



A Window of Opportunity for Newborn Screening

Donald B. Bailey Jr¹

Accepted: 7 April 2022 / Published online: 4 May 2022
© The Author(s) 2022

Abstract

Molecular diagnostics and therapies play a central role in an era of precision medicine, with the promise of more accurate diagnoses and more effective treatments. Universal newborn screening (NBS) identifies those health conditions that must be treated in early life and before clinical symptoms become apparent, to maximize effectiveness, prevent morbidity, and reduce or eliminate mortality. However, enthusiasm about NBS as the logical platform for early identification is tempered by the realization that NBS under public health authority exists in a complex ecology in which technology and medicine intersect with politics, ethics, advocacy, and resource constraints—a classic translational challenge that is exacerbated when considering the possible introduction of genome sequencing and molecular therapies in NBS. Substantial change is inevitable if the current model of NBS can be prepared for an envisioned future of greatly expanded molecular diagnostics and therapies. A window of opportunity for modernization now exists, but what changes are needed? The purpose of this commentary is to identify five major initiatives to stimulate focused discussion on how modernization might be achieved: (1) build systems for more rapid collection and integration of extant data relevant to NBS; (2) establish a national network of NBS research centers to design and conduct prospective research studies addressing critical NBS questions; (3) create a network of regional NBS laboratories to expedite state implementation of new methodologies or screening for newly recommended conditions; (4) establish a new stream of federal funding to provide financial support for states and incentivize national harmonization; and (5) integrate solutions in a way that is strategic and effective. Some aspects of these recommendations suggest that radical policy changes are needed to implement molecular testing in NBS and take advantage of emerging molecular therapies. I focus on recommendations for modernizing NBS in the US, some of which may be applicable in other countries.

Key Points

Despite its considerable success, newborn screening (NBS) is now facing a major set of challenges as a result of new therapies and options for genetic testing.

Specific solutions are needed to help NBS prepare for the future.

This paper suggests five strategies that could support modernization of NBS.

1 Introduction: The Newborn Screening Success Story

Virtually any discussion of newborn screening (NBS) begins by acknowledging that it has been and remains a remarkable public health achievement in the US, and indeed around the world [1]. And why not? More than 60 years ago, there was no such thing as NBS. Then a few US states began screening for one disorder—phenylketonuria. Today, every state operates a comprehensive NBS program, screening almost every newborn for health problems that can be identified in the presymptomatic stage and for which there are effective treatments that work best if provided before symptoms appear [2]. Universal screening as a public health mandate derives a long history of broader screening principles [3]. Although these principles continue to be discussed and revised [4, 5], their core guidance remains the same, emphasizing the importance of proven net benefit to children and the urgency of rapid treatment.

✉ Donald B. Bailey Jr
dbailey@rti.org

¹ RTI International, 3040 E. Cornwallis Rd.,
Research Triangle Park, NC 27709, USA

How did NBS in the US move from one health condition in a few states to where it is today? Much credit must be given to the tireless work of parents and patient advocacy organizations, who have persisted in raising funds for research, building awareness, and arguing for legislation to expand screening. Researchers and clinicians have developed ways to identify health conditions early, conduct research to understand disease pathophysiology and progression, and develop treatments and services to take advantage of earlier identification. Health departments have established screening laboratories, demonstrated standards of quality, validated protocols, and established follow-up systems. The federal government has supported national harmonization, built technical assistance networks, and provided funds for research, pilot studies, equipment, screening methods, and quality improvement. The US Department of Health and Human Services (DHHS) established the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) to conduct evidence-based reviews of nominated conditions, leading to a national Recommended Uniform Screening Panel (RUSP) [6].

Collectively, these and other factors (e.g., federal and state legislation, industry investments to advance technology and develop treatments, support from professional organizations) have led to screening programs that identify and provide early treatments for children with serious health conditions. Almost all babies born in the US are screened for 30–35 time-sensitive conditions that have been vetted and approved by the ACHDNC and DHHS. More than 12,000 babies each year receive a confirmed diagnosis of a screened condition, thus having the opportunity to access treatments that can significantly reduce morbidity and mortality [7, 8].

2 Does Newborn Screening Need to be ‘Modernized’?

Paradoxically, these accomplishments place NBS at a critical juncture in its evolutionary history, essentially a victim of its own success. NBS is the only viable mechanism to ensure universal identification of newborns who need early treatment for rare health conditions. This realization has led to a pent-up demand to greatly expand NBS in a more expeditious fashion. Parents want screening and treatments for more children with rare conditions. Clinicians want conditions to be identified earlier to avoid an expensive and often protracted diagnostic odyssey and provide appropriate treatments in a timely fashion. Furthermore, industry wants to justify expenses incurred when developing new testing methods or treatments. These expectations are magnified in the evolving arena of precision medicine, applying transformative treatments (e.g., gene therapy) based on an individual’s genetic profile [9].

