<https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6121a2.htm>

²<https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/meetings/condition-review-capacity.pdf>

³Kellar-Guenther, Yvonne, Sarah McKasson, Kshea Hale, Sikha Singh, Marci K. Sontag, and Jelili Ojodu. 2020. "Implementing Statewide Newborn Screening for New Disorders: U.S. Program Experiences" *International Journal of Neonatal Screening* 6, no. 2: 35. <https://doi.org/10.3390/ijns6020035>

⁴<https://www.newsteps.org/sites/default/files/resources/download/nbs-newsteps-2019-annual-report.pdf>

⁵<https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/resources/chair-letter-dmd-nominators.pdf>

⁶<https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/resources/chair-letterkrabbe-nominators.pdf>

review after re-submission were both welcomed votes at the August 2023 ACHDNC meetings, the positive update did not change how many within NBS view the current review process. The initial ACHDNC decisions left many patient advocacy communities feeling that the nomination process is untenable, and the criteria for condition evidence review ever-changing.

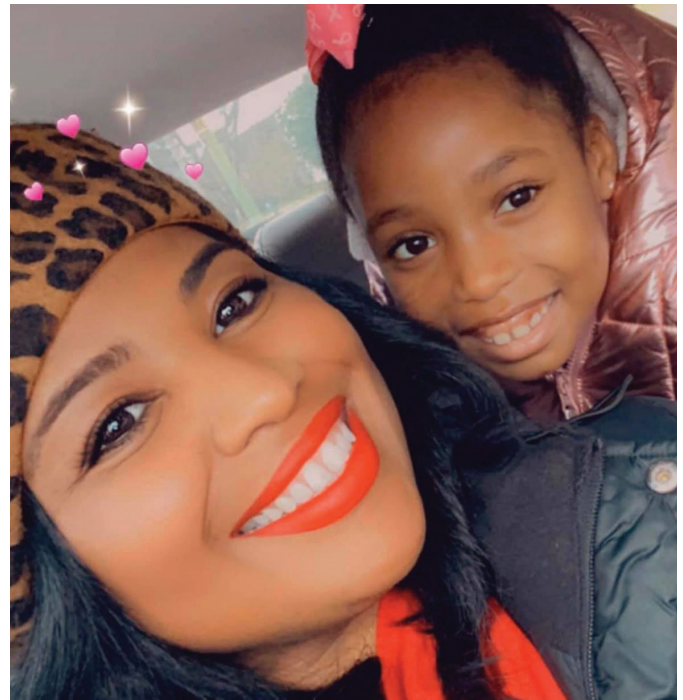
The current process for meeting the evidentiary requirements to be included on the RUSP is a long, arduous process. The evidentiary requirements should continue to remain high for addition to a review process that impacts a mandatory public program, but challenges surrounding that process must be addressed. This paper will focus on exploring solutions that address some of the issues the rare disease community identified to be of most critical urgency including the evidence review process, disparities across state lines, and challenges with implementing new screening methods. These are just a few of the challenges that the NBS program must address to ensure that it continues to be a successful public health program.

A Call for Continued Modernization of Newborn Screening

The challenges outlined above will continue to intensify as the progression of science results in the development of treatments and care standards for pediatric-onset conditions. Compared to the previous decade, the number of new drugs approved in the United States increased by 60 percent in the decade between 2010 and 2019.⁷ Additionally, the proportion of orphan designations for pediatric-onset diseases has increased in the most recent decade to 27 percent.⁸ The U.S. Food and Drug Administration (FDA) predicts that they will approve 10 to 20 cell and gene therapy products a year by 2025.⁹ Many of these developing therapies will allow new conditions to meet the current standards to be considered a good candidates for NBS.