In the US, these and other expectations place pressure on an already stressed system. Factors contributing to stress include new technologies, more effective treatments, disease complexity, insufficient national leadership, fragmentation of state or regional programs, restrictive state rules and regulations, inadequate resources, and lack of data to inform policy [10, 11]. In a recent study we asked a cross-section of NBS experts about the likelihood of RUSP approval and state implementation of 30 additional monogenic disorders with US FDA-approved transformative therapies in the next 10 years [12]. Most experts felt that this would be impossible without significant changes to NBS. A recent publication concludes that NBS as we know it is facing an ‘existential challenge’ [13].

The issues are now converging to such an extent that some would characterize it as a ‘perfect storm’, jeopardizing the entire US system. But now is also the ‘perfect window’ to reimagine the future of NBS, with special attention to how it fits into the larger landscape of precision medicine. The fundamental goal of screening—find babies with serious health conditions that need urgent treatment—will remain the same. We must retain an evidence-based system with high standards for quality, public acceptance, and responsible decision making, but NBS must move to a more nimble and adaptable state with robust systems to collect data needed to inform policy and enhance state capacity to add new conditions more quickly. Well-accepted principles of screening and screening policy must be consistent with and support modern technologies and treatments.

3 Five Strategies to Prepare NBS for an envisioned future of Screening

Modernizing NBS will require strategic planning, informed decision making, resources, and buy-in from multiple stakeholders. Many solutions are possible, but they vary in the extent to which they can truly impact the system and whether they are feasible, acceptable, and sustainable. The purpose of this commentary is to provide a set of concrete suggestions that could serve as the basis for national debate and hopefully advance modernization in a constructive way. I draw on the findings of our recent studies [12, 14] and other experiences to suggest five major initiatives: (1) build systems for rapid collection and integration of extant data; (2) establish a national network of NBS research centers to design and conduct prospective research studies; (3) create a national network of regional NBS laboratories to expedite state implementation of new methodologies; (4) establish a new stream of federal funding to support states and incentivize national harmonization; and (5) integrate solutions in a strategic and effective way. The discussion focuses primarily

on NBS in the US, in hopes that the issues and solutions raised here may have some relevance for other countries.

3.1 Implement Systems to Integrate and Analyze Extant Data

The US ACHDNC has provided invaluable guidance to states, using an Evidence Review Group (ERG) to conduct a comprehensive literature review and provide information that informs decisions about RUSP additions. However, since its inception in 2006, the Committee has only recommended seven new disorders, an unsustainable pace in light of rapid developments in technology and treatment [12].

By far the primary reason for the slow pace of decision making is the absence of critical data. Information is needed about natural history, screening methods, effective treatments, long-term outcomes, and state capacity. Data relevant to some of these questions may already exist, providing a rich and relatively inexpensive source of information; however, extant data are likely to be fragmented, having been collected by researchers, states, patient registries, or industry, with little incentive to harmonize measures or merge data across sites. The lack of a coordinated national data system puts the burden on advocacy groups, individual researchers, or the ERG, and may provide only partial answers to important policy questions. This problem is not unique to NBS, as similar challenges have been reported by the US Preventive Services Task Force [15, 16]. Denny and Collins [9] argue that “huge interoperable longitudinal cohorts”—big data augmented by sophisticated analytic capabilities—are needed to advance precision medicine.

In the interim, there is an immediate and attainable need for NBS to expand current data-sharing mechanisms and support collaboration among sites engaged in similar activities that may have comparable data. The Longitudinal Pediatric Data Resource [17] exemplifies a good first step, establishing common data elements for selected disorders and a voluntary program for clinicians and researchers to submit de-identified clinical data. The data are made available to eligible researchers under a data use agreement to allow previously impossible large-scale secondary research and data mining efforts to better understand disease characteristics and progression.

But this type of work could be expanded to a more proactive approach that answers specific questions about phenotype or about public health implementation for health conditions. For example, a gap in preparing fragile X syndrome (FXS) for the possibility of NBS was lack of data on natural history. To answer this question, we invited seven clinical research sites across the country to collaborate on a study to better understand early development in FXS, knowing that each had collected developmental assessments using the same instrument, but these data had not been entered into

any sort of repository. De-identified data on > 500 children across 1178 assessment occasions submitted to a central data analysis team resulted in a more definitive description of early development in FXS, fulfilling a key criterion for NBS decisions and providing baseline information that will be informative in evaluating future treatments [18].

Early collaboration among independent projects with a similar focus could not only enhance knowledge about health conditions but also provide information to support public health implementation. For example, at least four US state-based pilot studies on NBS for X-ALD have been published [19–22] and four for spinal muscular atrophy (SMA) [23–26], in addition to numerous studies in other countries. Each project published useful data, but the findings could potentially have been more powerful and informative if methods or measures had been harmonized or systematic differences were built in across sites to answer comparative questions, especially those related to implementation in the context of public health. Even after these projects had been completed, it would have been possible to link some of the data to increase statistical power and increase confidence in findings.