In a 2021 RTI International survey of NBS experts, including patient advocates, state public health officials, and academia, on the amount of change needed to add 30 conditions within the next decade, nearly half answered a nine or ten on a 0-10 scale, with 10 representing extensive change throughout the system.¹⁰ In addition, 100 percent of participants acknowledged that change, either small or large, was needed within the current NBS system.¹¹

In multiple other studies, there has been consistent agreement within the NBS community that changes need to be made to address the current and future challenges within NBS.^{12,13,14} In 2022, NBS stakeholders convened with the goal of developing policy solutions to modernize the NBS system. This committee was comprised of leadership from the American Society of Gene & Cell Therapy (ASGCT), Newborn Screening Translational Research Network (NBSTRN), Baby's First Test, Every Life Foundation (ELF), Sanofi, Sarepta Therapeutics, BioMarin, Traverre Therapeutics, PTC Therapeutics, and Orchard Therapeutics. The committee convened three separate Roundtables that included 108 participants across the NBS ecosystem in 2022 designed to hear from NBS experts from diverse backgrounds to develop consensus around actionable policy solutions to move NBS forward to address current and future challenges.



In a recent survey of newborn screening experts, 100 percent of participants acknowledged at least small changes were needed within newborn screening.

⁷United States. Congressional Budget Office. United States, 2021. Web Archive. <https://www.cbo.gov/publication/57025>

⁸Miller, K.L., Fermaglich, L.J. & Maynard, J. Using four decades of FDA orphan drug designations to describe trends in rare disease drug development: substantial growth seen in development of drugs for rare oncologic, neurologic, and pediatric-onset diseases. *Orphanet J Rare Dis* 16, 265 (2021). <https://doi.org/10.1186/s13023-021-01901-6>

⁹FDA Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies. January 15, 2019. <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics>

¹⁰<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2787589>

¹¹Ibid

¹²<https://jamanetwork.com/journals/jama/article-abstract/2275452>

¹³<https://pubmed.ncbi.nlm.nih.gov/32115905/>

¹⁴<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2787589>

Methods

Each of the three Roundtables was conducted virtually and utilized breakout rooms to allow for smaller group discussions to focus on different themes or possible policy solutions. The series began with an open public forum held on June 6, 2022, to ensure that the identified policy solutions were representative of the diverse community that comprises the NBS system. The second and third Roundtables, held on June 9 and July 14, 2022, were smaller, invite-only events comprised of experts representing key stakeholder groups within the NBS ecosystem. The invited participants were selected due to their leadership within the following NBS community stakeholder groups: patient advocacy organization representatives, industry representatives, state and federal officials, NBS academic researchers, clinical health care providers, and policymakers. For additional information, please see the Methods Appendix.



3

Roundtables held



108

Attendees at public meeting



40+

Experts identified actionable policy solutions



4

Key themes identified

Four Themes for Policy Action



THEME 1: Increase federal leadership, accountability, and transparency within federal newborn screening programs

Federal Role within Newborn Screening

The NBS system currently relies on input from federal, state, and patient advocacy organizations to successfully operate. States make the final decisions on how best to run and fund NBS in their state to ensure that the program fits the unique needs of each state. Patient advocacy organizations often lead the development of the infrastructure for NBS and evidence development for a review package, which requires significant levels of funding for screen development and validation, longitudinal data collection, clinical care guidelines, educational materials for patients and providers, population-based pilot studies, and follow-up programs and services. The major connecting element between these two key players is the various federal agencies outlined in the introduction.

Federal agencies must significantly evolve to create increased transparency, accountability, and coordination across both state and federal NBS programs. To modernize NBS nationwide, there must be a combination of both shared responsibilities among agencies as well as a clear leader within government. While this paper is not proposing which agency, there was broad consensus that a single federal agency must take the lead on making the necessary changes within the federal government to ensure that the NBS moonshot so many are calling for can succeed. The current model of informal coordination results in needed changes falling through the cracks and going unaddressed by the system.

Standards for the Federal Review Process

The ACHDNC has the responsibility of making recommendations regarding which conditions to add to the RUSP as well as the discretion to determine what characteristics are deemed important for addition to the RUSP. Each stakeholder within the NBS community has their own specific frustrations with the current review process, including the pace of reviews; evidentiary requirements that seem to overlook the challenges of collecting data from small, rare disease populations; and overestimating states' ability to add more conditions when they are struggling to add conditions that have been on the RUSP for many years.