Variations in funding sources, the desire for independent access to biospecimens or data, publication priorities, and privacy considerations when sharing data are among the many factors that make collaborations challenging. Proactive mechanisms are needed to rapidly locate extant data, especially in anticipation of upcoming policy decisions (e.g., review for a RUSP nomination). A trusted entity then needs to communicate with investigators or clinicians who control access to data. A standardized data use agreement would protect privacy and assure investigators that they will retain all rights to publication and coauthor publications arising from the collaboration. Data could be submitted to the trusted source for preparation, analysis, and working with sites to summarize and submit findings for publication as soon as possible to support the evidence review conducted by the ERG. Funding is needed to support coordinating activities and data preparation at participating sites.

3.2 Build a Network of NBS Research Centers

A rapid way to integrate extant data is certainly needed, but there is pressing need for coordinated prospective research. One of the most powerful changes that could be made to advance NBS is a coordinated national network of NBS research centers. These centers could not only focus on the usual questions for which policy makers need answers but also address two recent developments that have created a new sense of urgency for better and more precise evidence—a more nuanced understanding of complex diseases and new transformative treatments. This information is critical if the

promise of precision medicine is to be supported by NBS [9, 27].

Most health problems are multifaceted, and the more complicated they are, the more they challenge NBS. SMA, caused by a mutation in both copies of the *SMN1* gene, is a good example. Finding a mutation in the *SMN1* gene does not necessarily predict whether a child will have the most severe (and typically fatal) version of SMA that requires immediate treatment. Fortunately, severity is modified by the number of copies of the *SMN2* gene, providing critical information to determine urgency of treatment. But situations such as this will only grow as we develop a more nuanced understanding of diseases. In many cases, disease-modifying genes or other biomarkers will not be known, requiring longitudinal surveillance to determine when treatment should begin. X-ALD exemplifies this scenario. X-ALD is caused by a mutation in the *ABCD1* gene, with as many as eight types, some of which are quite rare. The childhood cerebral form has severe consequences and current treatment is a bone marrow transplant. The other types are milder and can have an onset in late childhood or even during the adult years. But the type of X-ALD cannot be discerned at birth, and periodic brain imaging is needed to detect changes that indicate when treatment is necessary [28].

Although all NBS conditions benefit from early detection, many children still experience developmental or health challenges [29]. New transformative treatments (e.g., cell therapies, gene therapy, gene editing) address the underlying cause of a condition rather than symptoms and have the potential to be curative or substantially disease-altering. SMA is the first condition on the RUSP for which there is a gene therapy treatment, and the pipeline for other transformative treatments in the next decade is substantial [30, 31]. New therapies bring tremendous hope for both common and rare disorders and are anxiously awaited by parents of affected children. A rapid expansion of approved therapeutics will immediately result in strong advocacy to add many new disorders to the RUSP, but this will be a challenge for states that struggle to add even one or two.

Extant data may inform these discussions, but a network of NBS centers would be more powerful. Federal agencies and institutes already fund many research networks, typically focusing on a single disease or health risk. But the networks range considerably in expectations for participation and coordination of activities. Coordinated sites collecting standardized data provide a source of important information, using much larger samples than would be possible at any single site. Even more impactful, however, are centers funded to collaborate not only on data collection but also to design and implement clinical trials or observational studies, as exemplified by the Neonatal Research Network (NRN) funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The NRN

involves multiple clinical sites, a steering committee, and a data coordination center, all dedicated to studying issues of relevance to clinical care of low-birthweight and premature infants, most of whom have been in neonatal intensive care. The clinical sites follow standardized protocols, the steering committee establishes research priorities, clinical trials are conducted, and the data coordinating center works with the network to standardize processes and analyze data. The NRN established a registry to collect descriptive information on very low birth weight infants, with >82,000 babies enrolled, and a follow-up database of >20,000 children who received multidimensional assessments of outcomes at 24 months of age. Since its inception, the NRN has published literally hundreds of publications to support evidence-based treatment (<https://www.nichd.nih.gov/research/supported/nrn>).

NBS urgently needs a research network similar to the NRN. Such a network should be disease agnostic, funded to conduct prospective collaborative research to enhance decisions about NBS policy and practice. High-impact findings would result from coordinated research projects, eliminating the need for post hoc efforts to standardize data across sites. For example, research sites could collaborate on natural history studies, examine biomarkers to predict disease subtypes or progression, conduct clinical trials to evaluate new treatments, evaluate public perceptions of screening for health conditions under consideration for NBS, or compare surveillance strategies to determine when and if a child needs treatment. A steering committee could evaluate research proposals submitted by consortium members, other researchers, or state or federal advisory committees. A coordinated NBS research network within the US, or even globally, would enhance statistical power for complex data analyses, encourage a priori specification of research questions, and ensure a nationally coordinated research resource to provide timely evidence in support of clinical or policy decisions.