The federal government has the discretion to determine what standards should be considered when adding conditions to the RUSP. Updating those standards will set a precedent on how best to add conditions to NBS panels in the future. Proposed solutions include:

Real World Example: A current example of a multi-agency coordination effort that addresses the full area of interest is the federal One Health program that serves as a collaborative approach to addressing zoonotic diseases that could impact national health.¹⁵ The One Health program is led out of the CDC, who then works with the Department of Agriculture and the Department of the Interior to develop plans to address the risk those diseases can pose to humans.¹⁶ When faced with the COVID-19 pandemic, the program expanded to include more than 20 federal agencies and 150 U.S. government partners to address how COVID-19 impacted their work.¹⁷ The effort resulted in multiple guidances about how to mitigate the potential impact to wildlife to try and limit the shifting of COVID-19 to other species.^{18,19} The flexibility highlights what could be utilized to begin to make meaningful change within the NBS programs if multiple agencies would formalize their coordination to ensure they are all working together to move forward in the same direction.

¹⁵<https://www.cdc.gov/onehealth/what-we-do/federal-coordination.html>

¹⁶Ibid

¹⁷<https://www.hhs.gov/sites/default/files/day2-05-behravesh.pdf>

¹⁸<https://www.naccho.org/blog/articles/report-u-s-one-health-zoonotic-disease-prioritization>

¹⁹<https://www.nature.com/articles/s41598-022-12619-1>

1. Creating a full-time review committee and/or ad-hoc working groups to generate a faster, more agile evidence review
2. Addressing challenges to collect data from small disease populations to ensure their inclusion in NBS panels
3. Bundling of conditions with similar screening methods into a single review to create a more efficient review process that will speed up the addition of conditions that are ready for nationwide screening
4. Increasing the weight placed on patient experience in the benefit- risk consideration during the review process to better elucidate the impact of adding conditions to panels for each community
5. Developing a path for screening conditions when a therapy is in development

The above solutions are a sample of a variety of ways that the review process can be addressed. Any proposed solution must address the pace at which conditions are added without sacrificing the evidentiary standards. The above solutions resolve the growing trend that there are conditions that many believe meet the criteria for NBS that have not yet undergone an evidence review. An innovative review process will ensure more conditions are added in a timely manner to NBS panels.

Proposed Newborn Screening User Fee Program

To help alleviate the costs of developing and submitting a RUSP nomination package, innovative policy ideas are required. A major policy solution identified at the Roundtable was the creation of a NBS user fee program, modeled after the existing FDA user fee programs. The current FDA user fee programs collect fees from drug and device developers to supplement FDA congressional funding. The User Fee programs are reauthorized every five years through an extensive process that includes pre-determined implementation commitments agreed negotiated and agreed upon by the FDA and regulated industry. User fee programs vary greatly based on the product area, with the application cost for certain devices costing \$19,870 and application for new prescription drugs costing \$4.048 million.^{20,21} User fees and the user fee process help ensure the agency is aligned with advances in science, funds key activities while also ensuring a predictable timeline for its review process through its support of the staffing needed for expeditious reviews.

In the context of NBS, a user fee program could help secure stable funding for the condition review process and adding new conditions to the RUSP. A sustainable funding source could provide assistance to the states, support a full-time federal review committee, fund population-based pilot studies and other activities. This support could alleviate the financial burden that typically falls on advocacy organizations who work to have their conditions reviewed by the ACHDNC and state NBS programs. Additional engagement with stakeholders is needed to conceptualize the user fee program as this could alter the federal review process. Any federal legislation on this issue would need to address:

- Timing, source, and structure of payments and related Congressional oversight
- To which government entity NBS user fees are paid and distribution mechanism
- Appropriate guardrails to ensure a system that is inclusive of smaller biotechnology companies and disease populations with fewer resources
- A pathway for conditions that have a care standard in place and not an FDA-approved treatment, limiting the resources available to pay a user fee
- Impact of potentially bundling conditions on user fees

A novel user fee program could benefit NBS through increased funding, resulting in higher capacity for condition review. Currently the ACHDNC is only budgeted for two evidence reviews a year and has conducted 13 evidence reviews since 2008.^{22,23} A user fee program could be designed as a part of a Congressionally-created national strategy on NBS, led by and accountable to the Secretary of HHS, with established NBS policy goals that would ensure federal agencies, state programs, public-private partnerships, and all stakeholders are working to maximize the reduction of preventable death and disability.



A sustainable funding source could provide assistance to the states, support a full-time federal review committee, fund population-based pilot studies and other activities.

²⁰<https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments>

²¹<https://www.fda.gov/industry/fda-user-fee-programs/medical-device-user-fee-amendments-mdufa>

²²<https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/meetings/condition-review-capacity.pdf>

²³<https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/summary-nominated-conditions.pdf>



THEME 2: Establish a regional lab network that provides state NBS programs with the opportunity to work together to ensure efficient and faster addition of newborn screening conditions

There are 51 discrete NBS programs in the United States, run by all 50 states and the District of Columbia, with each program varying dramatically across the country. For example, Alabama screens their newborns for 31 of the 37 recommended conditions and Minnesota screens for 63.²⁴ There are a multitude of factors contributing to these disparities, such as how NBS programs are funded, state regulations and protocols, and the way enabling statutes are written. These disparities between screenings in the states will only be compounded as more therapies and screening tests for conditions become available and some states struggle to keep up. Geographic location will continue to greatly influence the number of conditions that a newborn is screened for while also playing a role in determining health outcomes. A newborn's zip code should not increase preventable death and disability.

To address these differences and to promote health equity across all NBS programs, multiple regional laboratory networks could be leveraged to ensure all newborns are being screened for as many conditions as possible. The roles and capabilities of these regional laboratory networks could vary based on the needs of the various states participating in the region. For example, the laboratory of one region could focus on streamlining the integration of new conditions into state panels by leveraging the expertise of more advanced state laboratories, while another regional laboratory could focus on conducting pilot studies for new potential conditions looking to be added to the RUSP. This solution would require important focus on flexibility for the programs to meet the needs of the region, and collaboration among the state laboratories, as well as the federal government which can offer support. This federal support could be financial, administrative, or any other form of assistance, and would help to alleviate some of the pressure individual state laboratories face and thus aid in the faster implementation of new conditions to screening panels across the country.

Developing a network of regional laboratories would greatly impact the NBS system and help to ensure that no newborn in the U.S. misses a diagnosis and opportunity for treatment due to where they are born. The implementation of such a network will require advocacy and coordination at both the federal and state levels, as laws and regulations will need to be updated to establish the creation of these laboratories. Additionally, the design, function, and interaction of these regional laboratories within the current system will need further discussion. High-performing laboratories could be expanded into a formal regional laboratory or entirely new laboratories could be built to carry out the appointed tasks. When creating the regional laboratory networks, states and federal programs must communicate on how best to address funding, the increased volume of screenings for those states, workforce challenges, and education around the regional laboratories and their new roles. These are important questions that must be addressed to ensure that laboratories are screening for conditions based on if they are determined to be a good fit for NBS and not solely on if the resources are available to screen for new conditions.

When establishing these regional laboratory networks, it will be vital to include the perspectives and voices from various stakeholders involved throughout the system. These stakeholders include, but are not limited to, patient advocates, state laboratory representatives, providers, and local and federal government officials. Theme four will dive deeper into the considerations needed for how the expanded research and utilization of genetic testing will impact regional networks and how best to monitor and support these networks in the years to come.

Real World Example: The New England Newborn Screening Program screens about 500 newborns every day in Massachusetts, Maine, New Hampshire, Rhode Island, and Vermont.²⁵ Each individual state's public health department determines the conditions that are screened for in that state, and the Massachusetts lab carries out the actual screening. Additionally, the Massachusetts lab provides backup services to other NBS programs outside of New England and offers optional screenings, or pilot studies, for conditions that are not yet on the state or federal screening panel. This screening consortium, one of a few that currently operate in this country, could be analyzed, improved, and/or expanded and then used as a model to help develop other regional laboratory programs.



Developing a network of regional laboratories would help to ensure that no newborn in the U.S. misses a diagnosis and opportunity for treatment due to where they are born.