3.3 Establish a Network of Regional Screening Laboratories

A critical barrier for states trying to screen for new conditions is lack of equipment, staff, funding, or expertise related to new screening methods. For example, tandem mass spectrometry (also known as MS/MS) was introduced in the 1970s to multiplex NBS screening for many conditions at one time. Although MS/MS was a technological breakthrough, it was many years before all states had the capability to use it [32]. Likewise, two conditions (hearing loss and congenital heart defects) are hospital-based tests rather than dried blood spot tests performed in a state laboratory, which required public health to establish entirely new procedures and partnerships to achieve universal screening.

Biochemical testing has proven to be highly effective in NBS and almost certainly will continue to be an essential component of screening; however, the likely introduction of next-generation sequencing and genomic technologies in NBS will constitute a major shift for which NBS laboratories are largely unprepared [33]. Genetic testing is currently the first-tier test for only two disorders: severe combined immunodeficiency and SMA. It is used as a second-tier test for some disorders initially identified by MS/MS (e.g., cystic fibrosis, galactosemia) to reduce false-positive cases or provide additional information needed by clinicians and families [34].

The eventual incorporation of some form of genomic sequencing in NBS is inevitable. Exome or genome sequencing could provide a single platform for identifying literally hundreds of genetic disorders [35]. The cost of sequencing is dropping rapidly, and pilot studies have provided initial data about acceptability and utility [36, 37]. Many health conditions that could benefit from new transformative therapies will require genetic testing or sequencing to be identified, and there will be considerable pressure on states to fully embrace these technologies. However, much work needs to be done to evaluate feasibility, translation to practice, clinical implications, return of results, and a range of ethical and policy decisions [38–40].

Genome sequencing will inevitably evoke questions about how to identify complex disorders, including the possible use of polygenic risk scores (PRS) that predict the chances of future disease using a formula to weigh multiple genes. PRS would expand the potential for NBS to screen for complex diseases such as type 1 diabetes, but with much less specificity [41, 42]. A complex disease for which a PRS score is needed almost certainly would not be approved for the RUSP at this time, as much more work is needed to validate appropriate algorithms, parent support, and treatment/surveillance protocols [43], but as treatments are developed for complex diseases, pressure to add PRS to NBS will grow. The less-than-perfect prediction of future disease state will result in identification of many children who may never need treatment, requiring an expensive surveillance system and creating uncertainty for both parents and clinicians [44, 45]. NBS and associated follow-up programs are completely unprepared for such a scenario.

A network of regional NBS laboratories with cutting-edge expertise and equipment could expedite state implementation of genetic testing or other methods to screen for newly recommended conditions. Although some regional laboratories already exist, they do not operate as a coordinated network and are primarily designed to help states screen for disorders already on the RUSP. A truly national system of coordinated laboratories with sufficient funding could accomplish four major goals. First, the network could provide a bridge for states to offer screening for new disorders

before a state laboratory has the necessary equipment and technical capability. States could send de-identified blood spots to the regional laboratory and results then returned to states to coordinate follow-up services. Second, the network could conduct research and development activities to develop and validate screening methods, including systematic study of alternative screening methods and cut-off scores. This work would promote national harmonization of laboratory standards and practices. Third, the network could collaborate with the NBS research centers to study disease subtypes and the potential for genes or other biomarkers to identify which children have early onset severe forms of a disease. Finally, the network could provide individualized technical assistance to states to enhance screening capabilities.

3.4 Establish a New Stream of Federal Funding to States

NBS programs in the US are operated by states, a loosely connected set of programs that differ in the number of disorders screened, requirements for adding new disorders, funding, and expertise. Many state programs are underfunded, understaffed, and overly burdened by state legislation or regulations. As a result, it can take 3–5 years to implement screening for just one new disorder.

The federal government provides important resources and guidelines, but it does not have regulatory authority over states. The devolution of NBS authority to states has led to cross-state fragmentation, with limited options for federal influence. Ideally the US would have a national NBS program, with universal standards and the capability to quickly adopt new disorders or methodologies, but changing this state-based model to a national system will be virtually impossible. Assuming a future of NBS programs operated by states, what could the federal government do, beyond data integration, research centers, and a regional network of laboratories to appropriately guide and support national harmonization? The most effective approach would likely be a program offering substantial financial incentives to states, but with requirements that each state must fulfill to receive those funds.

A successful and sustainable precedent in the US exists in the form of the Part C early intervention program in the Individuals with Disabilities Education Act (IDEA). IDEA mandates free and appropriate education for individuals with disabilities ages 3–21 years. Services were not mandated for infants and toddlers with disabilities, therefore Part C was established in 1986 as a voluntary state program. Federal funding is available for states that meet a common set of requirements. For example, all children with a developmental delay or with a health condition likely to lead to a delay must be served in a timely fashion.

An Individualized Family Service Plan must be developed by an interdisciplinary team that includes families, and services must be provided according to that plan. States must annually submit data to the US Department of Education describing the number of children served, selected demographic characteristics (e.g., age of entry, race/ethnicity), and services provided. Outcomes for children and families are reported using a standardized rating system. Procedural safeguards must be in place for families and a comprehensive system of personnel development must be in place.

All states now participate in Part C and are eligible for funding based on the total number of children in the state ages birth through 2 years. Federal funding is significant—in 2020, the national allocation was \$477,000,000. California received the largest allocation (> \$55,000,000), whereas the smallest allocations (\$2,000,000–\$3,000,000) were received by small-population states such as Vermont, South Dakota, and New Mexico.

A comparable program could be established for NBS. Examples of state requirements to receive funds could include demonstrated ability to add a disorder within 12 months of RUSP approval; adoption of nationally standardized procedures and cut-offs for screening; achievement of quality indicators such as those collected by the Newborn Screening Technical Assistance and Evaluation Program [46] (e.g., timeliness of NBS activities, percentage of unacceptable dried blood spot specimens, percentage of missed cases by disorder); an established long-term follow-up program to determine outcomes for babies with screen-positive results; and standardized data submitted annually to the designated federal agency.

To make this happen, the federal government would need to establish regulations, designate a responsible federal agency, allocate funds, build oversight capabilities, and support states that have difficulty achieving all standards. If the Part C IDEA formula was used for NBS, the annual appropriation would be \$159,000,000 (one-third of the Part C allocation, based on annual birth rate rather than total number of children ages birth through 2 years). Using this formula, the allocation would be \$39.75 for each of the nearly 4,000,000 children born in the US each year. A state such as North Carolina, with 120,000 births per year, would be eligible for \$4,770,000 in federal funds if it met all federal requirements.

A program such as this would have the potential to accelerate state adoption of screening for new disorders and should lead to greater national harmonization. State legislation would be necessary, as was the case with Part C of IDEA, and it took several years before all states were part of the Part C program. Full adoption by states will take several years, and focused parent and professional advocacy for state participation would be needed.

3.5 Integrate Solutions in a Strategic and Effective Manner

Although the solutions suggested thus far could independently advance NBS, they will be far more effective if combined in an integrated initiative. Integration will be more complex than any one solution, but it must be achieved to truly transform NBS.

The question of leadership must be addressed first, and unfortunately there is no obvious choice. Who or what entity will be responsible? In the US, three federal agencies have major roles in NBS—the DHHS Health Resources and Services Administration, NICHD in the National Institutes of Health, and the Newborn Screening and Molecular Branch of the Centers for Disease Control and Prevention. Each agency makes unique and critical contributions to NBS, but none has a primary oversight or a coordinating role. Congress could identify one as the lead agency, but given their history and independence, success would only be achieved if the others fully embraced that choice. An alternative would be to establish a multi-agency collaboration model, which would likely have broader impact but would still require leadership. A radical but perhaps most effective long-term solution would be to create a new governmental entity and transfer all current and new NBS programs under a single umbrella. This solution would undoubtedly be disruptive, as it would be challenging for a single entity to embrace all aspects of NBS. Success would require the new entity to have the responsibility, authority, resources, and ability to provide trusted leadership for reform.

Second, any reform effort needs a clear specification of outcomes and a strategic plan. Many groups have a stake in NBS—parents, clinicians, policy makers, state laboratories, researchers, industry, patient advocacy groups—each of which has its own priorities. These groups must be able to view their existing priorities (e.g., developing a therapy for a specific indication, building marketable technology for screening, advocating for a single disease, promoting a single discipline, protecting agency or group identity) as unattainable without systems change, and work together for a common set of goals. Goals need to focus on those with high impact, are clear and specific, and have measurable outcomes to document achievement. ‘Modernization of NBS’ is an admirable and indeed desirable goal, but to what end? Agreement on outcomes by various stakeholder groups will be a necessary step before developing a strategic plan.

Third, focused and coordinated advocacy will be needed at the state and national level. Patient and professional groups will play an important role, since agencies, researchers, and industry will have perceived or real conflicts of interest that could compromise reform efforts. However, to be effective, this advocacy needs to be planned and coordinated. Federal agencies will not be allowed to lead or

participate in advocacy, therefore leadership will need to come from a trusted and unbiased source. A large, well-funded, disease-agnostic foundation with prior experience in effective communication, coordination, and advocacy is likely to be the most feasible and acceptable alternative.

Finally, the first four solutions suggested in this commentary should be considered in a synergistic and transactional manner. For example, if a nominated condition does not meet the standards for a RUSP recommendation, there should be clear identification of the data needed before the nomination can move forward. The Research Centers Steering Committee could be tasked with reviewing gaps and developing activities to answer each question, some of which could come from extant data, some from research conducted by the network, and some from the regional laboratories. If sufficient federal funding is not available, one solution could be a public–private partnership, one of the top solutions rated in our recent study of expert evaluation strategies to modernize NBS [12]. Proper oversight would be needed to manage potential conflicts of interest, but such a partnership would have the potential to augment federal funding to expedite definitive answers that would enable or decline a nomination for screening.