²⁴<https://newbornscreening.hrsa.gov/your-state>

²⁵<https://nensp.umassmed.edu/>



THEME 3: Increase access to population-level data both before and after newborn screening to facilitate the development and adoption of newborn screening conditions to federal and state panels

Increased access to data within multiple parts of the NBS system is key to making necessary policy and programmatic changes to the NBS system. The way the system was established, with state-run NBS programs with influence and support from multiple federal agencies and programs, has led to information silos among stakeholders and inconsistent data expectations across the board. These data deficiencies ultimately result in a less efficient and less equitable NBS system as it makes it harder to track trends and best practices within various state NBS programs. There is a critical need for increased data-sharing, as well as improved public access to population level, deidentified data.

To increase data-sharing capabilities throughout the system, there needs to be an established and uniform system for data collection and management related to NBS. NBS datapoints range from things like data about disease progression, NBS implementation in states, false positive and false negative rates of screening methods, and the impact of early diagnosis. The harmonization of these datapoints, and many others, will help to reduce barriers in the current system for implementing and screening for conditions. Laboratories, state and federal agencies, providers, patients, manufacturers, and the various other entities involved in the NBS process must be able to sufficiently communicate data to each other in the same language.

A cohesive data collection and management system will allow for information to be more easily shared, understood, and utilized to improve health outcomes for newborns. This improved data-sharing capability will allow for expanded research into important issue areas within NBS, such as the use of sibling data and natural disease histories to demonstrate the impact of early treatment, pilot studies that allow for more conditions to be added to the RUSP, best practices for adding new conditions to a screening panel, and the psychological impact of false positives on families. Establishing this improved data collection and management system will likely require federal leadership, as well as approval and buy-in from all the involved stakeholders during every step of the process.

As data collection is improved, it is important to ensure that access to publicly available data is also afforded, while ensuring data privacy protections. Public access to this data will allow for various stakeholders to expand the scope and depth of their important research and education goals regardless of their size or the financial resources available to them. Thus, increased public access to de-identified data will result in a more equitable NBS system. Additionally, while increased access to better data is crucial for modernizing NBS, we must continue to ensure that personal health data is still sufficiently protected.



THEME 4: Integrate next-generation, evidence-based neonatal sequencing into newborn screening in a manner that can be broadly implemented in all state newborn screening programs

A major change already impacting NBS is the rise in genetic testing as a tool for early detection of rare diseases. NBS has historically been accomplished through tandem mass spectrometry (MS/MS), a molecular test that allows for rapid screening of multiple inborn errors of metabolism with a single test. In most states a tiered strategy is performed in which MS/MS is completed first followed by genetic testing of conditions based on the positive results of the first tier. Current research does not suggest that genetic testing will replace metabolic testing but could act as an additional or complementary test to further grow the scope of NBS.²⁸ However, many have called for genetic testing to be included in first tier testing as genetic sequencing holds the promise of increasing the number of conditions screened at birth to as many as 400.²⁹

Although genetic testing has the potential to dramatically improve the diagnostic yield of NBS, there are still many questions left to answer before genetic testing is used as the primary screening

Real World Example: The Federal Government has recognized the data analytic challenges that NBS professionals in the U.S. face, ranging from a continued expansion of the number of conditions being screened for by NBS programs to difficulty in disease detection and matching disease markers with risk and severity.²⁶ In response to these challenges, the Enhanced Data-driven Disease Detection in Newborns (ED3N) pilot program has been established in order to assess the functionality of a CDC data platform in the Division of Laboratory Sciences Newborn Screening and Molecular Biology Branch.²⁷ The program aims to help improve disease detection in newborns and help newborn screening programs evaluate disease risk.

Increased public access to de-identified data will result in a more equitable NBS system.

²⁶<https://www.cdc.gov/nceh/dls/ed3n.html>

²⁷<https://www.cdc.gov/nceh/dls/ed3n.html>

²⁸<https://www.nature.com/articles/s41591-020-0966-5>

²⁹<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9502059/>

method within state's NBS system. There must be continued exploration to ascertain how genetic testing can most effectively and efficiently be integrated into the NBS system. For example, questions such as what type of genetic testing (whole genome sequencing, targeted sequencing, exome sequencing, etc.) would best serve the goals of NBS, what infrastructure and workforce capacity states would need to further implement genetic testing, the ability to maintain the same diagnostic accuracy for current conditions if switching from molecular to genetic testing, what ethical questions within NBS (such as health equity and consent) would arise from genetic testing, and what the public perspective is on the inclusion of genetic testing in NBS are all questions yet to be addressed.