4 Conclusion

Substantial change is inevitable if NBS as we know it today is to modernize itself to be NBS as we need it tomorrow. Incremental improvements over many years will not be sufficient. Radical changes in research, policy, oversight, resources, and implementation are needed, many of which will require national legislation and visionary leadership.

NBS is at a critical point in its evolutionary history, with a window of opportunity to envision a desired future state and do the hard work needed to achieve it. This commentary suggests five changes that could enable modernization. Other effective solutions almost certainly exist, but hopefully the recommendations suggested here will serve as an impetus for a focused effort to consider these and other possible solutions. Change will be difficult, but the need is immediate, so that the potential benefits of precision medicine in the context of NBS can be realized by children, families, and the professionals who care for them.

Declarations

Funding Preparation of this manuscript was supported in part by the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (Awards # UL1TR002489 and 1U01TR001792), and in part by Fellows discretionary funds provided by RTI International. The opinions expressed are those of the author and do not represent the official position of NCATS, RTI International, or any current or previous funders. No other sources of financial assis-

tance were used to conduct the study described in the manuscript and/or used to assist with the preparation of the manuscript. The open access fee was paid by RTI International.

Conflicts of interest Donald B. Bailey Jr discloses no conflicts of interest but reports other current funding to RTI International from The John Merck Fund, the Centers for Disease Control and Prevention, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and Janssen Pharmaceuticals. He reports recent but completed funding to RTI from Orchard Therapeutics, Sarepta Pharmaceuticals, BioMarin, Travere, and the EveryLife Foundation, as well as donated reagents and equipment from Asuragen.

Ethics and consent Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability Not applicable.

Code availability Not applicable.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

References

1. Boyle CA, Bocchini JA Jr, Kelly J. Reflections on 50 years of newborn screening. *Pediatrics*. 2014;133(6):961–3. <https://doi.org/10.1542/peds.2013-3658>.
2. Association of Public Health Laboratories. The newborn screening story: How one simple test changed lives, science, and health in America. Association of Public Health Laboratories; 2013. https://www.aphl.org/aboutAPHL/publications/Documents/NBS_2013May_The-Newborn-Screening-Story_How-One-Simple-Test-Changed-Lives-Science-and-Health-in-America.pdf.
3. Wilson JMG, Jungner G. Principles and practice of screening for disease. WHO papers No 34. WHO; 1968. <https://apps.who.int/iris/handle/10665/37650>. Accessed 9 Mar 2022.
4. Andermann A, Blancquaert I, Beauchamp S, Dery V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull World Health Organ*. 2008;86(4):317–9. <https://doi.org/10.2471/blt.07.050112>.
5. Downie L, Halliday J, Lewis S, Amor DJ. Principles of genomic newborn screening programs: a systematic review. *JAMA Netw Open*. 2021;4(7): e2114336. <https://doi.org/10.1001/jamanetwopen.2021.14336>.
6. Kemper AR, Green NS, Calonge N, Lam WK, Comeau AM, Goldenberg AJ, et al. Decision-making process for conditions

- nominated to the recommended uniform screening panel: statement of the US Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. *Genet Med.* 2014;16(2):183–7. <https://doi.org/10.1038/gim.2013.98>.
7. Association of Public Health Laboratories. NewSTEPS 2020 annual report. 2021. <https://www.newsteps.org/sites/default/files/resources/download/NewSTEPS%20Annual%20Report%209%2022%2021.pdf>.
 8. Sontag MK, Yusuf C, Grosse SD, Edelman S, Miller JI, McKas-son S, et al. Infants with congenital disorders identified through newborn screening—United States, 2015–2017. *MMWR Morb Mortal Wkly Rep.* 2020;69(36):1265–8. <https://doi.org/10.15585/mmwr.mm6936a6>.
 9. Denny JC, Collins FS. Precision medicine in 2030—seven ways to transform healthcare. *Cell.* 2021;184(6):1415–9. <https://doi.org/10.1016/j.cell.2021.01.015>.
 10. Bailey DB Jr, Gehtland L. Newborn screening: evolving challenges in an era of rapid discovery. *JAMA.* 2015;313(15):1511–2. <https://doi.org/10.1001/jama.2014.17488>.
 11. Bailey DB Jr, Zimmerman SJ. The future of newborn screening: why and how partnerships will be needed for success. *N C Med J.* 2019;80(1):28–31. <https://doi.org/10.18043/ncm.80.1.28>.
 12. Bailey DB Jr, Porter KA, Andrews SM, Raspa M, Gwaltney AY, Peay HL. Expert evaluation of strategies to modernize newborn screening in the United States. *JAMA Netw Open.* 2021;4(12):e2140998. <https://doi.org/10.1001/jamanetworkopen.2021.40998>.
 13. McCandless SE, Wright EJ. Mandatory newborn screening in the United States: history, current status, and existential challenges. *Birth Defects Res.* 2020;112(4):350–66. <https://doi.org/10.1002/bdr2.1653>.
 14. Andrews SM, Porter KA, Bailey DB Jr, Peay HL. Preparing newborn screening for the future: a collaborative stakeholder engagement exploring challenges and opportunities to modernizing the newborn screening system. *BMC Pediatr.* 2022;22(1):90. <https://doi.org/10.1186/s12887-021-03035-x>.
 15. Kemper AR, Krist AH, Tseng CW, Gillman MW, Mabry-Hernandez IR, Silverstein M, et al. Challenges in developing US Preventive Services Task Force Child Health Recommendations. *Am J Prev Med.* 2018;54(1S1):S63–9. <https://doi.org/10.1016/j.amepre.2017.08.023>.
 16. Krist AH, Wolff TA, Jonas DE, Harris RP, LeFevre ML, Kemper AR, et al. Update on the methods of the US Preventive Services Task Force: methods for understanding certainty and net benefit when making recommendations. *Am J Prev Med.* 2018;54(1S1):S11–8. <https://doi.org/10.1016/j.amepre.2017.09.011>.
 17. Brower A, Chan K, Hartnett M, Taylor J. The longitudinal pediatric data resource: facilitating longitudinal collection of health information to inform clinical care and guide newborn screening Efforts. *Int J Neonatal Screen.* 2021;7(3):37. <https://doi.org/10.3390/ijns7030037>.
 18. Wheeler AC, Gwaltney A, Raspa M, Okoniewski KC, Berry-Kravis E, Botteron KN, et al. Emergence of developmental delay in infants and toddlers with an FMR1 mutation. *Pediatrics.* 2021;147(5):e2020011528. <https://doi.org/10.1542/peds.2020-011528>.
 19. Hall PL, Li H, Hagar AF, Jerriss SC, Wittenauer A, Wilcox W. Newborn screening for X-linked Adrenoleukodystrophy in Georgia: experiences from a pilot study screening of 51,081 newborns. *Int J Neonatal Screen.* 2020;6(4):81. <https://doi.org/10.3390/ijns6040081>.
 20. Lee S, Clinard K, Young SP, Rehder CW, Fan Z, Calikoglu AS, et al. Evaluation of X-linked adrenoleukodystrophy newborn screening in North Carolina. *JAMA Netw Open.* 2020;3(1):e1920356. <https://doi.org/10.1001/jamanetworkopen.2019.20356>.
 21. Matteson J, Sciortino S, Feuchtbaum L, Bishop T, Olney RS, Tang H. Adrenoleukodystrophy newborn screening in California since 2016: programmatic outcomes and follow-up. *Int J Neonatal Screen.* 2021;7(2):22. <https://doi.org/10.3390/ijns7020022>.
 22. Wiens K, Berry SA, Choi H, Gaviglio A, Gupta A, Hietala A, et al. A report on state-wide implementation of newborn screening for X-linked adrenoleukodystrophy. *Am J Med Genet A.* 2019;179(7):1205–13. <https://doi.org/10.1002/ajmg.a.61171>.
 23. Hale JE, Darras BT, Swoboda KJ, Estrella E, Chen JYH, Abbott MA, et al. Massachusetts' findings from statewide newborn screening for spinal muscular atrophy. *Int J Neonatal Screen.* 2021;7(2):26. <https://doi.org/10.3390/ijns7020026>.
 24. Kay DM, Stevens CF, Parker A, Saavedra-Matiz CA, Sack V, Chung WK, et al. Implementation of population-based newborn screening reveals low incidence of spinal muscular atrophy. *Genet Med.* 2020;22(8):1296–302. <https://doi.org/10.1038/s41436-020-0824-3>.
 25. Kraszewski JN, Kay DM, Stevens CF, Koval C, Haser B, Ortiz V, et al. Pilot study of population-based newborn screening for spinal muscular atrophy in New York state. *Genet Med.* 2018;20(6):608–13. <https://doi.org/10.1038/gim.2017.152>.
 26. Kucera KS, Taylor JL, Robles VR, Clinard K, Migliore B, Boyea BL, et al. A voluntary statewide newborn screening pilot for spinal muscular atrophy: results from early check. *Int J Neonatal Screen.* 2021;7(1):20. <https://doi.org/10.3390/ijns7010020>.
 27. Garcia-Foncillas J, Argente J, Bujanda L, Cardona V, Casanova B, Fernandez-Montes A, et al. Milestones of precision medicine: an innovative, multidisciplinary overview. *Mol Diagn Ther.* 2021;25(5):563–76. <https://doi.org/10.1007/s40291-021-00544-4>.
 28. Kemper AR, Brosco J, Comeau AM, Green NS, Grosse SD, Jones E, et al. Newborn screening for X-linked adrenoleukodystrophy: evidence summary and advisory committee recommendation. *Genet Med.* 2017;19(1):121–6. <https://doi.org/10.1038/gim.2016.68>.
 29. Zengin Akkus P, Ciki K, Mete Yesil A, Ilter Bahadur E, Karahan S, Ozmert EN, et al. Developmental and behavioral outcomes of preschool-aged children with biotinidase deficiency identified by newborn screening. *Eur J Pediatr.* 2021;180(1):217–24. <https://doi.org/10.1007/s00431-020-03740-2>.
 30. Abreu NJ, Waldrop MA. Overview of gene therapy in spinal muscular atrophy and Duchenne muscular dystrophy. *Pediatr Pulmonol.* 2021;56(4):710–20. <https://doi.org/10.1002/ppul.25055>.
 31. MIT NEWDIGS. Updated projection of US durable cell and gene therapies product-indication approvals based on December 2019 development pipeline. 2020. <https://newdigs.mit.edu/sites/default/files/NEWDIGS-Research-Brief-2020F207v51-PipelineAnalysis.pdf>. Accessed 2 June 2021.
 32. Millington DS. The role of technology in newborn screening. *N C Med J.* 2019;80(1):49–53. <https://doi.org/10.18043/ncm.80.1.49>.
 33. Almannai M, Marom R, Sutton VR. Newborn screening: a review of history, recent advancements, and future perspectives in the era of next generation sequencing. *Curr Opin Pediatr.* 2016;28(6):694–9. <https://doi.org/10.1097/MOP.0000000000000414>.
 34. Smith LD, Bainbridge MN, Parad RB, Bhattacharjee A. Second tier molecular genetic testing in newborn screening for pompe disease: landscape and challenges. *Int J Neonatal Screen.* 2020;6(2):32. <https://doi.org/10.3390/ijns6020032>.
 35. Berg JS, Agrawal PB, Bailey DB Jr, Beggs AH, Brenner SE, Brower AM, et al. Newborn sequencing in genomic medicine and public health. *Pediatrics.* 2017;139(2):e20162252. <https://doi.org/10.1542/peds.2016-2252>.