Beyond testing, NBS programs will need to address logistical challenges such as increased data collection from genetic testing lab space. Stakeholders must not overlook how genetic testing and the potential use of genetic sequencing will impact education and follow-up services; and they must update standards of practice and education materials accordingly. When we address the remaining questions on how best to implement, genetic testing has the potential to have a profound impact on NBS.

To begin answering these questions, there must be a coordinated national public-private effort. Whether through a nationwide study, a national initiative led by the Secretary of HHS, or legislation, federal leadership must be taken to identify areas of support, improvement, and education required to ensure the most efficacious integration of genetic testing into a nationwide public health program such as NBS. Public discussions and papers like this have been a key step in the process, but national leadership is needed to take the theories into real-world situations to determine if newborn genetic screening is a possibility and, if yes, how it should be done.

Discussion

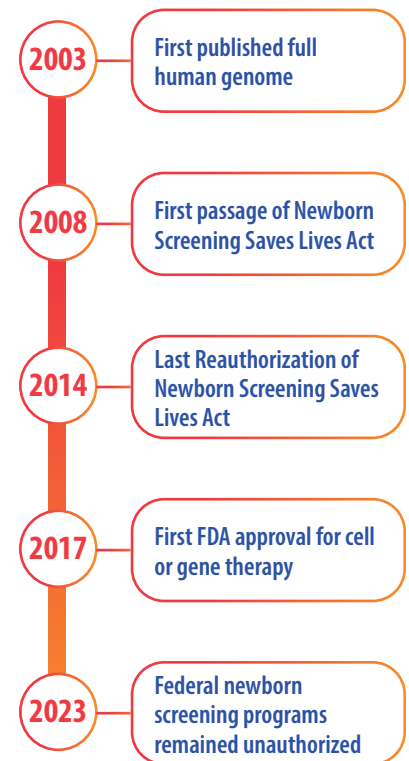
When the Newborn Screening Saves Lives Act (NBSSLA) was passed in 2008, significant enhancements to the NBS program were made. The law expanded the responsibilities of the ACHDNC to include such items as making recommendations for the RUSP. The law also established a clearinghouse of NBS information, reorganized the NIH NBS research under the Hunter Kelly Newborn Screening Research Program, established the ability for CDC to oversee quality of laboratories that run NBS tests, and greatly expanded the financial resources available to support state NBS programs.^{32,33} It was a defining moment in NBS, creating an avenue to help align NBS programs across the country.

We have again reached a similar defining moment in NBS policy. The 2008 passage of the NBSSLA was just five years after the publication of the human genome sequence and the first FDA-approvals for cell and gene therapy were still nine years in the future.^{34,35} The landscape of NBS has changed drastically in the 15 years since the original passage of the NBSSLA and the community must once again be willing to make large-scale changes to address current and future challenges.

The challenges outlined here are by no means the only issues facing the NBS ecosystem. Inequities in follow-up services, workforce challenges for NBS programs directly and the healthcare professionals that support diagnosis and treatment that follow NBS, and the difficulty in setting up pilot studies to generate evidence required for RUSP nomination packages are just a few of the issues of deep concern to the rare disease community, yet not addressed in this paper. In addition, throughout the paper funding for NBS was discussed in terms of specific solutions, but not addressed as an overall challenge within NBS. Federal NBS programs are currently funded at their highest levels and NBS fees continue to rise as does the number of conditions to add, so we cannot surmise that increased funding at the federal and state levels alone without reform will solve all NBS problems. Advocates and policymakers must think of innovative new and sustainable funding methods to ensure that resources are not the bottleneck to improving the NBS program.