36. Lewis MA, Paquin RS, Roche MI, Furberg RD, Rini C, Berg JS, et al. Supporting parental decisions about genomic sequencing for newborn screening: the NC NEXUS Decision Aid. *Pediatrics*. 2016;137(Suppl 1):S16-23. <https://doi.org/10.1542/peds.2015-3731E>.
37. Roman TS, Crowley SB, Roche MI, Foreman AKM, O'Daniel JM, Seifert BA, et al. Genomic sequencing for newborn screening: results of the NC NEXUS project. *Am J Hum Genet*. 2020;107(4):596–611. <https://doi.org/10.1016/j.ajhg.2020.08.001>.
38. Allen CG, Peterson S, Khoury MJ, Brody LC, McBride CM. A scoping review of social and behavioral science research to translate genomic discoveries into population health impact. *Transl Behav Med*. 2021;11(4):901–11. <https://doi.org/10.1093/tbm/ibaa076>.
39. Friedman JM, Cornel MC, Goldenberg AJ, Lister KJ, Senecal K, Vears DF, et al. Genomic newborn screening: public health policy considerations and recommendations. *BMC Med Genom*. 2017;10(1):9. <https://doi.org/10.1186/s12920-017-0247-4>.
40. Khoury MJ, Dotson WD. From genes to public health: are we ready for DNA-based population screening? *Genet Med*. 2021;23(6):996–8. <https://doi.org/10.1038/s41436-021-01141-w>.
41. Ferrat LA, Vehik K, Sharp SA, Lernmark A, Rewers MJ, She JX, et al. A combined risk score enhances prediction of type 1 diabetes among susceptible children. *Nat Med*. 2020;26(8):1247–55. <https://doi.org/10.1038/s41591-020-0930-4>.
42. Lambert SA, Abraham G, Inouye M. Towards clinical utility of polygenic risk scores. *Hum Mol Genet*. 2019;28(R2):R133–42. <https://doi.org/10.1093/hmg/ddz187>.
43. Wand H, Lambert SA, Tamburro C, Iacocca MA, O'Sullivan JW, Sillari C, et al. Improving reporting standards for polygenic scores in risk prediction studies. *Nature*. 2021;591(7849):211–9. <https://doi.org/10.1038/s41586-021-03243-6>.
44. Azzopardi PJ, Upshur REG, Luca S, Venkataramanan V, Potter BK, Chakraborty PK, et al. Health-care providers' perspectives on uncertainty generated by variant forms of newborn screening targets. *Genet Med*. 2020;22(3):566–73. <https://doi.org/10.1038/s41436-019-0670-3>.
45. Bell M, Biesecker BB, Bodurtha J, Peay HL. Uncertainty, hope, and coping efficacy among mothers of children with Duchenne/Becker muscular dystrophy. *Clin Genet*. 2019;95(6):677–83. <https://doi.org/10.1111/cge.13528>.
46. Ojodu J, Singh S, Kellar-Guenther Y, Yusuf C, Jones E, Wood T, et al. NewSTEPS: the establishment of a National Newborn Screening Technical Assistance Resource Center. *Int J Neonatal Screen*. 2017;4(1):1. <https://doi.org/10.3390/ijns4010001>.