The proposed solutions outlined above will interact with each other and require a variety of policy

Real World Example: The BabySeq project is the first clinical trial to employ genomic sequencing of healthy newborns during routine NBS.³⁰ Through this research protocol newborns undergo whole exome sequencing, one of the most comprehensive genetic tests clinically available. The study has produced 25 publications on issues such as psychosocial factors that influence parental interest in newborn genomic sequencing, the impact of providing a genomic result for an adult-onset condition, and multiple studies that discuss the interpretation of genomic sequencing results in newborns.³¹



³⁰<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6038274/>

³¹<https://www.genomes2people.org/publications/>

³²<https://www.nichd.nih.gov/health/topics/newborn/conditioninfo/history#f3>

³³https://www.aphl.org/aboutAPHL/publications/Documents/NBS_2013May_The-Newborn-Screening-Story_How-One-Simple-Test-Changed-Lives-Science-and-Health-in-America.pdf

³⁴<https://www.genome.gov/about-nhgri/Brief-History-Timeline#three>

³⁵<https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states>

actions to be fully formed and implemented. For example, the creation of a regional laboratory network would require advocacy efforts and policymaker leadership at both the state and federal levels to pass legislative and regulatory language that would establish the network. When creating that network, leaders in the field would have to consider how the growth in genetic testing will impact regional networks to complete their work and the best way to create the network. Stakeholders would need patient advocacy organizations and academic researchers included in any conversation on how to address a review system that can currently only handle two evidence reviews a year at the federal level.³⁶ To truly modernize the NBS system, a multi-faceted approach is required across the country to improve the entire system.

The Newborn Screening Modernization Roundtables provided a first of its kind opportunity to bring expert stakeholders together from a variety of backgrounds to discuss how to improve NBS in the United States. As the NBS community works to evolve and implement the concepts and solutions laid out in this paper, there must be continued multi-stakeholder engagement to ensure the actions taken will sustainably improve the system. This paper provides an overview of proposed policy options that could begin to modernize NBS processes for the benefit of generations to come. If we are to ensure that NBS remains one of the most successful public health programs in the country, continued cross-stakeholder engagement is the key to success.



Continued cross-stakeholder engagement is the key to success!

Methods Appendix

Roundtable #1 – Emerging Newborn Screening Topics

The first public Roundtable provided 108 NBS stakeholders the opportunity to share their thoughts and suggestions on how best to modernize the NBS system. Participants were divided into breakout rooms to discuss possible policy solutions for each of four themes:

- Entering NBS as an advocate
- Building an inclusive RUSP review process
- Public health infrastructure in NBS
- Emerging methods in NBS.

Participants were encouraged to review solutions identified in recent publications highlighting opportunities to modernize NBS, as well as draw inspiration from their experience providing clinical care, ongoing research, and their understanding of existing models to develop potential policy solutions to modernize the NBS system.

Roundtable #2 – Newborn Screening Policy Identification

Based on discussions from the first Roundtable, the planning committee compiled a list of actionable solutions to be discussed by participants in Roundtable #2. The actionable solutions were categorized based on the four themes. The 46 participants in the second Roundtable were asked to define and assess the viability of the identified potential actionable solutions. The Roundtable concluded with a full group discussion where participants were asked to provide policy solutions they thought would have a meaningful impact on successfully modernizing the system.

Roundtable #3 – Newborn Screening Policy Prioritization

The planning committee identified four modernization themes for the 41 participants to discuss and prioritize in Roundtable #3. These themes, which are largely reflected in the four priorities outlined below, were sent to participants in advance of the final Roundtable for their review. To start Roundtable #3, participants were asked to rank the listed actionable items for each theme based on prioritization, urgency, and feasibility. The rankings were recorded using a virtual polling platform so that the data could be collected and shared. Participants were then divided into four groups and each group rotated through the four modernization themes. As the groups cycled through the four themes, the ranking data was shared and participants were able to discuss the results, further analyze the feasibility, prioritization, and urgency of these policy solutions, and identify the policy solutions most necessary to modernize the NBS system.



About the EveryLife Foundation

The EveryLife Foundation for Rare Diseases is a 501(c)(3) nonprofit, nonpartisan organization dedicated to empowering the rare disease patient community to advocate for impactful, science-driven legislation and policy that advances the equitable development of and access to lifesaving diagnoses, treatments and cures. We do not speak for patients. We provide the training, education, resources and opportunities to make their voices heard. By activating the patient advocate, we can change public policy and save lives.

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³⁶<https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/meetings/condition-review-capacity.pdf>